Epidemiology of Hepatitis A and Hepatitis E in Brazil

Themis Reverbel da Silveira

Brasilia, 19-21 March 2014
BRAZIL

- Inhabitants ~200,000,000 million
- Extension: 85,142,153 km²
- Heterogenous population
- Ethnic miscigenation
- A developing country
- Significant economic growth
- Problems with sanitary conditions
- Striking regional differences

http://www.censo2010.ibge.gov.br
### Cases of Viral Hepatitis notified between 1999 and 2011 in Brazil

<table>
<thead>
<tr>
<th>Hepatitis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>138,305</td>
<td>40.2 %</td>
</tr>
<tr>
<td>B</td>
<td>120,343</td>
<td>34.9 %</td>
</tr>
<tr>
<td>C</td>
<td>82,041</td>
<td>23.8 %</td>
</tr>
<tr>
<td>D</td>
<td>2,197</td>
<td>0.64 %</td>
</tr>
<tr>
<td>E</td>
<td>967</td>
<td>0.28 %</td>
</tr>
<tr>
<td>Total</td>
<td>343,853</td>
<td></td>
</tr>
</tbody>
</table>
The majority of cases notified were in the North-East: 31.2% and North: 23.3% and North: 23.3%.

Children under 13 are the group most affected by Hepatitis A and account for 75% of cases.

www.datasus.gov.br
Hepatite A

Shifting susceptibility  
95% anti-VHA +  
Hadler et al, 1987

Prevalence  
~ 65 % anti VHA +  
Clemens et al, 2000
It is well known that HAV infection is strongly correlated with poverty and inadequate sanitation.

Despite the improvements in sanitary conditions, hepatitis A is still endemic and outbreaks may occur.
A large number of children from one-four years of age (74.1-90%) were susceptible to a HAV infection. The overall prevalence of anti-HAV antibodies was 12.1% (10-25.9%). Among those participants from one-18 years of age, the prevalence was 41.9% (39.8-49%).

Vitral et al, 2012
A significant decrease in HAV seroprevalence among children aged one-18 years old, indicates that the rates decreased from 70-40.4% in the span of 9 years ($p < 0.0001$).

The data suggest that a decrease in the infection rate of HAV may be occurring even among the lower socioeconomic groups in Brazil who live on the periphery of capital cities.
Declining prevalence of H A virus antibodies among children from low socioeconomic groups reinforces the need for the implementation of hepatitis A vaccination in Brazil

Claudia Lamarca Vitral et al

“Declining prevalence of H A virus antibodies among children from low socioeconomic groups reinforces the need for the implementation of hepatitis A vaccination in Brazil”

Mem Inst Oswaldo Cruz, 107(5): 652-658, August 2012
Shifting susceptibility to hepatitis A among children and adolescents over the past decade

The results suggest that the endemicity of hepatitis A in Porto Alegre has been declining over the past decade, and that children and adolescents, particularly those in the lowest socioeconomic strata, are more susceptible to the disease.

Hepatitis A

Reduction in the Incidence rate
(per 100,000 inhabitants)

2006 - 9.1
2010 - 3.6

www.datasus.gov.br
The drop of mortality in hepatitis A results from increases in the quality of health care and greater availability of liver transplantation in specialized centers in major urban cities.

Vitral CL, Gaspar AMC, Souto FJ. Mem Inst Oswaldo Cruz 2006; 101:119-127
Acute hepatic failure in 33 children.

HAV vaccination has been incorporated in the immunization programs of three countries.

In Argentina, the introduction of a single dose of HAV vaccine reduced cases by > 80% in a 2 year period.
It is still not included in the Brazilian National Program for Immunization.

Hepatitis A vaccine

It is offered at Reference Centres for Special Immunobiologicals for groups that are at high risk for HAV infection or at private immunization clinics.
Improvements in sanitary facilities represent a powerful method to reduce the transmission and the control of HAV but we cannot wait until the conclusion of the Brazilian Program of Basic Sanitation.
In countries that have experienced a reduction from high to medium HAV endemicity global immunization is likely to be cost-effective.

