Mitigation of the threat posed to transfusion by donors traveling to Zika-affected areas: a Canadian risk-based approach

Marc Germain,[1] Gilles Delage,[1] Sheila F. O'Brien,[2] Yves Grégoire,[1] Margaret Fearon,[2] and Dana Devine[2]

BACKGROUND: The recent spread of the Zika virus to the Americas and the recognition that it can cause severe disease in the developing fetus has prompted the adoption of measures to mitigate the risk that this virus might pose to transfusion safety. In nonendemic countries, the risk to transfusion results from donors traveling to an endemic region. Canada implemented a 21-day temporary deferral for prospective donors who traveled to such regions. We present the rationale for this policy, including a quantitative risk assessment supported by a Monte Carlo simulation.

STUDY DESIGN AND METHODS: The model considered the following parameters, each with specified values and ranges: the probability that a donor recently returned from a Zika-endemic region, the duration of travel to this region, the daily risk of acquiring Zika while in an endemic region, and the incubation and viremic periods. We ran the simulation 20 times, each with 10 million iterations.

RESULTS: In the absence of any travel deferral, 32 donors (range, 20-46 donors) would be able to donate while still being at risk of transmitting Zika, corresponding to a rate of 1:312,500 (range, 1:217,000 to 1:500,000). None of these donors would be viremic beyond 21 days after returning from their travel, with a risk estimated at less than 1:200,000,000.

CONCLUSIONS: A 21-day temporary travel deferral offers an extremely wide margin of safety for the possible transmission of Zika by a donation obtained from someone who recently returned from a country where the virus is circulating.

In early 2016, it became clear that the Zika virus had spread extensively to the Americas, particularly in Brazil.[1] More important, there were increasingly stronger indications that this otherwise relatively mild, acute, self-resolving infection might pose a major risk to the fetus when women became infected during their pregnancy. This was initially suspected when health officials from Brazil reported a surge in the number of children born with microcephaly at the same time and in regions where the Zika virus had reached epidemic levels.[2] Subsequent reports confirmed the causal link between Zika and several neurodevelopmental defects in the fetus.[3] Within the international health care community, these dire effects of Zika on the fetus have certainly raised the level of concern for this emerging infection. Because of the potential for transmission of Zika through blood components, this concern also extended to the transfusion community.[4,5]

The threat posed by the Zika virus to transfusion safety has prompted the quick adoption of mitigating strategies to protect the blood supply, in particular the deferral of donors who recently returned from regions affected by the virus. In February 2016, the US Food and Drug Administration (FDA) issued a guidance document in which it recommended that donors should be screened for recent travel to Zika-endemic regions and that such donors should be deferred for 28 days.[6] More recently, because of the occurrence of locally acquired Zika

From [1]Medical Affairs, Héma-Québec, Montréal, Québec, Canada; and [2]Canadian Blood Services, Ottawa, Ontario, Canada.

Address reprint requests to: Marc Germain, MD, FRCP(C), PhD, Medical Affairs, Héma-Québec, 1070, Sciences-de-la-Vie Avenue, Québec, QC, Canada, G1V 5C3; e-mail: marc.germain@hema-quebec.qc.ca

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infections in Florida, the FDA issued a recommendation to systematically screen all blood donors in the United States with a Zika-specific individual donor nucleic acid test.[7] In Canada, since February 2016, a 21-day temporary deferral has been applied to prospective donors who travel to any location outside the country, except the continental United States and Europe. This report presents the rationale for the policy that was adopted in Canada, including a quantitative risk assessment supported by a Monte Carlo simulation.

The risk of Zika transmission through transfusion in a nonendemic country depends on several factors that still remain poorly quantified. For example, there are still no robust data regarding the risk of infection in someone traveling to a country where Zika is circulating. Also, our knowledge of the biology of the virus is still incomplete, in particular regarding the maximum duration of infectivity in blood. However, based on the limited data available for Zika and the extensive experience with other similar arboviruses, we believe that it is possible and reasonable to make some assumptions that can be used to quantify the risk and decide on which actions, if any, need to be taken. The Monte Carlo approach allows us to take into account the uncertainties around these estimates, in addition to the inherent biological variability of the infectious process.

