Residual infectious risks in blood transfusion

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Estimating the risk of dengue transmission from Dutch blood donors travelling to Suriname and the Dutch Caribbean

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ABSTRACT

Background
The risk of dengue transmitted by travellers is known. Methods to estimate the transmission by transfusion (TT) risk from blood donors travelling to risk areas are available, for instance, the European Up-Front Risk Assessment Tool (EUFRAT). This study aimed to validate the estimated risk from travelling donors obtained from EUFRAT.

Methods
Surveillance data on notified dengue cases in Suriname and the Dutch Caribbean islands (Aruba, Curacao, St. Maarten, Bonaire, St. Eustatius and Saba) in 2001–2011 was used to calculate local incidence rates. Information on travel and donation behaviour of Dutch donors was collected. With the EUFRAT model, the TT risks from Dutch travelling donors were calculated. Model estimates were compared with the number of infections in Dutch travellers found by laboratory tests in the Netherlands.

Results
The expected cumulative number of donors becoming infected during travels to Suriname and the Dutch Caribbean from 2001 to 2011 was estimated at 5 (95% CI, 2-11) and 86 (45-179), respectively. The infection risk inferred from the laboratory-based study was 19 (9-61) and 28 (14-92). Given the independence of the data sources, these estimates are remarkably close. The model estimated that 0.02 (0.001-0.06) and 0.40 (0.01-1.4) recipients would have been infected by these travelling donors.

Conclusion
The EUFRAT model provided an estimate close to actual observed number of dengue infections. The dengue TT risk among Dutch travelling donors can be estimated using basic transmission, travel and donation information. The TT risk from Dutch donors travelling to Suriname and the Dutch Caribbean is small.
INTRODUCTION

Dengue fever is one of the most important mosquito-borne diseases in the world. It is caused by the Dengue viruses (DENV) of which four serotypes are known. Subsequent dengue infections can lead to a severe haemorrhagic shock syndrome [1]. In addition to mosquito bites, dengue can be transmitted via needle stick accidents, blood transfusion [2,3], bone marrow and kidney transplantation. Dengue is highly endemic in tropical and subtropical areas in Asia, Africa and America, which often are popular tourist destinations.

Travellers are increasingly at risk for dengue [4,5] because of the increasing prevalence of dengue worldwide driven by the wider spread of vectors, and the increasing worldwide travel [6]. Some studies estimated the number of new infections among travellers by means of mathematical models [7] or by testing blood samples of returning travelers [4]. The probability of Dutch travellers becoming infected with dengue while travelling has been reported specifically. Cleton and colleagues made an estimate of the proportion of dengue infections in travellers associated with the subgroup of travellers who visited tropical and subtropical regions in 2007 and 2010 of 0.02%–3.7% and 0.06%–7.6%, respectively [8]. Baaten and colleagues in 2006-2007 found an incidence rate of 1.46 (95% CI, 0.83- 2.39) per 100 person-months among the travellers to the tropics [4]. The Baaten study mentioned that travellers to South-East Asia were at higher risk than travellers to other regions but did not present the incidence per destination because of small sample sizes.

To date, no estimates of DENV transmission from travelling donors through blood transfusion has been put forward. The European Up-Front Risk Assessment Tool (EUFRAT), a web-based risk assessment tool made available by the European Centre for Disease Prevention and Control (ECDC) to quantify the risk of infectious disease transmission through blood transfusion (http://eufrattool.ecdc.europa.eu), can be used to assess the transmission risk from travelling donors [9]. In this study, we aim to validate estimates of number of Dutch donors that become infected when travelling to Suriname or the Dutch Caribbean (Aruba, Curacao, St. Maarten, Bonaire, St. Eustatius and Saba) in the years 2001 through 2011 obtained by the EUFRAT model, by comparing these estimates with the number of dengue infections among Dutch travellers in the general population obtained from a laboratory-based study [8]. In addition, we used the EUFRAT model to estimate the expected number of transfusion transmission cases from the infected travelling donors.

