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

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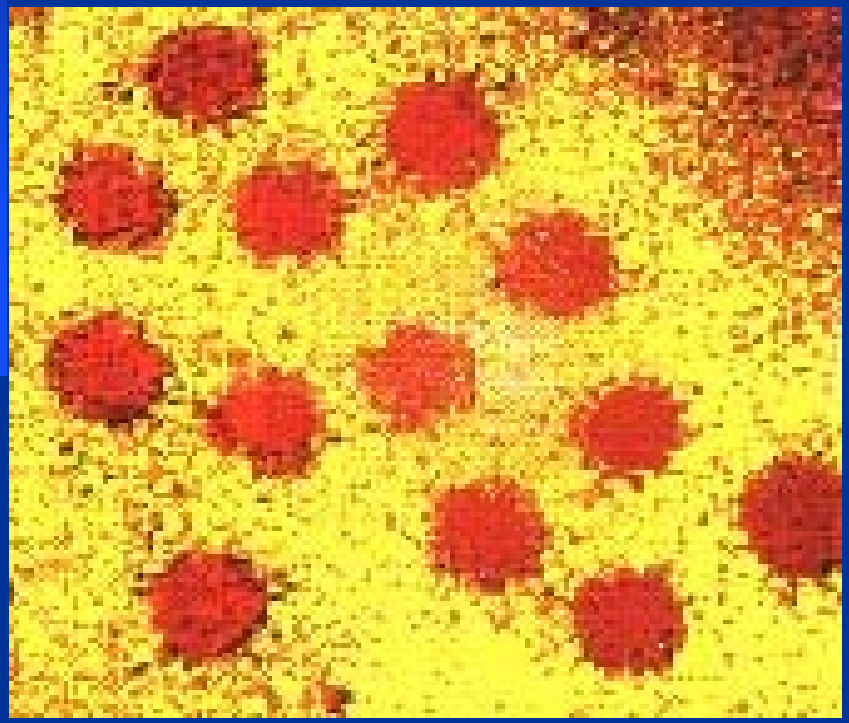
Argentina Pediatrics´ Society

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



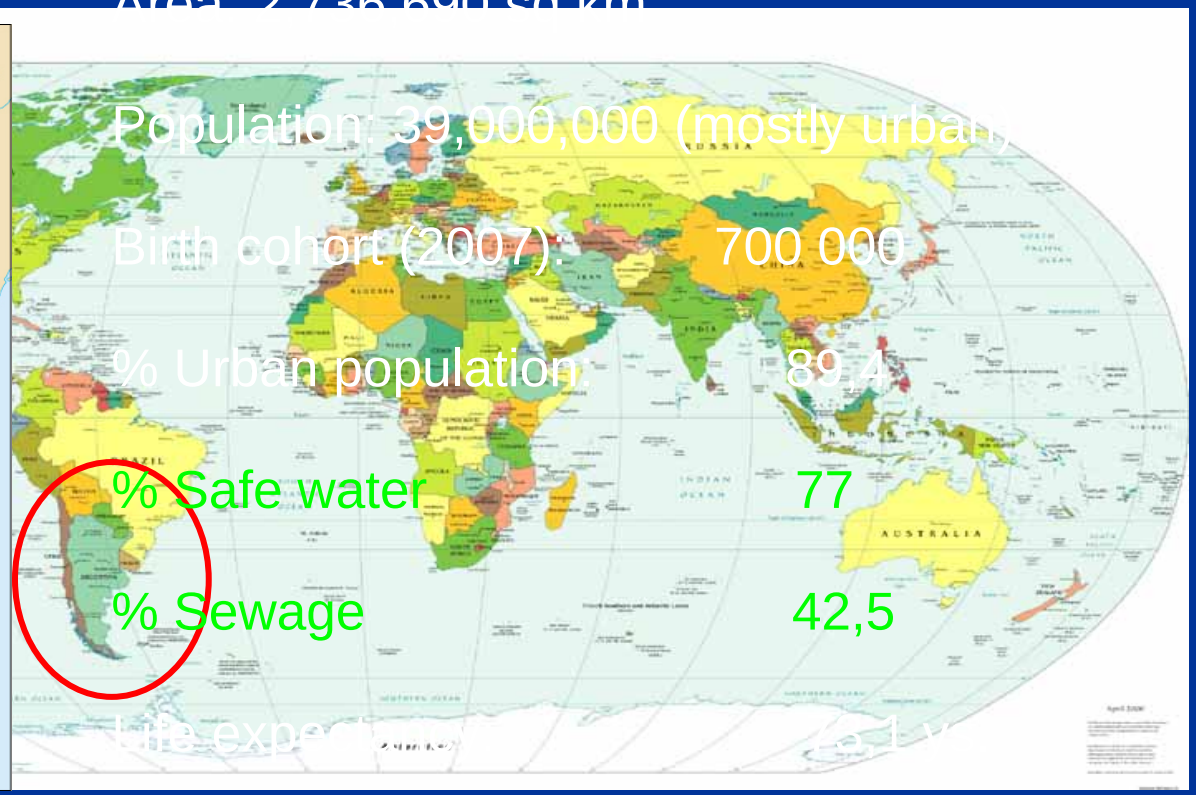
- RNA *Picornavirus*
  - Single serotype worldwide
  - Acute disease and asymptomatic infection
- Transmission
  - Close personal contact (e.g., household contact, sex contact, child day-care centers
  - Contaminated food, water (e.g., infected food handlers)
- No chronic infection
  - Protective antibodies develop in response to infection - confers lifelong immunity

Hepatitis A in Latin America

- Total Population: ≅ 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 ys. 3.000/year
- Acute liver failure: ~ 0.3-0.4%.

Stapleton JT and Lemon SM.: Hepatitis A and E, in Infectious Diseases (5th ed), eds Hoeprich P MC,Jordan MC and Roland AR, Lippincott Co. 1994. Pg 790-800

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 74,1

% Population with

Basic needs not satisfied 17,7

Introduction

- 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

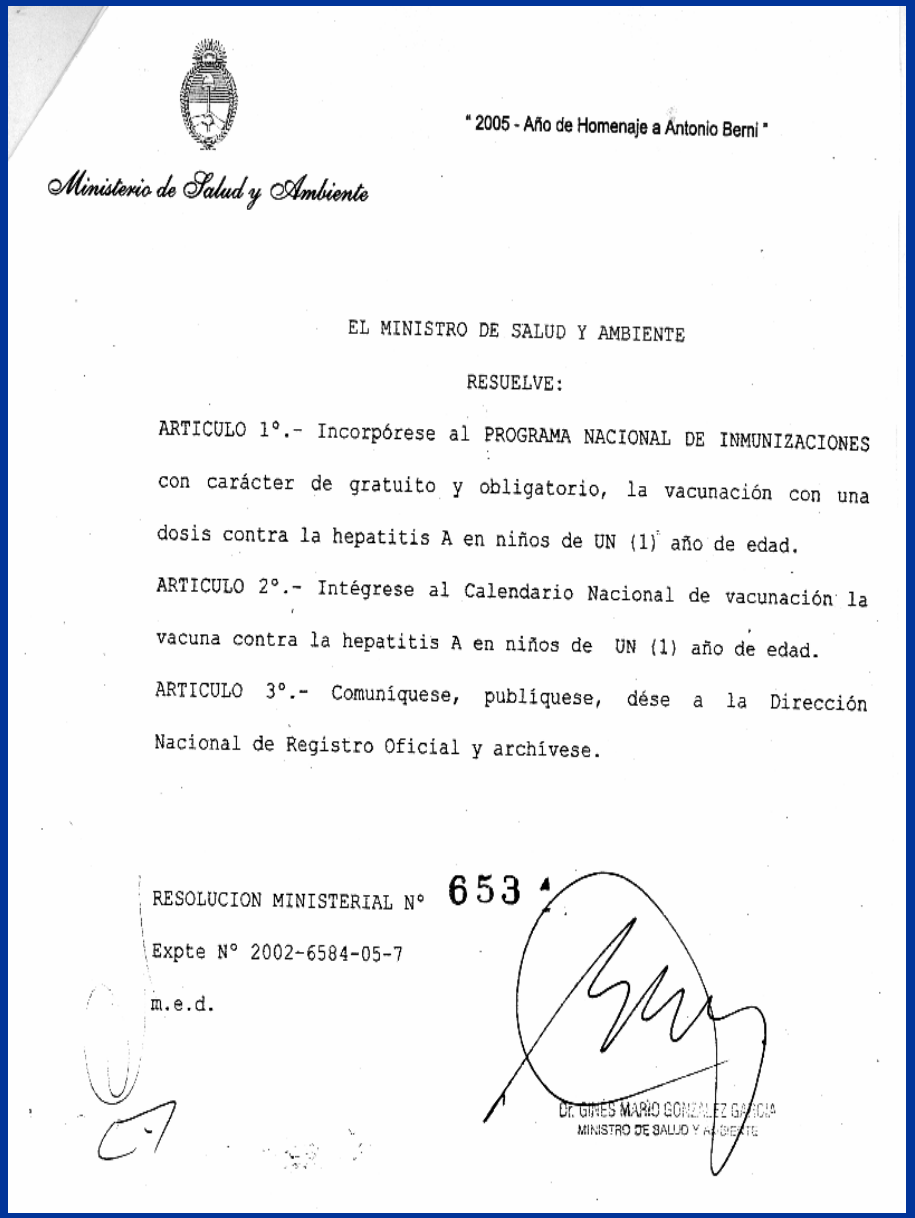
Tanno H, Fay OH, Rojman JA, Palazzi J. Biphasic form of hepatitis A virus infection: a frequent variant in Argentina. Liver 1988;8(1):53-57.

Background - WHO Position Paper

- 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 proportions 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

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.



" 2005 - Año de Homenaje a Antonio Berni "

Ministerio de Salud y Ambiente

EL MINISTRO DE SALUD Y AMBIENTE

RESUELVE:

ARTICULO 1°.- Incorpórese al PROGRAMA NACIONAL DE INMUNIZACIONES con carácter de gratuito y obligatorio, la vacunación con una dosis contra la hepatitis A en niños de UN (1) año de edad.

ARTICULO 2°.- Intégrese al Calendario Nacional de vacunación la vacuna contra la hepatitis A en niños de UN (1) año de edad.

ARTICULO 3°.- Comuníquese, publíquese, dése a la Dirección Nacional de Registro Oficial y archívese.

RESOLUCION MINISTERIAL N° 653

Expte N° 2002-6584-05-7

m.e.d.

