HHS Public Access

Author manuscript

Rev Soc Bras Med Trop. Author manuscript; available in PMC 2022 June 06.

Published in final edited form as:

Rev Soc Bras Med Trop. ; 52: e20180166. doi:10.1590/0037-8682-0166-2018.

Genotypes of clinical varicella-zoster virus isolates from Manaus, Brazil

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To the Editor: Varicella-Zoster virus (VZV), or human herpesvirus 3, is a member of the *Herpesviridae* family, subfamily *Alphaherpesvirinae*. Primary infection with VZV causes chickenpox (varicella), a febrile rash illness that usually follows a mild course but may be complicated by pneumonia, meningitis, bacterial superinfections among others (1, 2). The virus establishes latent infection in dorsal root ganglia and can reactivate to cause zoster, a dermatomally distributed rash illness that is often marked by severe pain (1).

In Brazil there were 2,334 deaths related to VZV from 1996 to 2011 during the pre-vaccination period. Of these, 66.9% occurred among children under 9 years of age. During the same period 62,052 hospitalizations due to VZV occurred, primarily in children <9 years old. More than 27% (~17,000) of varicella cases requiring hospitalization developed in children aged 1–4 (DataSUS: http://www2.datasus.gov.br/DATASUS). Data about the molecular epidemiology and circulating VZV genotypes in Brazil have been scant. The only available data prior to this report came from Muir, et al (3) and Loparev, et al (4), and were generated using genotyping methods that were less robust than those currently in use. Loparev and coworkers revealed the first evidence of recombination in VZV strains collected in Mexico and Chile, most of which were identified as genotype M (mosaic) (4).

Varicella vaccination has been shown to be both effective in safe in countries that routinely administer the vaccine; in the US, a 2-dose schedule of varicella vaccine prevented 87.5% of clinically diagnosed varicella and 97.3% of laboratory-confirmed varicella (5). Brazil began universal varicella vaccination in September 2013 through the National Immunization Program. The determination of VZV genotypes in this sample serves as a baseline of circulating strains in Manaus, Brazil prior to the introduction of routine immunization for varicella. As coverage levels increase in the coming years, we anticipate that reduced rates of transmission will lead to a shift in the profile of circulating VZV genotypes, as has was observed during virologic surveillance for other vaccination programs such as measles (6).

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The authors report no conflicts of interest.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Diseases Control and Prevention (CDC).

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During February–September 2013, vesicular lesion specimens for VZV genotyping were collected from 14 hospitalized patients with clinically diagnosed varicella or herpes zoster,or from CSF in patients with suspected CNS viral infection as part a study investigating the common viruses circulating in the Amazonas (7). All specimens were from clinically diagnosed cases in the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado, a tertiary and public health care center as well as a referral center for tropical and infectious diseases, located in the City of Manaus. This study was approved by the Ethics Committee of the FMT-HVD. Written informed consent was obtained from all the patients included in this study or from their responsible person(s).

DNA was extracted from the specimens using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. PCR amplification and sequencing of 3 variable VZV genome targets in ORF21, ORF22 and ORF50 were used to distinguish wild type VZV clades designated in 2010 (8) using the technique described by Loparev et al (9).

DNA amplification reactions were performed in a GeneAmp PCR 9700 (Applied Biosystems, Grand Island, NY), using the AmpliTaq Gold 360 MasterMix (Life Technologies, Grand Island, NY) in 50μl reaction volumes. PCR conditions were 95°C for 10m for 1 cycle, 40 cycles of 94°C for 30s, 55°C for 30s, 72°C for 30s, followed by 1 cycle of 72°C for 10m. PCR products were cleaned up using ExoSAP-IT (Affymetrix, Santa Clara, CA) and added to cycle sequencing reaction (20μl). Cycle sequencing conditions were 25 cycles of 96°C for 10s, 50°C for 5s, 60°C for 4m, followed by 72°C for 7m. These products were treated with CleanSeq beads (Beckman Coulter, Indianapolis, IN) and denatured. Denatured samples were sequenced on the ABI 3500 genetic analyzer (Applied Biosystems), and sequences were analyzed using Sequencher 5.4.6 software (Gene Codes Corporation, Ann Arbor, MI).

The VZV molecular epidemiology varies according to geographical region, likely reflecting both climatic conditions and geographic isolation of populations. Although these this trend is breaking down in countries with open immigration policies (9–11).

All of the collected specimens were VZV DNA positive and wild type (using vaccine: wild-type discrimination) (9). Genotypic analysis characterized 7 isolates as Clade 5 viruses (50%), 5 as Clade 1 (36%), and 2 as Clade 3 (14%). This is a similar distribution to the US except that Clade 1 predominates, followed by Clade 3, and then Clade 5 (CDC, unpublished observation). Clade 5 viruses comprise the predominant genotype circulating in Africa, and its dominance in Brazil may reflect large influxes of people from sub-Saharan Africa in the 16th century. The only other substantial study of VZV isolates in South America was conducted in temperate Argentina, in which exclusively European type viruses (Clade 1 or 3) were identified (10)

Monitoring of VZV genotypes in a susceptible population is important as a means for determining factors involved in the transmission and global dissemination of the virus. As varicella vaccination is adopted more broadly among developed and developing countries, the distribution of globally circulating varicella clades is expected to shift. Studies of

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various genotypes in the context of diseases may also lead to characterizing risk factors for complications in varicella and zoster, such as neurological disease, pneumonia, bacterial superinfection, and post-herpetic neuralgia. Of all regions of the world, South America has been investigated less than any other for the distribution of VZV clades. Broader studies among countries on this continent should add valuable information about transmission patterns and global trends for this common virus infection.

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