MATERIALS AND METHODS

The model and study design
Figure 1 illustrates the steps in determining the probability of a donor who visits an area where there is ongoing local transmission of a pathogen, becoming infected, returning to the Netherlands and presenting to donate while being infectious. Donors from an infection-free area are considered susceptible to infection before they travel to the area with risk of infection transmission. The likelihood of these donors becoming infected depends
on the duration of the visit and the force of infection, that is the rate at which susceptible individuals acquire an infectious disease (which varies over the beginning, peak, or end of the dengue season). The force of infection is assumed to be approximated by the incidence rate among the local population in the infection risk area. Next to the probability of the travelling donors becoming infected during their visit, the risk of transfusion transmission from a returning travelling donor also depends on the length of the incubation time, the infectious period, donation frequency and possibly also the type of donation. The transfusion transmission risk from travelling donors is estimated in terms of the expected number of infected travelling donors, and the resulting number of infected blood recipients. The estimated number of infected blood recipients is adjusted for the impact of existing safety measures, and the probability that a viraemic donation causes an infection in recipients.

The number of dengue transfusion transmission cases from travelling donors was estimated using the methodology of the EUFRAT model. The model has been elaborated elsewhere [9], and an update to the specific part in estimating the transfusion transmission risk from a group of travelling donors has been recently described [T Mapako, W Oei, M van Hulst, ME Kretzschmar, MP Janssen]. The model population includes active blood donors in the Netherlands who travelled to Suriname or to the Dutch Caribbean. We chose these countries because they are popular travel destinations for Dutch citizens.

Figure 1. Scheme of donors travelling to and returning from an infection risk area. Each box shows a list of model parameters used to estimate the transfusion transmission risk of donors who travel from an infection-free area to an area with an infection risk.
The dengue infection risk for the general Dutch population has been recently described by analysing dengue laboratory requests of the Dutch travellers in 2000–2011 [8]. From this laboratory-based study, we inferred the expected number of infected donors returning from Suriname or the Dutch Caribbean. We next compared EUFRAT’s estimates of infected donors with the number of dengue infections inferred from the laboratory-based study for model outcome validation.

For estimating the dengue transfusion transmission risk from travelling donors, the following input parameters are needed:

1. Dengue incidence rate in the infection risk area
2. Travel information of Dutch donors: frequency of travel to and length of stay in the risk area
3. Donation frequency and products derived from a donation
4. Disease-specific parameters for dengue (proportion of asymptomatic infections, duration of asymptomatic infectious period, incubation time)

Data collection

Surveillance data and incidence of dengue infection in the risk area

Dengue surveillance data as used in this analysis was collected by the different Epidemiology, Surveillance and Research Unit in the respective public health departments of Suriname and the islands of the Dutch Caribbean [personal communication with the respective public health officials]. The cases were notified following laboratory requests for patients who fulfilled the case definitions according to the Caribbean Epidemiology Centre CAREC [10], and further information on notification system in each public health department can be found in the Appendix. We assume that the notified cases represent all symptomatic infections.

We included cases notified in the period from 1 January 2001 to 4 May 2011 for analysis. The date of first symptom onset was used as the date of diagnosis. For those without date of first symptom onset, the date of diagnosis was estimated from other information (date of notification, date of laboratory test or date of hospital discharge). However, for 0.1% and 0.4% of cases in Suriname and the Dutch Caribbean (Aruba specifically), the date of symptom onset could not be derived because of lack of additional information. These cases were therefore removed from the analysis.

The monthly incidence rate was calculated using the number of cases notified in the same month divided by the size of the population at risk in the relevant year. The population data was obtained from a 10-year census for Suriname, but were available per year for the Dutch Caribbean. The incidence rate estimate was corrected for the proportion of asymptomatic infection to obtain an estimate of the total number of infections. A detailed description of the data collection and incidence rate calculations can be found in the Appendix.
Travel behaviour of Dutch blood donors

Information on travel behaviour was collected through a questionnaire conducted in 2010. Around 2000 donors were randomly selected and invited to report their travels throughout the preceding year: the destination, frequency, duration and timing of travel. The results from this questionnaire have been recently reported [11]. It has been shown that the travel behaviour of Dutch donors is similar to that of the Dutch population in general.

We extracted travel information of donors to Suriname and the Dutch Caribbean in 2009 and extrapolated these to predict their travel in 2001–2011. We calculated the rate of donors travelling to Suriname and the Dutch Caribbean by multiplying the proportion of donors travelling to these areas with the annual number of Dutch donors registered in 2001–2011.

