The epidemiology, the need for an evidence-based decision making process with regard to control of Hepatitis A

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Argentina Pediatrics´ Society
Agenda

– Brief introduction on the disease
– Hepatitis A in Latin America & WHO guidelines
– The Argentina’s experience: an evidence based example of vaccine introduction
Hepatitis A infection

- **RNA Picornavirus**
  - Single serotype worldwide
  - Acute disease and asymptomatic infection

- **Transmission**
  - Close personal contact (e.g., household contact, sex contact, child day-care centers)
  - Contaminated food, water (e.g., infected food handlers)

- **No chronic infection**
  - Protective antibodies develop in response to infection - confers lifelong immunity
Hepatitis A in Latin America

- Total Population: $\approx 500,000,000$
- Estimated annual incidence rate: 40-50/100,000
- Endemicity: intermediate (South Cone) and high (Tropical countries)
- Estimated cases by year: 350,000 - 400,000
- Mortality rate: under 15 yrs. 3,000/year
- Acute liver failure: $\sim 0.3-0.4\%$

Argentina in the World

Area: 2,736,690 sq km

Population: 39,000,000 (mostly urban)

Birth cohort (2007): 700,000

% Urban population: 89.4

% Safe water: 77

% Sewage: 42.5

Life expectancy: 73.1 years

% Population with Basic needs not satisfied: 17.7
Hepatitis A (HA) was an important public health problem in Argentina, being a leading cause of acute liver failure and liver transplantation in children.

Whereas HA is often asymptomatic in young children, in adolescents and adults produces extended morbidity. Jaundice, fever, malaise, anorexia, nausea, abdominal discomforts are the most common symptoms. The majority of HA patients recover but a small proportion develop acute fulminating liver multiple organ failure and death.
Illness typically lasts several weeks, but may persist for several months.

Some evidence suggests a bi-phase form of hepatitis A, in which symptoms reappear after apparent recovery, is more common in Argentina.

In highly endemic countries, almost all persons are asymptomatically infected with HAV in childhood, which effectively prevents clinical hepatitis A later in life. In these countries, large scale vaccination programs are not recommended.

In regions of low endemicity, vaccination is indicated for individuals with increased risk of contracting the infection, such as travelers to areas with higher endemicity.

In countries of intermediate endemicity, where a relatively large proportion of the adult population is susceptible, and where hepatitis A represents a significant public health burden, often with large outbreaks, large scale childhood vaccination may be considered as a supplement to health education and improved sanitation.

*Background* - WHO Position Paper

*Weekly Epidemiological Record* 5:38-44, 2000
Universal hepatitis A vaccination was implemented by Argentina Ministry of Public Health in June 2005 with a single dose at 12 months of age.
# National Immunization Schedule

**Argentina, Ministry of Public Health**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>2 meses</td>
<td>2ª dosis</td>
<td>1ª dosis</td>
<td>1ª dosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 meses</td>
<td></td>
<td>2ª dosis</td>
<td>2ª dosis</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>6 meses</td>
<td>3ª dosis</td>
<td>3ª dosis</td>
<td>3ª dosis</td>
<td></td>
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<td>12 meses</td>
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<td>1ª dosis</td>
<td>1ª dosis</td>
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</tr>
<tr>
<td>18 meses</td>
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<td>4ª dosis</td>
<td>4ª dosis</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 años</td>
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<td></td>
<td>Refuerzo</td>
<td>2ª dosis</td>
<td></td>
<td>Refuerzo</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>16 años</td>
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<td></td>
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<td></td>
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<tr>
<td>Cada 10 años</td>
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<td></td>
<td></td>
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<tr>
<td>Puerperio o post-aborto inmediato</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 dosis [4]</td>
</tr>
</tbody>
</table>
Considerations to introduce Vaccines in National Calendars

- Priority of the disease and its control
- Vaccine characteristic
- Programmatic Feasibility
- Vaccine supply
The decision was taken considering......

- 1- Disease Burden
- 2- Cost- effectiveness
- 3- Vaccine characteristics
- 4- Programmatic feasibility
- 5- Social acceptance
The decision was taken considering:

- 1- Disease Burden
- 2- Cost- effectiveness
- 3- Vaccine features
- 4- Programmatic feasibility
- 5- Social acceptance
Define the problem
Observe the magnitude of the problem

Burden of disease

Compare the immunization with other types of interventions

Have the immunization best benefits compared with other interventions?
Argentina Hepatitis A cases 1989-2004

5-14 Years: 60% (256.834) of cases

www.diripe.vigia.org.ar
What was the situation of the country?

Was the same situation in the whole country?
Hepatitis A

The rates increased (25%) during the period 2003-2004.

