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Clinical significance of intra-host variability of Dengue-1 virus in venous and capillary blood

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Dengue-1 intra-host variability and clinical outcomes

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ABSTRACT
Background
Dengue fever represents a major public health problem. Both viral and host immune factors are involved in severe infections. Humans and mosquito-vectors are infected with diverse viral populations that may play a role in viral adaptation and disease pathogenesis. Our

objective was to analyse the intra-host genetic variability of DENV-1 in the venous and capillary blood and its relationships with the clinical presentation of dengue.

Methodology/Principal Findings
Early serum samples were collected in 2009 from ten DENV-1 infected patients hospitalised in Santa Cruz de la Sierra, Bolivia. Partial viral envelope sequences were analysed at the inter- and intra-host level. For each patient, an average of 56 clone sequences was analysed both in the venous sector and the capillary sector (from right and left hands). The ten consensus sequences were highly similar. The intra-host DENV-1 genetic variability was significantly lower in the venous sector than in the capillary sector, and in patients with hemorrhagic symptoms than in those without hemorrhagic symptoms, particularly in capillary samples. No relation was found with sex, age, dengue IgG-serological status, day of serum sampling, or viral load.

Conclusions/Significance
Significant relationships were found between the clinical presentation of dengue and the variability of viral populations within hosts, particularly in capillary samples. The observed variability of envelope sequences at the early phase of dengue infection was not critically influenced by the previous dengue serological status of patients. An important part of viral microevolution may occur in the capillary sector and influence the mechanisms of severe forms.

INTRODUCTION

Dengue fever represents an increasing public health issue in the tropics and subtropics [1]. Infection with one of the four serotypes of dengue virus (DENV) can be subclinical or cause mild febrile syndrome to severe illness with bleeding and shock, providing a prolonged specific immunity against this serotype but not against the others [2].
Two physiopathological hypotheses –which are not necessarily exclusive- are debated, based on host immune factors and viral virulence factors.

The antibody-dependent enhancement theory relies on the observation that patients experiencing a second dengue infection have a higher risk for developing severe disease [3]. Pre-existing heterologous dengue antibodies, induced by a prior infection, would enhance the replication of DENV in mononuclear cells that secrete vasoactive mediators causing increased vascular permeability, hypovolemia and shock. More recently, factors involving cell-mediated immunity and host genetics have been shown to be determinants of disease severity [4,5].

Viral factors are also implicated. For example, several studies have shown that DENV-2 viruses belonging to the genotype “Southeast Asia” have a higher virulence and epidemic potential than viruses belonging to the “American” genotype [6,7], and residue E-390 has been shown to be key in the level of viral replication [8]. However, whilst genetic variations of viral populations observed within human-hosts and mosquito-vectors may play a role in viral adaptation to changing environments, their role in dengue pathogenesis remains unclear [9-18]. Relationships between DENV intra-host genetic diversity and clinical outcome have rarely been studied with conflicting results [10, 14, 17, 18].