Donation type and frequency in the home country

Sanquin's annual reports from 2001 to 2011 provide information on donation type and frequency. On average, a whole blood (WB) donor donates 1.7 times per year, whereas plasmapheresis donors for quarantine plasma (QP) donate up to 5.4 times per year [12]. As the proportion of WB and QP donors to total donors differs over the years, we accounted for these differences on an annual basis when estimating the donation risk from WB and QP donors.

Dengue characteristics

Dengue model parameters were extracted from a summary Factsheet [1]. A ratio of 4:1 (ranging from 2:1 to 13:1) of asymptomatic to symptomatic infections was used to correct for the number of notified cases. An incubation period of 5.5 (range: 3-14) days was used. A period of 5 (range: 2-12) days was used to describe the longest asymptomatic or pre-symptomatic infectious period of an infected individual, during which that person is able to transmit the infection through blood transfusion.

Dengue transmissions have been documented for various blood components (plasma, red cells and platelets) [1-3]. A blood donor study from Puerto Rico in 2007 found 29 out of 15,390 donations positive for dengue RNA [13]. Of the 29 positive donations, three recipients' serum samples could be traced and tested. Of these three, only one recipient, whom was transfused with red blood cells, developed febrile illness and both the donor’s and the recipient’s viruses had identical envelope sequences. This implies the transfusion transmission probability would therefore be 0.33. A recent study of a dengue outbreak in Brazil supported this by reporting a dengue transfusion transmission probability of 0.37 (95% CI, 0.15-0.65) [14].

Data analysis

A country-specific database of the dengue-notified cases was created in Microsoft Excel (edition 2007). The extracted information for donation type and frequency of Dutch donors was also tabulated in Excel. The raw data was organized, imported and analysed in the package for statistical computation R (version 3.0.3). A simulation for the estimation was done by drawing random values of the specified ranges of possible values of the input
parameters. A list of the parameter values, their ranges and the formulas used are provided in the Appendix.

**Model outcome comparison**

**Incidence of dengue among Dutch travelers**

Cleton and colleagues have recently presented the infection risk of dengue for Dutch travellers in general [8]. In this study, laboratory test results for dengue were included, as obtained during January 2000 to May 2011, from three major diagnostic laboratories in the Netherlands.

From this study, we extracted the cumulative number of IgM-positive tests among Dutch individuals travelling to Suriname or to the Dutch Caribbean in 2000–2011 (Fig. 3 supplement) [8]. We presume that these positive test results represent all symptomatic infections in the Netherlands and that the risk of infection among the Dutch travellers in general is similar to that of the Dutch travelling donors. We inferred the expected cumulative number of infected donors returning from Suriname and Dutch Caribbean during that period by multiplying this number of positive tests with the proportion of donors in the general population. Note that this donor risk estimate inferred from the general population was based on laboratory test results over a one-year longer observation period than the surveillance data in the risk areas, and it represents only 42% of travellers who were tested for DENV infection and reported their travel history. We presumed that this travel pattern is similar for those who did not report their travel history. We estimated the expected cumulative number of infected travelling donors and corrected the number of infections found for the proportion of asymptomatic infections, the underreporting of travel history and for the length of the observation period. The corrected number of infections derived from laboratory results was next compared to the cumulative number of infected donors estimated by EUFRAT.

**RESULTS**

**Surveillance data and the estimated monthly incidence rate**

Table 1 shows the characteristics of cases notified in Suriname and the Dutch Caribbean. The total number of notified cases in the Dutch Caribbean is five times higher than that in Suriname whereas its population is about a half, resulting in an average incidence rate in the Dutch Caribbean eight times higher than that in Suriname. This difference in case notification and thus the resulting incidence might be caused by registration effect (see Discussion).

The number of cases per month notified in Suriname and the Dutch Caribbean from 2001 to 2011, together with the estimated monthly incidence rate is shown in Fig. 2. The number of dengue cases peaked in 2005 and in 2009 in Suriname, whereas in the Dutch Caribbean there were several peaks with the highest peak observed in December 2008.
The highest and lowest monthly incidence rates were notified at (per 100,000 inhabitants) 192 (October 2005) and 0 (March 2004) for Suriname, and 3167 (December 2008) and 11 (January 2001) for the Dutch Caribbean, respectively.

