Summary of the major findings and conclusions of the Global Hepatitis A meeting, Miami December 2007

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Global Hepatitis A meeting

- Joint initiative
  - CDC, CEV, WHO, PAHO
- > 250 delegates from 46 countries
- PH representatives, epidemiologists, virologists, hepatologists, viral hepatitis and infectious disease experts, travel medicine doctors, …
- Abstract book & presentations: www.havmeeting.info

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Global Hepatitis A meeting: objectives

- To review surveillance systems, diagnostic tools, outbreak control, cost-effectiveness of hep A vaccination
- To discuss the changing epidemiology
- To review the hepatitis A immunization programmes
- To review the data needed to assess current hepatitis A prevention strategies

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Global Hepatitis A meeting:

- Country presentations on hepA epidemiology:
  - Brazil, Mexico, Saudi Arabia, Italy, Turkey, South-Africa, China, Korea, Thailand, India, Russia, & Ukaine
- Country presentations on prevention
  - Argentina, The Netherlands, Italy (Puglia), Israel, Spain (Calatlonia), Australia, Chile, Belarus, Russia, & China

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

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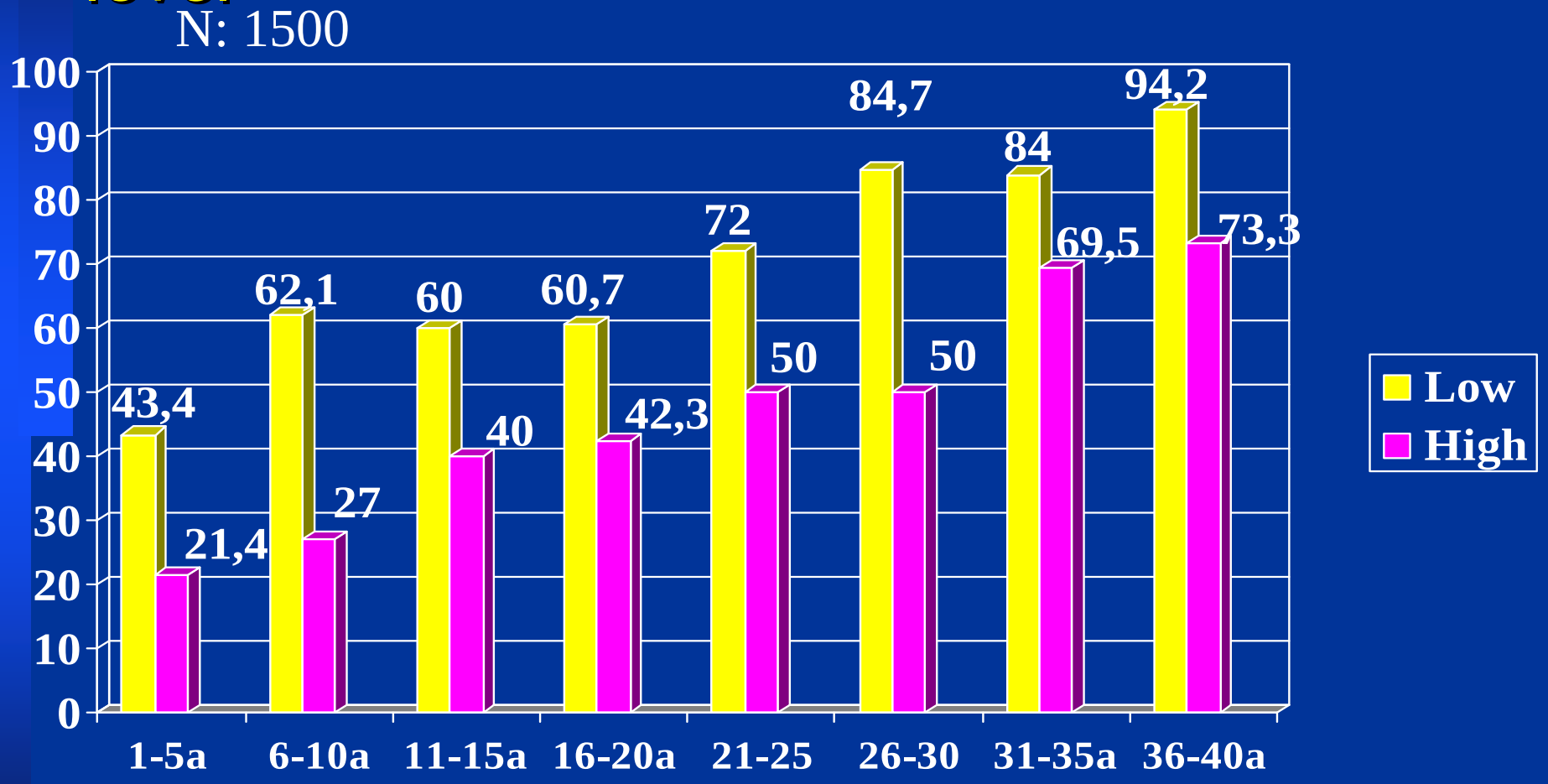
Argentina Pediatrics´ Society

