Residual infectious risks in blood transfusion
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The yield of temporary exclusion of blood donors, exposed to emerging infections abroad

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ABSTRACT

Background and objectives
Emerging infections abroad pose a threat to the safety of blood, donated by travelling blood donors. In this study, the yield of donor deferral after travelling was evaluated, by comparing the estimated numbers of infected donors returning from various affected areas.

Methods
A deterministic model was applied to calculate the number of infected donors, returning from six areas affected by outbreaks: Greece – Macedonia (West Nile fever), Italy – Emilia Romagna (West Nile fever), Thailand (chikungunya), Latvia (hepatitis A), central Turkey (Sicilian sandfly fever) and Italy – Tuscany (Toscana sandfly fever).

Results
The estimated number of infections among returning blood donors was surprisingly low, ranging from 0.32 West Nile virus-infected donors per year returning from Macedonia (Greece) to approximately 0.005 infected donors per year returning respectively from Tuscany (sandfly fever), Latvia (hepatitis A) and central Turkey (sandfly fever).

Conclusion
The yield of the temporary exclusion of blood donors travelling to a specific, affected area is low, but the continuous monitoring of emerging infections and the timely assessment of new threats are laborious and imperfect. Safety measures may be instituted after the greatest threat of a new outbreak has passed. A general deferral of travelling donors may be more appropriate than targeted measures. It can be argued that all donors who stayed outside their country or continent of residency should be deferred for 4 weeks.
INTRODUCTION

International travel is among the top 10 causes of emerging diseases [1]. During holidays, people may fall prey to infection and subsequently introduce the infection in their home country. Travelling donors who unknowingly import infections may endanger the safety of the blood supply at home [2]. To ensure the safety of blood, for each emerging infection the Dutch blood transfusion service (Sanquin) rapidly assesses whether measures must be taken to prevent blood-borne transmission of the agent involved. Since 2008, the Sanquin Working group for emerging blood-borne infections (WOBI) yearly evaluated several hundreds of signals on emerging infections, with possible implications for the safety of the blood supply. For example, WOBI monitors new and ongoing outbreaks of dengue, Q-fever, chikungunya, hepatitis A, West Nile fever, Rift Valley fever and tick-borne en-
Cephalitis. At present, donors are deferred after travelling to countries that are at risk for one or more agents. Fig. 1 shows that these cumulative measures lead to the temporary exclusion of donors travelling to almost all countries outside Europe. Only travel to Tunisia, Morocco, Japan, New Zealand, Kazakhstan and the United Arab Emirates do not lead to temporary exclusion. Although specific data on tourists to these countries are hard to find, this concerns a small proportion of Dutch tourists [3].

Many blood banks implemented a deferral policy for donors who travel to countries that pose a risk due to endemic or (re)emerging infectious agents. To this end, an extensive list with countries and regions that pose a threat to blood safety has to be maintained and readjusted constantly. For example, Emilia Romagna in Italy (in 2008) and Central Macedonia in Greece (in 2010) emerged as risk areas for West Nile virus (WNV), while Thailand became a risk area for chikungunya in 2009. In practice, once a region is on the list for temporary exclusion of travelling donors, it stays on the list for many years. The yield of the temporary exclusion of travelling blood donors is unclear. To evaluate the practice of donor deferral, we compared the estimated threat to the safety of blood of three outbreaks that caused the deferral of Dutch donors, to the estimated threat of three outbreaks that did not cause temporary exclusion of donors, although they concerned major tourist destinations.

**MATERIALS AND METHODS**

The number of infected blood donors was estimated, returning from the following six areas with a local outbreak: West Nile fever in Greece (2009), West Nile fever in Italy (2009), chikungunya in Thailand (2008–2009), hepatitis A in Latvia (2008), Sicilian sandfly fever in Turkey (2008) and Toscana sandfly fever in Italy (yearly 1995-2009). Temporary exclusion of blood donation was instituted for the first three of these outbreaks.

We applied a deterministic model to estimate the number of infected donors returning from the areas that had an outbreak (see Fig. 2). The sources and values of the parameters and estimators are documented in Table 1. First the local incidence of the six outbreaks was calculated, using the symptomatic vs. asymptomatic ratio of each infection. Subsequently the tourist incidence was calculated by adjusting the local incidence by two factors. Tourists stay in an affected area only during a limited period of time, and thus have less time to become infected as compared to the local residents. Furthermore, an infectious agent may be active only during a part of the year. For instance, if an agent is active during 3 months of the year, only one in four visitors may be in the affected area at the time of risk. We corrected for the seasonal activity of the infectious agents as obtained from literature. Finally we applied these results to the estimated number of donors visiting each affected area.