Table 2 summarizes the travel and donation behaviour of Dutch donors who travelled to Suriname or to the Dutch Caribbean. The proportion of donors who travelled to the Dutch Caribbean is more than three times higher than that of Suriname. Multiplied with the annual number of registered Dutch donors, on average we expect 1945 and 7131 donors travelling to Suriname and Dutch Caribbean annually, respectively. The length of stay is, however, higher for travels to Suriname than for the Dutch Caribbean. Table 2 also shows various characteristics of the Dutch whole blood and plasma donors. These data are also available per annum in the Appendix Table S2. This information was used to estimate the resulting number of infections in the recipients.
Table 2. Travel and donation behaviour of Dutch blood donors to Suriname and Dutch Caribbean based on data collected in 2010.

<table>
<thead>
<tr>
<th>Travel behaviour of Dutch donors</th>
<th>Suriname</th>
<th>Dutch Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of donors travel annually</td>
<td>0.5%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Average rate of travelling donors (donors/day)</td>
<td>5 (range: 4-7)</td>
<td>19 (range: 16-28)</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>26 (range: 1-90)</td>
<td>15 (range: 1-30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donation behaviour of Dutch donors</th>
<th>Whole blood</th>
<th>Quarantine plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of donors registered annually</td>
<td>403,402</td>
<td>30,963</td>
</tr>
<tr>
<td>Proportion of donations</td>
<td>93%</td>
<td>7%</td>
</tr>
<tr>
<td>Frequency (times/donor year)</td>
<td>5.6</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Estimated risk of dengue infection for donors travelling to Suriname or to the Dutch Caribbean.

Estimated travelling donors’ risk using the EUFRAT model

Figure 3 shows the estimated monthly number of travelling donors infected with dengue during travel to either Suriname or the Dutch Caribbean. The average monthly number of donors becoming infected during travels to Suriname was estimated at 0.04, with a maximum of 0.3 (95% CI, 0.1-0.6) in October 2005. The average monthly number of infected donors travelling to the Dutch Caribbean was 0.7, with a maximum of 8 (95% CI, 4-17) in December 2008. The annual estimates are presented in Appendix Figure S1.
The cumulative number of donors travelling to Suriname or the Dutch Caribbean and becoming infected with DENV from 2001 to 2011 was estimated at 5 (95% CI, 2-11) and 86 (95% CI, 45-179), respectively. The cumulative number of donors travelling to Suriname or the Dutch Caribbean during that period is estimated to be 20,377 and 74,716. This means on average we expect 25 (95% CI, 12-56) and 115 (95% CI, 61-239) infections per year per 100,000 donors travelling to Suriname and the Dutch Caribbean, respectively. The annual estimates of this proportion of infected travelling donors are available in the Appendix.

The resulting cumulative number of infected recipients from travelling donors from 2001 to 2011, given an average donation frequency, and without temporary deferral of returning donors, was estimated at 0.02 (95% CI, 0.001-0.06) for Suriname and 0.4 (95% CI, 0.01-1.4) for the Dutch Caribbean. The estimated number of infections in recipients for specific donation types can be found in the Appendix Table S2.

Incidence of dengue infection among Dutch travellers
Cleton and colleagues found 85 and 129 IgM-positive tests among 385 and 375 individuals who travelled to Suriname or the Dutch Caribbean for more than a decade (2000-2011). Assuming the proportion of donors in the population at 2.3%, the expected cumulative number of Dutch donors getting infected with dengue for over a decade from that study would be 19 (95% CI, 9-61) and 28 (95% CI, 14-92), respectively.

Comparing EUFRAT estimates with serology outcomes
The comparison between the number of donors becoming infected by travelling to Suriname or the Dutch Caribbean estimated using the EUFRAT and that inferred from Cleton’s laboratory-based study is summarized in Table 3. With the EUFRAT model, we estimated the cumulative number of Dutch travelling donors becoming infected in Suriname and the Dutch Caribbean throughout 2001–2011 to be 5 and 86. Compared with the laboratory-based inferred estimates, the estimates from EUFRAT are three times smaller for Suriname and three times higher for the Dutch Caribbean. Given that these estimates used completely independent information from various sources (surveillance in the risk area, and results from a survey on travel behaviour of the donor population), the differences with the number of infections found in the general population are remarkably small.

