Hepatitis B and Delta in Latin America

Epidemiological Aspects

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Hepatitis B Virus (HBV)
History - HBV

Baruch Samuel Blumberg
(New York, July 28th, 1925 – April 5th, 2011)

1976 - Nobel Prize of Physiology and Medicine
PRESENÇA DO ANTÍGENO “AUSTRÁLIA” (Au) EM POPULAÇÕES DO INTERIOR DO ESTADO DO AMAZONAS — BRASIL

Gilberta Bensabath (1) e Jorge Boswell (2)

RESUMO

A pesquisa do antígeno Au no soro de pessoas residentes ao longo do rio Purus, Estado do Amazonas, mostrou-se positiva em 17,9% dos indivíduos com hepatite ou história de hepatite, e em 5,1% dos indivíduos sem história de hepatite. Foram testados ao todo 506 indivíduos, com um percentual de positividade, nos dois grupos, igual a 9%.
Epidemiology - HBV

The number of HBsAg-positive people increased from 223 million in 1990 to 240 million in 2005

Brazilian Ministry of Health in 2011
Estimation of 600,000 HBsAg Chronic Carriers
HBsAg = 0.37%
Low Endemicity

Epidemiology - HBV

Adapted from:
HBV Genotypes – Brazil

4. Santos AO, ... PINHO JR, ... Salcedo JM. *Viral J* (2010) 7:315
5. Ribeiro NR, ... PINHO JR, ... Lyra AC. *Liver Int* (2006) 26: 1

Processos FAPESP nº 2010/51208-2 e 2010/50081-9

“Prevalência de resistência primária aos antivirais utilizados no tratamento da hepatite B entre pacientes com infecção crônica pelo vírus da hepatite B não submetidos a tratamento”

Trabalho de Doutorado de Michele S Gomes-Gouvêa

Participants:

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5. Rosamar EF Rezende – Secretaria Municipal da Saúde, Ribeirão Preto, SP
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12. Marcio K Oikawa – Universidade Federal do ABC, Centro de Matemática, Computação e Cognição, São Paulo, SP
13. Luciano V de Araújo, Escola de Artes, Ciências e Humanidades-Universidade de São Paulo, SP
HBV SubGenotypes – Latin America

10. Alvarado-Mora MV, ..., Carrilho FJ, PINHO JR. Mem Inst Oswaldo Cruz (2011) 106: 495
Detection of Hepatitis B virus subgenotype A1 in a Quilombo community from Maranhão, Brazil

Mônica V. Alvarado-Mora, Lúcia Boteho, Michele S. Gomes-Couveia, Vanda de Souza, Maria C. Nascimento, Gaudio S. Pinniu, Flávio J. Carlinho and João R. Pinto
HBV Genotype F – Latin America

Molecular characterization of the Hepatitis B virus genotypes in Colombia: A Bayesian inference on the genotype F
Mónica Viviana Alesardey-Mate1**, Camila Hilda Romano1, Michelle Ismael Gómez-González1, María Fernanda Gutierrez1, Luisa Bombard1, Iralu Isabel Cardona1, Iesha Ramirez-Robledo Pardo1

Genotype F was the most prevalent in this population (77%) – subgenotypes F3 (75%) ©

BMC Microbiology

Research article
Hepatitis B virus genotypes circulating in Brazil: molecular characterization of genotype F isolates
Francisco CA Mello1,2, Francisco JD Souto1, Letícia C Nabuco1, Cristiane A Villela-Nogueira1, Henrique Sergio M Coelho1, Helena Cristina F Franz1, João Carlos P Saraiva1, Helaine A Virgolinino1, Ana Rita C Motta-Castro1, Mabel MM Melo2, Regina MB Martins2 and Selma A Gomes1

New perspectives on the evolutionary history of hepatitis B virus genotype F
Cássia Torres, Flavia Guadalupe Piñeiro y León, Silvana Claudius Peszans, Viviana Andrea Mhiyel, Redolfo Hietz Carpes

