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Using routine diagnostic data as a method of surveillance of arboviral infection in travellers: A comparative analysis with a focus on dengue

Natalie Cleton [a,d,*], Chantal Reusken [a], Jean-Luc Murk [b], Menno de Jong [c], Johan Reimerink [a], Annemiek van der Eijk [d], Marion Koopmans [a,d]

[a] National Institute for Public Health and the Environment, Centre for Infectious Disease Research, Diagnostics and Screening, A. van Leeuwenhoeklaan 9, P.O. Box 1, 3720 BA Bilthoven, The Netherlands
[b] University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
[c] Academic Medical Centre, Department of Medical Microbiology, Meibergdreef 9, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands
[d] Erasmus Medical Centre, Virology Department, 's Gravendijkwal 230, P.O. Box 2040, 3000 EA Rotterdam, The Netherlands

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Summary *Background:* In a large part of the developing world, limited infectious disease surveillance is performed. In laboratory information management systems data on diagnostic requests is available and may be amenable to trend analyses. We explored this potential, using DENV diagnostic requests as a model.
Method: Test results and anonymised information provided by clinicians were received for 8942 patients from diagnostic centres in the Netherlands from January 2000 to May 2011. The data were evaluated for completeness of a predefined minimal dataset and trends in DENV positive results by travel destination. Population travel data were obtained from a commercial registry, and dengue case notification data by country from WHO DengueNet.
Results: Vaccination history was rarely reported (0.4%); travel destination was completed for 42% of requests; trends in diagnostic requests and IgM positive tests for this subset correlated to the WHO DENV notifications for the three main travel destinations, with some discrepancies. Additionally, this approach may provide information on disease outbreaks with other

* Corresponding author. National Institute for Public Health and the Environment, Centre for Infectious Disease Research, Diagnostics and Screening, A. van Leeuwenhoeklaan 9, P.O. Box 1, 3720 BA Bilthoven, The Netherlands. Tel.: +31 (0) 30 274 7521; fax: +31 (0) 30 274 4418.
E-mail addresses: natalie.cleton@rivm.nl (N. Cleton), chantal.reusken@rivm.nl (C. Reusken), j.murk@umcutrecht.nl (J.-L. Murk), m.d.dejong@amc.uva.nl (M. de Jong), a.vandereijk@erasmusmc.nl (A. van der Eijk), marion.koopmans@rivm.nl (M. Koopmans).

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pathogens causing diseases clinically similar to DENV. PCR data proved to be insufficient for trend monitoring by country.
Conclusion: This approach is not straightforward, but shows potential for use as a source of additional information for surveillance of disease.

Introduction

New diseases continue to emerge across the world, due to a complex array of factors relating to demographics, increasing demand for animal protein, deforestation, and a steep increase in international travel and trade [1,2]. Vector-borne diseases, with the exception of West Nile and Dengue virus, are considered neglected tropical diseases and no or little surveillance is performed in a large part of the developing world. Systematic evaluation of health complaints through travel clinics has shown a high incidence of health complaints (8–10%) [3,4]. As a consequence, international travellers can be seen as sentinels and sources of introduction for infectious diseases occurring worldwide [5–8]. Developing diagnostic tools and approaches to monitor health complaints in returning travellers could provide an interesting addition to traditional surveillance [8]. Geosentinel clinics form an international network that collects data on diseases in travellers. However, the number of clinics participating is limited and the reporting system depends on the extent to which clinicians actively upload information. A large amount of diagnostic data is therefore available in diagnostic laboratories but remains unused for surveillance purposes. This had led us to explore the use of routine laboratory submission data and results for additional monitoring of trends of illness through international travellers. Here, we set out to explore this potential by using dengue virus as an example.

Dengue virus (DENV) is considered one of the most important arboviruses globally, with 2.5 billion people at risk of infection according to the World Health Organization (WHO) [9]. It is a well-recognized disease in travellers to tropical and subtropical regions and therefore diagnostic tests are requested frequently [10–12]. Surveillance is done in many countries that are popular travel destinations, and DENV probable and confirmed cases are notified on voluntary basis to the WHO. This currently provides the best insight into the DENV situation per country and therefore offers a potential comparison and addition to data provided by diagnostic laboratories [13,14]. Routine diagnostic information in travellers coupled to travel history and symptoms could potentially be used as an already in-place cost-effective additional information source for monitoring the demographics of disease and exposure trends where no surveillance in available [15].