MATERIALS AND METHODS

Our risk assessment was based on the premise that prospective donors could only become infected while traveling outside Canada, that is, with the assumption that the virus cannot be acquired locally, because the main mosquito viral vectors, *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*, are not endemic to Canada. The risk posed by donors who might become infected by sexual contact with a person infected abroad is not addressed in detail here; however, this particular risk was also evaluated, and the results of this assessment will be considered when discussing our findings.

Our approach was to build a simple stochastic model in which a prospective donor would have a certain probability of having traveled to a Zika-affected region. In turn, this donor would have a given probability of having been infected while traveling. An infected donor would then have a variable period of time during which the virus would be present in his or her blood in the absence of any sign or symptom that would preclude a blood donation. The Monte Carlo approach allowed us to randomly vary each of these parameters—independent from each other and between donors—in such a manner that all possible combinational scenarios might happen, according to probabilities specified for each parameter in the model. After having run this simulation for a very large number of prospective donors, the final output of the model is the distribution of lengths of time during which prospective donors might still be at risk of transmitting the virus after returning from a Zika-affected country.

The assumptions underlying our model and the values assigned to the various parameters were the following:

1. Maximum period at risk for infectivity in blood: We only considered travel for which the date of return was 56 days ago or less at the time of donation. Infections that might have happened more than 56 days before donation are considered to represent zero risk, that is, it was assumed that the duration of infectivity in blood would never extend beyond this time period.
2. Risk of exposure through travel: Donors in Canada have a 6.35% probability of having visited a Zika-affected country in the 56-day period before their donation. This parameter was obtained from a 2015 travel survey conducted among blood donors at the Canadian Blood Services; in the Monte Carlo simulation, this probability was allowed to vary uniformly between 5.87 and 6.88, which were the 95% confidence limits for the point estimate. It should be noted that, in the simulation, we assumed that donors were just as likely to donate on any given day, regardless of when they returned from their travel. In other words, we did not take into account the possibility that donors might be less likely to donate in the early period after their return from travel.
3. Duration of travel in Zika-affected countries: The usual duration of travel in a Zika-endemic region was assumed to be around 10 days; in the simulation, we used a triangular distribution, centered at 10 days, with extremes of 7 and 14 days; these durations are based on reports published by a government agency regarding international travel by Canadian citizens.[8]
4. Risk of Zika infection while traveling in an endemic region: The risk of having acquired the infection during travel to a Zika-endemic country was derived from another study that estimated the risk of acquiring Dengue while traveling to Singapore during the epidemic that affected that country in 2007; the risk was calculated to be 0.0017 for a travel duration of 1 week, that is, a daily risk of 0.000243.[9] We adjusted this risk to take into account the magnitude of the Zika epidemic in the Americas relative to the Dengue epidemic in Singapore. In the Americas, there had been 130,689 cases of symptomatic, suspected Zika infections reported, annualized to a 1-year period, in a population of 647,959,953;[10] assuming that only 20% of all infections were symptomatic, this translates into 653,445 cases, for an attack rate of 0.10%. The attack rate of Dengue in Singapore during the 2007 epidemic reportedly was 0.33% (14,006 cases in a population of 4,265,800).[11] Therefore, the daily risk of acquiring Zika in the Americas was adjusted accordingly: $0.000243 \times (0.10\%/0.33\%) = 0.0000736$. In the Monte Carlo simulation, the total risk of acquiring Zika

was allowed to vary from 0.0522151 to 0.104432%, depending on the randomly assigned number of days of travel for a particular donor.