Therefore, as per WHO recommendations, HAV vaccination in children ≥ 1 year old is encouraged.
Endemicity for Hepatitis E Virus

Levels of Endemicity for Hepatitis E Virus (HEV)
- **Highly Endemic**
  - (water-borne outbreaks or confirmed HEV infection in ≥ 25% of sporadic non-A, non-B hepatitis)
- **Endemic**
  - (confirmed HEV infection in < 25% of sporadic non-A, non-B hepatitis)
- **Not Endemic**
Geographic distribution of the HEV genotypes in swine and humans

Péres-Gracia MT, Suay B. et al., Infect Genet Evol. 22, 40–59 2014
• Evidence of historical outbreaks as early as 1794 (Teo, 2012)

• Currently, the infection with HE virus represents the most frequent cause for acute hepatitis and jaundice in the world

• According to WHO around 2 billion people live in endemic areas!

Data on HEV infections in Brazil are scarce
Transmission routes of HEV

Péres-Gracia MT, Suay B. et al., Infect Genet Evol. 22, 40–59 2014
The majority of the 967 anti-HEV IgM+ were in Southeast region (48.6%). Between 2,000 – 2,001 86 deaths related to VHE.
Prevalence of serum IgG anti-hepatitis E antibody + in normal populations in different Brazilian regions

<table>
<thead>
<tr>
<th>Population/study</th>
<th>Region</th>
<th>N of cases</th>
<th>IgG anti-HEV (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold miners / Pang et al</td>
<td>Amazon basin</td>
<td>97</td>
<td>6.1</td>
</tr>
<tr>
<td>General population/Souto et al</td>
<td>Amazon basin</td>
<td>299</td>
<td>3.3</td>
</tr>
<tr>
<td>Blood donors /Parana et al</td>
<td>Northeast-Salvador</td>
<td>200</td>
<td>2.0</td>
</tr>
<tr>
<td>Pregnant women/Trinta et al</td>
<td>Southeast –Rio</td>
<td>304</td>
<td>1.0</td>
</tr>
<tr>
<td>Blood donors/Gonçales (ALT&gt;2UNL)</td>
<td>Southeast – Campinas</td>
<td>40</td>
<td>7.5</td>
</tr>
<tr>
<td>Individuals from rural areas from urban areas/Trinta et al</td>
<td>Southeast – R.de Janeiro</td>
<td>145</td>
<td>2.1</td>
</tr>
<tr>
<td>Blood donors/Gonçales (ALT&gt;2UNL)</td>
<td>Southeast- R. de Janeiro</td>
<td>260</td>
<td>0</td>
</tr>
<tr>
<td>Low socioecon.community/Santos</td>
<td>Southeast – R.de Janeiro</td>
<td>699</td>
<td>2.4</td>
</tr>
<tr>
<td>Low socioecon.community/Silveira</td>
<td>South – Porto Alegre</td>
<td>830</td>
<td>5.9</td>
</tr>
<tr>
<td>Children (2 – 9 years old) Assis et al</td>
<td>Amazon basin (MT)</td>
<td>487</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0 – 7.5 %)</td>
</tr>
</tbody>
</table>
# Epidemiology of hepatitis A and E virus infection in Brazil

Prevalence of serum IgG anti-hepatitis E vírus (HEV) in São Paulo city, Southeastern Brazil, by age

<table>
<thead>
<tr>
<th>Age interval (years)</th>
<th>Positive serum total anti-HEV</th>
<th>No. of cases</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td></td>
<td>61</td>
<td>0.0</td>
</tr>
<tr>
<td>5-9</td>
<td></td>
<td>108</td>
<td>0.0</td>
</tr>
<tr>
<td>10-14</td>
<td></td>
<td>104</td>
<td>1.05 (0.0-3.04)</td>
</tr>
<tr>
<td>15-17</td>
<td></td>
<td>58</td>
<td>1.63 (0.0-4.98)</td>
</tr>
<tr>
<td>18-29</td>
<td></td>
<td>250</td>
<td>1.63 (0.07-326)</td>
</tr>
<tr>
<td>30-39</td>
<td></td>
<td>184</td>
<td>2.19 (0.05-4.32)</td>
</tr>
<tr>
<td>40-49</td>
<td></td>
<td>123</td>
<td>243 (0.0-5.19)</td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td>81</td>
<td>2.25 (0.0-5.56)</td>
</tr>
<tr>
<td>&gt;60</td>
<td></td>
<td>90</td>
<td>3.09 (0.0-6.74)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1059</td>
<td>1.68 (0.91-2.46)</td>
</tr>
<tr>
<td>Population/study</td>
<td>Region</td>
<td>N of cases</td>
<td>IgG anti-HEV (+)</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Acute NANBNC Hepatitis/Souto Paraná et al</td>
<td>Amazon basin</td>
<td>16</td>
<td>12.5</td>
</tr>
<tr>
<td>Acute hepatitis A/ Paraná et al. Lyra et al.</td>
<td>Northeast-Salvador</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Acute hepatitis A/ Paraná et al. Lyra et al.</td>
<td>Northeast – Salvador</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Acute hepatitis C/ Paraná et al</td>
<td>Northeast – Salvador</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Acute hepatitis B/ Paraná et al</td>
<td>Northeast – Salvador</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>Cleaning service workers/Gonçales et al</td>
<td>Northeast – Salvador</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Health care workers</td>
<td>Northeast – Salvador</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Women at risk for HIV</td>
<td>Northeast – Salvador</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Prostitutes</td>
<td>Southeast-Campinas</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Southeast-Campinas</td>
<td>117</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Southeast-Campinas</td>
<td>193</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Southeast-Campinas</td>
<td>21</td>
<td>14</td>
</tr>
</tbody>
</table>
Hepatitis E antibodies IgG in farm workers of Mato Grosso, Brazil