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

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.

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

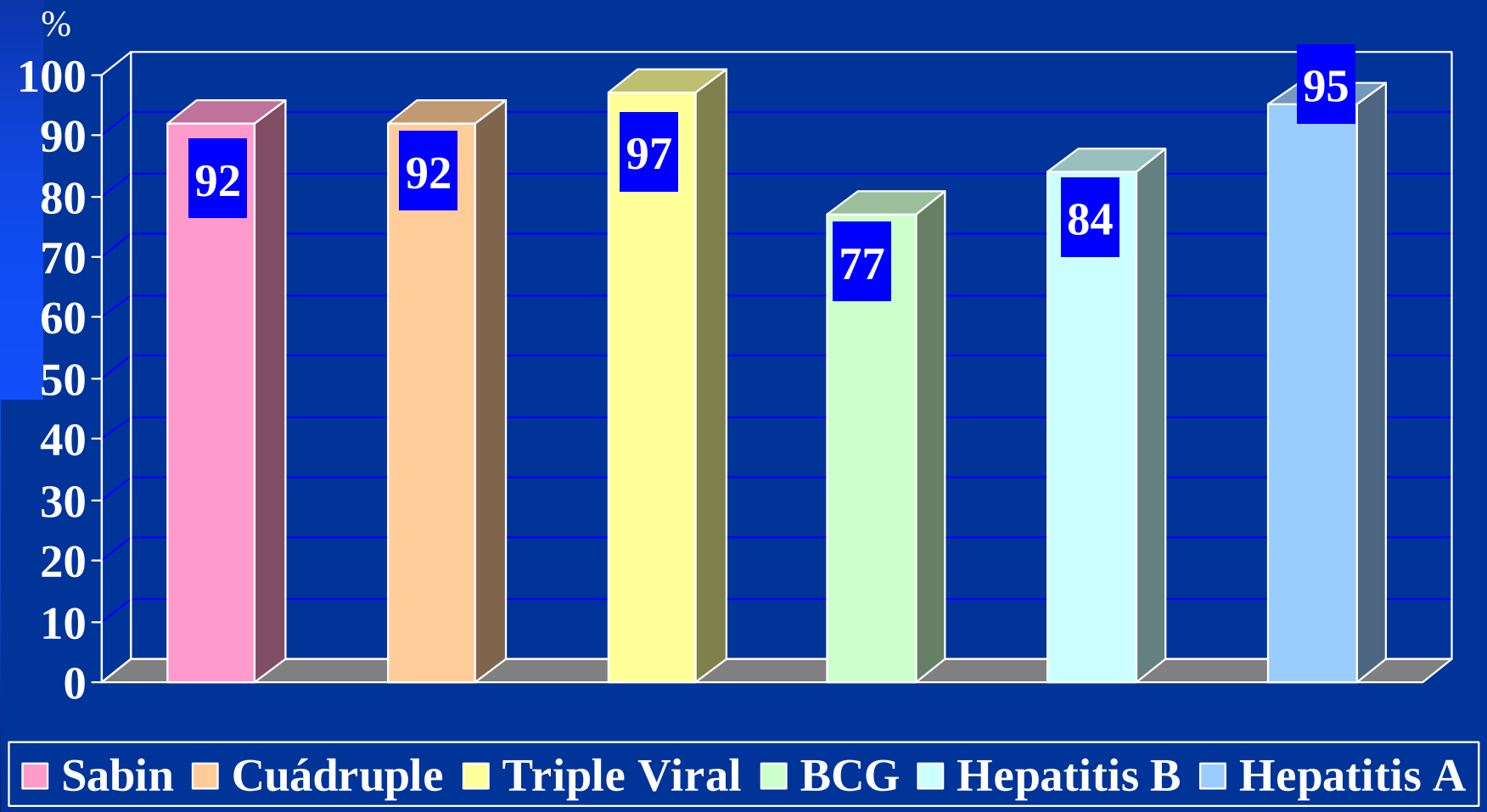