DR. GINES MARIO GONZALEZ GARCIA
MINISTRO DE SALUD Y AMBIENTE

National Immunization Schedule Argentina, Ministry of Public Health

EDAD	BCG	Anti-hepatitis B (HB)	Cuádruple (DTP- Hib)	Sabin (OPV)	Triple viral (SRP)	Anti-hepatitis A (HA)	Triple bacteriana (DTP)	Doble bacteriana (dT)	Doble viral (SR)
Recién nacido	Única dosis [1]	1ª dosis [2]							
2 meses		2ª dosis	1ª dosis	1ª dosis					
4 meses			2ª dosis	2ª dosis					
6 meses		3ª dosis	3ª dosis	3ª dosis					
12 meses					1ª dosis	1 dosis			
18 meses			4ªdosis	4ª dosis					
6 años				Refuerzo	2ª dosis		Refuerzo		
11 años		Iniciar o completar esquema [3]			Refuerzo [4]				
16 años								Refuerzo	
Cada 10 años								Refuerzo	
Puerperio o post-aborto inmediato									1 dosis [4]

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

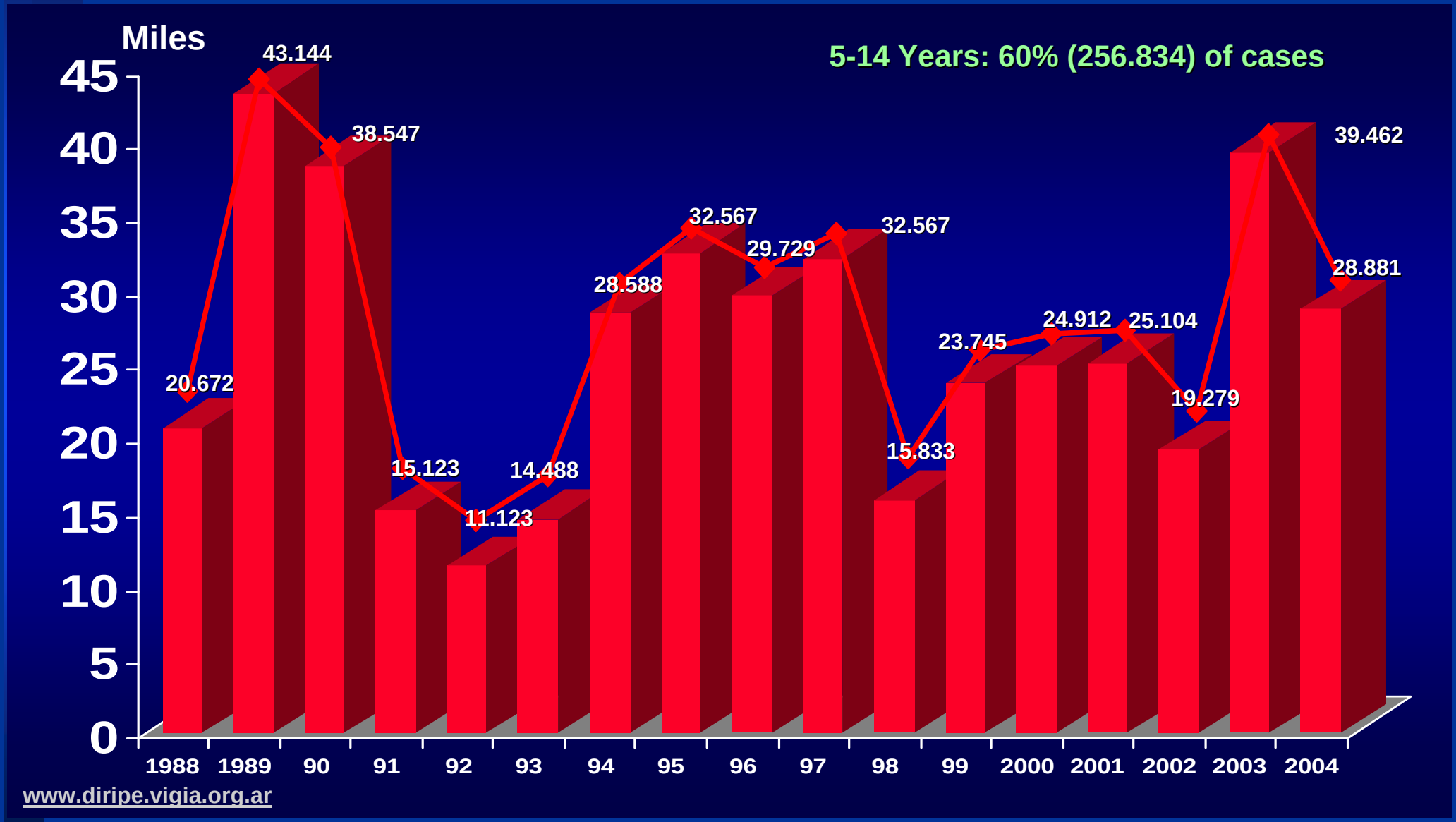
- Define the problem
- Observe the magnitude of the problem

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

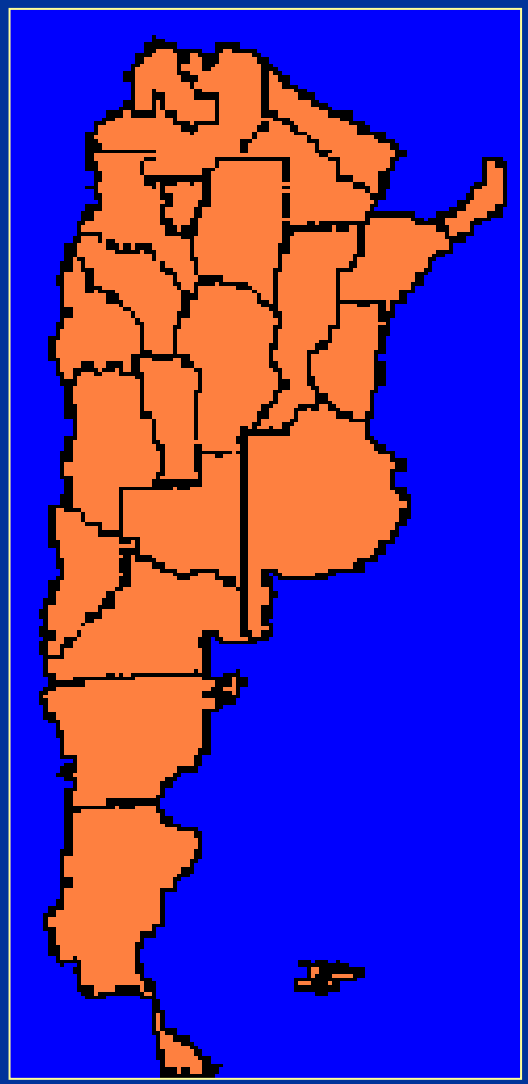


www.diripe.vigia.org.ar

Boletín Epidemiológico 1999, 2002, 2003, 2004

What was the situation of the country?

Was the same situation in the whole country?



Hepatitis A

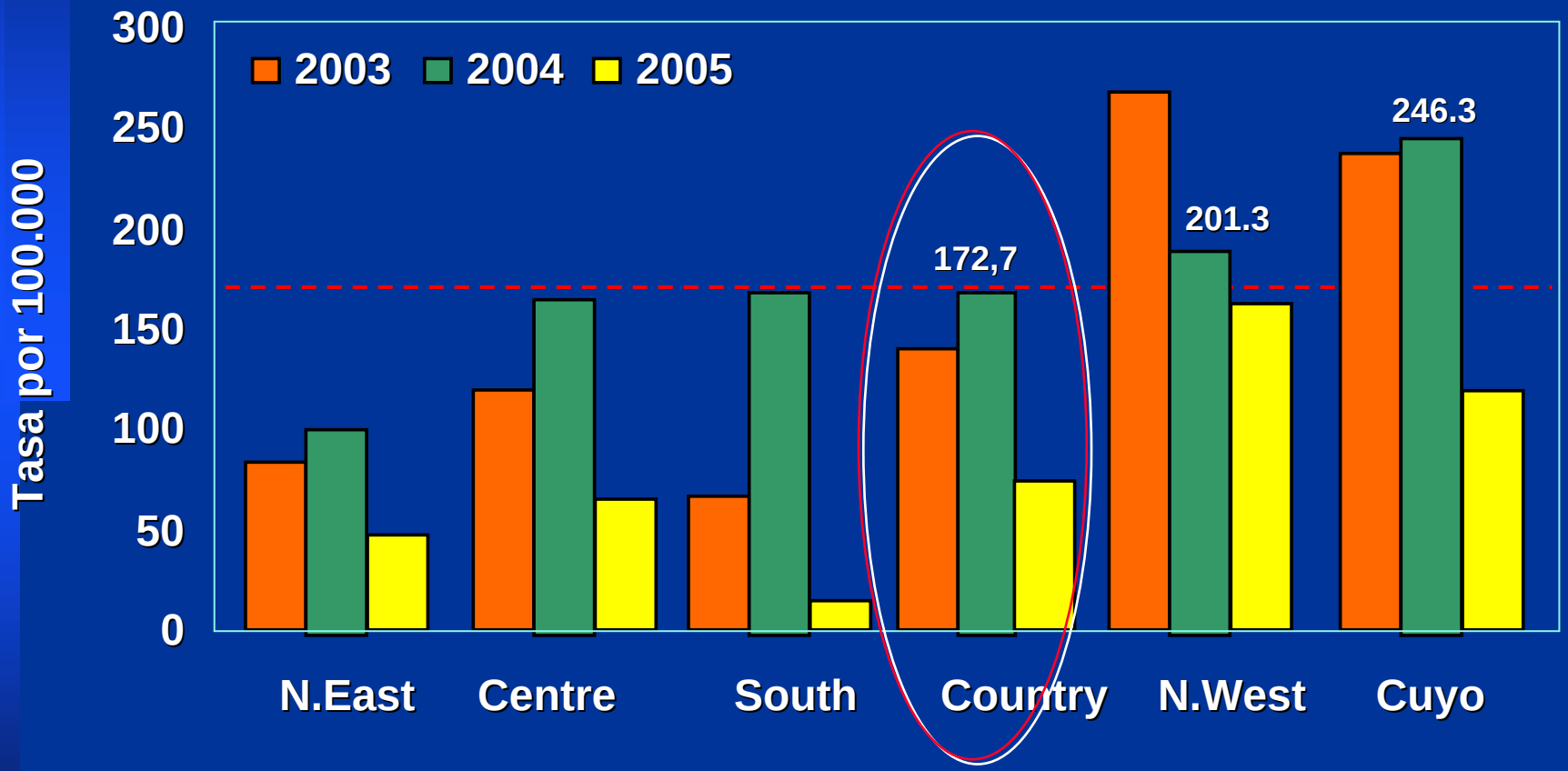
The rates increased (25 %) during the period 2003-2004

West region (NOA) presented the highest incidence rate.

