PhD defence Ralph Huits

Challenges in diagnosis and management of chikungunya and Zika virus infections.

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Summary:

Chikungunya virus (CHIKV) and Zika virus (ZIKV) have emerged as pathogens of global importance. They belong to different virus families (*Togaviridae* and *Flaviviridae*, respectively), but both arboviruses are primarily transmitted by widely distributed *Aedes* species mosquitoes. The studies in this doctoral thesis aim to advance our understanding of the risk factors, clinical presentation and diagnosis of *CHIKV and ZIKV* infections.

The sera of 498 patients with suspected CHIKV infection during the 2014-2015 outbreak of an Asian genotype of CHIKV in Aruba, were retrospectively tested at the Institute of Tropical Medicine in Antwerp (ITM). 269 CHIKV cases were identified, 210 by antibody detection and in addition 59 (28%) cases using real-time reverse transcription polymerase chain reaction (RT-PCR). This finding highlights a substantial risk of under-diagnosis in field settings where RT-PCR is not available and follow-up samples are not easily obtained. 171 patients were interviewed. Joint pains, fever and skin rash were the dominant acute phase symptoms. 26% of cases with joint pains suffered from persisting pains that lasted longer than one year. Persistence of joint pains was predicted by female gender of the patient (odds ratio 5.9), the pattern and number of joints involved in the acute phase of infection (odds ratio 7.4) and viremia beyond 7 days of symptom onset (odds ratio 6.4). The considerable burden of long-lasting sequelae of CHIKV infection and the poor performance of antibody detection-based assays in the acute phase, emphasize the need for improved diagnostics.

We evaluated a prototype rapid diagnostic test that uses mouse antibodies to capture the envelope protein E1 of CHIKV. When evaluated in a panel of clinical samples from returning travellers that contained Eastern/Central/Southern African (ECSA) genotype CHIKV (different lineages), the test had fair diagnostic sensitivity (88.9%), but the sensitivity for samples from Aruba, containing Asian genotype CHIKV was low (33.3%). The overall specificity of the test against sera from patients with other febrile conditions or sera that contained other alphaviruses or flaviviruses was poor (83.1%). Further development of a rapid test for CHIKV requires the use of antibodies that react across CHIKV genotypes and such a new assay should be evaluated against different CHIKV genotypes.

Zika virus was considered a cause of mild illness or, in 80% of cases, asymptomatic infection. However, its emergence in French Polynesia (2013) and the Americas (2015) has unveiled associations of ZIKV infection with neurological disease and, when pregnant women are infected, with microcephaly and other birth defects. In addition, the notion that this arbovirus can be transmitted from person to person by sexual intercourse, has caused great concern among scientists, health professionals and the general public. Clinicians and laboratories were overwhelmed by the demand for diagnostic evaluations for ZIKV. In returning travellers, the evidence base for diagnosis and management of ZIKV infection, particularly in regard to family planning, was small.

In a prospective cohort study among 55 adult participants who traveled to areas with epidemic vector-borne transmission in the Americas in 2016 the risk

of ZIKV infection was 17.0% per month of travel, and during the outbreak it ranked second only to travellers' diarrhea among travel-associated health hazards. Symptomatic infection presented with a skin rash, rather than with a fever. Only one of 9 ZIKV-cases (11.1%) was asymptomatic, suggesting that asymptomatic ZIKV infection in travellers is much lower than previously reported in studies from endemic areas.

ZIKV had been detected in high loads in semen, and it was isolated from semen samples for up to 69 days after the onset of symptoms. The potential for sexual transmission of ZIKV seems therefore closely associated to viral persistence in semen, which was studied in symptomatic returning travellers with confirmed ZIKV infection. ZIKV RNA was detected by RT-PCR in the semen of nine out of 15 participants (60%). It remained detectable for (median) 83 days post symptom onset (DPSO), and the longest duration of viral shedding in semen recorded in our cohort was 144 DPSO. ZIKV was successfully isolated from one sample only, but as long as viral RNA can be detected in semen, the potential for sexual transmission of ZIKV cannot be excluded. Microscopic analysis of semen samples of 11 participants showed presence of leukocytes (n=11), red blood cells (n=10) and oligospermia (n=6). These abnormalities may indicate some degree of tissue damage to the male reproductive tract.

In a cross-sectional cohort analysis, ITM's approach to the diagnosis of Zika infection in non-pregnant travellers during the ZIKV outbreak in the Americas was evaluated. At ITM, symptomatic travellers were tested with a ZIKV-specific RT-PCR on serum samples upon presentation within 7 DPSO and on urine within 14 DPSO and with ZIKV-specific antibody detection assays (ELISA). All positive or equivocal serological results were considered diagnostic only when confirmed by ZIKV virus neutralization testing. Asymptomatic travellers were tested using ELISA only, preferably from 20 days after the last exposure. ZIKV infection was confirmed in 49 of 462 travellers. It was frequent in symptomatic cases (46/227, 20.3%), but not in asymptomatic persons (3/235, 1.3%). Asymptomatic travellers had similar baseline characteristics, but they had reproductive concerns more often (75.8% vs. 24.2%). Rash (positive likelihood ratio (LRP) 5.6) and conjunctivitis (LRP 10.8) predicted ZIKV infection. The post-test probability of a negative ELISA result at 20-25 days was below 0.1%. Testing for ZIKV-specific antibodies within this timeframe is a safe strategy to rule out ZIKV infection and could be particularly valuable in the management of returning travellers who wish to conceive.