The decision was taken considering……

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

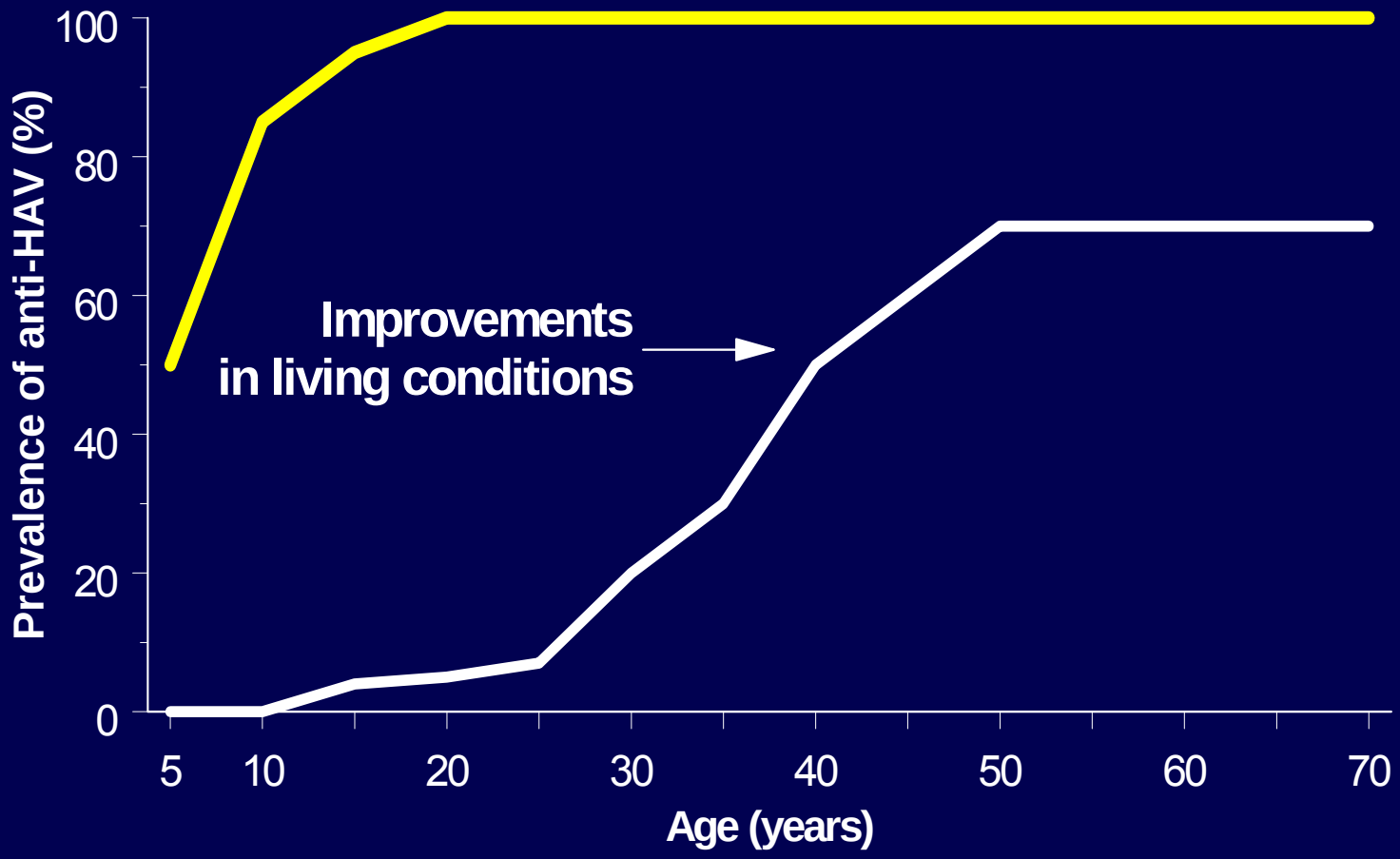
National Immunization Schedule Argentina, Ministry of Public Health

