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Scientific evidence for the use of one dose

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VHPB Technical Meeting:

*Addressing Hepatitis A in Europe in 2026:
Challenges, Strategies, and Opportunities*

13-14 October 2026, Antwerp, Belgium

Status Quo of single-dose / double dose pediatric UMV



New since 2021/22*

Single dose

- Libya
- Peru
- Tunisia
- Oman ?

Double-dose

- Cayman Islands
- El Salvador
- Guam
- Jordan
- Mongolia
- Mariana Islands

* WHO Country Profiles
(accessed Sept. 2026)

2020: n= 13 countries 2 dose-UMV
n= 8 countries 1 dose -UMV

How evolved the efficacy evidence since the 1990s ---> 2012 ?

Randomised controlled single dose studies

Werzberger NEJM 1992: (USA, June - Dec 1991) **RCT (1 : 1 vs placebo):** planned summer-fall HAV outbreak intervention; assumed $\geq 80\%$ efficacy $\Rightarrow$ n= **1037 seroneg. children** (2-16 yrs), **1 dose** (VAQTA 25U): **100% protection** after ≥ 50 days, **4.5 months follow-up**

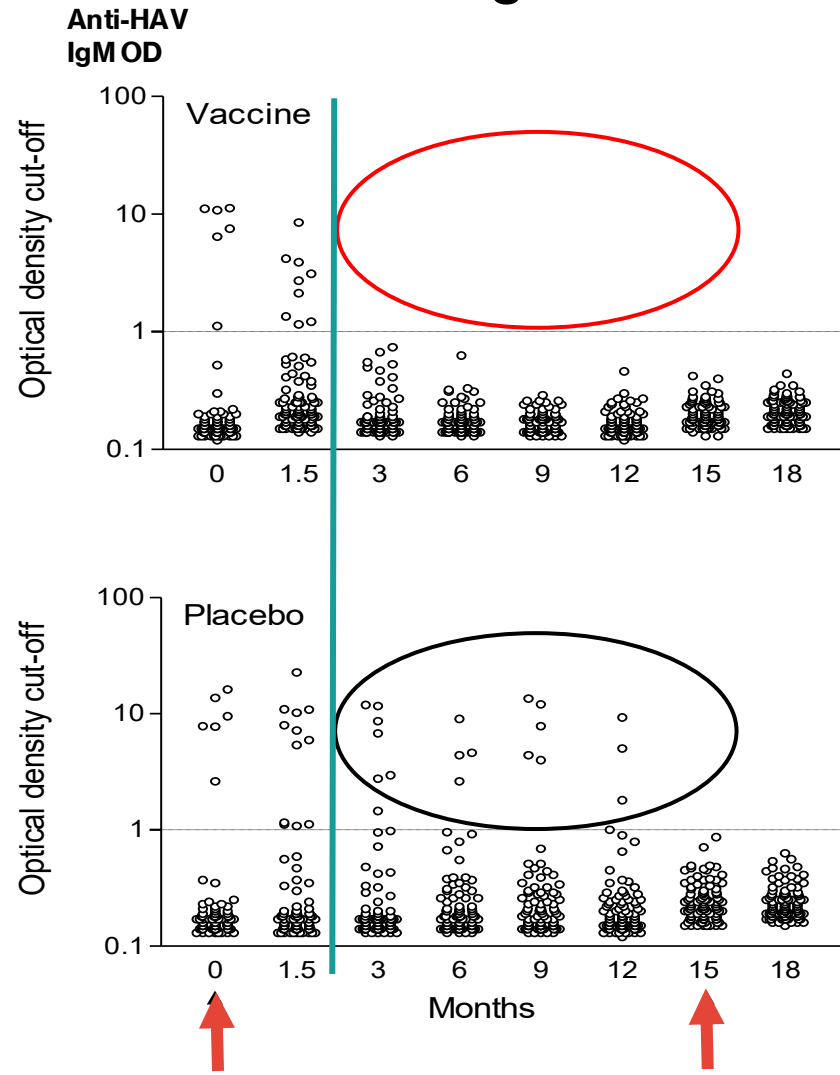
FACIT: "... a single dose is highly protective against clinical apparent hepatitis A"

Mayorga J Infect Dis 2003: (Nicaragua, 1995-1996) **RCT (1 : 1 vs placebo)** field efficacy trial: assumed yearly attack rate of $\geq 10\%$ and 90% efficacy $\Rightarrow$ n=**274 seroneg. children** (1.5-6 yrs), **1 dose** (Epaxal 0.5 mL): **100% protection** (IgM pos) after ≥ 6 weeks; **15 months follow-up**

FACIT: "A single dose ... protects young children against HAV infection."