Following these steps, the expected number of infected returning donors was calculated, taking into account the following assumptions:

1. Tourists travel randomly throughout the year and a trip abroad lasts on average 2 weeks. In Dutch travel data, seven periods of travelling can be distinguished: au-
The yield of deferral of travelling blood donors

By autumn, Christmas, spring, Easter, pre-season, high season and past season [3]. As a consequence, the current number of donor deferrals is relatively stable throughout the year, with a moderate increase in week 31–35 (see Fig. 3). On average, 542 donors per week (2.7% of all donors) are deferred for travelling to countries that are at risk for the selected infectious agents.

(2) Although in general Dutch donors are healthier than the average Dutchmen and are aged between 18 and 70 years, they travel as much as the average Dutchmen and to the same destinations, with an average travel duration of 2 weeks. The percentage of donors in the Dutch population is 2.4%. (The number of donors is 404,184 [4] and the Dutch population is 16,574,989 [5].

(3) Dutch travellers visit the same regions in a country as tourists from other countries do.

(4) The data on local incidence, based on notifications or hospitalizations, are an underestimation of the real incidence. Based on literature for each agent, the amount of underreporting was estimated (Table 1).

![Figure 2. Model for calculation of travelling donors at risk for infection.](image)

**Table 1.** Characteristics of emerging infectious diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage asymptomatic</th>
<th>Seasonal activity</th>
<th>Transfusion Transmissible</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Nile virus</td>
<td>70-80%, ≤1% neuroinvasive [6-11]</td>
<td>13 weeks [21,22]</td>
<td>Yes [32–34]</td>
</tr>
<tr>
<td>Sicilian sandfly fever</td>
<td>≥80% [15,16]</td>
<td>36 weeks [15,28,29]</td>
<td>Unknown, not documented [18,29]</td>
</tr>
<tr>
<td>Toscana sandfly fever</td>
<td>70%-90% [17-20]</td>
<td>26 weeks [17,18,30,31]</td>
<td>Unknown, not documented [18,31]</td>
</tr>
</tbody>
</table>
We selected the six outbreaks for this study based on the availability of data and because newly emerging infections were involved. To limit the number of estimators, and thus the amount of uncertainty, we did not include subsequent estimations for the fraction of infected donors that actually would donate while being infectious; nor did we estimate the morbidity and mortality that various transmitted agents subsequently would cause via different blood components, in various categories of recipients. The variation that was found in literature for the parameters is shown in Table 1. If different values for parameters in the calculations were available, the values were used that would lead to the highest estimation of the number of infected donors.

RESULTS

To assess the risk of infections, introduced by travelling blood donors, we analysed six emerging infections abroad. For each outbreak, the incidence for the local population and for visiting Dutch donor tourists was calculated, as illustrated by the following example for WNV in Greece:

The yearly number of Dutch donors visiting Central Macedonia was obtained by adjusting the number of Dutch tourists to Greece (730,000) for the percentage of foreign-
ers in Greece travelling to Central Macedonia (17%) (P1). Neuro-invasive West Nile disease is thought to represent approximately one in 244 of all WNV infections [10], including mild and silent cases; thus, the 84 hospitalizations in Central Macedonia represent 20,496 infections. For a population of 1.8 million people, this means a local incidence (P2) of 20,496/1,874,597 = 1093.35 per 100,000 inhabitants per year. The tourist incidence was calculated at 10.51 per 100,000 by adjusting for the weeks West Nile virus is active (13/52 = 0.250; see Table 1) and the time a tourist is in the area (2 weeks a year or 2/52 = 0.38). Thus, among the infected Dutch tourists, 10.51/100,000*3026 = 0.32 infected Dutch donors (P3) can be expected per year.

The local incidence ranged from 1093 cases of WNV infection per 100,000 inhabitants in central Macedonia (Greece) to seven cases of Toscana virus (TOSV) infection per 100,000 inhabitants in Tuscany (Italy). The estimated tourist incidence ranged from 10 cases of WNV infection per 100,000 travellers in Central Macedonia (Greece) to 0.13 cases of TOSV infection per 100,000 travellers in Tuscany (Italy), see Table 2.

Table 2. Yield of exclusion of travelling blood donors.