The goal of our study is to investigate the usability of diagnostic information of returning travellers on travel history, symptoms and diagnostic results provided by routine diagnostic laboratories as complementary information usable in surveillance for disease in travellers, providing information on public health threats by possible introduction of viremic patients and trends in local disease activity. We use DENV as an example since WHO surveillance information is available for some countries as comparison and complementary data.

Methods

Diagnostic data

During a consensus meeting between the diagnostic laboratories and responsible researchers, a minimal dataset needed for data analysis was proposed and discussed based on the question what minimal information was essential for use in surveillance of disease in travellers and the countries they visit. The defined minimum dataset was age, sex, travel date and destination, description of clinical symptoms, vaccination history, diagnostic results and test(s) used. *Age and sex* were considered to be of importance in order to identify risk groups and make results compatible between diagnostic centres. Information of *travel history and dates* were needed to correlate demographic distribution of infections in Dutch travellers to current known and unknown outbreaks. This information was also needed for interpreting results as new or old infections and possible cross-reactions with co-circulating cross-reactive arboviral infections [16–19]. Records of *clinical symptoms* were needed to evaluate the usefulness of the clinical data for syndromic surveillance [20]. Finally, vaccination history was considered essential for the data analysis since a number of flavivirus vaccinations (Tick-borne encephalitis virus, Japanese encephalitis virus, Yellow fever virus) are known to cross-react causing false positive IgG diagnostic results [16,19]. Data containing the diagnostic results, interpretation, and the information provided by clinicians with the requests for DENV diagnostics were retrospectively extracted from the laboratory information management systems (LIMS) from the three main arboviral diagnostic labs in the Netherlands from 2000 to 2011. This represents the vast majority of all DENV diagnostic requests in the Netherlands. The information was provided in excel format as raw data. As there is no standardized testing for DENV infections, each laboratory provided the interpretations of the results. Diagnosis was based on determination of IgM and IgG antibodies by rapid lateral flow Immunochromatographic Test (ICT) by Panbio (Brisbane, Australia) (one laboratory), immunofluorescence assay (IFA) by Progen (Heidelberg, Germany) and Scimedix (Denville, New Jersey, USA) (one laboratory) and Enzyme-linked immunoassays (ELISA) from Focus (Cypress, CA, USA) (two laboratories). Each laboratory provided a cut-off for defining if a diagnostic result was considered positive or negative.

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Laboratories using IFA and ELISA tests used a higher but comparable cut-off than recommended by the manufacturer to increase specificity. These cut-offs were defined by validation prior to implementation of the assays in the diagnostic routine. In compliance with the medical ethical guidelines, no personal identifiers were included.

Data analysis

A database was created in Microsoft Excel (edition 2007). The raw data was organized and imported into 'R' (version 2.14.0) for further analysis. The data was evaluated for completeness of the minimal defined dataset and for trends in DENV positive results by travel destination. These trends were compared with those based on data collected by WHO DengueNet 2001 to 2011 that are published by the WHO regions online (South-East Asia only published data until 2010)

Travel data

Data were obtained from a commercial research registry 'ContinuVakantieOnderzoek' (CVO) that follows travel trends by interviewing, every three months, 10,000 out of a panel of 150,000 Dutch homes about their travel behaviour [21]. The research has been conducted since the 1980's and is used for monitoring Dutch travel behaviour in the tourist and travel industry. Basic information is requested on number and length of vacations within and outside the country (if any), location and lodging, activities, method of transport and booking. Information is analysed in condensed form for reports and raw data is available in an online database HolidayTracker [21].

Estimation of the proportion of DENV infections in travellers, 2010

As travellers may be seen as a source of introduction of arboviral infections, we tried to use the available data to provide an estimate range for the possible proportion of travellers infected with Dengue during one year. For this, the lower limit estimate was made by:

$$E_{low} = (P * 4)/N$$

Where E_{low} is the lower estimate of DENV infections, P is the number of DENV IgM positive patients, 4 is the multiplication factor assuming 25% of all cases are symptomatic [22], and N is the number of travellers to DENV endemic countries.