5. Incubation period: At the time of our risk assessment, there were limited data to inform us on this parameter; by analogy, we used the extensive data that exist for the West Nile virus. For that virus, the experimentally measured incubation period was no longer than 2 days,[12] although it may be somewhat longer in natural infection.[13] Therefore, we assumed conservatively that the usual duration of the incubation period for Zika was 5 days; in the simulation, we used a log-normal distribution, with a mode at 5 days, and the 99th upper percentile of this distribution at 12 days.
6. Duration of viremia: The usual duration of Zika viremia was assumed to be 5 days, based on the limited data that were available.[14,15] Also, by analogy with the West Nile virus, in the simulation, we used a log-normal distribution, with a mode at 5 days, and the 99th upper percentile of this distribution at 18 days.
7. Proportion of symptomatic infections: We assumed that Zika is symptomatic in only 20% of cases.[16] In our model, donors with a symptomatic infection had a period of viremia of 2 days before the appearance of symptoms; beyond this time, donors would no longer be at risk of transmitting their infection through blood donation, because their symptoms would make them ineligible.
8. Risk of transmission through blood during viremic phase: We assumed that a donor had a 100% risk of transmitting Zika throughout their period of asymptomatic viremia. We did not consider the possible mitigating effect of neutralizing antibodies appearing at some point after the acute infection and before the end of detectable viral nucleic acid.

We used SAS Enterprise Guide 4.1 (SAS Institute, Inc.) to program the model and run the Monte Carlo simulations. We ran the model 20 times, each time with 10 million iterations; each of these iterations corresponded to a donor presenting for donation.

RESULTS

With a very large number of iterations (n = 10,000,000), Fig. 1 illustrates distribution according to the total duration of infection, that is, from the time of infection until the end of detectable viremia, among donors who might have been infected while traveling to a Zika-affected country. The pattern of this distribution is log-normal, as would be expected from the model. The modal duration is approximately 10 days but can be as long as several weeks in the most extreme cases, which would represent "worst case scenarios" in the simulation.

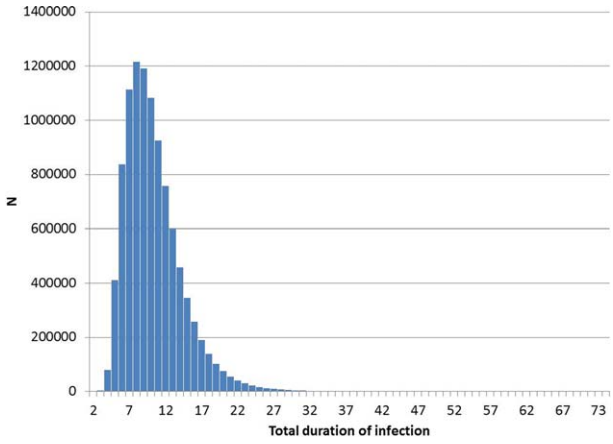

Fig. 1. Distribution of days of infection (incubation + viremia) according to the Monte Carlo simulation. The model assumes a log-normal distribution for both the incubation and viremic phases, each with a mode at 5 days, and the 99th upper percentile at 12 and 18 days, respectively. [Color figure can be viewed at wileyonlinelibrary.com]

The results were summarized by averaging all 20 simulations. Based on 10 million iterations per simulation, and in the absence of any temporary deferral that would target donors who returned from Zika-endemic regions, we observed that, on average, 32 donors (range, 20-46 donors) would be able to donate while still being at risk of transmitting Zika, corresponding to a rate of 1:312,500 (range, 1:217,000 to 1:500,000).

Figure 2 illustrates the distribution, for all 20 simulations combined, of the number of days that would remain until the end of viremia among the 632 donors who would not have yet reached this point at the time of return from their travel. This graph shows that a temporary deferral period of 21 days would interdict all of these donors. Given that the simulations were performed on a total of 200,000,000 iterations, this means that the risk of obtaining a donation from a viremic individual, under a scenario of a 21-day deferral, is less than 1:200,000,000. With a 14-day temporary deferral, only seven donors out of 632 infected donors would have been able to donate beyond the deferral period while still being viremic, for a risk of 1:28,571,000.