South region (SUR) increased twice the incidence rates.

	2002		2003		2004	
	Casos	Tasas x 100.000	Casos	Tasas x 100.000	Casos	Tasas x 100.000
Total país	25558	70,5	50399	139,0	62633	172,7
Centro	12127	50,9	28243	118,5	40209	168,7
NOA	5506	132,1	11188	268,4	8392	201,3
Cuyo	4106	143,7	6790	237,6	7039	246,3
NEA	2484	73,8	2815	83,6	3530	104,8
Sur	1335	65,5	1363	66,9	3463	170,0

Hepatitis A Regional Incidence Rate in Argentina 2003-2005



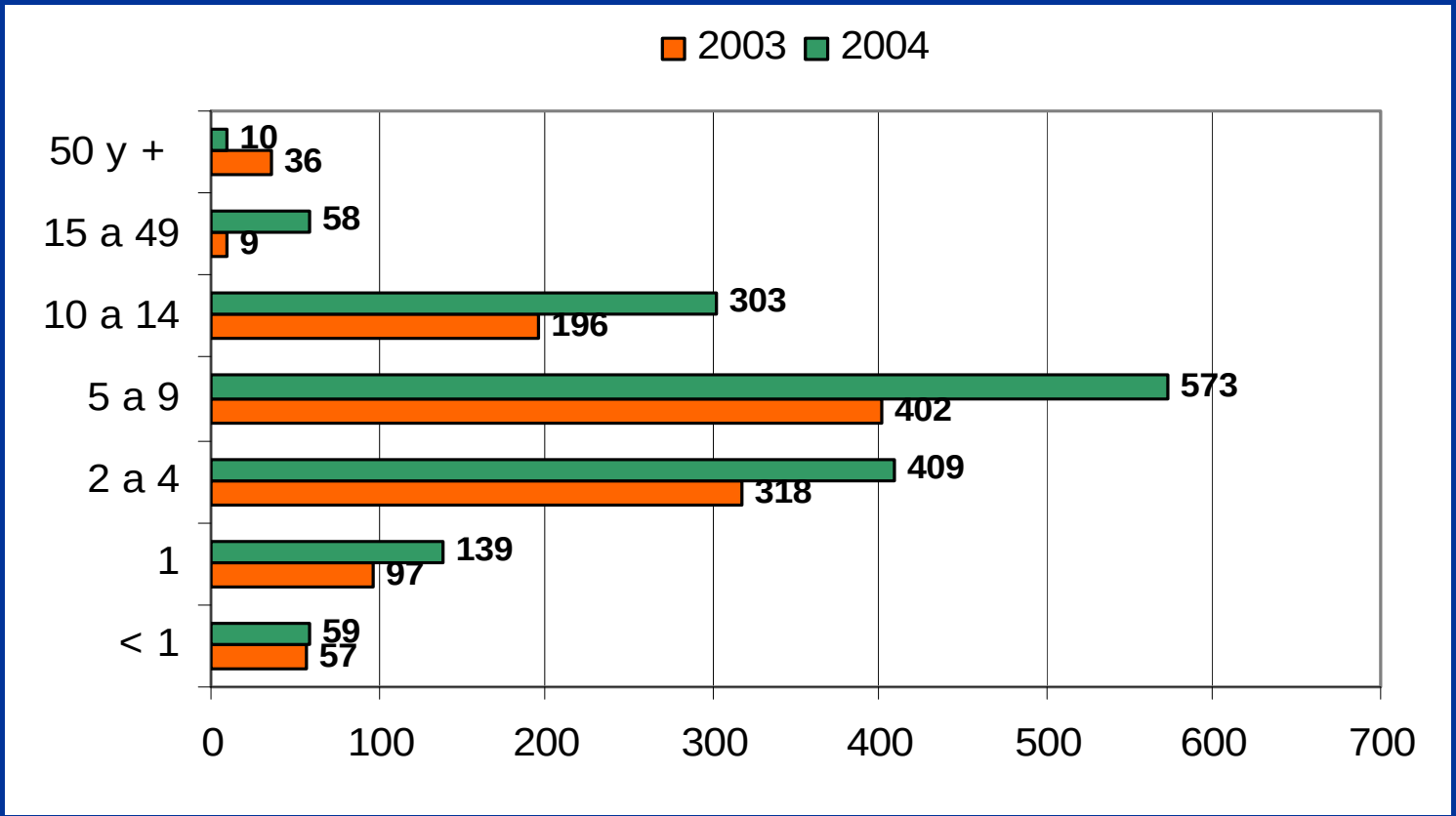
Ministry of Public Health

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

Hepatitis A

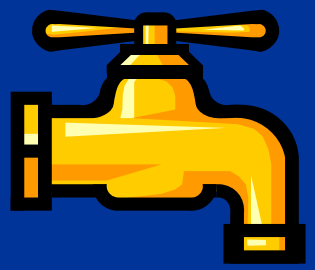
More than 75% of the cases in 2004, occurred in children of 2-14 yrs. old.

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

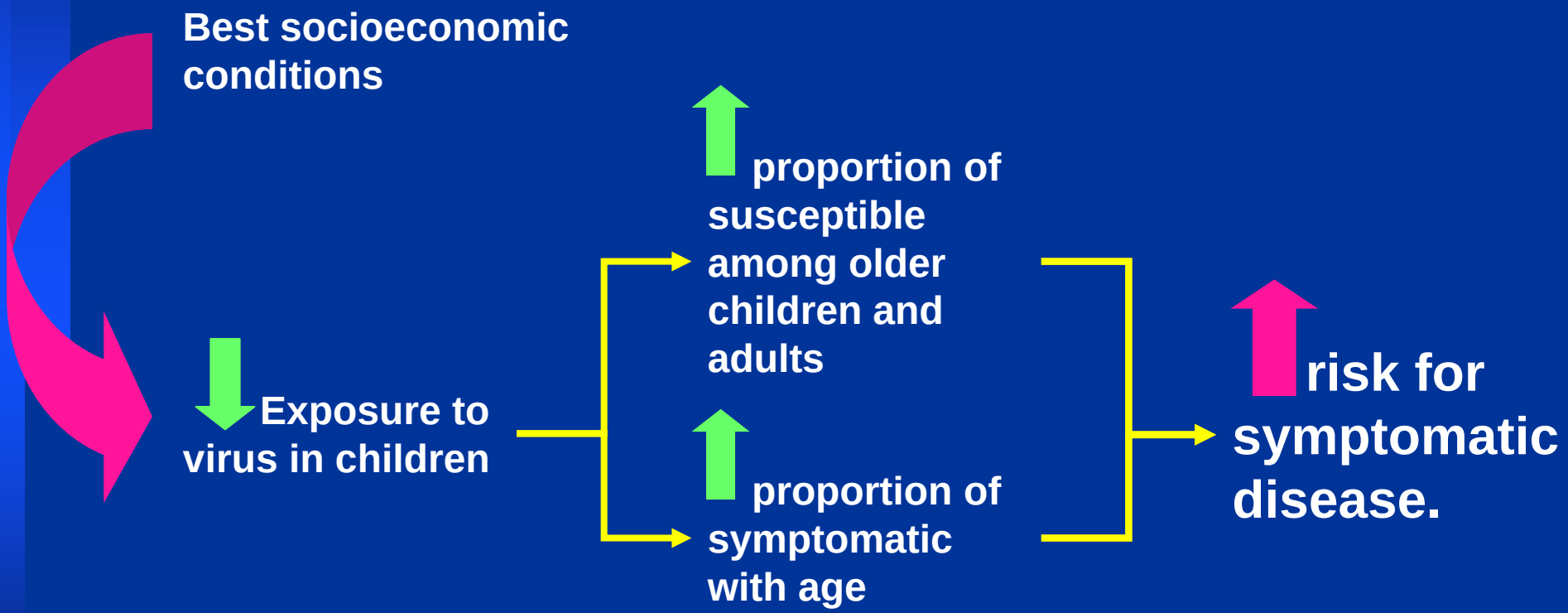


The transmission being mainly person to person through oral-fecal route

- **health education**
- **sanitation**
- **Sanitary control of food.**

Hepatitis A endemicity is declining in Argentina, as in much of Latin America overtime because the sanitary conditions are improving but…..

