Residual infectious risks in blood transfusion

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Travel behavior and deferral of Dutch blood donors: consequences for donor availability

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ABSTRACT

Background
Donors returning from areas with outbreaks of infectious diseases may donate infectious blood back home. Geographic donor deferral is an effective measure to ensure the blood safety, but donor deferral may pose a threat for the blood supply especially after holiday seasons. Insight into the travel behavior of blood donors is a first step to define appropriate deferral strategies. This study describes the travel behavior of Dutch donors, the actual deferral, and the consequences of deferral strategies on donor availability.

Study design and methods
A questionnaire designed to assess travel behavior (destination, frequency, and duration of travels) was sent to 2000 Dutch donors. The impact of travel deferral policies on donor availability was calculated, expressed as proportionate decrease in donor availability. The deferral policies considered were 1) deferral based on entire countries instead of affected regions where an infection is prevalent and 2) deferral after any travel outside Europe ("universal deferral").

Results
Of the 1340 respondents, 790 (58.9%) donors traveled within Europe only, 61 (4.6%) outside Europe only, and 250 (18.7%) within and outside Europe. The deferral for entire countries and universal deferral would lead to 11.1 and 11.4% decrease in donor availability, respectively.

Conclusion
Most Dutch donors traveled outside the Netherlands, while 23.2% traveled outside Europe. Universal deferral resulted in an additional decrease in donor availability of 0.3% compared with deferral for entire countries instead of affected regions where an infection is prevalent. Thus, the universal deferral could be considered as a simpler and safer measure.
INTRODUCTION

Blood donors traveling to a country where an outbreak of an infectious disease is present, may contract the infection during their visit [1-4]. Subsequently, exposed blood donors may donate in an asymptomatic phase of the infection, resulting in infected blood products and the risk of infecting the recipient. Temporary donor deferral for the duration of the asymptomatic phase of an infection after visiting a risk area is therefore an effective precautionary measure. The blood establishment in the Netherlands (Sanquin) has defined risk areas for six infectious diseases (West Nile fever [WNF], Crimean Congo hemorrhagic fever [CCHF], chikungunya, dengue, malaria, and leishmaniasis). Deferral related to leishmaniasis has been set to 1 year; deferral for malaria is 6 months for visitors and 3 years for former residents or for persons having had an episode of malaria. Former residents can shorten their deferral if antibody testing at least 4 months after return turns out negative. Deferral for the other infections has been set to 28 days [5,6]. Donor deferral for malaria, leishmaniasis, and WNF risk does not apply to plasma donations used for fractionation.

The definition of the risk areas within countries has to be updated constantly as infections spread, and epidemics appear and disappear. More complex deferral policies lead to more errors, noncompliance, and confusion among donors and donor physicians. Examples are donors forgetting about visits to relevant areas or incorrectly estimating the time period spent. We therefore explored the possibility of simplifying the deferral rules. Deferral for any travel outside Europe, referred to as universal deferral, is considered an alternative. Belgium introduced the 28-day geographic deferral for candidate donors after travel outside Europe in 2007 [7]. The advisory board estimated that this might lead to an additional donor deferral of 0.5%, but this additional measure is a proactive approach for future epidemics.

Insight into the travel behavior of donors is necessary to enable the estimation of the impact of simplified deferral rules on the blood supply. As little was known about the number of trips and destinations of Dutch blood donors, we studied the travel behavior of Dutch donors by means of questionnaire. We used these data to calculate the consequences of two deferral policies (entire countries vs. universal deferral) for the blood supply.

MATERIALS AND METHODS

Study population
A random sample of 2000 Dutch active repeat whole blood and plasma donors was drawn from the donor database in March 2011 (Table 1).

Donor questionnaire
A questionnaire on travel behavior included questions about final destinations, frequency, duration, and season of the year of traveling as well as the nature of the visits. Areas
within countries were not queried, because this would complicate and lengthen the questionnaire. The questionnaire was distributed by regular mail in March 2011. Donors were asked to report on travels for each country they had visited, with a maximum of five countries within Europe and five outside Europe. A postage-paid return envelope was included in the mailing. All returned questionnaires were checked for obvious errors and illegible responses. If it was clear that a visit concerned a transit (because a donor mentioned this in the questionnaire), the transit was left out of the analysis. If it was questionable whether travel concerned a transit country or not, this country was included in the analysis.