DISCUSSION

Our model suggests that, in the absence of any donor deferral, the risk of obtaining a contaminated donation from a Canadian donor returning from a Zika-affected country is small, on the order of 1:300,000. A 21-day deferral period brings down this risk to almost zero, with a residual risk on the order of less than 1:200,000,000. We believe that some assumptions made in this model were

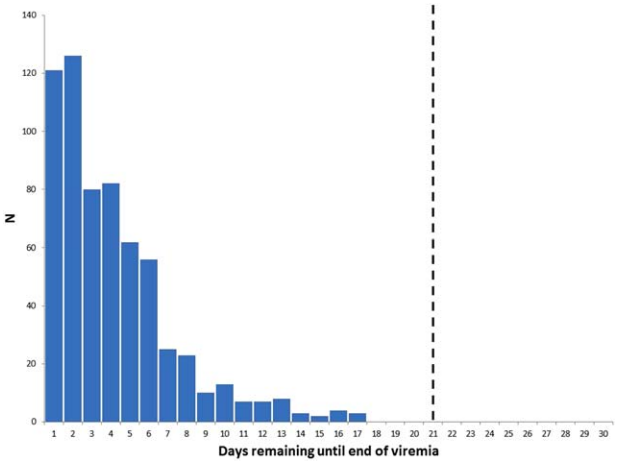

Fig. 2. Distribution of days remaining until the end of viremia among 632 infected donors returning from a Zika-endemic region, after running the Monte Carlo simulation 20 times with 10 million iterations each time. In the absence of any deferral, each of the 20 simulations resulted in an average of 32 donors (range, 20-46 donors) who would donate while still being at risk of transmitting Zika, for a baseline risk of 1:312,500 (range, 1:217,000 to 1:500,000). [Color figure can be viewed at wileyonlinelibrary.com]

likely to overestimate the real risk posed by Zika to transfusion in Canada.

First, the risk that a traveling donor will acquire Zika is likely to be much lower than we assumed. The model considers this risk to be equal in all countries that were declared to be endemic; however, the risk is likely to vary between countries and also over time; in countries that are more frequently visited by our donors (e.g., Mexico, Cuba), the risk is likely much lower compared with that in countries where there is more intense Zika activity, such as Brazil and Colombia. According to our survey, our donors rarely travel to these high-risk countries. Finally, the living conditions of traveling donors are probably such that their risk of infection is lower compared with that in the local population.

Second, the duration of the phase of potential infectivity in blood after a Zika infection is probably shorter than that used in our model. We assumed that the incubation and viremic periods were somewhat longer compared with those for West Nile, but the Zika-specific data suggest that these periods are shorter, especially for viremia. In a study by Gourinat and colleagues, viremia became undetectable after no more than 5 days after the onset of the rash in all six patients who were tested, suggesting that the mean duration of viremia was even shorter.[14] In a study of the Yap epidemic by Lanciotti and coworkers, 157 acute-phase blood specimens were tested by polymerase chain reaction (PCR), and only 17 patients were PCR-positive.[15] Of those 17 samples, the majority had been taken only a few days (range, 1-5 days) after the onset of symptoms, and only one patient had a PCR that was positive 11 days after the onset of symptoms. A study of 747 patients who presented with suspected acute-phase Zika virus infection during the 2013 and 2014 French Polynesian Zika virus outbreak also revealed that only 28.1% tested positive by reverse transcriptase-PCR.[17] Taken together, these data do not indicate that the potentially viremic phase of Zika will extend beyond 10 to 20 days after the infection, at least for the vast majority of infected individuals. A recently published review of these and other data concurred with this assumption.[18] Also, our model did not take into account the true infectivity of the virus present in blood, which is likely to be mitigated by the early appearance of neutralizing antibodies. In support of this notion, a recent study demonstrated that nine of 12 patients who received transfusions with Zika RNA-reactive blood products did not seroconvert; none of those 12 patients developed signs or symptoms consistent with Zika infection.[19] Therefore, our assumption of 100% transmissibility is likely to be overestimated. Finally, another recent report indicated that the proportion of symptomatic Zika infections may be approximately 55%, which is higher than what we assumed in our model and, if true, would further reduce the risk of collecting contaminated blood from asymptomatic donors.[20]