The higher estimate was made by:

$$E_{high} = ((N * 0.1) * (P/T))/N * 4$$

Where 4, N and P are as indicated above, 0.1 is the estimated proportion of travellers returning with febrile illness [3,4,23,24], and T is the number of samples tested.

Statistical analysis

Proportions were tested with Pearson's chi-squared test for equality of proportions. Trend lines were tested with F-test and R^2 and correlations were calculated using Spearman's rank correlation coefficient for describing independence between variables (r_s).

Results

Completeness of diagnostic data

In total, data were received on 10,540 diagnostic samples from 8942 patients from the three diagnostic centres in the Netherlands from January 2000 until May 2011. Each laboratory provided diagnostic result and interpretation per patient.

The completeness of data ranged from 0.5% for vaccination history to 98% and 99% for sex and birth date. Some basic clinical information was provided with 75% of requests, but only 42% of the requests mentioned information on travel history (Table 1). Only 0.2% of diagnostic requests contained all parameters.

Trends in diagnostic requests and results

Between 2000 and 2011 RT-PCR for detection of DENV viral RNA was performed on 275 samples (3%) of DENV diagnostic requests. More than 50% of the RT-PCR requests have occurred in the last three years and the percentage of positive samples has dropped from 30% to 13% (data not shown). RNA was more often detected in IgM positive (23%) than in IgM negative patients (9%).

The annual number of serological diagnostic requests for DENV has increased significantly over time (Fig. 1). In correspondence, the proportion of travellers with diagnostic requests has also increased (Fig. 1). Correlation between the number of requests, and IgG and IgM positive samples per year was very high ($r_s = 0.82$ to 0.99 and $P < 0.01$). The proportion of patient samples testing positive for DENV IgG or IgM antibodies fluctuated, with peaks in 2005 and in 2009/2010. IgG and IgM proportions show a reasonably strong correlation ($r_s = 0.70$ and $P < 0.01$). When studying trends in more detail, the increase relative to the previous year of IgG positives compared to IgM was higher in 2005 than in 2009, which indicates some independence between IgG and IgM proportions. A third peak was observed in 2002 but this is less clear as the total number of diagnostic requests was too low to draw conclusions based on this.

Table 1 Information provided with diagnostic requests per patient population for 8942 patients.

Parameter	Percentage available
Sex	98%
Birth date	99.9%
Clinical history	75%
Travel history	42%
Sex, Age, Clinical, Travel history	38%
Vaccination history	0.5%
Clinical, Travel, Sex, Age, Vaccination	0.2%
Total patients	8942

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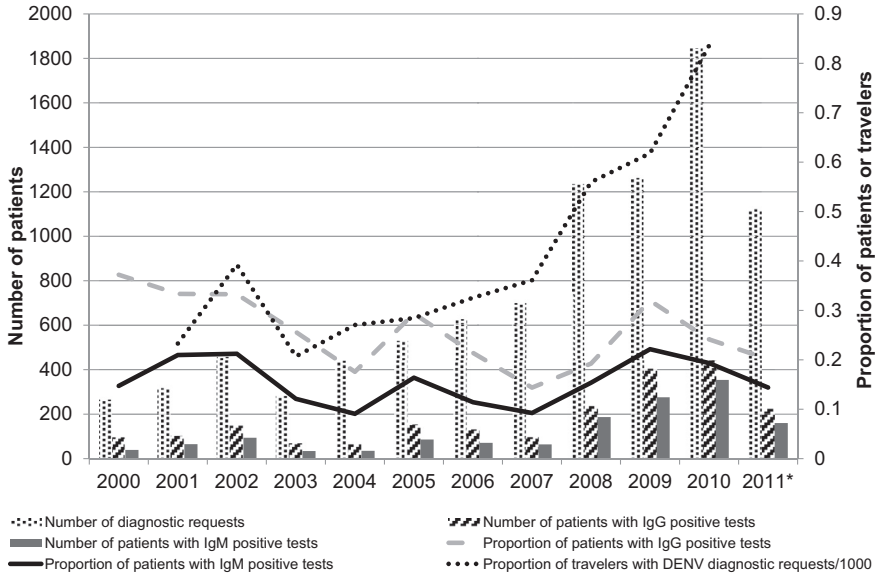

Figure 1 Trends in diagnostic requests for evaluation of patients with suspected dengue virus infection from 2000 through May 2011(*) in The Netherlands in absolute counts (bars, first *Y* axis) and in proportions (lines, second *Y* axis).

