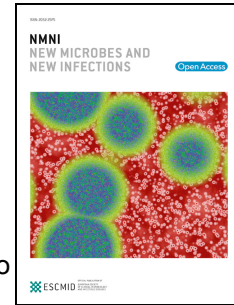


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Simultaneous outbreaks of dengue, chikungunya and Zika virus infections: diagnosis challenge in the returning traveler with non-specific febrile illness

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1 **Simultaneous outbreaks of dengue, chikungunya and Zika virus infections: diagnosis challenge in the**
2 **returning traveler with non-specific febrile illness**

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13 Running title: Dengue, chikungunya and Zika virus infections

14 Key words: dengue, chikungunya, Zika, outbreak, diagnostic algorithm

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16

17 **Abstract**

18 Zika virus is an emerging flavivirus that is following the path of dengue and chikungunya. The three *Aedes*-
19 borne viruses cause simultaneous outbreaks with similar clinical manifestations which represents a diagnostic
20 challenge in ill-returning travelers. We report the first Zika virus infection case imported in Switzerland and
21 present a diagnostic algorithm.

22

ACCEPTED MANUSCRIPT

23 Dear Editor,

24 On November 19th 2015, a 29-year-old woman attended our clinic with a four-day flu-like syndrome after a trip
25 in Colombia from October 30th-November 15th. During her trip home, she developed a feverish feeling with
26 diarrhoea; 24 hours later, she noted a pruritic rash on her trunk. Over the coming days, she presented retro-
27 orbital headache and arthralgia involving her wrists and interphalangeal joints. On physical examination, there
28 was a maculopapular rash on her trunk and limbs. Full blood count was normal. Because of her stay in a region
29 with concurrent arbovirus epidemics, as well as clinical presentation and incubation time, differential diagnosis
30 included dengue (DENV), chikungunya (CHIKV) and Zika (ZIKV) viruses infection. Given the absence of
31 concerning clinical signs, the patient received symptomatic treatment and was followed up as an outpatient.
32 Blood smear, malaria (SD BIOLINE Malaria Ag P.f/Pan) and dengue rapid tests (SD BIOLINE Dengue Duo
33 IgG/IgM/NS1Ag) were negative. On serum collected on November 20th (5 days after symptoms onset),
34 chikungunya IgM/IgG (immunofluorescence commercial test CHIKV (Euroimmun, Germany)) was negative,
35 but real-time ZIKV RT-PCR was positive (38 C_i; method developed by national reference center for arboviruses,
36 service de santé des armées, Marseille, France). Urine collected 12 days after symptoms onset was positive for
37 ZIKV by real-time RT-PCR with a higher viral load than in serum collected 7 days before (34 C_i). At the last
38 medical visit, 20 days after symptoms onset, she described progressive relief from the arthralgia and urine real-
39 time RT-PCR was negative. This was the first imported case of ZIKV infection in Switzerland.

40 Clinical manifestations of ZIKV infection are similar to dengue and chikungunya (fever, exanthema,
41 conjunctivitis, retro-orbital headache and arthralgia) [1]. Identification of the virus has specific management
42 implications for clinicians. In the case of dengue, a close follow-up for thrombocytes and haematocrit should be
43 done. In the case of chikungunya, high prevalence of chronic arthralgia should be discussed. In the presence of
44 ZIKV, potential sexual and materno-foetal transmission (risk of congenital microcephaly) should be presented
45 [2].

46 A reliable immunochromatographic rapid diagnostic test makes DENV infection easy to rule out in acutely ill
47 travellers [3]. NS1 antigen is highly specific but, in the presence of DENV IgM only, cross-reactivity between
48 the two flaviviruses, DENV and ZIKV, has been described [4]. CHIKV can be detected by PCR in blood and
49 serology by immunofluorescence is expected to be positive after ≥ 5 days of symptoms. Cross-reactivity between
50 flaviviruses limits the use of serology for ZIKV diagnosis which relies on viral RNA detection by PCR in blood,
51 preferably less than five days after symptoms onset (short viraemic period 3-5 days). As illustrated in our case,
52 viral RNA in urine persists for longer periods (15-20 days) and can be useful to confirm infection [5]. Virus can

53 also be detected in saliva during the viraemic period [6]. To support clinicians in their diagnostic work-up, we
54 present in the Figure a diagnostic algorithm for travelers with non-specific febrile illness returning from regions
55 experiencing simultaneous outbreaks of DENV, CHIKV and ZIKV.