DISCUSSION
Our study shows that it is possible to use the EUFRAT model to obtain a reliable estimate of the number of infections among donors who travel to risk areas. The calculation requires basic information concerning transmissions in the risk area, relevant disease characteristics and the number of travelling donors and their duration of stay. Risk estimates obtained can support decision-making concerning blood safety interventions and risk communication. The estimated risk of DENV transfusion transmission by Dutch donors travelling to Suriname and the Dutch Caribbean is small.
Dengue transmission risk from travelling donors

Note that the estimated number of infected recipients presumes absence of temporary deferral. However, in practice all Dutch donors who travelled to outside Europe will be deferred for 28 day [11]. The proportion of donors who may donate soon upon return had the measure not been in place is unknown, and thus in the analysis, we assume that donors will donate independently of their travel history. This implies that the recipient risk may be overestimated.

The number of travelling donors becoming infected estimated by EUFRAT was compared to the number of infected donors inferred from the number of dengue infections found among Dutch travellers in general. There are various potential factors that might cause differences between these estimates:

- The infection risk was estimated by EUFRAT 17 times larger for travel to the Dutch Caribbean than to Suriname which was not observed in the laboratory-based study, but might be the result of a difference in health cost reimbursement systems, that is the bulk of the costs for dengue diagnostics in the Dutch Caribbean during the study period was covered by government whereas not all laboratory test in Suriname was covered, which would cause fewer patients in Suriname seeking diagnosis test [personal communication].

- The donor survey used by EUFRAT revealed an annual proportion of 1.6% Dutch donors (equivalent to 20 donors per day) travel to the Dutch Caribbean. This is in agreement with the report of the central bureau for statistics (CBS) in the Netherlands (3% in the summer and 1% in the winter) [15]. It is possible that recall bias occurred in the travel behaviour study in questionnaire participants, that is those who travelled would be more likely to participate, which causes a high estimate of number of travellers. However, the CBS reported that in 2012, 150 thousand tourists flew to the Dutch Caribbean, of which >60% are Dutch citizens [16,17]. Given these tourism statistics and assuming 2.3% donors in the Dutch population, the reported number of Dutch travelling donors (i.e. 19, see the Appendix for the calculation) is close to the EUFRAT estimate. Unfortunately, information on the number of Dutch travellers to Suriname is not available.

### Table 3. Travel and donation behaviour of Dutch blood donors to Suriname and Dutch Caribbean based on data collected in 2010.

<table>
<thead>
<tr>
<th>Estimated number of infections for Dutch donors travelling to dengue risk areas</th>
<th>Suriname (95%CI)</th>
<th>Dutch Caribbean (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative number of infected travelling donors in 2001-2011 estimated by EUFRAT model</td>
<td>5 (2-11)</td>
<td>86 (45-179)</td>
</tr>
<tr>
<td>Cumulative number of infected travelling donors in 2001-2011 inferred from infections in the general Dutch population (laboratory-based study)(a)</td>
<td>18 (9-60)</td>
<td>28 (14-92)</td>
</tr>
<tr>
<td>Ratio EUFRAT: laboratory-based study estimates</td>
<td>0.3</td>
<td>3.3</td>
</tr>
</tbody>
</table>

\(a\) This estimate represents the expected number of infections as conveyed by the laboratory test results of the Dutch population given their travel to Suriname or Dutch Caribbean, and presuming that the risk of infections among Dutch donors is identical with that of general Dutch population. This estimate is corrected for the proportion of asymptomatic infections, underreporting of travel history, and the length of observation period.
• Dengue transmission in the Caribbean follows a seasonal pattern with low transmission reported in March-June and high in August-November [18]. Contrarily, travel information showed more travel in summer (up to August) than in winter. We would therefore expect fewer transmissions in practice than estimated by EUFRAT, which assumes a constant travel rate throughout the year.

