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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

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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

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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.