Statistical analysis
The answers to the questionnaire were compiled and analyzed with computer software (SPSS, IBM SPSS Statistics, Version 19, IBM, Armonk, NY). To evaluate whether the study population was representative of the donor population, basic characteristics of the respondents, such as age, sex, and donation type, were compared with the nonrespondents and with the whole active donor population. Travel and destinations of the respondents were analyzed within Europe and outside Europe. Detailed travel behavior (frequency, duration, time or season of visit, and type of visited surroundings) was analyzed for each of the top 10 most visited countries (results not presented in this article). The top 10 countries visited outside Europe were compared to a previous assessment in 2007, to see whether travel pattern had changed over time [8]. A comparison was also made with data from the national bureau of statistics (CBS), regarding holiday destinations of Dutch inhabitants [9].

Deferral policies
The deferral policies we studied were:
1. Deferral based on entire countries instead of affected regions where an infection is prevalent (Fig. 1A).
2. Universal deferral for any travel outside Europe whereas deferral for countries within Europe with infections remains the same. We defined Europe as all countries located on the European continent, excluding the countries located mainly on the Asian continent (Turkey, Azerbaijan, Kazakhstan, Russia, and Georgia; Fig. 1B).

### Table 1. Characteristics of the sample and all Dutch active blood donors in 2010.*

<table>
<thead>
<tr>
<th>Basic characteristics</th>
<th>Questionnaire responders (N=1340)</th>
<th>Nonresponders (N=660)</th>
<th>Donor population (N=332,083)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.5 (±13.4)</td>
<td>40.2 (±13.0)</td>
<td>45.3 (±13.6)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>642 (47.9)</td>
<td>300 (45.5)</td>
<td>161,678 (48.7)</td>
</tr>
<tr>
<td>Whole blood donation</td>
<td>1102 (82.2)</td>
<td>591 (89.5)</td>
<td>273,941 (82.5)</td>
</tr>
<tr>
<td>Plasma donation for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractionation</td>
<td>197 (14.7)</td>
<td>56 (8.5)</td>
<td>49,891 (15.1)</td>
</tr>
<tr>
<td>Quarantine</td>
<td>41 (3.1)</td>
<td>13 (2.0)</td>
<td>8,251 (2.5)</td>
</tr>
</tbody>
</table>

* Data are reported as mean (±SD) or number (%).
Figure 1. (A) Policy 1: Deferral based on entire countries instead of affected regions where an infection is prevalent. (B) Policy 2: Universal deferral.
To estimate the effect of the deferral policies on donor availability we calculated the decrease in donor availability (i.e., the proportion of donors that would be unavailable due to travel deferral on any given day in a year) for leishmaniasis, malaria, and other infections and in total.

As fractionation plasma donors are not deferred after traveling to countries with malaria, leishmaniasis, or WNF, we did calculations separately for each donor group.

To estimate the decrease in donor availability we multiplied the proportion of donors deferred for only one infection risk with the number of days the deferral was for (length of deferral). For those with more than one deferral, we corrected for multiple deferrals by adjusting the number of days available in a year for a subsequent deferral. The deferral per donor was calculated with the formula:

\[
\text{Duration of deferral}_x = \frac{\text{Duration of deferral}_{x-1} + \text{Length of deferral}_x \times \frac{365 - \text{Duration of deferral}_{x-1}}{365}}{365}
\]

where \( x \in \{1, \ldots, n\} \) is the sequence of \( n \) subsequent deferrals in 1 year and Duration of deferral\(_x\) is the total deferral for that donor from travels in that year.

Length of deferral is the defined deferral for each infection, that is, 365 days for leishmaniasis, 182.5 days for malaria, and 28 days for other infections, and duration of the deferral is the calculated deferral corrected for overlap. For example, the duration of deferral for donors traveling once to countries where malaria occurred is 182.5 days (= 0 + 182.5 \times (365 − 0)/365). For two travels, the duration of deferral would be 273.75 days (= 182.5 + 182.5 \times (365 − 182.5)/365) and for three it would be 319.375 days (= 273.75 + 182.5 \times (365 − 273.75)/365). These deferral durations were then multiplied with the proportion of donors with that number and combination of travels. This gives us the mean number of days donors are unavailable for donation due to travel.

We divided the mean number of deferral days by 365 to calculate the mean proportionate decrease in donor availability on any given day in a year for the six infections. Confidence intervals (CIs) for those proportions were determined by bootstrapping the observed survey data (2000 samples). Variability in donor unavailability was determined by sampling of random timing and frequency of travel for each donor.

The decrease in donor availability with the deferral policies was calculated under the following assumptions:

- Each country visited could only lead to one deferral period. The longest period applicable was taken for countries with multiple infectious diseases.
- Since different deferral periods exist for malaria (travelers, residents, or history of malaria), we assumed that whole blood and quarantine plasma donors would be deferred from donation for 6 months after return from a malaria risk area [5,6].
- Donors contribute 365 potential donor days a year and therefore could not be deferred for more than 365 days.
- Other deferral reasons were independent of deferral because of travel.
• Travels were assumed to be mutually independent in time and randomly occurring over the year.
• Duration of travel would lead to donor unavailability as well, but this was not taken into account as this is not deferral caused.