Hepatitis A: The shift of endemicity and risk of infection

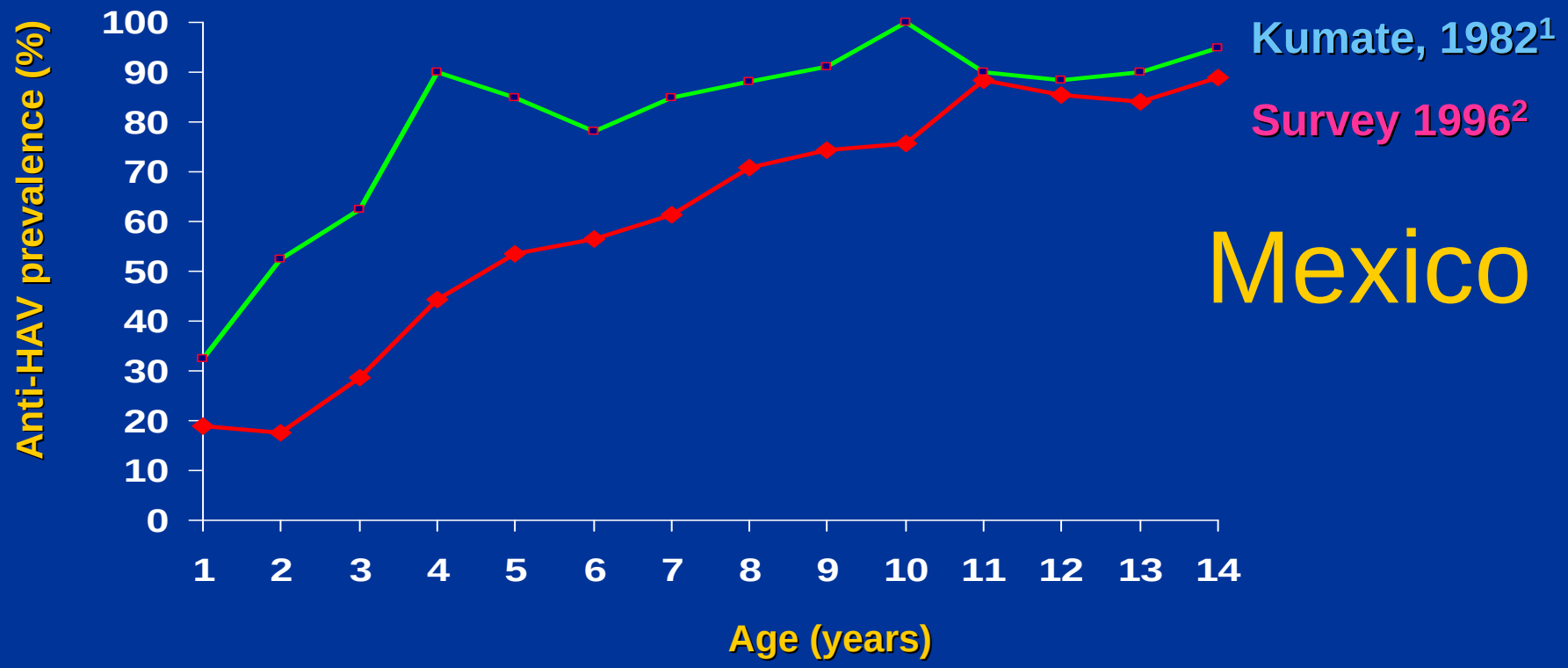


Van Damme P *et al. Expert Rev Vaccines* 2004; 3:249–67;

Villar LM *et al. Braz J Med Biol Res* 2004; 37:1779–87; WHO, 2000.

Ron Dagan, pers. communication

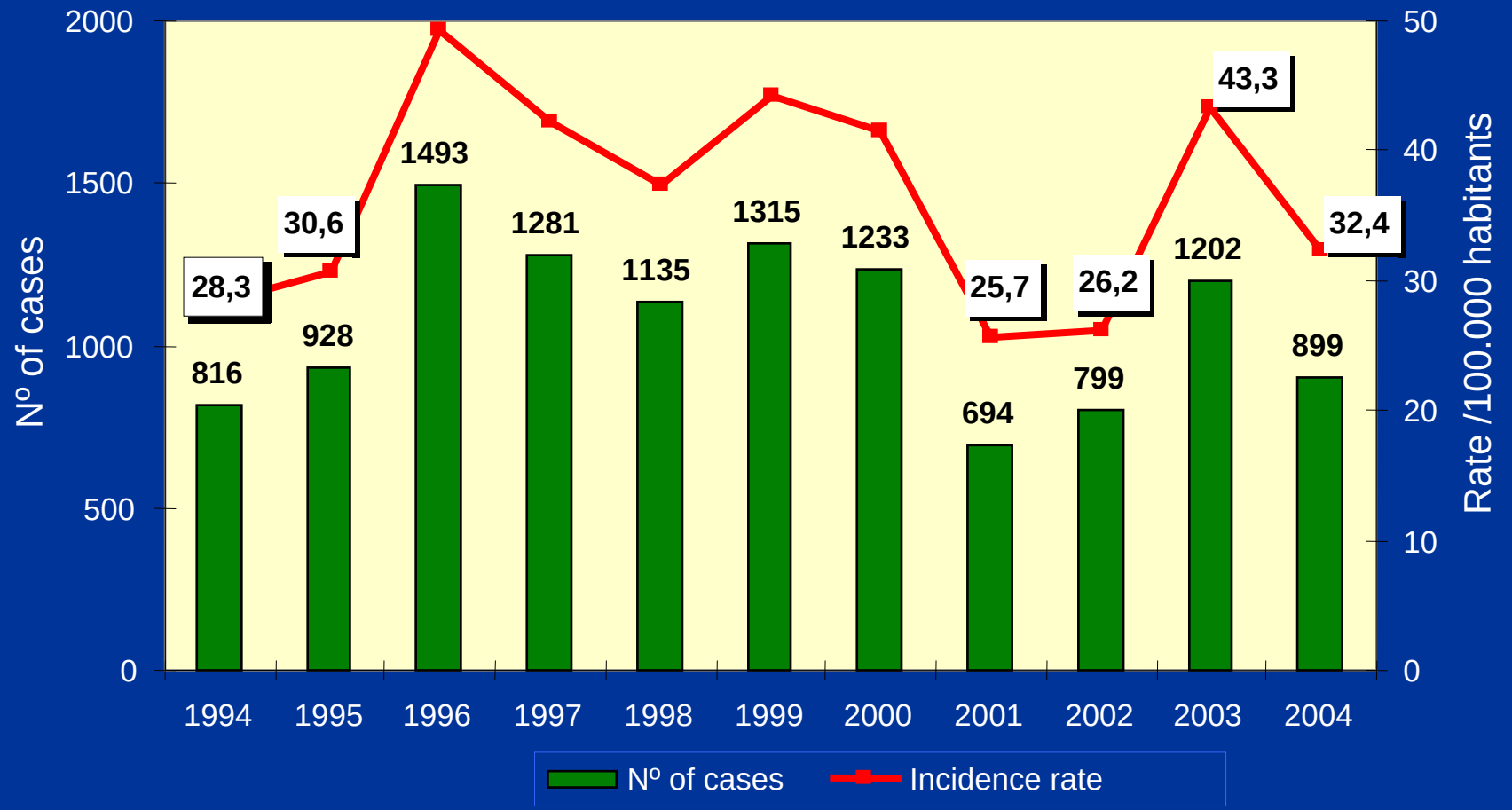
Changes in epidemiological Hepatitis A pattern



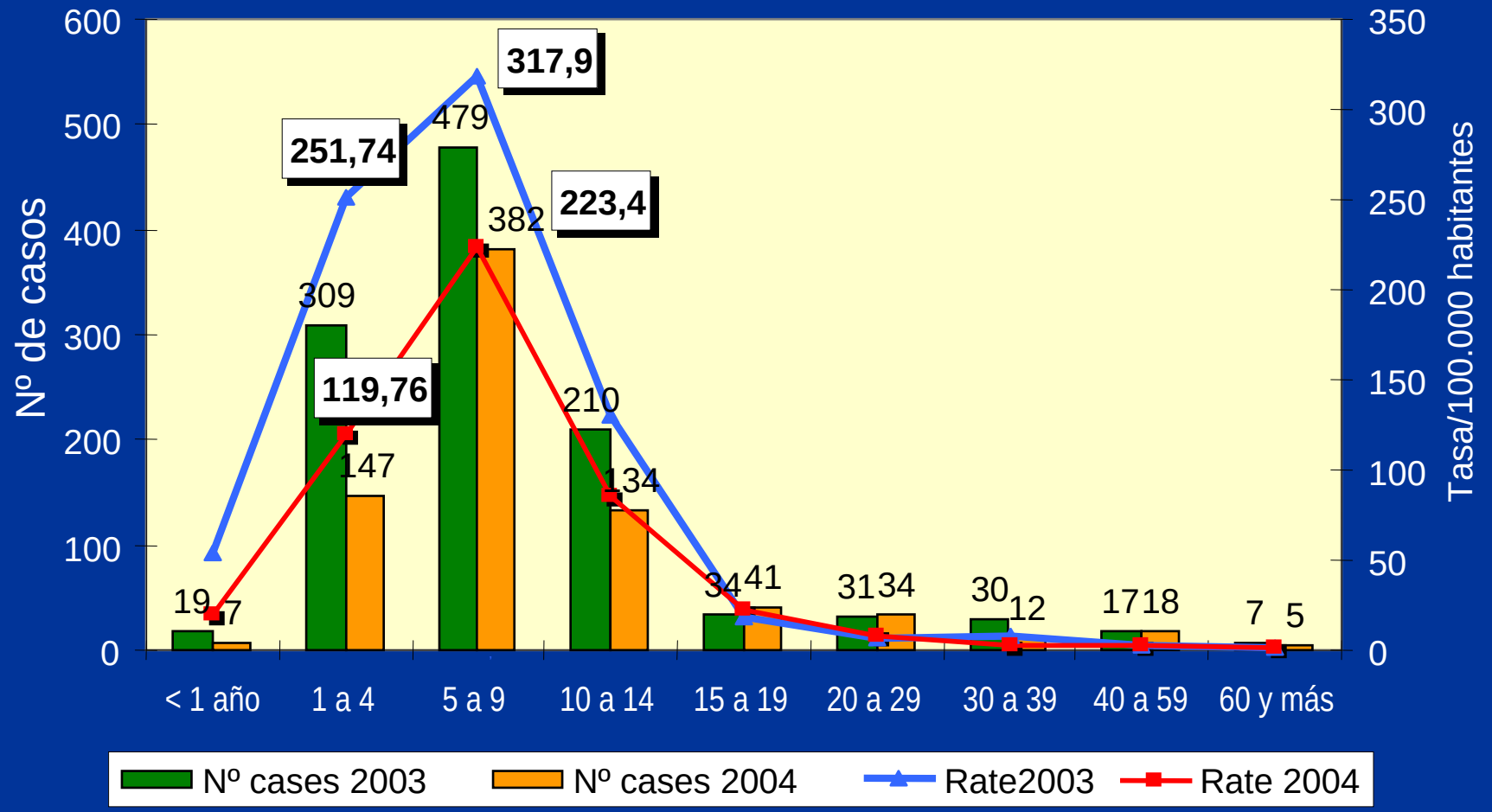
1. Kumate J et al. Bull Pan Am Health Organ 1982;16:156–60;

2.Tapia-Conyer R et al. Am J Trop Med Hyg 61(5) 1999 825-29.