West region (NOA) presented the highest incidence rate.

South region (SUR) increased twice the incidence rates.

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
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<tr>
<td></td>
<td>Casos</td>
<td>Tasas x 100.000</td>
<td>Casos</td>
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<tr>
<td>Total país</td>
<td>25558</td>
<td>70,5</td>
<td>50399</td>
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<td>Centro</td>
<td>12127</td>
<td>50,9</td>
<td>28243</td>
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<tr>
<td>NOA</td>
<td>5506</td>
<td>132,1</td>
<td>11188</td>
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<td>Cuyo</td>
<td>4106</td>
<td>143,7</td>
<td>6790</td>
</tr>
<tr>
<td>NEA</td>
<td>2484</td>
<td>73,8</td>
<td>2815</td>
</tr>
<tr>
<td>Sur</td>
<td>1335</td>
<td>65,5</td>
<td>1363</td>
</tr>
</tbody>
</table>
Hepatitis A Regional Incidence Rate in Argentina 2003-2005

Ministry of Public Health

Tasa por 100.000

N.East  Centre  South  Country  N.West  Cuyo

2003  2004  2005

172.7  201.3  246.3

2003  2004  2005
Incidence rates of Hepatitis A (100 000 habitants) according to age groups, Argentina 2003-2004.

Hepatitis A

More than 75% of the cases in 2004, occurred in children of 2-14 yrs. old.

The incidence rate in this age group increased more than 40% compared with 2003.
Control measures

To improve the hygiene (hand washing) and sanitary conditions, namely:

- The transmission being mainly person to person through oral-fecal route
- health education
- sanitation
- Sanitary control of food.
Hepatitis A endemicity is declining in Argentina, as in much of Latin America over time because the sanitary conditions are improving but.....
Hepatitis A: The shift of endemicity and risk of infection

Best socioeconomic conditions

- Exposure to virus in children
- Proportion of susceptible among older children and adults
- Proportion of symptomatic with age

Risk for symptomatic disease.


Ron Dagan, pers. communication
Changes in epidemiological Hepatitis A pattern

In spite of good sanitary conditions….. Cases and incidence rate of Hepatitis A in Buenos Aires city were observed during 1994-2004.
In spite of good sanitary conditions….. Cases and incidence rate of Hepatitis A in Buenos Aires City. 1994-2004
Serological studies
Children HAV infection in argentinian population

- Tucumán 81,4% \( n: 3699 \)
- San Justo 57,8% Age: 1-10 ys.
- Rosario 46,5%
- Trelew 41,9%
- Buenos Aires 29,4%

Mean rate: 51,5%

Hepatitis A prevalence in Argentina according to age and socioecosocial level

### IgG antiHAV Prevalence

#### Good Socioeconomical Level Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Total</th>
<th>IgG antiHAV(+)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>RR (95% IC)</td>
</tr>
<tr>
<td>Day care attendance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7.6</td>
<td>28</td>
<td>36.8</td>
</tr>
<tr>
<td>No</td>
<td>352</td>
<td>87</td>
<td>24.7</td>
</tr>
<tr>
<td>Kindergarten</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>301</td>
<td>89</td>
<td>29.5</td>
</tr>
<tr>
<td>No</td>
<td>126</td>
<td>25</td>
<td>19.8</td>
</tr>
<tr>
<td>Extrascholar activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>134</td>
<td>45</td>
<td>33.5</td>
</tr>
<tr>
<td>No</td>
<td>294</td>
<td>69</td>
<td>23.4</td>
</tr>
</tbody>
</table>


Acute Hepatitis A

Complications

Extrahepáticos
- Skin
- Hematologics
- Renal
- Pancreatics
- Neurologics

Autoimmunidad
- Autoimmune Hepatitis

Acute liver failure

FHA
ALF : Argentina experience

May 1982 - September 2002
N: 210 patients

- **Age**: (mean ± SD): 5.33 years (r: 12 m-17.4 y)
  - 87% < 10 years
  - 63.5% < 5 years

- **Gender**: (masc/ fem): 107/103

ALF: Argentina experience

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Number (%)</th>
<th>Alives</th>
<th>Deaths</th>
<th>LxT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis A</strong></td>
<td>128 (61)</td>
<td>40 (31.2)</td>
<td>33 (25.8)</td>
<td>55 (43.0)</td>
</tr>
<tr>
<td><strong>Indeter.</strong></td>
<td>68 (32)</td>
<td>11</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td><strong>Autoimmune</strong></td>
<td>5 (3)</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Otros</strong></td>
<td>9 (4)</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total (%)</strong></td>
<td>210 (100)</td>
<td>59 (28)</td>
<td>61 (29)</td>
<td>90 (43)</td>
</tr>
</tbody>
</table>