Trends in travel history by region

The 3751 (42%) patients that had information on travel history provided with their diagnostic requests were subdivided into the geographical regions Africa, Americas, Europe and Asia-Oceania. For 263 patients, travel history was stated as 'Tropics' (228), 'No' (12) or 'Yes' (23) and these could not be assigned into a geographical category. Patients ($n = 219$) that had travelled to more than one region were included multiple times in the subdivision. Most patients traveling outside of Europe had travelled to Asia-Oceania followed by the Americas and then Africa (Table 2). The prevalence of DENV IgM and IgG positive patients differed significantly for travellers from different regions (Table 2, $P < 0.01$). Only 29% (79) of the samples tested with PCR were accompanied by travel information (Table 2).

Trends in travel history by country

In total 131 different countries were listed in the travel history of patients. The top five travel destinations were Indonesia, Thailand, Surinam, India and the combination of the former and current Dutch Caribbean Islands, i.e. Bonaire, St Eustatius and Saba (BES islands), St Maarten, Aruba and Curacao (2000 patients, 53%). Travellers from Surinam were most frequently DENV IgG positive (Fig. 2 and Supplement Fig. 3(A)). The Dutch Caribbean islands were the travel destination associated with the highest number of patients with DENV IgM positive tests (129 patients). Results are plotted for all countries that had been listed for at least 50 persons (Supplement Fig. 3(A)) or 20 persons (Supplement Fig. 3(B)) as travel destination. The proportion of DENV positive patients differed greatly between travel destinations. Large differences were observed in percentage IgM positives for patients returning from different countries. This is partly explained by the low number of diagnostic requests for travellers to these countries (Supplement Fig. 3(A)&(B)). Per top five travel destinations only one or two patients were PCR positive, but did show a higher than average number of positive samples compared to other destinations (20%).

Table 2 Reported travel destinations by region for returning travellers with suspected DENV clinical disease, and proportion with positive IgM serology, IgG serology, or both.

Travel destination	Number of patients	% Requests	% IgG	% IgM	% IgG and IgM
Africa	643	17	11	5	3
Americas	1283	34	34	20	15
Asia-Oceania	1744	46	21	16	10
Europe	37	1	8	0	0
P-value			<0.01	<0.01	<0.01

Trends in DENV IgM positive results by country compared to WHO DENV notifications

Data representing the number of Dutch patients with DENV positive tests was combined with data representing the WHO reported DENV cases per country for the pooled data from patients returning from the top five travel destinations.

WHO notifications preceded the trends in DENV diagnoses from the pooled dataset by one year (data not shown). When analysing trends by country, however, clear differences were observed. For the Dutch Caribbean islands, Suriname and Thailand, the diagnostic data and the number of WHO reported cases show a high correlation, although the timing differed. The data from Thailand corresponded almost perfectly with the WHO