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



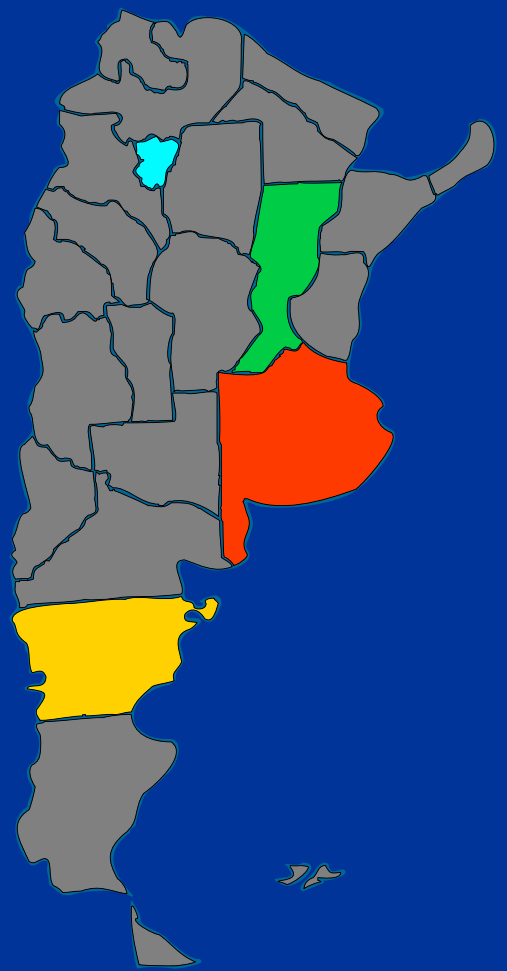
Serological studies

Children HAV infection in argentinian population

- Tucumán 81,4%
- San Justo 57,8%
- Rosario 46,5%
- Trelew 41,9%
- Buenos Aires 29,4%

n: 3699

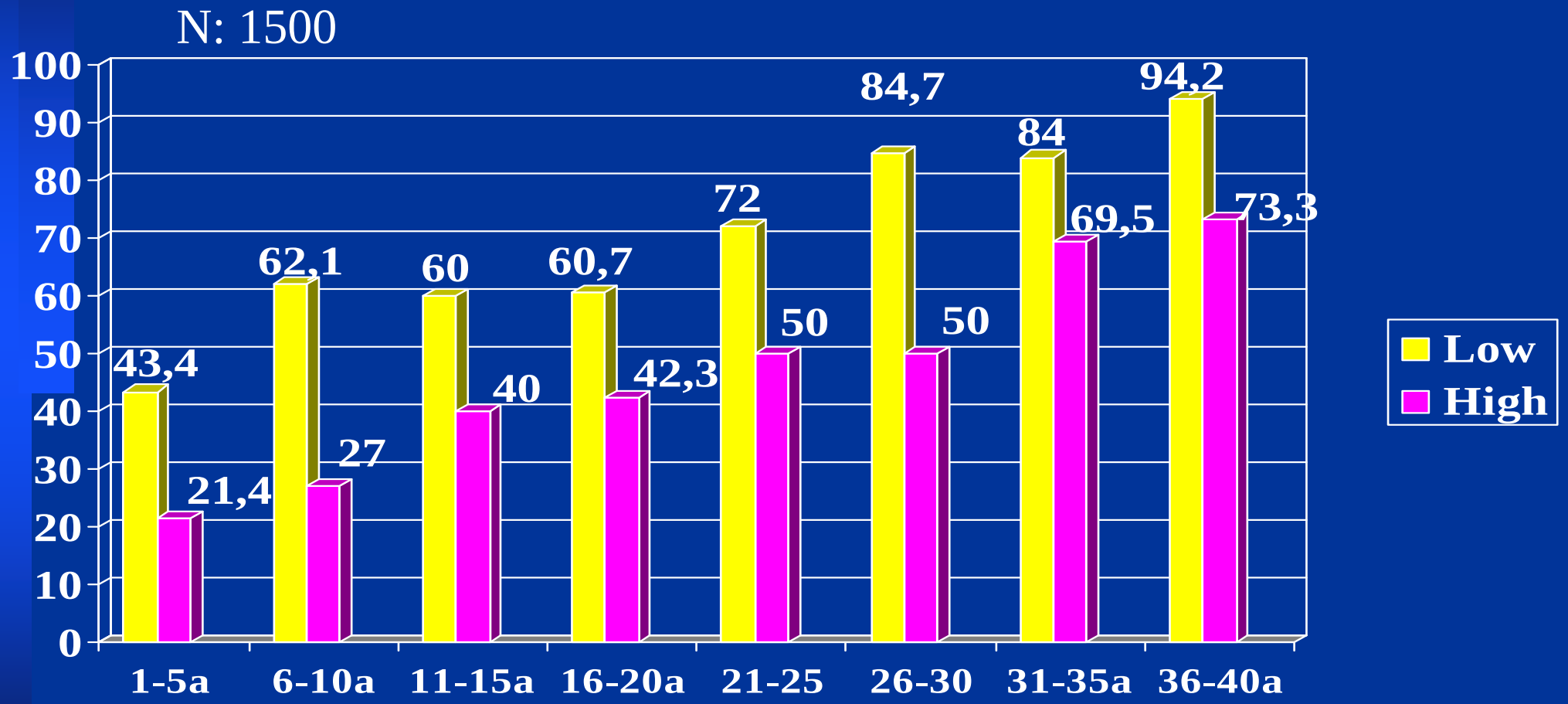
Age: 1-10 ys.



Mean rate: 51,5%

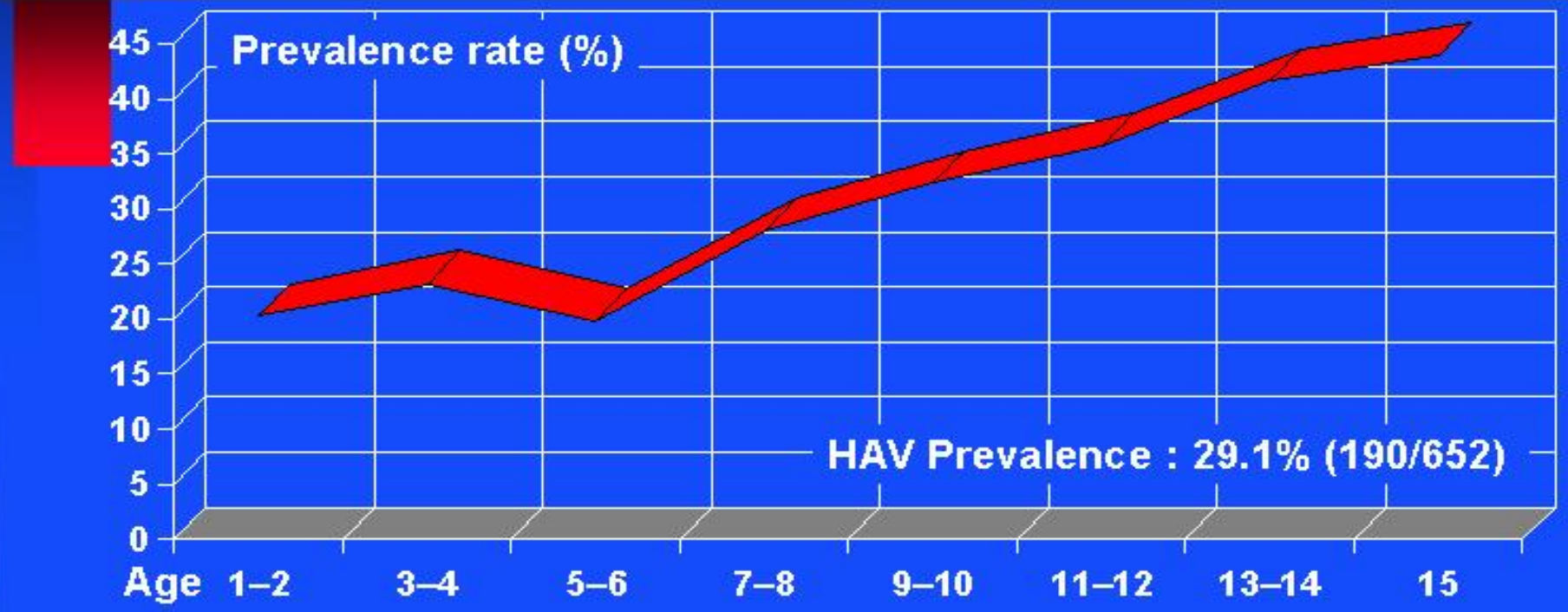
González J, Fay O, Cañero-Velasco C, Fernandez E, Carchio E, Moreiro R, et al. Infección por virus de hepatitis A (HAV) en niños en Argentina. Ensayo piloto. Acta Gastroenterol Latinoam 1997;27(5):331-334.

Hepatitis A prevalence in Argentina according to age and socioeconomical level



Gentile A y col. Lausanne ECCMID1997 , Tapia-Conyer R et al. Am J Trop Med Hyg 61(5) 1999 825-29.

IgG antiHAV Age Prevalence



Age	1–2	3–4	5–6	7–8	9–10	11–12	13–14	15
Total	54	86	121	100	99	95	72	25
%	20.3	23.2	19.8	28	32.3	35.7	41.6	44.0

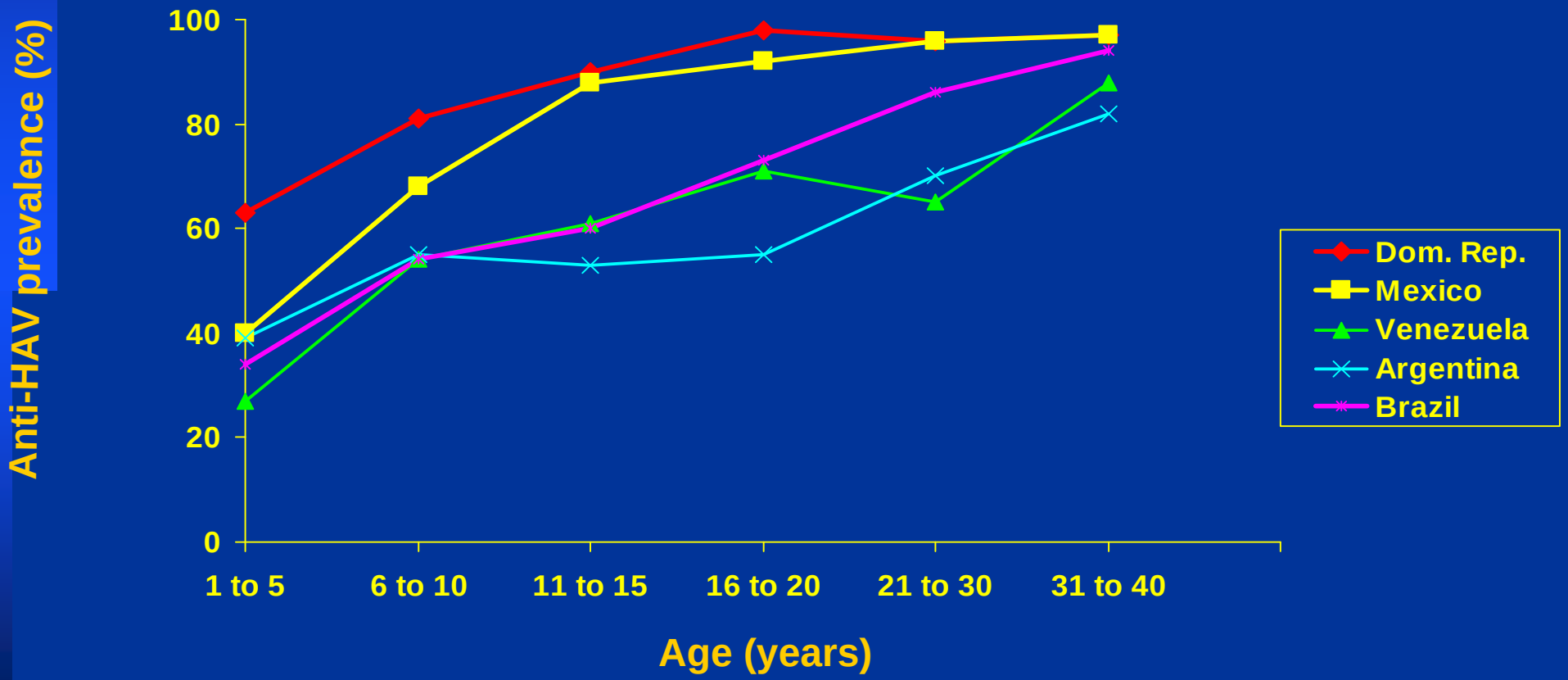
Gentile A, Martínez Iriart E.; Joaquín W.; Lamy, P.; Galoppo, C.; Badía I.; Dayan, G.; Ceraci, P.; "Hepatitis A virus prevalence in Argentine children" 37 th ICAAC,1997