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Greece</th>
<th>Italy</th>
<th>Thailand</th>
<th>Latvia</th>
<th>Turkey</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>WNV</td>
<td>WNV</td>
<td>Chik</td>
<td>HAV</td>
<td>SFSV</td>
<td>TOSV</td>
<td></td>
</tr>
<tr>
<td>Inhabitants of affected regiona</td>
<td>1,874,597</td>
<td>4,337,979</td>
<td>67,070,000</td>
<td>2,261,300</td>
<td>9,228,204</td>
<td>3,707,818</td>
<td></td>
</tr>
<tr>
<td>Number of notificationsb</td>
<td>-</td>
<td>-</td>
<td>23,847</td>
<td>2,817</td>
<td>260</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Number of hospitalizationsb</td>
<td>84</td>
<td>9</td>
<td>23,847</td>
<td>2,817</td>
<td>260</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Local Incidence/100,000/year</td>
<td>1093.35</td>
<td>50.62</td>
<td>59.26</td>
<td>166.10</td>
<td>14.09</td>
<td>6.74</td>
<td></td>
</tr>
<tr>
<td>Adjusted tourist incidence/100 000/year</td>
<td>10.51</td>
<td>0.49</td>
<td>1.52</td>
<td>1.06</td>
<td>0.36</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Dutch travellers to countryc</td>
<td>730,000</td>
<td>1,020,000</td>
<td>183,347</td>
<td>19,000</td>
<td>760,000</td>
<td>1,020,000</td>
<td></td>
</tr>
<tr>
<td>Percentage tourist to regiond</td>
<td>17%</td>
<td>10%</td>
<td>100%</td>
<td>100%</td>
<td>5%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Number of Dutch donors to region</td>
<td>3026</td>
<td>2512</td>
<td>4471</td>
<td>463</td>
<td>1001</td>
<td>2761</td>
<td></td>
</tr>
<tr>
<td>Expected number of infected donors/year</td>
<td>0.318</td>
<td>0.012</td>
<td>0.068</td>
<td>0.005</td>
<td>0.004</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Bold in last 2 lines indicates the (important) outcome numbers of the estimation.

aData on number of inhabitants in affected region, obtained from statistical offices: Greece [37], Italy [38], Thailand [39], Latvia [40], Turkey [41].

bData on number of notified cases or hospitalizations: West Nile virus (WNV) in Central Macedonia Greece [42], WNV in Italy [43], chikungunya (chik) in Thailand [23], hepatitis A (HAV) in Latvia [25, 26], sandfly fever Sicilian fever (SFSV) in Turkey [27] and Toscana virus (TOSV) in Italy [17, 44].


Regarding the yield of the temporary exclusion of travelling blood donors, two factors are important: the number of returning donors to be excluded and the number of infections among the excluded donors. The expected annual number of returning donors from the six affected areas ranged from 463 donors returning from Latvia to 4471 donors returning from Thailand (see Table 2). The estimated number of infections among the returning donors is surprisingly low and ranged from 0.32 WNV-infected donors per year returning from Greece, to 0.004 sandfly fever Sicilian virus-infected donors respectively 0.004 TOSV-infected donors returning from Turkey respectively Italy. The relatively high number of expected WNV-infected donors from Macedonia was caused by the high number of tourists visiting this area combined with a high local incidence.

Nevertheless, only one WNV-infected donor can be expected to return from Macedonia every 3 years.

DISCUSSION

In this study, the number of infected Dutch blood donors was estimated, returning from areas affected by an outbreak respectively of West Nile fever (in Greece and Italy), chikungunya (in Thailand), hepatitis A (in Latvia) or sandfly fever (in Italy and Turkey). The modelled infection risk for travelling donors exposed to these emerging infections appears to be very low. Although the yield of temporary donor exclusion for the six small regional outbreaks is low, the number of expected infected returning donors travelling to these areas cannot be neglected.

We estimate that deferral of donors who travelled to Central Macedonia excludes at most one WNV-infected donor every 3 years, and the deferral of donors returning from Thailand excludes one chikungunya virus-infected donor every 15 years. For West Nile fever in Emilia Romagna, hepatitis A in Latvia and sandfly fever in Tuscany and Turkey, the deferral of returning donors would exclude at most one infected donor in 80-300 years, for each infection. The actual yield of donor deferral is lower, because this study is limited to the number of donors acquiring infection abroad. These incidences are smaller than the estimated residual window risk for transmission of HIV after introduction of nucleic acid-based screening of blood donations in the Netherlands [4]. In addition, it must be considered that we applied conservative estimators in our analysis. In the unlikely event that we underestimated some parameters, this does not affect the order of magnitude of our estimations. In our calculations, the travel characteristics of the general population were projected to the donor population. This approach is practical and timesaving, as general travel data are readily available, and probably are sufficiently indicative to be used in a risk analysis for a rapid decision regarding the safety of blood donations, after the first notification of a new outbreak.