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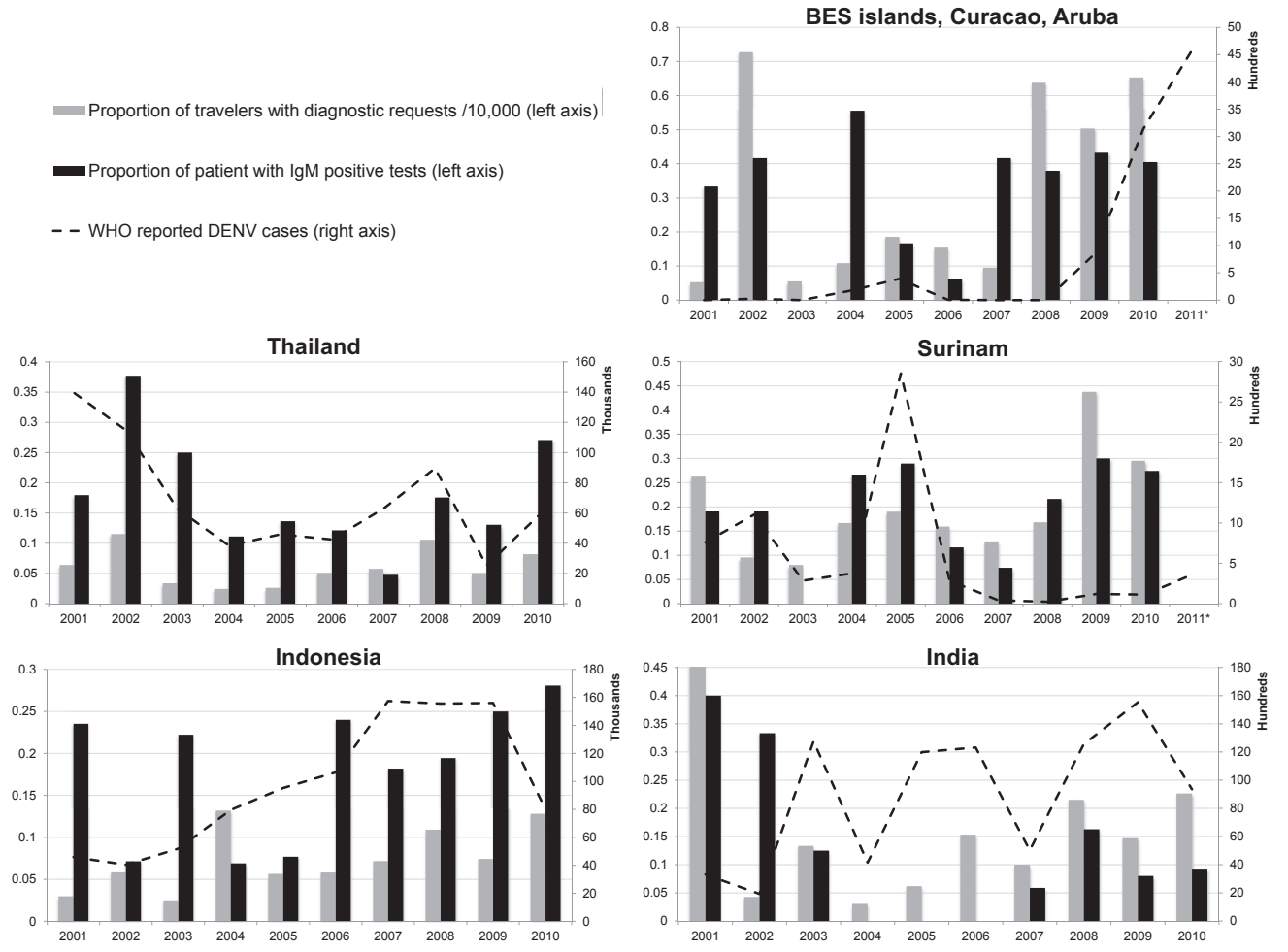

Figure 2 Trends in number of patients with requests and IgM positive tests (bars, first *Y* axis), WHO reported DENV cases and number of travellers (lines, second *Y* axis) per country from 2001 through May 2011(*).

data. For the Caribbean islands, the diagnostic trends preceded the increase seen in WHO reporting by one to two years. For the data from travellers to Surinam, the increase in the diagnostic trend line from 2008 onwards was not seen in WHO notifications (Fig. 2). For Indonesia, the diagnostic IgM trend showed some dependency with the WHO data but seemed to lag behind by one year in 2004–2005. Finally, the proportion of IgM positive samples for India did not show any correlation with the WHO reported cases or the proportion of travellers with diagnostic requests. However, the proportion of requests did show a correlation with the WHO data. All these observed correlations (r_s = 0.7–0.9) were significant ($P < 0.01$).

Estimation of the proportion of DENV cases in travellers, 2007 and 2010

As travellers may be seen as a source of introduction of arboviral infections, we tried to use the available data to provide an estimate range for the possible number of dengue cases during one year, as described in the methods section. By this approach, the lower estimate, assuming that all clinical DENV imported cases would be detected, was 0.02% for 2007 and 0.06% for 2010 of travellers to tropical or subtropical regions. The higher estimate, made based on the assumption that the current diagnostic requests reflect a fraction of all febrile travellers, was 3.7% for 2007 and 7.6% for 2010 of travellers to tropical or subtropical regions. We did not perform further calculations using the number of viremic travellers because of the low number of travellers tested by RT-PCR.