Efficacy of Virosome Hepatitis A Vaccine in Young Children in Nicaragua: Randomized Placebo-Controlled Trial

[Mayorga O et al. J Infect Dis 2003;188:671-7]



Epaxal

Not a single vaccinated child was infected after week 6 (= end of potential incubation period)

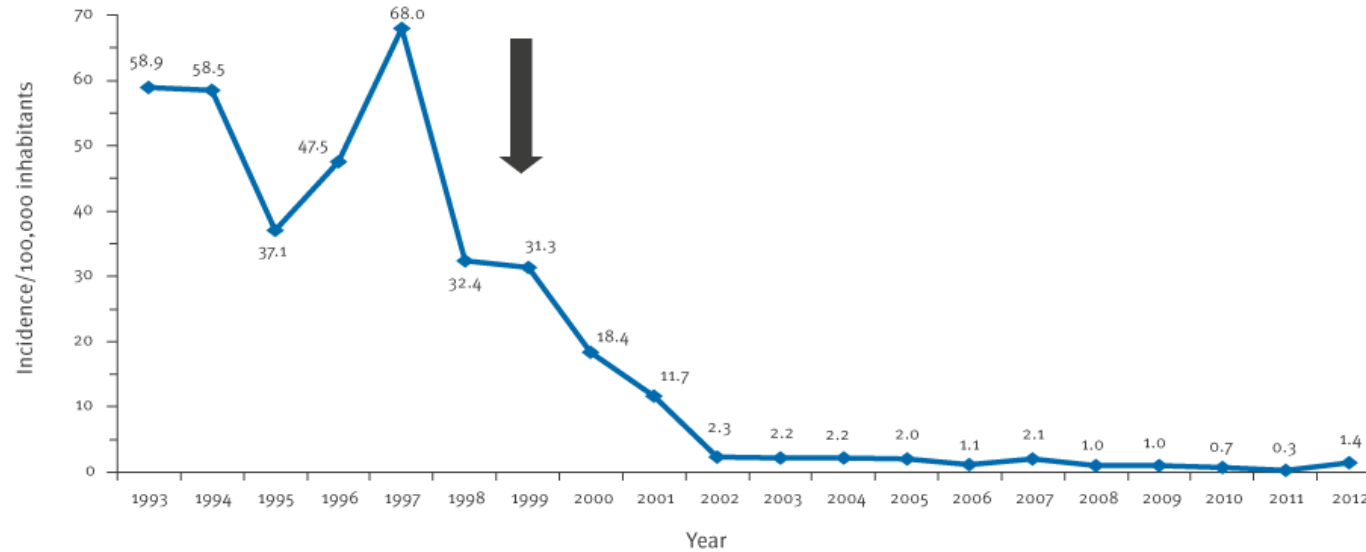
Placebo

12.4% of the non-vaccinated children were infected (IgM pos.) within 15 months

Implementation of pediatric UMV

Israel was in 1999 first country with pediatric, nationwide 2-dose UMV

Annual incidence rates of hepatitis A
per 100,000 population, Israel, 1993-2012