IgG antiHAV Prevalence
Good Socioeconomical Level Risk Factors

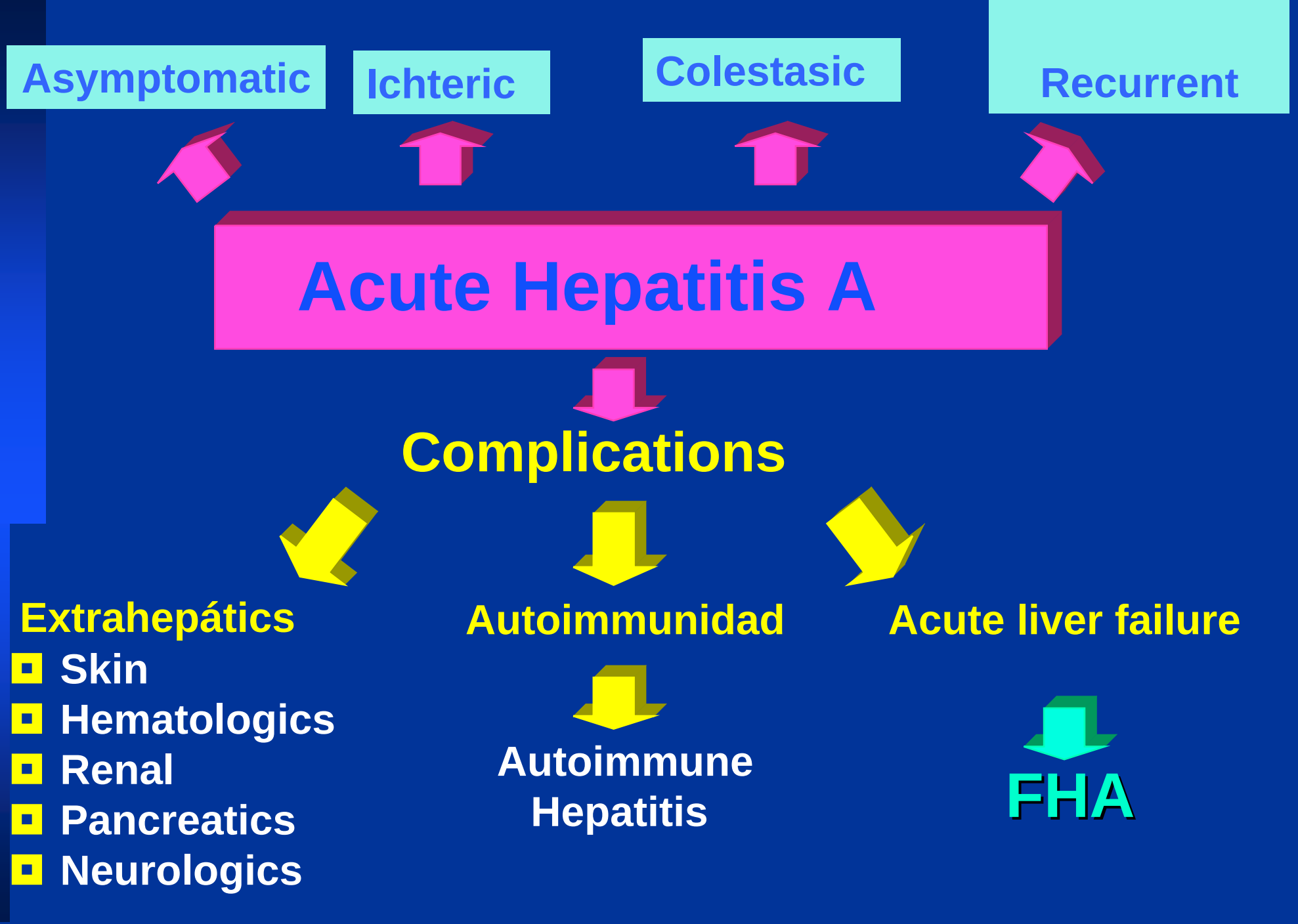
Risk Factor	Total	IgG antiHAV(+) No.	IgG antiHAV(+) %	Significance RR (95% IC)
Day care attendance				
Yes	7.6	28	36.8	1.46 (1.03-2.07)
No	352	87	24.7	p=0.05
Kindergarten				
Yes	301	89	29.5	1.49 (1.01-2.21)
No	126	25	19.8	p=0.05
Extrascholar activities				
Yes	134	45	33.5	1.49 (1.09-2.03)
No	294	69	23.4	p=0.01

Gentile A, Martínez Iriart E.; Joaquín W.; Lamy, P.; Galoppo, C.; Badía I.; Dayan, G.; Ceraci, P.; "Hepatitis A virus prevalence in Argentine children" 37 th ICAAC,1997

Hepatitis A seroprevalence in Argentina, Brasil, Rep. Dominicana, México y Venezuela, 1996–1997



Tapia-Conyer R et al. Am J Trop Med Hyg 61(5) 1999 825-29.


Asymptomatic
Ichteric
Colestasic
Recurrent
Acute Hepatitis A
Complications
Extrahepátics
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 ys.)***

  87% < 10 years

  63,5% < 5 years

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

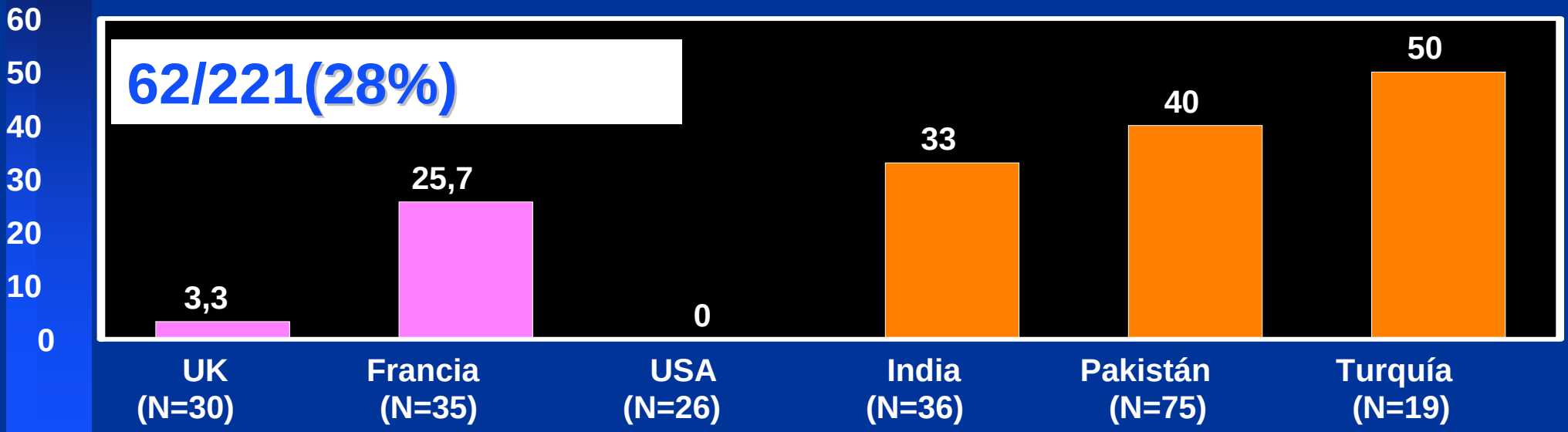
Ciocca M, Ramonet M. et al,.J Pediatr Gastroenterol Nutr 39: 2004