Discussion

Completeness of diagnostic data

We explored the potential use of diagnostic request data for systematic monitoring of trends in arboviral disease in Dutch travellers around the world, using DENV diagnostic data as a model [15]. We received information on 10,540 diagnostic samples from 8942 patients. Only 42% of the diagnostic requests provided information on travel history thereby limiting the usable amount of data to a large extent. Because of such a large amount of requests this loss of usable data seemed to be partially compensated as

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analysis still provided results. The literally complete lack of vaccination background data is of concern, as this information is essential for interpretation of serological diagnostic results of patients. The envelope protein of flavivirus is the main target for immune response [25–27]. Many common epitopes on the envelope protein cause cross-reactivity between flaviviruses in diagnostic tests [18,28,29]. Recent vaccination could cause cross-reactive antibody titres against other flaviviruses, mainly for IgG antibodies [16,19,30]. Although this factor has been taken into account when validating the cut-offs per laboratory for travellers to countries where YFV vaccination is compulsory (parts of South America) or highly recommended (Central Africa), this possible confounding factor could not be excluded when evaluating the IgG test results [16]. We tried to reduce the influence of this possible confounder by focusing further analysis on IgM data. This lack of information should however be further investigated to identify probable causes along the diagnostic request chain, for example (1) shortage of time by physicians to complete request forms, (2) the lack in understanding of how vital this information is for interpretation or (3) the lack in knowledge of the usability of this data of surveillance. The use of digital request forms with compulsory fields might prove beneficial for improving completeness of diagnostic data. Lack of additional information on travel times of individual patients could be compensated by extending the national information used on travel destinations into seasons and link these to the of diagnostic trends per month. This approach can only be used when sufficient diagnostic requests are available, reflecting travel behaviour of the patient population that is subject to national preferences. Potentially combining information on an international level might provide a better spread in data per country and strengthen the data per visited country. This data could provide laboratory and background parameters for surveillance supplementary to what is already done through the Geosentinel system [6,7].

Trends in diagnostic requests and results

The low number of requests for PCR is also of concern, especially because of the high percentage of PCR positive samples in both IgM positive and negative samples. In the Netherlands diagnostic samples may only be tested based on what the physician specifically requests. The lack in PCR requests is therefore probably based on the assumption that travellers are frequently not viremic anymore on time diagnosis. The number of PCR positive samples is therefore so low (one or two per destination) that no surveillance on travel destination is possible, but show that potentially a large number of viremic travellers return to the Netherlands annually.

There was a clear increase in the DENV requests and IgM positive patients over recent years (Fig. 1), similar to what was observed in other countries across the EU like Germany and the United Kingdom [31–33]. The proportion of travellers with diagnostic requests has increased (Fig. 1). This may reflect true increase in DENV prevalence or more awareness of DENV risk among Dutch physicians.

Trends in travel history per region

Although most diagnostic requests involved patients returning from Asia, the most positive samples came from the Americas, possibly for the reasons given above, whereas DENV was rarely diagnosed in travellers returning from Africa (Table 1). This is interesting as DENV is endemic in a large part of Africa. Possibly physician awareness might play a role in requesting dengue testing in travellers to Africa.

Trends in travel history per country

Three of the five top travel destinations for Dutch travellers have a colonial past with the Netherlands and therefore the high number of travellers in part are explained by citizens visiting friends and relatives. Such specific groups of travellers may bias results for two reasons: the local population might have more up to date knowledge of currently circulating diseases and might inform the visitors of possible DENV when they get ill. Secondly, the higher contribution of frequent visitors may influence the proportion of IgG-only positive patients as can be seen for Surinam where the percentage of IgG positive patients was higher than for other travel destinations (Fig. 2). However, Surinam is also a yellow fever endemic country where vaccination is recommended. The high IgG proportion could therefore also be due to yellow fever vaccination cross-reactivity [16,19,30]. From this data alone, it is difficult to distinguish between these possibilities because of a small percentage of patients with vaccination history. The high frequency of IgG positive samples also emphasizes the need for a convalescent sample for identification of a recent infection. This does support focusing trend monitoring more on IgM results and less on IgG until information on vaccination history is provided more regularly.