The threshold of the number of expected infected donors, above which targeted safety measures like donor deferral should be implemented, is unclear. It appears that blood transfusion services follow their own procedures regarding the monitoring of infectious threats to their blood supply, and the implementation of safety measures. Only recently,
a common approach has been proposed regarding the increasing occurrence of WNV in Europe. According to a recommendation in an ECDC report of a WNV expert meeting in 2011 [50], donors should be deferred for 4 weeks if they return from an area where an autochthonous case of neuro-invasive West Nile fever occurred. However, then extent of the area to be banned remains undefined. As an result, national blood transfusion services define their own deferral areas. To limit the impact on the blood supply, some apply a piecemeal approach for the area to be banned, before the country is banned as a whole. An affected area may be a popular tourist destination for one country but an uncommon destination for another country. If the affected area hardly is visited, donor deferral will hardly contribute to blood safety, and a blood transfusion service may decide to ignore the risk and refrain from donor deferral.

The working group for the monitoring of emerging infectious diseases (WOBI) of the Dutch blood transfusion service continuously screens signals and reports on possible outbreaks. For each outbreak abroad, the consequences of imported infections for the safety of blood have to be assessed, although for many agents insufficient data are available regarding their transmission via blood transfusion. Currently, the Dutch blood transfusion service defers donors if they travelled to regions where one or more of the following infections occur: Congo–Crimean haemorrhagic fever, chikungunya, dengue, leishmaniasis visceralis, malaria and West Nile fever. In practice, the areas where these infections occur cover most of the world outside of Europe (see Fig. 1). Within Europe, the area affected by West Nile fever has expanded the last few years. Our analysis shows that the yield of deferring donors, who return from a specific affected area, is low. In addition, blood safety measures may be implemented at the time that the greatest threat of an outbreak is over, due to the delays caused by the local detection and confirmation of infections, and the subsequent international notification of the outbreak. On the other hand, many areas representing a small risk together represent a more substantial risk, and in addition concurrent emerging infections, including outbreaks that not yet have been reported, may be present in the same area. Regarding the management of the threat of imported infections, a more proactive policy is possible, reducing the risk posed by delayed and incomplete information. Expanding the current practice of targeted deferral to universal deferral of 4 weeks after each stay abroad would cover most emerging viral infections, while at the same time the import of infections is prevented during yet unreported outbreaks.

Arguments in favour of general donor deferral are as follows. No longer the implementation of safety measures is late or absent because of delayed or missing reports on outbreaks. A general deferral of 4 weeks after travelling would cover most of the known and unknown viral import infections. No longer must hasty assessments be made while data on the new outbreak are incomplete. General deferral is easier to implement and easier to explain to travelling donors, and prevents the continuous updating of guidelines within blood banks. Finally, in reality the areas where emerging infections such as dengue, West Nile fever and chikungunya occur, necessitating donor deferral together already cover most of the non-Western world (Fig. 1).

Drawbacks of general donor deferral include the reduced availability of donors during the holiday season. Adequate donor management, compensating the lower donor
availability, is essential to prevent blood shortages. For the Netherlands, exclusion of all countries outside Europe would only cause an estimated 5% increase of deferrals (unpublished data), resulting in the deferral of 570 donors (2.8% of all donors) per week instead of 542 donors (2.7%) per week. General deferral for 4 weeks does not cover the risk of infections such as malaria and leishmaniasis; the need for monitoring of emerging infections persists, albeit for far less agents.

Emerging infectious diseases are a threat to the blood supply. A systemic research found nearly 90 new human pathogens since 1980 [51]. To allocate our limited resources, attempts are undertaken to prioritize infectious diseases, regarding their relevance for blood transfusion [52]. To guarantee the safety of the blood supply, a proactive policy seems required, reducing the risk posed by delayed information on emerging infections. Interactive universal risk assessment tools may be helpful in evaluating emerging threats. However, essential input parameters for such risk analysis often are not at hand at the time of a newly emerging outbreak. Alternatively, instead of the current practice of continuous risk analysis and targeted donor deferral, a simplified general deferral of all donors who stayed outside their country or continent of residence can be considered.

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REFERENCES