A new clade of hepatitis B virus subgenotype F1 from Peru with unusual properties
Markus van Molter1, Silvia Vásquez1, Juangun Sun1, Ulrike C. Wendt2, Anja May1, Wolfram H. Gerlich1, Monika Richtle1, Stephan Schäfer2

Phylogenetic Analysis of Hepatitis B Virus Genotype F Complete Genome Sequences From Chilean Patients With Chronic Infection
Mauricio Yenega3,1, Monica Y. Alvarez4,5, Bastenys A. Villanueva4, Jose R. Rebollo Pardo6,7, Peter J. Cremer8,9, Néstor Laurencin10,11, Lilly Yuen12, and Javier Bravo13

genotype F is the most prevalent in the country
HBV Genotypes – Latin America

- Buenos Aires, Argentina: Pezzano et al., 2010
  - HBV/F: 47%
  - HBV/A: 28%
  - HBV/D: 22%
  - HBV/C: 2%
  - HBV/B: 1%

- Bogotá, Colombia: Alvarado-Mora et al., 2011
  - HBV/F: 77%
  - HBV/G: 8%
  - HBV/A: 13%

- Venezuela: Machado et al., 2010
  - HBV/F: 98%
  - HBV/A: 2%

- Costa Rica, Nicaragua, Honduras, El Salvador and Guatemala: Arauz-Ruiz et al., 1997
  - HBV/F: 79%
  - HBV/A: 14%
  - HBV/D: 6%
  - HBV/C: 1%

- Santiago, Chile: Di Lello et al., 2009
  - HBV/F: 67%
  - HBV/B: 5%
  - HBV/A: 7%
  - HBV/D: 13%
  - HBV/C: 8%
The subgenotype F1 was found in Alaska, Argentina, Chile and Bolivia.

Genotype F strain subdivide into two subgenotypes, F1 and F2, each characterized by specific substitutions in the S gene product, Leu\textsuperscript{45} and Thr\textsuperscript{45}, respectively.

Arauz-Ruiz et al., 2002; Norder et al., 1993; Arauz-Ruiz et al., 1997
HBV Subgenotype F1b – Chile

Fig. 1. The Maximum Clade Credibility (MCC) tree was estimated by a Bayesian analysis of 290 complete genome sequences of hepatitis B virus strains. The posterior probabilities of the key nodes are shown above the respective nodes. The HBVF samples obtained from Chile (n = 21, HCUCH) were analyzed together with other strains from around the world. The clusters containing the strains of other HBV genotypes collapsed.

HBV Subgenotype F2 – Venezuela
Molecular characterization of the Hepatitis B virus genotypes in Colombia: A Bayesian inference on the genotype F

Mónica Viviana Alvarado Mora a,*, Camila Malta Romano b, Michele Soares Gomes-Gouvêa a, Maria Fernanda Gutierrez c, Livia Botelho a, Flair José Carrilho a, João Renato Rebello Pinho a

a Laboratory of Gastroenterology and Hepatology, São Paulo Institute of Tropical Medicine and Department of Gastroenterology, School of Medicine, University of São Paulo, Brazil
b São Paulo Institute of Tropical Medicine, Department of Infectious and Parasitic Diseases (LIM12), School of Medicine, University of São Paulo, Brazil
c Laboratory of Virology, Department of Microbiology, Pontifícia Javeriana University, Bogotá, Colombia