With these assumptions, the decrease in donor availability is interpretable independent of the actual number of days available, that is, deferrals after donation or for other reasons do not change the proportionate decrease in donor availability due to travel reasons.

RESULTS

Population
Of 2000 questionnaires, 1340 (67%) were returned and available for analysis. Because of the high response rate no reminder was sent to the nonresponders. Of the donors that responded, 1101 (82.2%) had traveled outside the Netherlands in 2010: 790 (58.9%) traveled within Europe only, 61 (4.6%) traveled outside Europe only, and 250 (18.7%) traveled both in- and outside Europe. Donors traveled with a similar frequency as the Dutch inhabitants in the same age categories (82.2% vs. 82.4%) [9].

Characteristics of responders, nonresponders, and all donors are shown in Table 1. Responders were somewhat older and more frequently male than nonresponders or the donor population. Responders’ characteristics were more similar to those of the donor population in general than to those of the nonresponders.

Travel behavior
Table 2 shows the top 10 countries within and outside Europe visited by the respondents. Traveling was very similar for plasma and whole blood donors, both in frequency and in destinations. In comparison with results of the earlier study, the travel destinations outside Europe were very similar, but travel outside Europe of current responders was somewhat more frequent in 2010 than it was in 2007 (23.3% vs. 21.1%). As information on travel destinations for all Dutch inhabitants was unavailable, we compared with holiday visits of all Dutch inhabitants. Although, of course, frequency of travel was higher than frequency of holidays, the top 10 list of countries visited was similar [9].

In 2010, 20% of donors traveled to countries with malaria, 30% to countries with WNV, 15% to countries with dengue, 10% to countries with chikungunya, 6% to countries with CCHF, and 0.5% to countries with leishmaniasis. However, since most countries with dengue also had malaria, there is considerable overlap (Fig. 1). All leishmaniasis countries have a malaria risk area as well. Countries further away from the Netherlands were less frequently visited than neighboring countries and duration of stay was longer. The season of visits correlated strongly with the destinations.
Deferral policies

Table 3A summarizes the estimated decrease in donor availability of the two deferral policies. Table 3B presents the estimated CIs obtained by bootstrapping.

**Policy 1: deferral based on entire country instead of affected region where an infection is prevalent**

The estimated total decrease in donor availability for all reasons combined, corrected for overlap, would be 11.1% (95% CI, 9.8-12.2). Among 1143 whole blood and quarantine plasma donors, seven (0.6%) traveled to leishmaniasis countries, all only once. With a deferral of 365 days per visit, deferral for leishmaniasis would have occurred for an average of 2.3 days (=0.6% × 365) or a decrease in donor availability with 0.6% (=2.3/365). Furthermore, 221 donors (19.3%) had traveled to a malaria country, on average 1.2 times, with 16.8% of donors traveling once, 2% of donors traveling two times, and 0.5% three times. Deferral for malaria occurred for an average of 37.8 days (=0.168 × 182.5 + 0.02 × 273.75 + 0.05 × 319.375). This deferral would constitute a decrease with 10.4% (=37.8/365) of donor availability. Finally, 275 donors (24.1%) visited countries without malaria or leishmaniasis, but with CCHF, chikungunya, dengue, and/or WNF an average of 1.1 times. A total of 7.6 donor days would be lost due to deferral for these infections decreasing donor availability with 2.1%.

Forty-seven fractionation plasma donors (23.9%) visited countries with CCHF, chikungunya, and/or dengue an average of 1.4 times, resulting in an average of 9.1 deferrable days (2.5% decrease in donor availability). No further deferral would occur among this donor group.
Travel and deferral of Dutch donors

Policy 2: universal deferral for any travel outside Europe

The estimated total decrease in donor availability for all reasons combined, corrected for overlap, would be 11.4% (95% CI, 10.1-12.5). The estimated total deferral for whole blood and quarantine plasma donors would amount to 46.9 donor days or a decrease in donor availability with 12.8%. Nothing would change for travel to leishmaniasis or malaria countries; thus 0.6 and 10.4% of donors would be unavailable per day on average for these reasons, respectively. However, an additional 64 travels to countries outside Europe without outbreak would lead to additional deferral for 28 days in 59 donors, 34 of whom had no previous deferrals, resulting in a loss of 9.1 donor days or 2.5% of donor availability.