• The surveillance data used in EUFRAT were based on the number of clinical cases for which laboratory testing was requested, whereas the infection risk in the general Dutch population was based on positive test results. A comparison of both approaches would be desirable. However, only less than half of the notified cases in the risk areas were further confirmed by laboratory tests (38% for Suriname and 42% for the Dutch Caribbean), and the access to laboratory testing varied for different islands. We considered that using all notified cases would be more representative for the total number of symptomatic cases than using positive test results. In the Netherlands, on the other hand, dengue cases are notified only when there is a positive test result. Since testing for infectious diseases is considered equally accessible for Dutch citizens, test results can be considered representative of symptomatic cases among travellers. If we had used the laboratory test results for both analyses, the ratio of EUFRAT and the laboratory-based inferred estimates would have been 8.7 times smaller for Suriname and 1.4 times higher for the Dutch Caribbean.

Despite the factors mentioned here that might affect the risk estimates, the differences found lie within reasonable bounds: the observed number of infections in the home population lie within a factor of three within the predicted number while the 95% confidence intervals of the estimates are partially overlapping. Considering the fact that two completely independent sources of data were used and high-level population-level statistics (observed infections in a foreign country, local laboratory test results and general tourism statistics), such a difference can be considered remarkably small. Therefore, the EUFRAT model seems to be sufficient to provide an ‘order of magnitude’ estimate of risk. Further validation of the model in terms of the actual number of infected donations or recipients remains difficult. This would be only possible by screening the blood of travelling donors for arbovirus RNA.

The estimated cumulative number of infected travelling donors and potentially infected transfusion recipients in 2001-2011 were small. This estimate reflects the infection risk in the risk area and the travel behaviour of Dutch donors. The surveillance data in the risk area, however, do show a consistent increasing dengue risk, which has been observed and reported by others [19]. Trends in travel behaviour of Dutch donors are not readily available, but nevertheless, the number of Dutch tourists visiting the Dutch Caribbean and the number of general tourists to Suriname have increased every year [17,20]. If travel of Dutch donors is similar to that of the Dutch population (which is likely the case), the risk of dengue transmission would on average increase by 13% per year for Suriname and 7% for the Dutch Caribbean. Recent identification of *Aedes albopictus* as a potential vector for dengue transmission in the Netherlands [21] implies that further transmissions or local outbreaks by infected travelling donors might also be possible. This means that continuous monitoring of diseases and travel behaviour remains warranted.
CONCLUSION

The risk of dengue transfusion transmission from Dutch travelling donors can be estimated with the EUFRAT model using basic population, transmission, disease, travel and donation information. The transfusion transmission risk in the Netherlands is very low but possibly increasing. The estimated number of infected donors obtained from EUFRAT was consistent with a laboratory-based study. This indicates that the model can be used to support decision-making concerning safety interventions related to travelling donors and for risk assessment regarding transfusion recipients.

ACKNOWLEDGMENTS

WO analysed the data, applied the model and wrote the manuscript. RL collected the donor data and wrote the manuscript. MK helped improve the model, supervised the analysis and reviewed the manuscript. HZ supervised the donor data and reviewed the manuscript. RC co-ordinated data collection and reviewed the manuscript. ME and BJ provided data from Suriname and reviewed the manuscript. YH and IG provided data from the Dutch Caribbean and reviewed the manuscript. EM and MT provided data from Aruba and reviewed the manuscript. MJ supervised data analysis, improved the model and improved the manuscript.
REFERENCES


Dengue transmission risk from travelling donors

Dengue surveillance description

Dengue cases were notified to the surveillance system in Suriname and the islands of the Dutch Caribbean. The cases were notified following the CAREC [10 case definitions: a person with acute onset of fever and two or more of the following: headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, or supportive serology. In Suriname the notified cases represent hospitalised suspect patients whereas in the Dutch Caribbean the notified cases represent symptomatic patients that requested laboratory tests. For the islands of the Dutch Caribbean, Aruba’s surveillance data was initially reported separately. Over a decade there are 6,368, 18,381, and 17,046 dengue cases notified in Suriname (1 Jan 2001-8 Nov 2012), Aruba (14 Oct 2000-23 Dec 2013), and the Dutch Caribbean (1 Jan 2001- 31 Dec 2013), respectively. We selected an overlapping period of data collection from 1 January 2001 to 4 May 2011 for analysis.