Genotype F was the most prevalent in this population (77%) – subgenotypes F3 (75%) and F1b (2%)
The phylogeny showed that subgenotype F3 (adw4) was most prevalent in this population: 39 (75%) out of 52 sample sequences clustered together with F3 reference sequences. Genotypes G (adw2) (4–7.7%), A2 (adw2) (8–15.3%), and F1b (adw4) (1–2%) were also found in this population.
<table>
<thead>
<tr>
<th>Dataset genotype F</th>
<th>HBV TMRCA (years; 95% HPD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.6 $\times$ 10^{-4}</td>
</tr>
<tr>
<td>77 sequences of HBV S/POL region with 1306 bp</td>
<td></td>
</tr>
<tr>
<td>Genotype F</td>
<td>150.9 (73.1–250.2)</td>
</tr>
<tr>
<td>F1</td>
<td>56.8 (28.3–93.4)</td>
</tr>
<tr>
<td>F2</td>
<td>73.8 (31.6–131.1)</td>
</tr>
<tr>
<td>F3</td>
<td>118.6 (60.6–194.4)</td>
</tr>
<tr>
<td>F3 Colombia</td>
<td>60 (35.7–89.2)</td>
</tr>
<tr>
<td>F4</td>
<td>39.3 (16.8–63.6)</td>
</tr>
<tr>
<td>283 sequences of HBV S/POL region with 681 bp</td>
<td></td>
</tr>
<tr>
<td>Genotype F</td>
<td>96 (28.9–361.6)</td>
</tr>
<tr>
<td>F1</td>
<td>37.1 (14.8–66.8)</td>
</tr>
<tr>
<td>F2</td>
<td>39.8 (12.7–93.5)</td>
</tr>
<tr>
<td>F3</td>
<td>73.1 (22.2–151.2)</td>
</tr>
<tr>
<td>F3 Colombia</td>
<td>22.9 (11.5–37.6)</td>
</tr>
<tr>
<td>F4</td>
<td>19.1 (9.9–31.5)</td>
</tr>
</tbody>
</table>
New perspectives on the evolutionary history of hepatitis B virus genotype F

Carolina Torres, Flavio Guadalupe Piñeiro y Leone, Silvana Claudia Pezzano, Viviana Andrea Mbayed, Rodolfo Héctor Campos

Cátedra de Virología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Argentina

Table 2

Co-estimation of substitution rates and tMRCA\(^4\).

<table>
<thead>
<tr>
<th>Group</th>
<th>Complete genome</th>
<th>Nonoverlapping regions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tMRCA (years)</td>
<td>HPD95% (years)</td>
</tr>
<tr>
<td>F1</td>
<td>91</td>
<td>46–150</td>
</tr>
<tr>
<td>F1a</td>
<td>55</td>
<td>33–82</td>
</tr>
<tr>
<td>F1b</td>
<td>23</td>
<td>16–31</td>
</tr>
<tr>
<td>F2</td>
<td>70</td>
<td>41–109</td>
</tr>
<tr>
<td>F3</td>
<td>62</td>
<td>39–93</td>
</tr>
<tr>
<td>F4</td>
<td>69</td>
<td>37–110</td>
</tr>
<tr>
<td>F</td>
<td>284</td>
<td>120–501</td>
</tr>
<tr>
<td>Substitution rate (s/s/y)</td>
<td>$1.67 \times 10^{-4}$</td>
<td>$9.42 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>$2.37 \times 10^{-4}$</td>
<td>$3.08 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

\(^4\) Mean substitution rates and tMRCA\(_s\) corresponding to the Bayesian coalescent analysis performed under the UCLN-BSP model by calibration with time-stamped sequences of HBV/F for the complete genome and the nonoverlapping regions.

![Evolutionary tree diagram](image)
High prevalence of HBV/A1 subgenotype in native south Americans may be explained by recent economic developments in the Amazon

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b Laboratory of Tropical Gastroenterology and Hepatology “João Alves de Queiroz and Castorina Bittencourt Alves”, Institute of Tropical Medicine, Department of Gastroenterology, University of São Paulo School of Medicine, São Paulo, SP, Brazil
c VIZLab — Advanced Visualization Laboratory, UNISINOS, São Leopoldo, RS, Brazil
d Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
Table 1: Characterization of a sample of 38 Native South American populations included in this study.

