Abstract title: Zika virus dynamics and immune response in patients with acute infection

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Background:
Limited data are available on the presence of Zika virus (ZIKV) in body fluids and the antibody response during acute infection. Information on the dynamics of the early stages of infection would be useful to optimize diagnostic algorithms.

Material/methods:
Acute ZIKV infection was diagnosed in 13 travellers returning from affected areas in Central America in the period from January to August 2016. The most common symptoms were rash and arthralgia; one patient was asymptomatic. The median time from symptom onset to diagnosis was 5 days, range 1-19 days. Follow-up was performed to monitor ZIKV RNA load in blood, urine, and saliva by qRT-PCR and IgM and IgG antibody titres by ELISA and virus neutralization test. Saliva and urine samples were collected daily, while blood samples were collected weekly. The duration of follow up ranged from 30 to 287 days.

Results:
At the time of diagnosis, ZIKV RNA was detectable in plasma and saliva about 50% of cases and in urine in 83% of cases. Viral load in plasma was low (mean, 100 copies/mL) and of short duration (mean 4.6 days after onset; maximum 13 days). In two patients, ZIKV RNA load was monitored both in plasma and in whole blood, showing higher RNA load in whole blood than in plasma and for a longer time, up to 44 days after onset. ZIKV RNA load in urine and saliva was relatively high (range, 10^3-10^6 copies/mL) and of longer duration than in plasma (mean 14.2 and 17.6 days; maximum 35 and 52 days after onset, respectively). The patient with asymptomatic infection had ZIKV shedding in urine for over 15 days after exposure. A patient had persistent shedding of ZIKV RNA in semen for over 9 months after symptom onset. Serum IgM antibodies were detectable in 41.7% of cases at diagnosis. Mean times to IgM and IgG seroconversion were 5.4 and 9.7 days, respectively. In three patients IgM became negative within two months. ZIKV-specific neutralizing antibodies appeared within two weeks and reached titres of 1:128 to1:1024. A patient with acute ZIKV infection and a history of previous dengue virus infection had already high levels of ZIKV IgG antibodies at the first days after symptom onset, but never developed ZIKV IgM antibodies.

Conclusions:
The pattern of ZIKV shedding and antibody response varied among patients, conceivably due to differences in individual immune response. ZIKV-RNA testing should be done in whole blood, urine, and saliva collected within one month after onset, but positive results may be observed for longer times. Negative serology results are common within the first week after onset and require confirmation in follow-up samples. Serology testing may be inconclusive in patients with acute ZIKV infection secondary to another flavivirus infection.