For Suriname and Aruba, all dengue cases were individually notified to the surveillance system together with basic information such as age, gender, laboratory test results, and date of symptom onset, hospitalization, and notification. Only a proportion of 67.86% and 2.34% cases, respectively, were presented with complete information on date of infection. A proportion of 21.17% and 77.65% cases did not have information on the date of symptom onset, which was used for analysis (thus were imputed from other information such as date of notification, laboratory test or hospital discharge), and a proportion of 0.1% and 0.4% of cases did not have any date information at all. The

Table Appendix 1. Parameter input values used in estimating the travellers’ risk using the EUFRAT model.

<table>
<thead>
<tr>
<th>No</th>
<th>Symbol</th>
<th>Dimension</th>
<th>Description</th>
<th>Suriname</th>
<th>Dutch Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do = t_{ob}</td>
<td>Time</td>
<td>Duration of the transmission observed: In this study monthly observation period was used.</td>
<td>30.44 days</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>-</td>
<td>Number of infections: number of cases notified during the defined monthly period.</td>
<td>Varies per month (See Figure 2)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>\lambda = I/ND_{o}</td>
<td>1/time</td>
<td>Incidence rate: the rate of infection accruing in the infection risk area.</td>
<td>Varies per month (See Figure 2)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>D_{o}</td>
<td>Time</td>
<td>Length of incubation period: the time between a traveller getting infected and becoming infectious.</td>
<td>5.5 (3-14) days</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>D_{i}</td>
<td>Time</td>
<td>Length of infectious period: the time in which a traveller is infectious.</td>
<td>5 (2-12) days</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>\tau</td>
<td>1/time</td>
<td>Rate of donors travelling to the infection risk area: number of donors entering the outbreak area per day.</td>
<td>5.4 (4.3-7.5) donors/day 19.5 (15.6-27.6) donors/day</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>\phi</td>
<td>1/time</td>
<td>Donation rate: average number of whole blood and plasma donations per unit time.</td>
<td>0.005 per day*</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>D_{v}</td>
<td>Time</td>
<td>Duration of visit: length of stay of visitors in the outbreak area.</td>
<td>25.6 (1-90) days 15.1 (1-30) days</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>T</td>
<td>Transfusion transmission: the probability of an infected donor infecting a recipient.</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This is calculated as an average rate of whole blood and quarantine plasma donations, given the frequency per donor year.
latter proportions of cases were therefore removed from the analysis. For the Dutch Caribbean the number of cases was presented cumulatively per week instead.

A proportion of these notified cases were further confirmed with laboratory test results based on the criteria according to the regional surveillance guidelines (Pan American Health Organization/World Health Organization). The proportion of confirmed cases (IgM positive tests) in Suriname, Aruba, and the Dutch Caribbean was 37.97%, 35.09%, and 41.51%, respectively. Since the proportion of confirmed cases depended on the access to laboratory test, which varied for different islands and countries, we chose to use all notified cases (assumed to be representing the symptomatic infections) to determine the incidence rate of dengue infection. The incidence rate estimate was next corrected for a range of proportion of asymptomatic infection.

The monthly incidence rate was calculated using the number of cases notified in the same month divided with the size of the population at-risk in the relevant year. The number of notified cases in Aruba that was initially reported separately was used to calculate the weighted (by population size) average incidence rate in the Dutch Caribbean. So the number of cases in Aruba was first aggregated weekly, added to the reported cumulative number of cases in the Dutch Caribbean in the corresponding week, and then divided with the total population of the Dutch Caribbean (including Aruba). The population data was obtained from 10-year census for Suriname, and annually for the Dutch Caribbean.

Travel and donation of Dutch blood donors
The Sanquin questionnaire in 2010 revealed that 6 and 22 out of 1340 Dutch active blood donors travelled to Suriname or to the Dutch Caribbean the preceding year. Out of 6 who went to Suriname, 5 stayed for 1 week to 1 month, and 1 stayed for more than a month. Out of the 22 who went to the Dutch Caribbean, 1, 4, and 17 stayed for <1 day, 1 day to 1 week, and 1 week to 1 month, respectively. Applying the proportion of travel to the annual number of donors, we obtained the annual number of donors travelling to Suriname or the Dutch Caribbean, assuming that the travel pattern stayed the same. The annual number of registered Dutch donors and their donation frequency are listed in the table below.