<table>
<thead>
<tr>
<th>No.</th>
<th>Population</th>
<th>Linguistic classification</th>
<th>Region</th>
<th>Sampling Year</th>
<th>First contact with non-native populations</th>
<th>+HBV/n (%)</th>
<th>Genotype</th>
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<tr>
<td>01</td>
<td>Kal'na</td>
<td>Carib</td>
<td>Amazon</td>
<td>1991</td>
<td>1923</td>
<td>01/20 (5.0) Not determined</td>
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</tr>
<tr>
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<td>Tirijó</td>
<td>Carib</td>
<td>Amazon</td>
<td>1970</td>
<td>1955</td>
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<td></td>
</tr>
<tr>
<td>03</td>
<td>Wayampi</td>
<td>Tupi</td>
<td>Amazon</td>
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<td>1900</td>
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<td>04</td>
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<td>Arawakan</td>
<td>Amazon</td>
<td>1976</td>
<td>1846</td>
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<tr>
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<td>Wai-Wai</td>
<td>Carib</td>
<td>Amazon</td>
<td>1988</td>
<td>1838</td>
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<tr>
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<td>Carib</td>
<td>Amazon</td>
<td>1983</td>
<td>1933</td>
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<td>Amazon</td>
<td>1983</td>
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<td>1968</td>
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<td>Mura</td>
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<td>Amazon</td>
<td>1986</td>
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<td>15</td>
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<td>1952</td>
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<td>Parintintin</td>
<td>Tupi</td>
<td>Amazon</td>
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<td>1922</td>
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<td>Arauan</td>
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<td>1796</td>
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<td>Amazon</td>
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<td>Tupi</td>
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<td>1969</td>
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<td>Amazon</td>
<td>1970</td>
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<td>27</td>
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<td>1965</td>
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<td>1986</td>
<td>1981</td>
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<td>Tupi</td>
<td>Amazon</td>
<td>1987</td>
<td>1954</td>
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<td>Brazilian Central Plateau</td>
<td>1974</td>
<td>1798</td>
<td>12/22 (54.5) A1 (05)</td>
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<tr>
<td>32</td>
<td>Xavante</td>
<td>Macro-Ge</td>
<td>Brazilian Central Plateau</td>
<td>1990</td>
<td>1960</td>
<td>00/28 (0) -</td>
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<td>33</td>
<td>Ayoreo</td>
<td>Zamucoan</td>
<td>Chaco</td>
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<td>1952</td>
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<td>Macroian</td>
<td>Chaco</td>
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<td>1950</td>
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<td>Chaco</td>
<td>1997</td>
<td>1968</td>
<td>02/30 (6.7) F4 (01)</td>
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<td>Southern Brazil</td>
<td>1988</td>
<td>1792</td>
<td>01/27 (3.7) A1 (01)</td>
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<td>37</td>
<td>Kaingang</td>
<td>Macro-Ge</td>
<td>Southern Brazil</td>
<td>1988</td>
<td>1808</td>
<td>00/25 (0) -</td>
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<tr>
<td>38</td>
<td>Mapuche</td>
<td>Araucanian</td>
<td>Southern South America</td>
<td>1990</td>
<td>1877</td>
<td>00/28 (0) -</td>
<td></td>
</tr>
</tbody>
</table>
Geographical location of 38 Native American populations included in this study.

Each color represents a region, and symbols indicate linguistic classifications.

Populations were numbered from North to South, according to the region where they are located: Amazon (green), Brazilian Central Plateau (orange), Chaco (purple), South Brazil (yellow) and Southern South America (blue).
Prevalence and HBV genotypes observed in a sample of Native Americans according to the year of first contact with non-Native populations.

Circle sizes are proportional to the prevalence of HBV in each population.

Populations negative for HBV are shown in white.

Different symbols indicate different genotypes, as indicated.
**Bayesian Skyline Plots of the population dynamics of HBV/A1.**

The thick red solid line is the median estimate, and the thick grey lines show the 95% highest posterior density limits.

a) Strains isolated from Native American individuals.

b) Strains isolated from urban Brazilian individuals.
Patients infected with HBV/D4 presented a higher frequency of HBeAg positive status than those infected with HBV/A1 [8/29 (28%) vs. 8/80 (10%), p = 0.02] and were more frequently found in the immune tolerance stage of chronic HBV infection [7/29 (24%) vs. 3/80 (4%), p = 0.003]. There was no significant difference in gender, age and viral load median.
Santos MDC, Gomes-Gouvêa MS, Nunes JDC, Romano CM, Sousa MT, Barros LMF, Carrilho FJ, Ferreira ASP, Pinho JRR. A high prevalence of the rare subgenotype D4 of Hepatitis B virus supports the peculiar pattern of slave trade to Maranhão State, Northeast Brazil. (submitted)