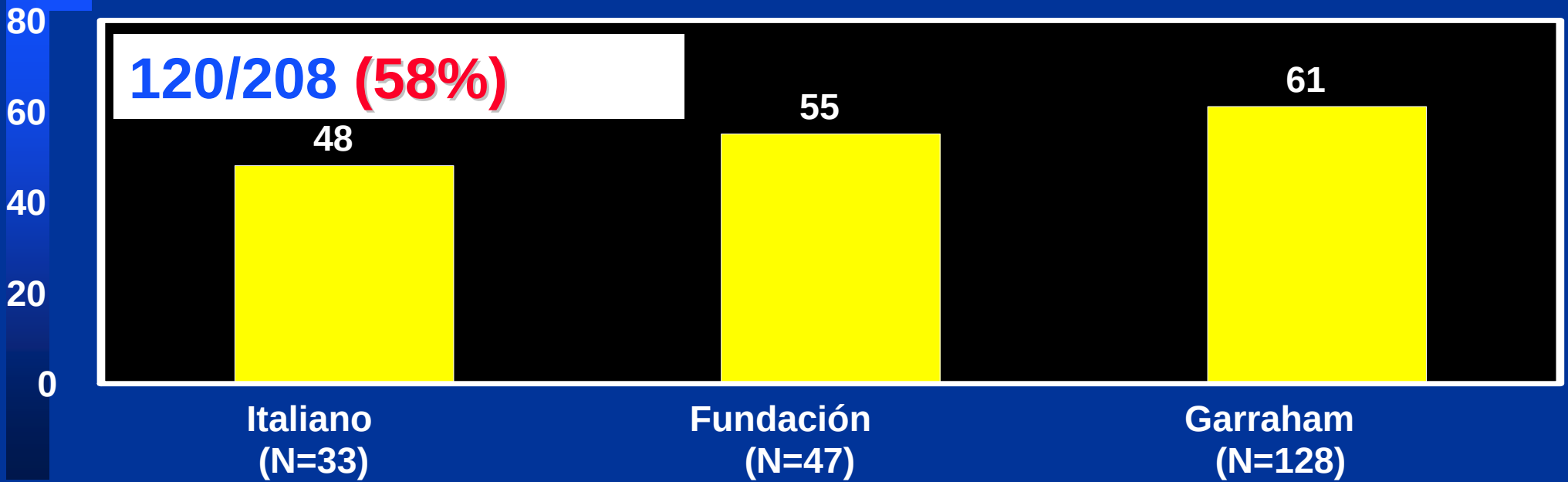
ALF : Argentina experience

Diagnostics	Number (%)	Alives	Deaths	LxT
Hepatitis A	**128 (61)**	**40 (31.2)**	**33 (25.8)**	**55 (43.0)**
Indeter.	68 (32)	11	25	32
Autoinmune	5 (3)	2	1	2
Otros	9 (4)	6	2	1
Total (%)	**210 (100)**	**59 (28)**	**61 (29)**	**90(43)**

Ciocca M, Ramonet M, et al JPediatr Gastroenterol Nutr,31, 2004

Acute liver failure due to hepatitis A in children



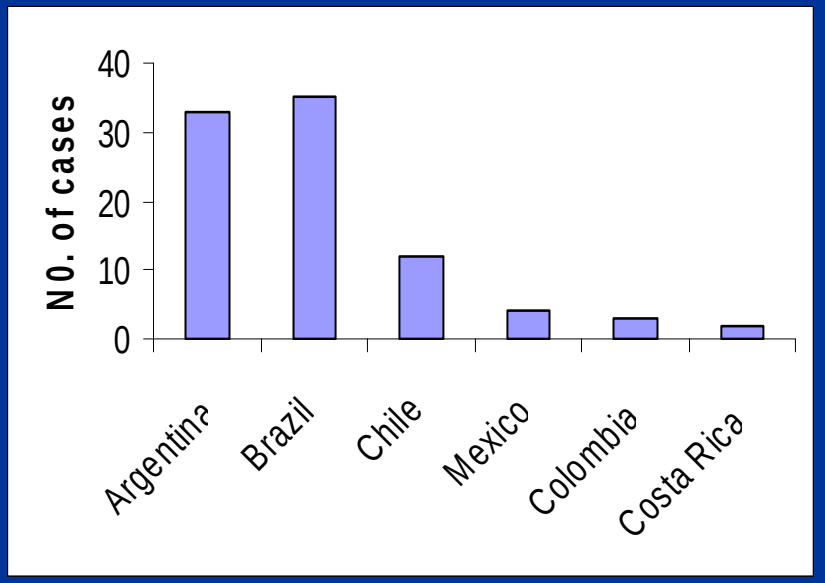


ALF: Latin american experience

- 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 all 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 efectiveness of Vaccination in Argentina

Table 4. The overall health outcomes and cost-effectiveness of a universal vaccination program in toddlers in Argentina: base-case scenario

	No vaccination	Vaccination
Disease burden[a]		
Vaccinated children (*n*)	0	652123
Hepatitis A infections (*n*)	380278	27873
Symptomatic infections (*n*)	134026	12439
Hepatitis A-related deaths (*n*)	474	46
Economic burden[b]		
Vaccination costs (US$)	0	9477097
Direct costs (US$)	26330501	5084646
Indirect costs (US$)	15264639	3043433
Total costs (US$)	41595140	17605176
Life-years lost (US$)	8701	1704
Cost–benefit[b]		
Cost difference	—	23989963
Cost per life-year gained	—	3429

[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 Gastroenterogy 2007;42:152-160

The cost efectiveness 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$ 3429per 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 efectiveness 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 efectiveness 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

Study interval	Virus HA infection		Efficacy (%)	IC 95%	p
	Vaccinates	Placebo			
Previous (138-366 days) booster (< 12 m)	2 / 19.037	32 / 19.120	94	79-99	< 0.0001
Post booster (367-532 days) (> 12 m)	0 / 18.217	6 / 18.270	100	54-100	0.02
Accumulated (138-532 d)	2 / 19.037	38 / 19.120	95	82-99	< 0.0001

Innis B et al. JAMA 1994;271:1363-4 A, vol. 271:1328-34, 1994 N Engl J Med 1992;327:453-7

Hepatitis A Vaccines

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

Beck BR et al. Clin Infect Dis, 2003;37: 126-8

- Long time protection

Van Damme P. Lancet 2003

- Safety in all ages
- Easy to administrate with others vaccines
- Different types of recipient.

