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Seroepidemiology of dengue in travellers: A paired sera analysis

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Summary *Background:* Dengue is a frequent cause of fever in travellers. The true extent is unknown as many infections are asymptomatic or undiagnosed.
Methods: We used paired sera, with pre- and post-travel specimens from Swiss travellers to tropical destinations, to evaluate the seroepidemiology of travel-related dengue. Post-travel specimens were tested for the presence of IgG and IgM antibodies to dengue antigen serotypes (1, 2, 3 and 4) using an indirect enzyme-linked immunosorbent assay (ELISA). All post-travel sera that screened as positive for dengue IgG or IgM antibodies were re-tested with the corresponding pre-travel sera as paired assays in order to detect seroconversion.
Results: There were 285 travellers with specimens available for analysis. Two hundred and fifty seven of the 285 individuals (90.2%) had negative dengue serology post-travel. Of the remaining 28 cases, 25 were dengue IgG positive and 3 had equivocal results. This corresponds to IgG seropositivity in 8.9%. Eighteen of these 25 individuals had a pre-travel specimen available for testing, of which 15 were positive for IgG consistent with possible past exposure. Three of the 18 had negative serology pre-travel, indicating possible recent infection. This corresponds to an attack rate of possible dengue of 1.1% and an incidence rate of 6.7 per 1000 person-months (95% CI 0–60.0). Two of these three individuals had received yellow fever vaccine for their trip, raising the potential of cross-reactivity. The confirmed dengue attack rate therefore was 0.23% with a corresponding incidence rate of 2.2 per 1000 person-months (95% CI-0–33.1).

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Conclusions: Seroepidemiology provides additional evidence of an appreciable risk of acute dengue infection among travellers to tropical destinations.

Introduction

It is estimated that there are approximately 100 million cases of dengue fever worldwide each year, with expansions in the geographic distribution of dengue in recent times. Among travellers, dengue is increasingly being recognised as a common cause of fever, especially among those returning from Asia [1]. However, the exact risk for the individual traveller is difficult to quantify for a number of reasons. Firstly, dengue infection may be asymptomatic and therefore unrecognised by the traveller. Secondly, even if symptoms occur, dengue's short incubation period means that illness may develop during travel so a healthcare visit may not be sought. Thirdly, even if the traveller sees a doctor during their trip or after return home, depending on the timing of presentation in relation to development of symptoms, a specific diagnosis of dengue infection may not be possible. Finally, the risk will vary according to timing, year, duration and destination of travel, as well as with the success of any mosquito avoidance measures employed.

Here we report results of a study assessing the risk of dengue infection among international travellers.

Methods

A cohort of Swiss travellers who travelled to a tropical destination between May 1998 and January 2000 were enrolled in a prospective study. At enrolment all participants had their vaccination history taken and received standard travel health advice. Pre- and post-travel blood specimens were collected. Testing for influenza seroconversion on these travellers has been reported previously [2]. A random subset had a sufficient quantity of stored serum (−20 °C) available for retrospective testing of dengue antibodies.

Available specimens were sent to the Victorian Infectious Disease Reference Laboratory (VIDRL; North Melbourne, VIC, Australia). Post-travel specimens were tested for the presence of IgG and IgM antibodies to dengue antigen serotypes (1, 2, 3 and 4) using an indirect enzyme-linked immunosorbent assay (ELISA), Dengue IgG Indirect ELISA and Dengue IgM Capture ELISA (PanBio Diagnostics, Brisbane, QLD, Australia). This assay has reported sensitivities in non-endemic populations as follows: IgM in primary infection of 94.7% (95% CI: 85.4—98.91%); IgM in secondary infection of 55.7% (95% CI 46.6—64.7%); IgG in primary infection of 91.4% (95% CIs not provided); IgG in secondary infection of 97% (range: 73.8—99.7%) (http://panbiodengue.com/product/dengue-igg-indirect-elisa; http://www.alere.com/us/en/product-details/panbio-dengue-igg-indirect-elisa.html) [3]. The assay's specificity is reported to be close to 100% (range: 91—100%) (http://panbiodengue.com/product/dengue-igg-indirect-elisa; http://www.alere.com/us/en/product-details/panbio-dengue-igg-indirect-elisa.html) [3]. All post-travel sera that screened as positive for dengue IgG or IgM antibodies were re-tested with the corresponding pre-travel sera as paired assays in order to detect seroconversion. Identical methods for testing were used as reported in a study assessing dengue seroconversion in Australian travellers to Asia [4]. Cross-reactivity with Japanese encephalitis (JE) was assessed by using an in-house immunofluorescence JE-specific antibody assay. No serological testing for yellow fever (YF) or tick-borne encephalitis (TBE) was performed.

In travellers who did not receive JE, YF or TBE vaccine at enrolment, confirmed acute primary dengue infection was defined as seroconversion from a negative anti-dengue IgM in the pre-travel sample to a positive anti-dengue IgM in the post-travel sample or seroconversion from a negative anti-dengue IgG in the pre-travel sample to a positive anti-dengue IgG in the post-travel sample, if the post-travel IgM was negative. For travellers who did receive JE, TBE or YF vaccine at enrolment, this definition of seroconversion was interpreted as indicating possible primary dengue infection. Secondary dengue infection was defined as a positive anti-dengue IgM in the post-travel sample if both the pre- and post-travel samples were anti-dengue IgG positive. Presumed past dengue infection was defined as positive pre- and post-travel anti-dengue IgGs and a negative post-travel anti-dengue IgM [4].

The study protocol was approved by the Zürich Ethics Committee and by Melbourne Health Human Research Ethics Committees. The field study was self-funded by the Institute of Social and Preventive Medicine, University of Zurich, Switzerland and the additional serological testing was funded by an investigator initiated unrestricted grant from Sanofi-Pasteur.

Results

There were 285 travellers with specimens available for analysis. Of these, 140 (49.1%) were male and 140 (49.1%) were female (gender missing in 5 cases). The mean age was 36.3 years (median: 31, range: 17—83 [age missing in 7 cases]). Sixteen of these travellers were VFRs, 31 were travelling for business, and the remainder were tourists (reason missing in 21 cases). Eighty five (29.8%) travelled to Africa, 117 (41.1%) to Asia, 72 (25.3%) to Latin America/Caribbean and 4 (1.4%) to the Middle East (>1 region: $n = 2$, region missing in 5 cases). Mean duration of travel was 49.6 days (median: 28 days, range: 2—247 days [duration missing in 14 cases]). Post-travel bloods were taken a mean of 52.2 days after return (median 42, range: 2—214, [missing: $n = 73$]).

Two hundred and fifty seven of the 285 individuals (90.2%) had negative dengue serology post-travel and no traveller was positive for IgM (Fig. 1). Of the remaining 28 cases, 25