3,860 samples
92 (2.38%) HBsAg-positives
50 HBV DNA positives
Subgenotypes:
  A1: 14%; 8/50
  D4: 86%; 42/50
Hepatitis Delta Virus (HDV)
Immunofluorescence detection of new antigen-antibody system (δ/anti-δ) associated to hepatitis B virus in liver and in serum of HBsAg carriers

M. RIZZETTO, M. G. CANESE, S. ARICÒ, O. CRIVELLI, C. TREPO, F. BONINO, AND G. VERME

From the Department of Gastroenterology, Ospedale Mauriziano Umberto I, Turin, Italy; the Electron Microscopy Centre of the Faculty of Medicine, University of Turin, Italy; and INSERM U45, Laboratory of Hygiene, University Claude Bernard, Lyon, France

δ agent: Association of δ antigen with hepatitis B surface antigen and RNA in serum of δ-infected chimpanzees

(M. rizzetto, b. hofer, m. G. canese, J. wai-Kuo shih, r. H. purcell, and J. L. Gerin)

*Division of Molecular Virology and Immunology, Department of Microbiology, Georgetown University Schools of Medicine and Dentistry, Washington, DC 20037, and Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20010

Communicated by Robert M. Claman, June 9, 1980
Hepatitis Delta Virus Infection and Labrea Hepatitis

Prevalence and Role in Fulminant Hepatitis in the Amazon Basin

Gilberta Bensabath, MD; Stephen C. Hadler, MD; M. C. Pereira Soares, MD; Howard Fields, PhD; Leonidas B. Dias, MD; Hans Popper, MD, PhD; James E. Maynard, MD, PhD

JAMA (1987) 258:479
Epidemiology - HDV

Epidemiology – HDV - Brazil

Lábrea/Amazonas
HBsAg 3.3%
(30% Anti-HD +) \(^{(3)}\)

Pará
HBsAg /Anti-HBc isolated (557)
3.4% (19/557) Anti-HD + \(^{(6)}\)

Amazonas
HBsAg 9.7%
(13.4% Anti-HD +)
in 7 Indians Tribes \(^{(2)}\)

Maranhão
133 HBsAg +
3.8% (5/133) Anti-HD Pos \(^{(1)}\)

Acre/Amazonas
Communities from Acre and Purus Rivers
66.6% Anti-HD pos. among HBsAg pos. \(^{(4)}\)

Acre
2002: HBsAg 3.3% (20% Anti-HD +) \(^{(5)}\)

Mato Grosso
Immigrants from South of Brazil
HBsAg 3.9% (0% Anti-HD +) \(^{(7)}\)

Epidemiology – HDV - Brazil

- Metropolitan Area of São Paulo City (ABC Region & SP)
  - HDV-RNA -
  - 1/137 (0.7%) Anti-HD +

- Minas Gerais
  - 2/164 (1.2%) Anti-HD +

- Paraná
  - 2/25 (8%) Anti-HD +

- Rio Grande do Sul
  - 0/84 Anti-HD +

- Ribeirão Preto
  - 0/184 Anti-HD +

- Bahia
  - 0/25 Anti-HD +

619 HBsAg +
0.8% (5/619) Anti-HD +

Viral Genetic Diversity - HDV

Viral Genetic Diversity
HDV Genotypes in the World

HBV/A/D/F

HDV genotypes III and HBV genotype F

These results confirm the predominance of HDV-3 in South America

HDV-3/HBV-A co-infection

control of HDV/3 spreading in South America

Venezuelan isolates belong to genotype III
Hepatitis delta in HIV/HBV co-infected patients in Brazil: is it important?