Acute liver failure due to hepatitis A in children

62/221 (28%)

120/208 (58%)
ALF: Latin American experience

- Patients aged 1–20 years
  - Admitted to participating referral hospitals
  - Presenting with ALF defined as the occurrence of jaundice and encephalopathy with prolonged prothrombin time [O’Grady, 1993]

- Subjects without encephalopathy but who had a liver transplant were also included

- Exclusion: chronic HBV with ALF as part of the natural progression of the disease

Themis et al, WSPID Chile Nov. 2002
Study Countries: LA experience

N: 88 patients
Viral Markers

- 37 (43%) anti-HAV IgM+
- 2 HBs-Ag+, 1 anti-HBc IgM+ (all were also anti-HAV IgM+)
- 0 HCV

Outcome of anti-HAV IgM+ cases

- Transplanted: 17 (46%)
- Died: 15 (41%)
- Discharged without transplant: 9 (25%)
- Transferred to another hospital: 4 (11%)

None of the anti-HAV IgM positive cases were vaccinated against HAV

Themis et al. WSPID Chile Nov. 2002
Burden of disease

- Argentina was a country with intermediate endemicity with areas of high endemicity
- High incidence rates in 2003-2004 (outbreak)
- Seroprevalence among children 1-15 years is about 54%, by adolescence nearly half the population lacks immunity from a common disease
- HAV plays a major role in ALF in children and adolescents
The decision was taken considering:

1. Disease Burden
2. Cost-effectiveness
3. Vaccine features
4. Programmatic feasibility
5. Social acceptance
The cost effectiveness of Vaccination in Argentina

<table>
<thead>
<tr>
<th>Table 4. The overall health outcomes and cost-effectiveness of a universal vaccination program in toddlers in Argentina: base-case scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease burden</strong></td>
</tr>
<tr>
<td>Vaccinated children (n)</td>
</tr>
<tr>
<td>Hepatitis A infections (n)</td>
</tr>
<tr>
<td>Symptomatic infections (n)</td>
</tr>
<tr>
<td>Hepatitis A-related deaths (n)</td>
</tr>
<tr>
<td><strong>Economic burden</strong></td>
</tr>
<tr>
<td>Vaccination costs (US$)</td>
</tr>
<tr>
<td>Direct costs (US$)</td>
</tr>
<tr>
<td>Indirect costs (US$)</td>
</tr>
<tr>
<td>Total costs (US$)</td>
</tr>
<tr>
<td>Life-years lost (US$)</td>
</tr>
<tr>
<td><strong>Cost–benefit</strong></td>
</tr>
<tr>
<td>Cost difference</td>
</tr>
<tr>
<td>Cost per life-year gained</td>
</tr>
</tbody>
</table>

*a* Average annual cases over 100 years

*b* Average annual costs = discounted costs over 100 years/discounted number of years (31.6)

Lopez E, Debbag R, et al.

J Gastroenterology 2007;42:152-160
The cost effectiveness of Vaccination in Argentina

A two dose program with 95% coverage rate (annual decrease in infection 1%):

- Reduce the number of HA infections by 352405 annually, avoiding 212587 symptomatic cases and 428 deaths.
- Costs: US$ 9477097 over a 100 year time period.
- Prevent the loss of 6997 life-years
- The vaccination program would save US$ 3429 per life year gained.

The break-even cost per dose of HA vaccine (the point at which the costs of vaccination program and the disease are equal) was US$ 25, three times the public current costs of US$ 7 per dose.
The cost effectiveness of Vaccination in Argentina

Four immunization options were assessed

1) no hepatitis A vaccination;
2) hepatitis A vaccination at age 12 months only
3) hepatitis A vaccination at ages 12 and 72 months
4) hepatitis A vaccination at ages 12 and 18 months.

The analysis considers the different regions of the country

Ellis A, Ruttimann R. Jacobs J et al.
Rev Panam Publica/Pan Am/ Public Health 21(6) 2007
The cost effectiveness of Vaccination in Argentina

- Regional variation in vaccination cost effectiveness -
  - the first dose provides greater benefit in more developed regions
  - the second dose provides greater benefit in less developed regions of the country.

- A second dose at age 18 months would be acceptably cost effective in each region, and reduce costs in Cuyo. If the duration of protection with 1 dose is less than anticipated, the second dose would be more cost effective.