56

57 **Acknowledgements**

58 We thank J. Helfer from the medical outpatient clinic for clinical care. We are grateful to S. De Vallière and B.
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60 PCR.

61 All authors have made substantial contributions to the manuscript, for literature search, writing and figure.

62 No conflicts of interest.

63

64 **Figure legend**

65 Diagnostic algorithm for travelers with non-specific febrile illness returning from regions experiencing
66 simultaneous outbreaks of dengue, chikungunya and Zika virus infections.

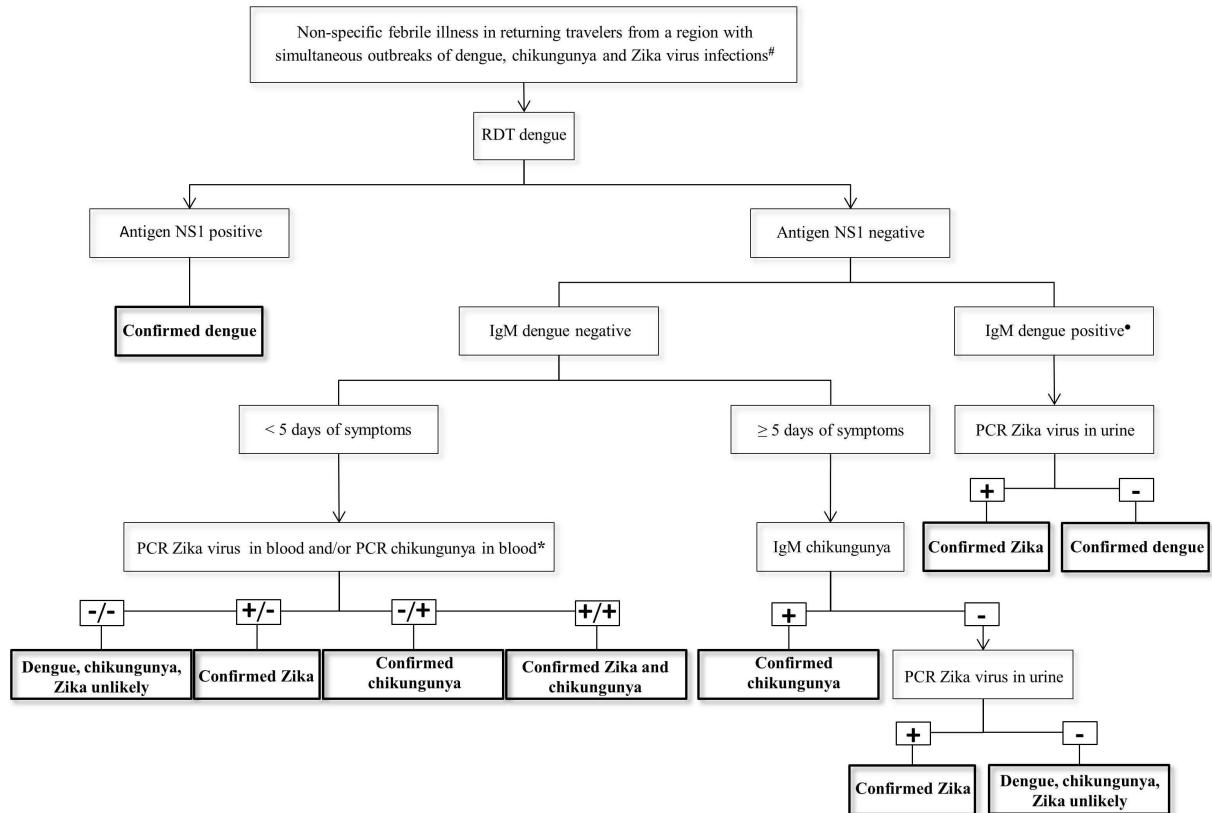
67 Abbreviation: RDT: rapid diagnostic test

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First, exclude malaria with a rapid diagnostic test.

* Cross-reactivity between flaviviruses.

*Sequential testing is an alternative in the absence of concerning clinical signs.