It is worth noting that the risk of transmission by transfusion estimated by our model, in the absence of any travel deferral, was very small, although it was not negligible. If this is the true risk, and given the increased awareness of the medical community concerning this infection, then we would expect that at least a few cases would be reported worldwide. In the United States alone, more than 20 million components are transfused each year, and many donors traveled to regions at risk for Zika before the implementation of any mitigating measure, yet not a single case of transmission by transfusion has ever been reported in a nonendemic country, including in North America. The very few cases of documented transmission all have been identified in Brazil, where the epidemic has been quite intense.[21,22]

There are no data to indicate that the transmission of Zika by transfusion, if and when it happens, can lead to more severe clinical outcomes compared with the mosquito-borne infection, which is most often benign. One potential situation in which the transfusion of a contaminated component might represent a significant risk is during early pregnancy, a situation which represents a very small fraction of all transfusions, likely less than 1%.[23] Guillain-Barre is another severe potential complication of Zika; however, this is also a rare occurrence and reportedly happens in less than 1 in 1000 infections.[24] Therefore, the clinically significant risk of transfusion-associated Zika can be further discounted by at least two orders of magnitude.

Some studies have demonstrated that the genetic material of the Zika virus can be recovered several weeks if not months after the acute infection in a variety of tissues from infected individuals, including blood from infected pregnant women.[25,26] A more recent study of symptomatic Zika infections in Puerto Rico reported that the 95th percentile of the distribution of detectable RNA in serum was 54 days, which is longer than what we assumed in our model in terms of infectivity.[27] Similarly, Galel and colleagues demonstrated that, when using sensitive, single-unit RNA testing, blood donors who had likely become infected in an endemic country tested positive between 6 and 71 days after returning from their travel.[28] These findings are in contrast with earlier studies, which reported shorter periods of detectable viremia[14,15]; this is likely because of the much higher sensitivity of the assays used in the more recent studies. It has not yet been determined whether this prolonged period of detectable viral RNA correlates with infectivity. However, by analogy with West Nile virus, it seems more likely that this prolonged detectability is because of inactive residues of the viral genetic material. Hopefully, future studies will help to resolve this issue. In the meantime, epidemiological data do not suggest that individuals can transmit for such long periods, at least not through blood components. Given the persistence of Zika RNA in serum, when someone is known to have been infected with Zika, it would seem prudent to defer this person from donating blood for a period longer than 21 days; the FDA, for example, recommends a 120-day deferral.[29] In these situations, the a priori probability of infection is obviously much higher compared with that of a random donor whose only risk factor is recent travel to an endemic region.

It should be noted that the 21-day deferral policy implemented in Canada is not only targeting regions that are currently identified as being endemic for Zika; it also applies to all regions outside of Canada, the continental United States, and Europe. The reason for this extended geographic coverage is because of the unknown future spread of Zika, which could very well happen in other tropical and subtropical areas of the globe. Indeed, Zika has previously been active in regions other than those currently identified as being at risk. Also, this policy will have the benefit of protecting the blood supply against other similar arboviruses, such as Dengue and Chikungunya, which have been shown to spread haphazardly in these same regions; this proactive approach will afford an increased level of protection against these unforeseen epidemics, assuming that these might pose a real threat to transfusion safety.

It has been demonstrated that Zika can be transmitted sexually, which raises the concern that prospective donors might become infected through this route. However, in a separate evaluation, we calculated that this risk was so small as to be negligible, on the order of 1:8,000,000.[30] Therefore, we did not consider the implementation of a screening question that would specifically target donors who might have been exposed in this manner.

Local transmission of Zika has been documented in regions of the United States not currently targeted by the Canadian travel deferral policy.[31] However, the extent of local transmission has remained very limited in the United States, and we calculate that the risk posed by Canadian donors traveling to these areas does not warrant any additional mitigating measures. It remains to be seen whether this level of risk will increase to a point that our current policy will need to be modified.

In conclusion, the results from this risk-modeling exercise support the notion that a 21-day temporary travel deferral offers an extremely good margin of safety for the possible transmission of Zika by the transfusion of a blood component obtained from a donor who recently returned from a country where the virus is active. This approach was reviewed and approved by Health Canada, the agency that regulates blood operators in our country. We continue to monitor the situation closely, and this policy will be modified if and when new data may warrant such a revision.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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