A transversal study in 54 farms in Mid-West, Brazil to estimate the prevalence of anti-HEV IgG +

310 exposed to pigs and 101 blood donors
Test MP Diagnostics Biomedical Asia Pacific, Singapura - Kit commercial ELISA (genotypes 1 and 2)

The associations with age, history of blood transfusion and contact with other farm animals, access to potable water and sanitary conditions were analysed.

Silva S & Souto F, 2012
Hepatitis E antibodies IgG in farm workers of Mato Grosso, Brazil

A logistic regression model was constructed

- 310 exposed to pigs - 8.4% anti-HEV+
- 101 blood donors from urban area - 4% anti HEV+

No association was observed between positivity and contact with pigs.

In this rural region the exposition to swines was not a risk factor for HEV infection.
Chronic hepatitis, cirrhosis, acute-on-chronic liver failure have been described in immunocompromised individuals

Davern, 2013

A single acute case has been confirmed

Lopes dos Santos et al., 2010

HEV genotype 3 infections are common in Brazilian swine livestock

Vitral et al., 2005; dos Santos et al., 2009, 2011; de Souza et al., 2012
A cross-sectional study was conducted among recyclable waste pickers from all 15 recycling cooperatives in Goiânia City. (Midwest).

The participants were tested for serological markers indicative of HEV infection. (Recomwell HEV IgG and IgM, Mikrogen GmbH, Neuried, Germany). Positive ELISA results were confirmed by immunoblot analysis.
Conclusions: These findings demonstrated that the prevalence of HEV antibodies among recyclable waste pickers in Central Brazil is relatively low and increased with age.
A retrospective study was performed with 96 serum samples from renal transplant recipients with unexplained liver enzymes ↑

Three confirmed cases of HEV infection identified that lacked seroconversion to HEV IgG antibodies using a sequence analysis the strains were classified as genotype 3 with a low percent identity to previously characterized strains.

Prevalence 3,1 % and a novel genotype 3 subvariant may be circulating !

Evidence of Hepatitis E Virus Infection in Liver Transplant recipients from Brazil

284 liver transplant patients
Serum samples collected between January and May 2013
Tested for the presence IgG and IgM (ELISA – Mikrogen, Neuried, Germany)

Anti-HEV IgG positive in 23 / 284 - 8.1 %
Anti-HEV IgM positive in 6 / 230 - 2.6 %
1 pt. was IgM and IgG positive with normal ALT/AST

The prevalence of anti-HEV antibodies is higher in liver transplant recipients than that previously observed in immunocompetent populations in Brazil
• Epidemiology complex and still incompletely understood

• In developing countries the infection occurs both as sporadic and an epidemic disease.

• Anti-HEV antibody rates increases with age

• Persons who handle swine had a higher risk for hepatitis E (farmers, veterinarians).

• Approximately **11%** of commercial pig livers sold in US contain infectious HEV *(Davern, 2013)*
Prevention on HEV Infection

Cooking Pork

Heat higher than 56°Celsius for at least 20 minutes! (Barnaud, 2012)

Consider HEV screening when transferring blood to susceptible patients
The morbidity and mortality associated with HEV may be preventable.

A vaccine has been developed and tested in a trial of 1,794 Nepalese and showed good efficacy (95%) in preventing genotype 1.

Recombinant genotype in China (over 100,000 volunteers). Efficacy 100%, both genotype 1 and 4 infections prevented.

Hecolin-Park, 2012
“We must plan for the future, because people who stay in the present will remain in the past”.  
Abraham Lincoln