Trends in DENV IgM positive results by country compared to WHO DENV notifications

WHO notification data on the Caribbean, Central America and the northern part of South America indicate large DENV outbreaks in 2007, 2009, 2010 and high DENV activity in 2008 [34]. This corresponds to our diagnostic findings for Surinam from 2007 onwards, but does not correspond to the WHO dengue data reported on Surinam itself. It seems implausible that all Surinam surrounding countries would experience outbreaks and Surinam would remain unaffected. Possibly, reporting of DENV cases to the WHO was affected for some reason during this period. Monitoring based on diagnostic results with WHO notification therefore has a clear added value.

The diagnostic results for travellers from Indonesia and India show less correlation. Both these destinations are less popular than the previously mentioned three. Dutch travellers focus their travels mainly on Borneo, Bali and Java islands making them less representative for all Indonesia. Focusing outbreak information on only these three islands may prove to be more accurate in relation to travellers.

Occasionally, a deviation from the trend indicated presence of high numbers of patients with dengue-like

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symptoms, for instance in the data for India for 2005 and 2006. This may indicate an outbreak of another disease with symptoms comparable to DENV (hence the DENV diagnostic request) but that causes no cross-reactivity (thus probably not a flavivirus). Outbreak reports suggest a possible increase in chikungunya infections in this area from 2005 onwards that might influence the increase in probable DENV clinical cases reported [35,36]. The data from the WHO is dependent on reporting of local health institutes and laboratories, each using different diagnostic methods, and not always based on diagnostic confirmation. For some regions the reliance on clinical case notifications might influence DENV trends of clinical syndromes overlap, as for instance is the case for Chikungunya virus infection.

Estimation of the proportion of DENV cases in travellers, between 2007 and 2010

The estimated proportion of dengue cases in travellers was found to be between 0.02%–3.7% and 0.06%–7.6% of all travels to DENV risk countries in 2007 and 2010. This estimation seems to be in accordance with earlier prospective studies by Cobelens et al. in 1991–1992 who found 1.7–5.1% incidence rate of dengue for travellers to high risk countries in Asia, and Baaten et al. in 2006–2007 who found that 1.2% of travellers to the tropics seroconverted [33,38]. The calculation of the number of infected travellers showed a 100-fold difference between lower and higher estimates, but indicated that the chances of DENV importation into the Netherlands due to viremic travellers are potentially high. The information does provide some overview of potential risks. This may become relevant in case of mosquito invasions, as were observed in Italy with the outbreak of chikungunya due to introduction by a traveller and subsequent transmission through mosquitoes that were competent for transmission of alphaviruses [39]. Tilston et al. used the estimated number of viremic travellers flying into Europe from known chikungyna outbreaks areas to identify high risk regions in Europe for chikungunya outbreaks. They proposed an enhanced traveller-based surveillance in parts of Europe supported by this estimation [40]. Our data could be a further addition to this surveillance approach.

Our study also has weaknesses: the dataset is biased because (a) recruitment is dependent on a patient developing symptoms severe enough to seek out medical care, (b) diagnostic requests are based on awareness of physicians, (c) completeness of data provision by physicians influences the usefulness for surveillance, and (d) travel behaviour is specific to the Netherlands.

Conclusion

We showed that trends in diagnostic requests and results can be identified and correspond partially to the WHO DENV reports on DENV outbreaks per country for the three top popular travel destinations of Dutch travellers. Occasional discrepancies were seen that could be explained either by underreporting of data to the WHO, or under-diagnosis of DENV as a cause of illness in travellers. The data offers a wide range of additional parameters that can be used as a source of information not only on current possible outbreaks, but also changes in awareness as well as high or low risk countries or populations. Secondly, this approach may also provide information on disease outbreaks with other pathogens causing diseases that are similar to DENV clinically. Currently, the number of PCR tested samples is too low and provides insufficient data for trend analysis based on travel destination, but shows that potentially a large number of viremic travellers return to the Netherlands annually.

Competing interests

None declared.

Conflict of interest

None declared.

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None.

Ethical approval

In accordance with the Dutch law on medical research (WMO), article 1.

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Appendix A. Supplementary data

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