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]

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



Epidemiologic Shift in Prevalence of Antibodies to Hepatitis A Virus



Hepatitis A: Transition from High to Intermediate Endemicity Features

- Lower prevalence among children
  - Increase in average age of infection
  - Increased morbidity
- Outbreak potential
  - Circulating virus
  - Cohorts of susceptible older children, adolescents, and adults
- Variability in incidence
  - Within regions
  - Within countries and cities
    - urban/rural
    - socioeconomic status

Current data limited

- Old
- Missing country, regional data
- Developed-country data used to estimate proportion of acute hepatitis as hepatitis A; age distribution of cases; distribution of severity of cases (including case fatality rate)

Describing the epidemiology of HAV: Prevalence vs. Incidence

	Prevalence	Incidence
Assess population immunity and susceptibility	+++	+
Monitor trends in incidence of and risk factors for disease	++	+++
Assess burden of disease	-	++
Identify and control outbreaks	-	+++
Identify infected persons and at-risk contacts for preventive interventions (i.e. post-exposure prophylaxis)	-	+++

Rationale for Surveillance for Acute Viral Hepatitis A (and other types)

- Quantify burden of disease
- Measure risk of acute hepatitis A in all age groups
- Evaluate risk factors for HAV infection
- Define the need for and identify target groups for vaccination programs
- Measure the impact of vaccination strategies
- Provide basis for further investigations of HAV epidemiology: case/control studies, outbreak investigations

The EUROHEP.NET Project is a European Commission-funded feasibility study for a future network on surveillance and prevention of vaccine-preventable hepatitis

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In summary:

1. All countries have surveillance systems for burden of disease in place but a **wide diversity of surveillance** systems exists among them due to different local situations.

2. The surveillance data on burden of disease **are not collected in a standardized way:** different data sources for hospital admission and mortality due to HAV and HBV are in place.

3. In some countries the data on total number of hospital admissions and deaths due to HAV and HBV are not available. Sometimes the data sources are present, but data are not immediately accessible or complete.

4. Data on days of hospitalization, total number of liver transplants and the proportion due to hepatitis A, B and C are not often included in the current surveillance systems of burden of disease.

5. There is not a **unique adoption of ICD-10 code** to report the diagnosis of hepatitis for hospital admission or death.

   ICD-10 came into use in WHO Member States since 1994,. Many countries had not yet adopted this standard several years later (more countries adopted it since then)

6. In some countries, available data on burden of disease are gathered only for remuneration reasons, not for epidemiological purposes. Sometimes only data from extemporary studies are available, without a routine registration system

7. In a number of countries, **data are collected regionally** and there is no centralised national data collection, or their aggregation at the central level is not timely

8. Blanks or missing data in the answers to the EUROHEP.NET survey, unless otherwise specified, can either be due to non-available/traceable information in the country or to non-availability of such information to the country correspondent at the time of the survey. In the latter case, this does not necessarily mean that the information does not exist.

country	Endemicity Age-specific sero-prevalence	outbreaks	HepA vacc policy	coverage	impact
South Africa	High-Intermediate > 90% HAV+ lower s-e class	outbreaks	Target risk groups		
Argentina	High-Intermediate Pre: 139/100.000 post: 28.3/100.000	Large outbreaks in 2003-04	Universal hepA vacc in 2005 Single dose	95% Reg. Variations: 60-90%	No new outbreaks >80% reduction in incidence
Brazil	High-Intermeidate 7.5/100.000 but underrep.	Small outbreaks	No vacc policy Improve hygienic conditions		