Table Appendix 2. Dutch blood donors and their donations in 2001-2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of donors</th>
<th>Total donors</th>
<th>Frequency of donation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole blood</td>
<td>Quarantined plasma</td>
<td>Whole blood</td>
</tr>
<tr>
<td>2001</td>
<td>572 000</td>
<td>42 000</td>
<td>614 000</td>
</tr>
<tr>
<td>2002</td>
<td>491 946</td>
<td>40 700</td>
<td>532 646</td>
</tr>
<tr>
<td>2003</td>
<td>453 885</td>
<td>15 024</td>
<td>468 909</td>
</tr>
<tr>
<td>2004</td>
<td>446 384</td>
<td>15 919</td>
<td>462 303</td>
</tr>
<tr>
<td>2005</td>
<td>407 249</td>
<td>12 338</td>
<td>419 587</td>
</tr>
<tr>
<td>2006</td>
<td>385 930</td>
<td>9 416</td>
<td>395 346</td>
</tr>
<tr>
<td>2007</td>
<td>349 369</td>
<td>10 652</td>
<td>360 021</td>
</tr>
<tr>
<td>2008</td>
<td>336 203</td>
<td>10 580</td>
<td>346 783</td>
</tr>
<tr>
<td>2009</td>
<td>331 738</td>
<td>62 073</td>
<td>393 811</td>
</tr>
<tr>
<td>2010</td>
<td>333 439</td>
<td>61 827</td>
<td>395 266</td>
</tr>
<tr>
<td>2011</td>
<td>329 283</td>
<td>60 067</td>
<td>389 350</td>
</tr>
</tbody>
</table>

Reported travel of Dutch population to Suriname and the Dutch Caribbean
The CBS reported in 2012 a total of 150 thousand tourists flying to the Dutch Caribbean. In Bonaire alone, about 10.5 thousand tourists per month came by plane, for which >60% are Dutch citizens. This means >6.3 thousand Dutch travellers per month arrive in Bonaire by plane only or it equals 5 Dutch travelling donors per day (assuming 2.3% donors in Dutch population). Including by boat there will be at least 10 Dutch donors per day arriving in Dutch Caribbean [16]. For Curacao, the number of visitors from the Netherlands in 2012 is reported at 138,555 [17], equivalent to 9 Dutch travelling donors per day. It was also shown that the number of visitors increases each year. Detailed number of Dutch visitors in other islands of the Dutch Caribbean is unfortunately not readily available. However, from the Bonaire and Curacao statistics alone, the number of travelling donors (10+9=19) is close to what is estimated by the EUFRAT (19, range: 16-28).
Formulas for estimating the travellers’ risk

1. Estimating the number of infected travelling donors:
\[ N_v = \frac{D_v \cdot E \cdot I}{N} \]

2. The number of infected blood recipients was estimated using the following formula.
   a. For duration of infectivity > length of stay \((D_i > D_v)\):
   \[ IR_v = N_v \cdot \varphi_T \left( D_i - \frac{1}{2} D_v \right) \]
   b. For duration of infectivity < length of stay \((D_i < D_v)\):
   \[ IR_v = \frac{1}{2} N_v \cdot \varphi_T D_i \]

The formula can be applied to estimate the risk for specific blood donation type (whole blood or plasma). The estimated cumulative number of infections among the recipients who received whole blood donations is presented in the table below.

Table Appendix 3. Estimated cumulative number of infections in blood recipients of whole blood and plasmapheresis donations from travelling donors infected in Suriname or to the Dutch Caribbean over the time period 2001-2011.

<table>
<thead>
<tr>
<th>Estimated cumulative number of infections from travelling donors</th>
<th>Suriname</th>
<th>Dutch Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood recipients (95%CI)</td>
<td>0.02</td>
<td>0.3 (0.0004-0.05)</td>
</tr>
<tr>
<td>Quarantine plasma recipients (95%CI)</td>
<td>0.004</td>
<td>0.1 (0.0001-0.01)</td>
</tr>
</tbody>
</table>

Figure Appendix 1. Estimated annual number of infections for Dutch donors travelling to Suriname or the Dutch Caribbean (left y-axis), and the proportion of infected travelling donors (right y-axis).