A universal deferral for all plasma donors would lead to an additional five deferrals in three donors, one of whom had not previously been deferred. A total of 48 donors with 71 travels would lead to deferral for 9.7 donor days or a decrease in donor availability of 2.7%.

In summary, the consequences of deferral for entire countries where an infection is prevalent (Policy 1) are that the decrease in donor availability would amount to 11.1% of all donors on average. Universal deferral (Policy 2) would result in an additional decrease with 0.3% (95% CI, 0.13-0.44) of donor availability.

Table 3A. Calculation of decrease in donor availability due to travel in 2010.

<table>
<thead>
<tr>
<th>Travel related infection risk leading to deferral (duration)</th>
<th>Number of travels per donor</th>
<th>Travelling donor (%)</th>
<th>Decrease in donor availability days (%)</th>
<th>No. of travels per donor</th>
<th>Travelling donor (%)</th>
<th>Decrease in donor availability days (%)</th>
<th>Difference in donor availability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood and quarantine plasma donors</td>
<td>n=1143</td>
<td></td>
<td></td>
<td>n=1143</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis (12 months)</td>
<td>1.0</td>
<td>7 (0.6)</td>
<td>2.2 (0.6)</td>
<td>1.0</td>
<td>7 (0.6)</td>
<td>2.2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Malaria (6 months)</td>
<td>1.2</td>
<td>221 (19.3)</td>
<td>37.8 (10.4)</td>
<td>1.2</td>
<td>221 (19.3)</td>
<td>37.8 (10.4)</td>
<td></td>
</tr>
<tr>
<td>CCHF/Chikungunya/Dengue/WNF (4 weeks)</td>
<td>1.1</td>
<td>275 (24.1)</td>
<td>7.6 (2.1)</td>
<td>1.2</td>
<td>309 (27.0)</td>
<td>9.1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>431 (37.7)</td>
<td>45.8 (12.5)</td>
<td>450 (39.4)</td>
<td>46.9 (12.8)</td>
<td>1.1 (0.31)</td>
<td></td>
</tr>
<tr>
<td>Fractionation plasma donors</td>
<td>n=197</td>
<td></td>
<td></td>
<td>n=197</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCHF/Chikungunya/Dengue (4 weeks)</td>
<td>1.4</td>
<td>47 (23.9)</td>
<td>9.1 (2.5)</td>
<td>1.5</td>
<td>48 (24.4)</td>
<td>9.7 (2.7)</td>
<td>0.6 (0.17)</td>
</tr>
<tr>
<td>All donors</td>
<td>n=1340</td>
<td>478 (35.7)</td>
<td>40.4 (11.1)</td>
<td>498 (37.2)</td>
<td>41.4 (11.4)</td>
<td>1.0 (0.29)</td>
<td></td>
</tr>
<tr>
<td>All infections</td>
<td>n=1340</td>
<td>478 (35.7)</td>
<td>40.4 (11.1)</td>
<td>498 (37.2)</td>
<td>41.4 (11.4)</td>
<td>1.0 (0.29)</td>
<td></td>
</tr>
</tbody>
</table>

* Deferral of donors according to guidelines of 2010, deferral based on the continuous monitoring of outbreaks for entire countries where an infection is prevalent.
† Universal deferral: after travel to any country outside Europe.
This study describes the travel behavior of Dutch active donors in 2010 obtained with a questionnaire and its impact on donor availability. The basic characteristics of the questionnaire respondents show that they were representative of the whole donor population. Most of the respondents (82.2%) traveled outside the Netherlands in 2010. Of them, almost a quarter (22.3%) traveled to countries outside Europe where outbreaks of emerging infections had been reported and deferral was indicated. We estimated the impact of travel deferral on donor availability using these data. This resulted in an estimated decrease with 11.1 and 11.4% of donor availability for deferral of entire countries and universal deferral, respectively. The additional decrease in donor availability associated with universal deferral was considered acceptable. Therefore, universal deferral of donors after travels outside Europe was introduced in the Netherlands in December 2012. We are currently evaluating the actual impact of this policy on deferral for travel. As it is well known that donors who are deferred on site are approximately 20% less likely to return when invited for the next donation [10], we will also monitor return rates.