Compared with no vaccination, the 1-dose schedule would save $US15.3 millions with regional variations.
The decision was taken considering:

- 1- Disease Burden
- 2- Cost- effectiveness
- 3- Vaccine characteristics
- 4- Programmatic feasibility
- 5- Social acceptance
Hepatitis A vaccine immunogenicity

**Adults**
- > 95% immunogenic with one dose
- 100% immunogenic with two doses

**Children and adolescents**
- > 97% immunogenic with one dose
- 100% immunogenic with two doses

Booster dose confers long lasting protection for 20-30 years.
Hepatitis A vaccine efficacy

<table>
<thead>
<tr>
<th>Study interval</th>
<th>Virus HA infection</th>
<th>Efficacy (%)</th>
<th>IC 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccinates</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous (138-366 days) booster (&lt; 12 m)</td>
<td>2 / 19.037</td>
<td>32 / 19.120</td>
<td>94</td>
<td>79-99</td>
</tr>
<tr>
<td>Post booster (367-532 days) (&gt; 12 m)</td>
<td>0 / 18.217</td>
<td>6 / 18.270</td>
<td>100</td>
<td>54-100</td>
</tr>
<tr>
<td>Accumulated (138-532 d)</td>
<td>2 / 19.037</td>
<td>38 / 19.120</td>
<td>95</td>
<td>82-99</td>
</tr>
</tbody>
</table>

Hepatitis A Vaccines

- Good and quick protection
- One dose schedule with flexible boosters


- Long time protection

Van Damme P. Lancet 2003

- Safety in all ages
- Easy to administrate with others vaccines
- Different types of recipient.
The decision was taken considering……

- 1- Disease Burden
- 2- Cost- effectiveness
- 3- Vaccine features
- 4- Programmatic feasibility
- 5- Social acceptance
National Immunization Program

- It covers the whole country

- All the vaccines included in National vaccination schedule are gratuitous and obligatory.

- The Ministry of Public Health acquires and distribute the vaccines and other inputs (syringes, needles etc.) for covering all the cohort. (approximately 700,000 children)

- Safe cold chain
Argentina: National Immunization coverage in first year of life, 2006

- Sabin: 92%
- Cuádruple: 92%
- Triple Viral: 97%
- BCG: 77%
- Hepatitis B: 84%
- Hepatitis A: 95%

National Immunization Programme
Political commitment to sustain hepatitis A vaccine (one dose)
Issues to sustain a National Immunization Program

(V Wright et al, Vaccine, 2006)
Social Acceptance
Hepatitis A vaccine coverage. 2005-2006

Coberturas de vacuna contra Hepatitis A
Argentina, 2005 - 2006

Jurisdicción

Cobertura

2005
2006
• In Argentina, highly susceptible populations live side by side with populations in which HAV is widely circulating (Intermediate endemicity)
• Disease occurs mostly after 1 year of age
• HAV plays a major role in ALF in children and adolescents
• Our experience tells us that to maximize effectiveness, vaccines must be given below 2 yrs of age
• It is assumed that the main source of transmission of HAV are toddlers - so that vaccination given at this age may protect both younger and older subjects.
Hepatitis A y SE. Casos y Tasas por 100 000 habitantes. Argentina. Años 1995 - 2006

<table>
<thead>
<tr>
<th>Año</th>
<th>Hep. A</th>
<th>Hep S/E</th>
<th>Hep. A y S/E</th>
<th>%SE</th>
<th>% Rel Hep A</th>
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<tr>
<td>1995</td>
<td>17383</td>
<td>15184</td>
<td>32557</td>
<td>46,6</td>
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<td>17617</td>
<td>12112</td>
<td>29729</td>
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<td>1,3</td>
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<tr>
<td>1997</td>
<td>19084</td>
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<td>32494</td>
<td>41,3</td>
<td>8,3</td>
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<td>1998</td>
<td>15833</td>
<td>9949</td>
<td>25782</td>
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<td>1999</td>
<td>23745</td>
<td>8268</td>
<td>32013</td>
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<td>50</td>
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<td>2000</td>
<td>28527</td>
<td>11876</td>
<td>40403</td>
<td>29,4</td>
<td>20,1</td>
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<td>6524</td>
<td>31636</td>
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<td>6199</td>
<td>25558</td>
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<td>2003</td>
<td>39462</td>
<td>10937</td>
<td>63006</td>
<td>21,7</td>
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<td>2004</td>
<td>52637</td>
<td>10369</td>
<td>10308</td>
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<td>33,4</td>
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<td>2005</td>
<td>22578</td>
<td>5266</td>
<td>27773</td>
<td>19</td>
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<tr>
<td>2006</td>
<td>7220</td>
<td>3088</td>
<td>10308</td>
<td>30</td>
<td>-68</td>
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</table>

Fuente: Dirección de Epidemiología - MSAL
The main global issue is that Hepatitis A virus (HAV) infection remains the most commonly reported vaccine-preventable disease in many parts of the world despite the availability of vaccines.
Thank you for your attention!!