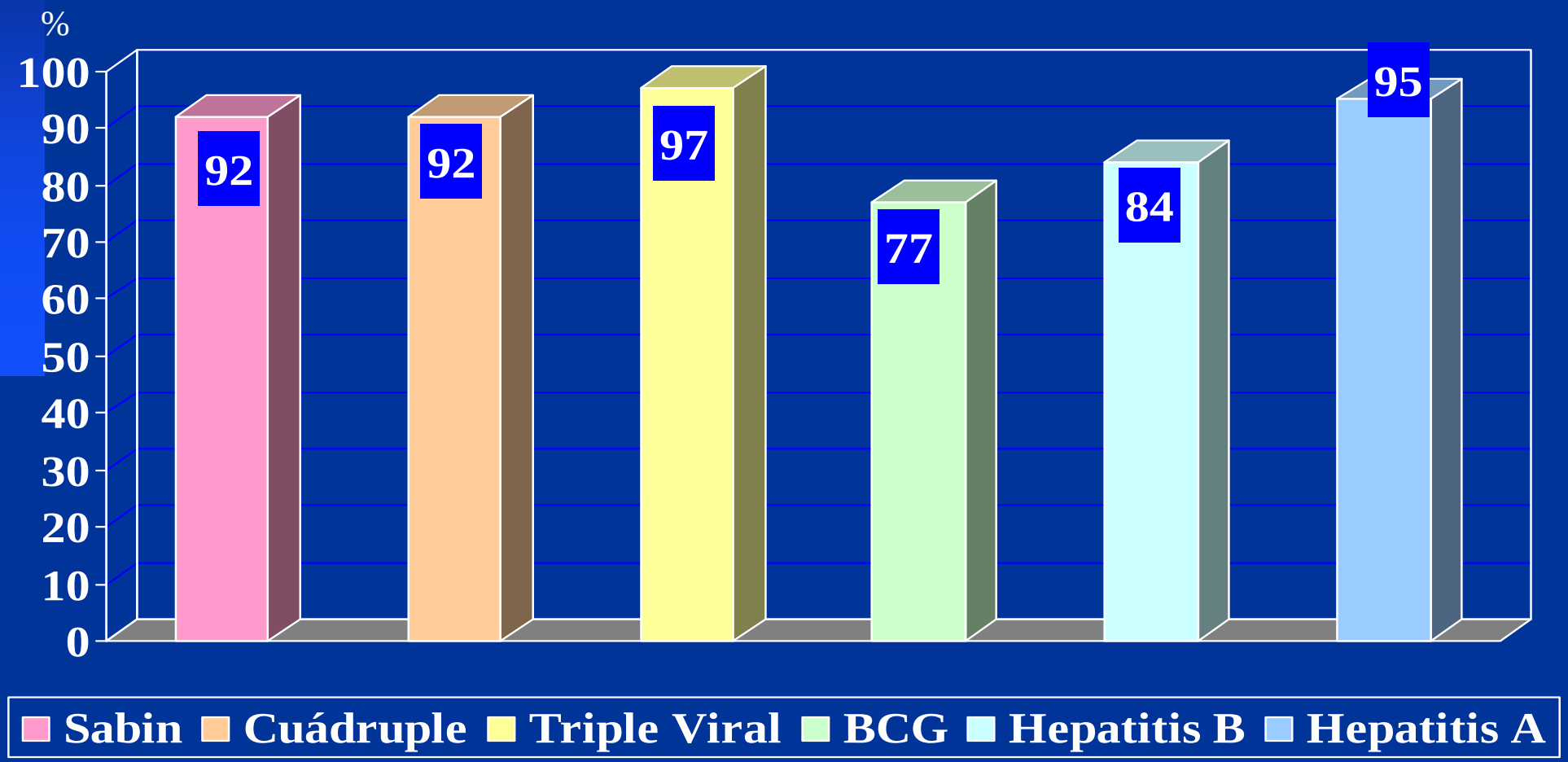
The decision was taken considering……

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

National Immunization Program

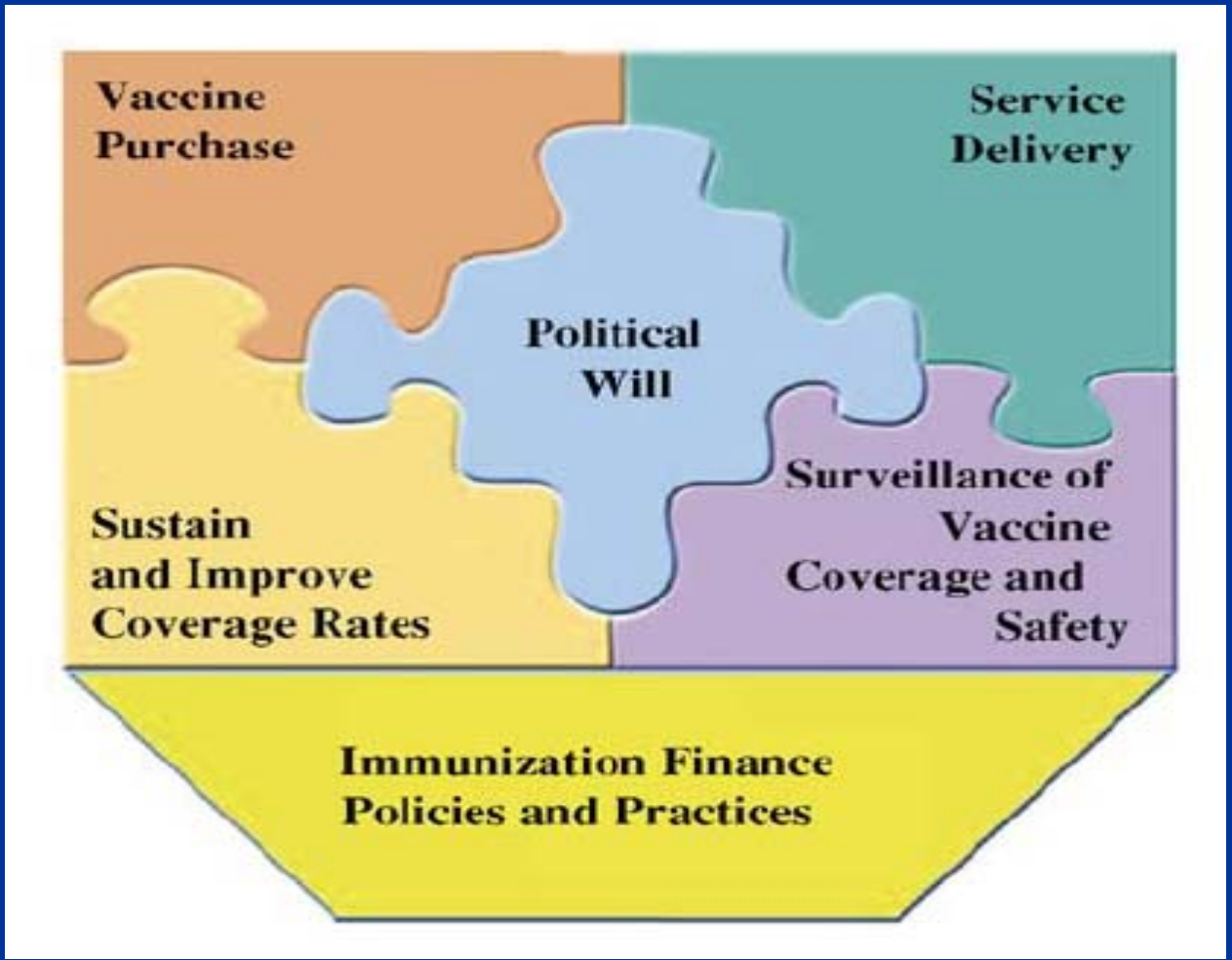
- It covers the whole country
- All the vaccines included in National vaccination schedule are gratuitous and obligatory.
- The Ministry of Public Health acquires and distribute the vaccines and other inputs (syringes, needles etc.) for covering all the cohort. (approximately 700.000 children)
- Safe cold chain

Argentina: National Immunization coverage in first year of life , 2006



Political commitment to sustain hepatitis A vaccine (one dose)

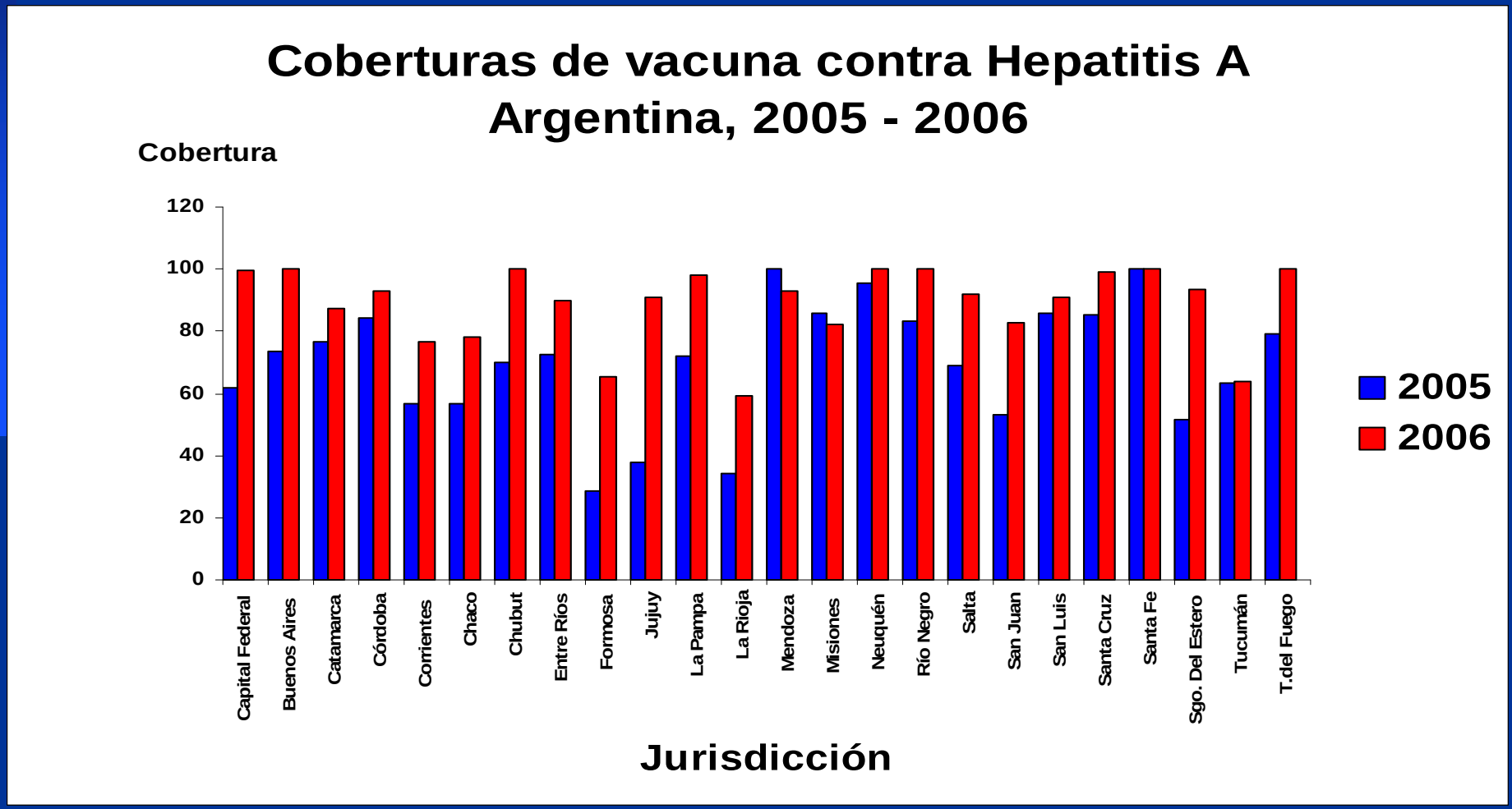
Issues to sustain a National Immunization Program



(Wright et al, Vaccine, 2006)

Social Acceptance

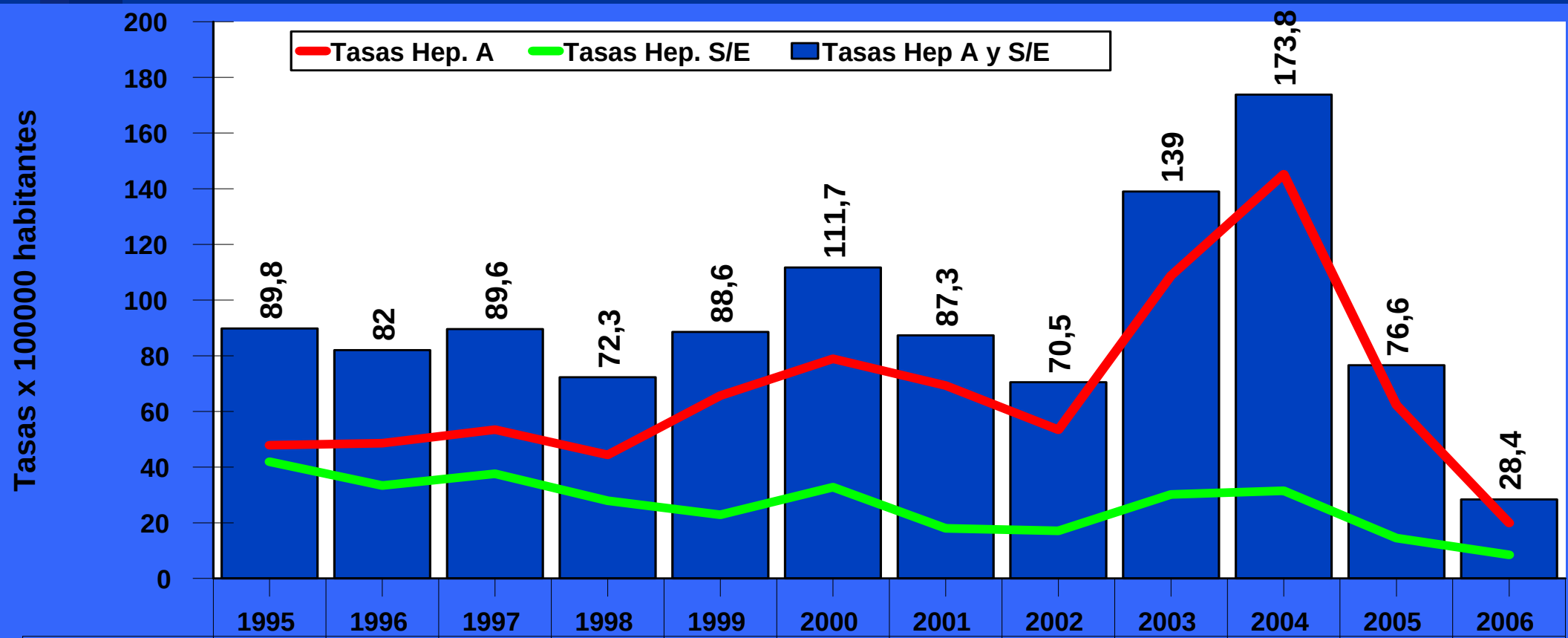
Hepatitis A vaccine coverage. 2005-2006



Rationale for Universal HAV Vaccination in Argentina

- 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



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Hep. A	17383	17617	19084	15833	23745	28527	25112	19359	39462	52637	22578	7220
Hep S/E	15184	12112	13410	9949	8268	11876	6524	6199	10937	10369	5266	3088
Hep. A y S/E	32557	29729	32494	25782	32013	40403	31636	25558	50399	63006	27773	10308
%SE	46,6	40,7	41,3	38,6	25,8	29,4	20,6	24,3	21,7	16,5	19	30
% Rel Hep A		1,3	8,3	-17	50	20,1	-12	-22,9	103,8	33,4	-57,1	-68

Fuente: Dirección de Epidemiología - MSAL

HEPATITIS A

A CALL FOR ACTION !!!

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!!