country	Endemicity Age-specific sero-prevalence	outbreaks	HepA vacc policy	coverage	impact
Chile	30-60/100.000 High-intermediate	Increasing number of cyclic outbreaks	Improve hgienic conditions		
Mexico	High-Interm. HAV+ > 97% of > 20 y olds Large cohort of pre-school children HAV-		No data		
US	Low Pre: 10-15/100.000 Post: 1.2/100.000	Large outbreaks every 10-15 years	'99: universal vacc policy in 17 states 2006: nationwide	Coverage : 13-71%	Decline in hops. (69%), mortality rates (32%)

country	Endemicity Age-specific sero-prevalence	outbreaks	HepA vacc policy	coverage	impact
India	High-Intermediate Sero-survey to be started in 2008 90-100% HAV+ in rural adults	Several large outbreaks	No national imm. policy		
Thailand	High-Intermediate 27.4% HAV+, increasing with age	Several outbreaks	Vaccine cost do not justify univ. Imm programme		
Belarus	Intermediate 95/100.000 >45y age: 85%	No data			

country	Endemicity Age-specific sero-prevalence	outbreaks	HepA vacc policy	coverage	impact
Israel	Intermediate 50.4/100.000	Pre: 10/y Post: none	1999: toddlers	85-90%	98% reduction in incidence
Italy	Low 1995: 4/100.000 2006: 1.4/100.000	Large outbreak in Puglia (1997)	Risk groups Surveillance of shellfish retail Univ. policy in Puglia (1998) Toddlers + ado's	60-70%	0.7/100.000
Spain Catalonia	Intermediate-Low Pre: 5.51/100.000 Post: 2.98/100.000	No data	1995: risk groups 1998: Univ. Policy: pre-ado's		Incidence red. 45-73%

country	Endemicity Age-specific sero-prevalence	outbreaks	HepA vacc policy	coverage	impact
Russ Fed.	High-intermediate 50-170/100.000 Decreasing immunity in younger pop.	Periodic large outbreaks	No universal policy		
Netherlands	Low 2/100.000 Import MSM transmission	Small n° of outbreaks Import related	Risk group policy Travel-import Related		
Turkey	Low-Intermediate-High Overall: 71.3% HAV+	No data	Vaccine in private sector		

country	Endemicity Age-specific sero-prevalence	outbreaks	HepA vacc policy	cove rage	impact
Ukraine	High-intermediate Increasing susc. In younger ones	Several outbreaks	hepA vacc. Planned to be included in NIP by 2011		
Saudi Arabia	High-Intermediate 9-14/100.000	Several outbreaks	2000: risk group –childhood imm in private schools 2008: univ. Policy (18m olds).		
Australia	Pre: 31.1-75/100.000 Indigenous pop. Post: 1.8/100.000	Oister-related MSM, IVDU, …	Risk group 1999: For indigenous children (N-Queensland) 2005: in high incidence states		95% red. in incidence

country	Endemicity Age-specific sero-prevalence	outbreaks	HepA vacc policy	cover age	impact
China	High-intermediate Pre:> 50/100.000 Post (2005-2006): 5/100.000	Shangai (1988)	Vacc policy since 1992 Plans to include vacc in routine programme by dec 2007 (18m)		Incidence decrease: 90% red in infection risk
Korea	High-intermediate 9.8/100.000 10-19y & 20-29y are most susceptible		Childhood vacc recommended but not universal	40%	

Uses of Molecular Epidemiology

- **Sources of Virus Transmission in outbreaks**
  - Food / water / other environmental
  - Risk factors – MSM, IDU
  - Blood / Blood Products
- **Transmission Patterns within Populations**
- **Monitoring Vaccine Effectiveness**

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- Examples of molecular epidemiological studies were presented:
  - HAV outbreak in European travelers returning from Egypt

(routine) monitoring of circulating HAV strains useful to:

- detect widely dispersed outbreaks and hidden clusters
- demonstrate links between imported and autochthonous cases

  - Used to detect HAV in urban sewage
    - F.u. of epidemiological patterns of excretion of HAV

Postexposure policy changes…

- In much of Europe and Canada, hepatitis A vaccine becomes recommended after exposure, but recommendations vary:
  - In countries where immune globulin was not used
  - In some countries vaccine is recommended over IG
  - In the UK, vaccine is recommend if it can be given early while IG is considered preferable later/for those with higher risk of serious outcome.

