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Intercurrent Flaviviral Viremia and *Plasmodium ovale* Infection in Ill Returned Travelers to Ontario

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Abstract:

Similar epidemiology and clinical presentations of arboviral infections and malaria coupled with the typically sequential approach to diagnostic testing, where malaria is confirmed or excluded urgently in febrile returned travelers, may mask the true epidemiology of co-infections. Flaviviruses are known to trigger relapsing forms of malaria, including *Plasmodium ovale*, long after primary malaria infection, and this may delay the diagnosis of malaria. We aim to understand the incidence of intercurrent flaviviral infection in confirmed *Plasmodium ovale* infection. DNA and RNA from biobanked isolates of *P. ovale* detected in whole blood at the Public Health Ontario Laboratory between 2006 and 2018 were extracted and screened for intercurrent flaviviral infections using previously validated real-time PCR (qPCR) assays targeting multiple flaviviruses (pan-FLAV) and, specifically, dengue virus types 1-4 (DEN1, DEN2, DEN3, DEN4). One-hundred seventeen unique isolates of *P. ovale* were identified, of which 64 had sufficient remaining specimen for further molecular analysis. Males accounted for 51.6% (n=33/64) of *P. ovale* cases, while females accounted for 43.8% (n=28/64), and sex was unassigned in 4.7% (3/64). Median age of *P. ovale* cases was 28.8 years (range 22 mos - 72 years; IQR 18.8 - 40.1 years). Median parasitemia was < 0.01% (range < 0.01% - 0.8%). Thirty (46.9%) *P. ovale* cases had documented travel history exclusively to Africa, with Nigeria as the most common source country (23/30 [76.7%]). Pan-FLAV assay yielded a 1.6% (1/64) positivity rate, while no specimens were positive on the DEN assays. *P. ovale* infections are most commonly imported to Ontario from West Africa, and Nigeria, specifically. Intercurrent flaviviral viremia was noted in at least 1.6%, which may suggest that primary flaviviral infection triggered a relapse of *P. ovale*. Alternatively, such co-occurrence may suggest primary infection with both organisms known to cause fever in returning travelers. Consideration of flaviviral co-infection should be given to the *P. ovale* patient with deep thrombocytopenia, lymphopenia, and high-yield arboviral symptomatology such as rash and retro-orbital headache.