Table 3B. Bootstrapping results with confidence intervals (95%)

<table>
<thead>
<tr>
<th>Travel related infection risk leading to deferral (duration)</th>
<th>Policy 1: deferral on entire countries instead of affected regions*</th>
<th>Policy 2: universal deferral†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of travels per donor</td>
<td>Travelling donor (%)</td>
</tr>
<tr>
<td>Whole blood and quarantine plasma donors n=(1117-1167)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis (12 months)</td>
<td>1.0-1.0</td>
<td>2-13</td>
</tr>
<tr>
<td>Malaria (6 months)</td>
<td>1.1-1.2</td>
<td>195-249</td>
</tr>
<tr>
<td>CCHF/ Chikungunya/Dengue/WNF (4 weeks)</td>
<td>1.1-1.2</td>
<td>246-304</td>
</tr>
<tr>
<td>Total</td>
<td>398-465</td>
<td>41-51</td>
</tr>
<tr>
<td>Fractionation plasma donors n=(172-224)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCHF/ Chikungunya/Dengue (4 weeks)</td>
<td>1.2-1.6</td>
<td>34-61</td>
</tr>
<tr>
<td>Total</td>
<td>444-513</td>
<td>36-44</td>
</tr>
</tbody>
</table>

* Deferral of donors according to guidelines of 2010, deferral based on the continuous monitoring of outbreaks for entire countries where an infection is revalent.
† Universal deferral: after travel to any country outside Europe.

DISCUSSION

This study describes the travel behavior of Dutch active donors in 2010 obtained with a questionnaire and its impact on donor availability. The basic characteristics of the questionnaire respondents show that they were representative of the whole donor population. Most of the respondents (82.2%) traveled outside the Netherlands in 2010. Of them, almost a quarter (22.3%) traveled to countries outside Europe where outbreaks of emerging infections had been reported and deferral was indicated. We estimated the impact of travel deferral on donor availability using these data. This resulted in an estimated decrease with 11.1 and 11.4% of donor availability for deferral of entire countries and universal deferral, respectively. The additional decrease in donor availability associated with universal deferral was considered acceptable. Therefore, universal deferral of donors after travels outside Europe was introduced in the Netherlands in December 2012. We are currently evaluating the actual impact of this policy on deferral for travel. As it is well known that donors who are deferred on site are approximately 20% less likely to return when invited for the next donation [10], we will also monitor return rates.
Globally monitoring all new outbreaks of infectious diseases, with continuous monitoring and risk assessments, is a time-consuming activity and leads to variable donor deferral rules over time. Furthermore, interventions are frequently only implemented after the outbreak has occurred. Applying universal deferral for 4 weeks after travels outside Europe seemed to be a more sensible proactive approach in terms of maintaining a safe blood supply.

The calculations were carried out under the assumption that travels were mutually independent. However, it is very likely that travels further away included several destinations, with almost complete overlap of deferral periods and a smaller decrease in donor availability than that calculated.

If we examine donor visits as samples of donor days available, the proportion of visits resulting in deferral for travel should be similar to the proportion decrease in donor availability. The actual deferral in our study was much lower, however. The proportion of visits with travel-related deferral was 2.6% in total among whole blood donors: 1.6% for malaria, 0.1% for leishmaniasis, and 1.7% for other infections. Total deferral was 0.9% among fractionation plasma donors.

There are several possible explanations for this discrepancy. First, donors are not invited to donate the day after their return and thus are not deferred for the standard period, but for the time remaining. Furthermore, donors who are deferred for a long period will not receive an invitation for donation and, thus, lower the number of deferrals on record. Furthermore, self-deferral of donors would lower the frequency of deferrals on file as well. Donors might also reschedule donation visits to just before a trip, introducing dependence of deferrals for travel with the donation lag. For viral infections, the dependence will probably be small, given that a new invitation is unlikely to be sent within 28 days of a previous visit for those deferred as well as for those not deferred. However, a new invitation will be sent to nondeferred donors and not to donors deferred for malaria or leishmaniasis in the 6 or 12 months after deferral. This lowers the proportion of visits with deferral but not the proportion decrease in donor availability.

Finally, with the estimation of deferrals we assumed whole countries were at risk for infectious diseases, while in practice donors were deferred based on regions within a country they traveled to. However, it was not feasible to accurately measure visits to areas or regions with infection risks with the questionnaire. A case in point is Turkey, where malaria risk is present only in the mountains across the northeastern border, while almost all travelers only visit the seaside resorts in the south west. A quarter of the donors traveling outside Europe visited Turkey. Recalculation, as if Turkey were a nonmalarial country, would reduce the mean decrease in donor availability from 11.1% to 10.5% for Policy 1 and from 11.4% to 10.8% for Policy 2.

In this analysis we studied the impact of travel deferral policies on the donor availability. The next step to explore could be the impact of travel deferral on the actual number of transmissions that would be prevented by these deferral policies. To investigate this, future research needs to examine the duration of the travel, the timing of donation since the last travel, the infection pressure in the visited areas, and the actual incidence of infections among the returning donors.
REFERENCES