### HDV Genotypes – Maranhão State

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Race</th>
<th>Origin (city)</th>
<th>HBeAg/ Anti-HBe status</th>
<th>HBV DNA levels (log)</th>
<th>HDV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>8127</td>
<td>M</td>
<td>41</td>
<td>Pardo</td>
<td>Urbanos Santos</td>
<td>Neg./Pos.</td>
<td>3.43</td>
<td>Pos.</td>
</tr>
<tr>
<td>8103</td>
<td>F</td>
<td>61</td>
<td>Pardo</td>
<td>Urbanos Santos</td>
<td>Neg./Pos.</td>
<td>4.74</td>
<td>Neg.</td>
</tr>
<tr>
<td>8135</td>
<td>M</td>
<td>53</td>
<td>Black</td>
<td>São Luís</td>
<td>Neg./Pos.</td>
<td>2.63</td>
<td>Neg.</td>
</tr>
<tr>
<td>8022</td>
<td>M</td>
<td>78</td>
<td>Pardo</td>
<td>Urbanos Santos</td>
<td>Pos./Pos.</td>
<td>4.91</td>
<td>Pos.</td>
</tr>
<tr>
<td>8141</td>
<td>F</td>
<td>50</td>
<td>Pardo</td>
<td>São Luís</td>
<td>Neg./Pos.</td>
<td>2.49</td>
<td>Pos.</td>
</tr>
</tbody>
</table>

5/133 (3.8%) anti-HD (+) em pacientes HBsAg +
• Ninety-two individuals who were positive for HBsAg serological marker among 3860 individuals, from five municipalities in Northeastern Maranhão, participated in this study.
• Among the 92 individuals screened for anti-HD antibody, eight were positive (8.7%).
• Samples from these eight positive individuals were submitted to PCR. Half of them were positive for a fragment sequence of the delta antigen and submitted to sequencing.
• Only two of them (50%) had detectable HBV DNA and had the HBV subgenotype determined.
### Table 1
Demographical characteristic HBV/HDV co-infected individuals described in this study.

<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Race*</th>
<th>Age</th>
<th>Origin</th>
<th>Zone</th>
<th>FamilyIncome(MW)</th>
<th>HDV-genotype</th>
<th>HBV-subgenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1015</td>
<td>M</td>
<td>Black</td>
<td>23</td>
<td>Morros</td>
<td>Rural</td>
<td>&lt;1 MW</td>
<td>HDV-8</td>
<td>ND</td>
</tr>
<tr>
<td>2231</td>
<td>M</td>
<td>Black</td>
<td>25</td>
<td>H. Campos</td>
<td>Rural</td>
<td>&lt;1 MW</td>
<td>HDV-8</td>
<td>D4</td>
</tr>
<tr>
<td>2321</td>
<td>M</td>
<td>Black</td>
<td>49</td>
<td>H. Campos</td>
<td>Rural</td>
<td>&lt;1 MW</td>
<td>HDV-8</td>
<td>D4</td>
</tr>
<tr>
<td>3959</td>
<td>F</td>
<td>Mestizo/Mullato</td>
<td>39</td>
<td>U. Santos</td>
<td>Urban</td>
<td>&lt;1 MW</td>
<td>HDV-8</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Self-declaration; M-Male; F-Female; MW- Minimum Wage; ND-Not determined.
Viral hepatitis B and Delta still remain a serious problem in Latin America.

Data from the 1980s indicated that HBV and HDV infection are the main causes of chronic hepatitis. However, the spread of HBV infection could be controlled through the implementation of immunization programmes.

Different countries from Mexico to Argentina display marked differences in terms of HBV genotype distribution. HBV genotype F has been identified as the most frequent in most Latin America countries, except for Mexico and Brazil, where genotypes H and A are the most frequent, respectively.
Take Home Messages

• HDV is present worldwide but its distribution pattern is not uniform. HDV was recently detected in novel geographic regions, reinforcing that it is a very serious health threat in under-developed countries.

• The main prevalence areas are the Mediterranean basin, the Middle East, central and northern Asia, western and central Africa, the Pacific islands and Latin America, MAINLY in the Amazonian basin (Brazil, Peru, Venezuela and Colombia).

• Novel strategies to increase HBV immunization in the Latin American population are needed to warrant thorough coverage in the rural areas.
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Thank you for your attention!