Study in Kazakhstan compared the efficacies of hepatitis A vaccine and IG in the prevention of laboratory-confirmed symptomatic hepatitis A when given within 14 days of exposure to a symptomatic index case of hepatitis A.

Study concluded:

hepA vacc. had high efficacy, similar to that of IgG.

Updated ACIP Recommendations (abbreviated)

- For healthy persons age ≥ 12 months to 40 years, hepatitis A vaccine is preferred to IG.
- For persons > 40 years, IG is preferred. (Vaccine can be used if IG cannot be obtained.)
- For children age < 12 months, immunocompromised persons, persons with chronic liver disease, and persons for whom vaccine is contraindicated, IG should be used.

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Conclusions: HEpatitis FLoridA

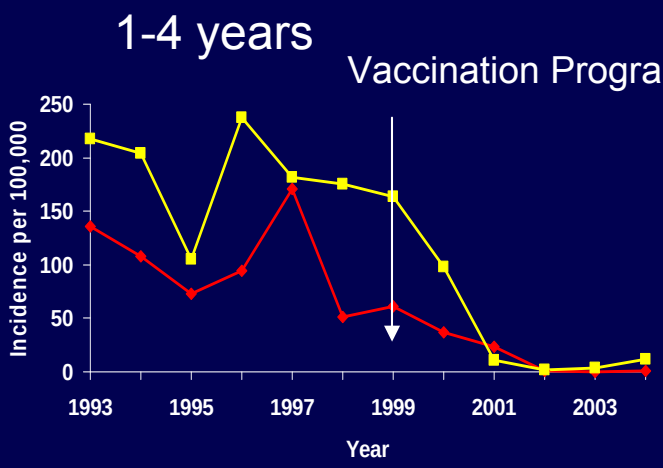
- Highly immunogenic
  - Non-response in > 99%
  - Rapid seroconversion
  - Long-term antibody persistence
- Excellent safety profile
- Freedom to choose
  - Coadministration / combination vaccines
  - Flexible vaccination schedule
  - Interchangeability
- Long-lasting protection
  - Beyond antibody persistence (life-long)
  - Proven effectiveness, even post-exposure
- After single dose? How long protected?

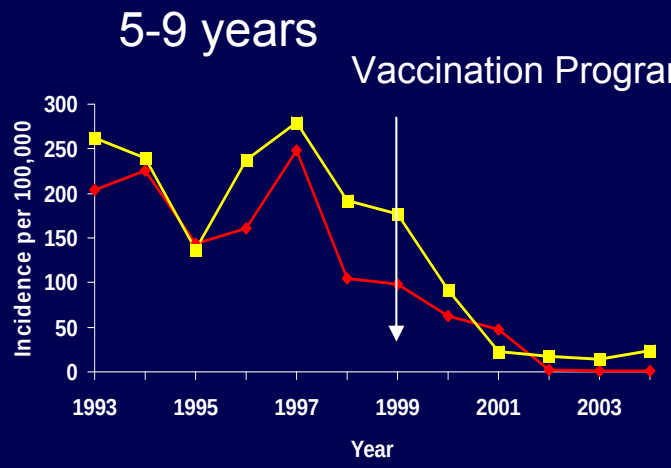
Selected Countries with Routine Childhood Hepatitis A Vaccination Programs; 2007

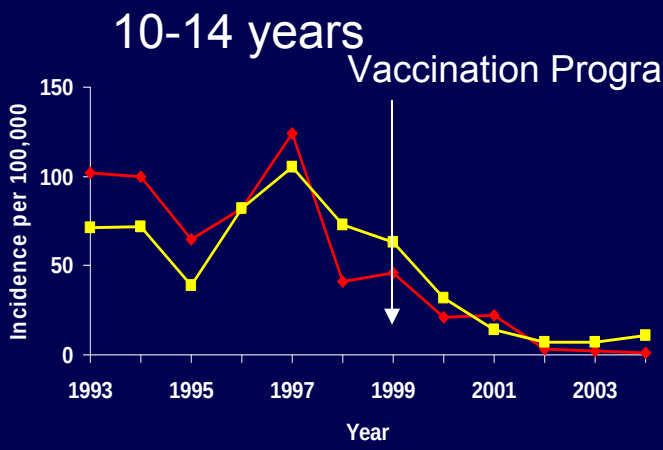
Country	Target Ages	Year Begun	Comments
Zhejiang Province, China	1-15 years	1992	Single dose live attenuated vaccine
North Queensland, Australia	18 months; catch-up to age 6 years	1999	Indigenous population
United States	2-18 (regional)	1999	2006 - national (12 months)
Catalonia, Spain	12 years	1998	A/B vaccine
Puglia Region, Italy	15 months 12 years	1997	A/B vaccine for adolescents
Israel	18 months	1999	
Argentina	12 months	2005	Single dose

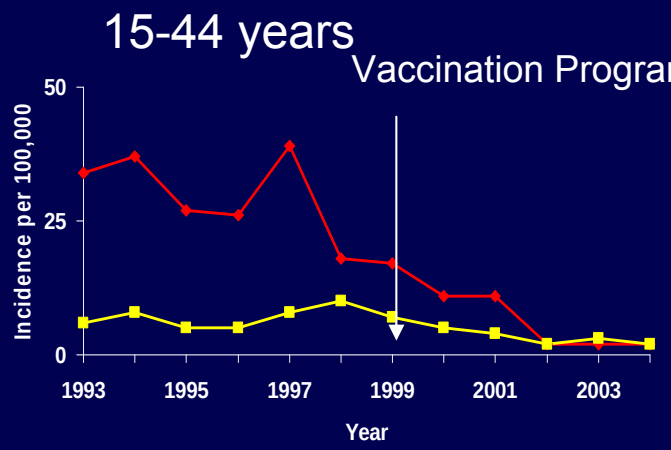
CDC

Hepatitis A Incidence, by Age and Population Group, Israel, 1993-2004









Jews

Non-Jews

Source: Dagan et al, JAMA 2005

Impact on Health Care Utilization, U.S. 1996-2004 Medstat MarketScan Database

Comparing baseline (1996-97) to 2004, statistically significant declines:

- Hospitalizations – 69%
- Ambulatory visits – 42%

Adjusted to US population, medical expenditures for hospitalizations and ambulatory visits declined:

- $29.1 million (baseline) to $9.3 million (2004)
  - 68% reduction

CDC

Source: Zhou et al. Vaccine 2007.

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Conclusions

- Hepatitis A is a significant cause of morbidity in the world
- Mortality due to hepatitis A is low but is the leading cause of liver transplant for acute viral hepatitis:
  - Surprising rates of fulminant hepatitis A in younger ones (e.g. in Korea, Brazil, Argentina)
- Lack of recent country data!
- need for improved surveillance – standardized systems of data collection and case definition
  - To produce accurate BOD data
  - To document the increased n° of susceptibles
  - Through low cost methods (cross sectional data, …)

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Conclusions

- The changing epidemiology is vizualizing the clinical features of the disease and its consequences
- Investment in improved sanitation, makes high endemicity countries move to intermediate situation, … this should go hand in hand with the implementation of universal hepatitis A immunization programmes.

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conclusions

- data on circulating strains need to be shared globally and within the regions
- Vaccination of travellers need to be stressed (prevention of HAV importation)
- Low endemicity country: most HE analysis have shown hep A risk group vaccination to be cost-effective
- Low endemicity country: routine vaccination studies have been inconclusive
- However, recent analysis have shown more favourable results
  - With reduced vaccine costs
  - Using dynamic models taking the indirect effect of herd immunity into consideration

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Conclusions

- Consensus reached on a stepwise strategy at country-level:
  - Invest in accurate surveillance
    - Document level of endemicity/outbreaks/…
  - Secure political support
  - Conduct HE analysis
- The need to control HAV globally was emphasized
- The need to place HAV disease in the context of global health priority was stressed

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Future

- Revisite the WHO position paper
- Put HAV on the international agenda
- Next edition of a similar meeting over 1 or 2 years
  - Update the situation
  - Review what has been achieved in the meantime