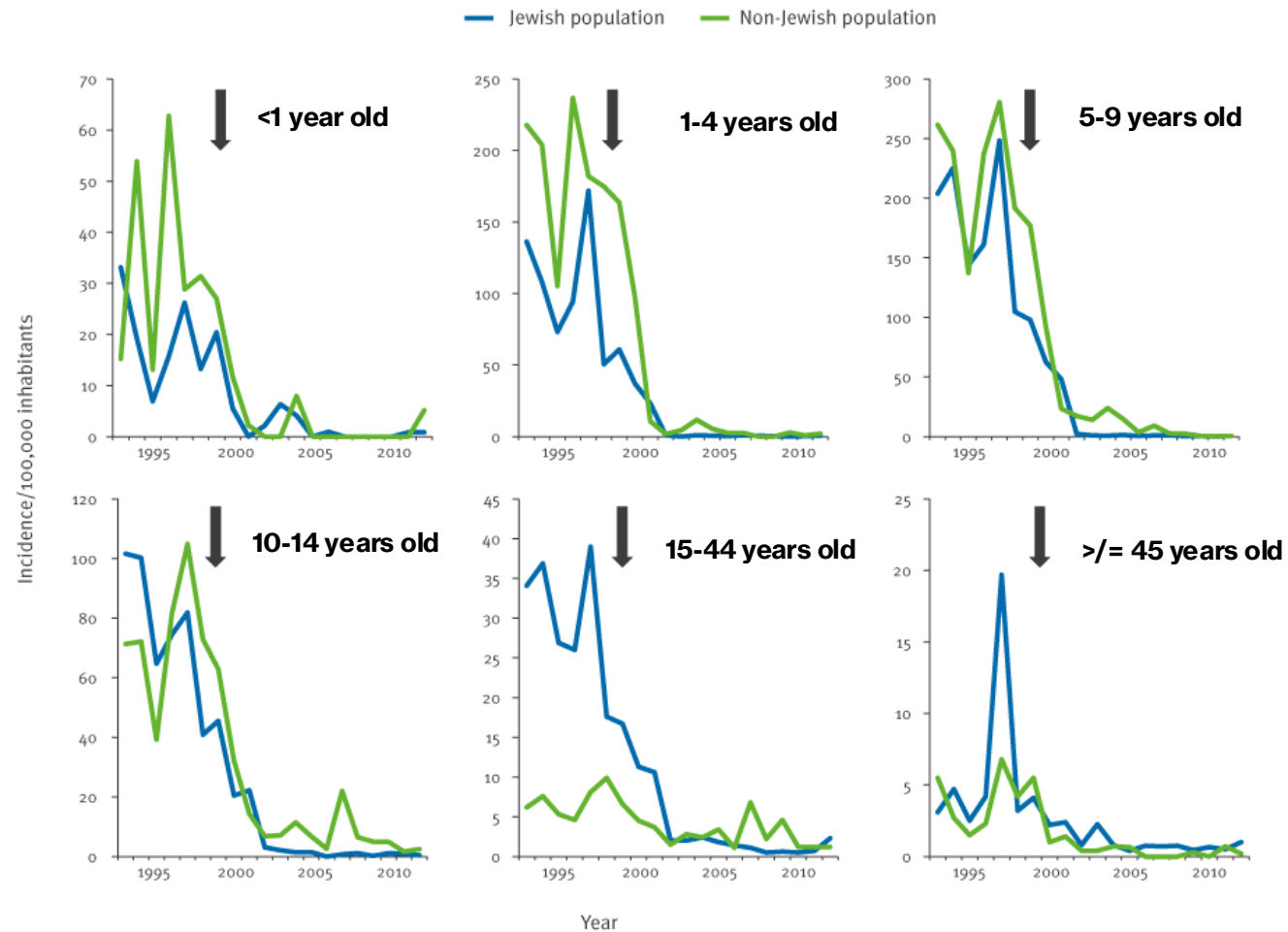


Israel UMV 1999-2012 ---> Hep A incidence decreased quickly

[Levine H et al. Eurosurveillance 2015;20:pii_21040]

Israel UMV 1999 - 2012:

---> Herd effect documented in all age groups



[Levine H et al. Eurosurveillance 2015;20:pii_21040]

Delayed second dose studies in adult travellers

Publication	Subjects	Seroprotection rate (%)		GMC (mIU/mL)		Delay (months)
		Pre-boost	Post-boost	Pre-boost	Post-boost	
Landry 2000	n=124	68%	100%	116	2242	24-66
Beck 2003	n= 97	71%	100%	na	2385	18-54
Iwarson 2004	n= 52	65%	100%	na	2160	47-96
Hatz 2011	n= 130	59%	100%	17	1557	18-128

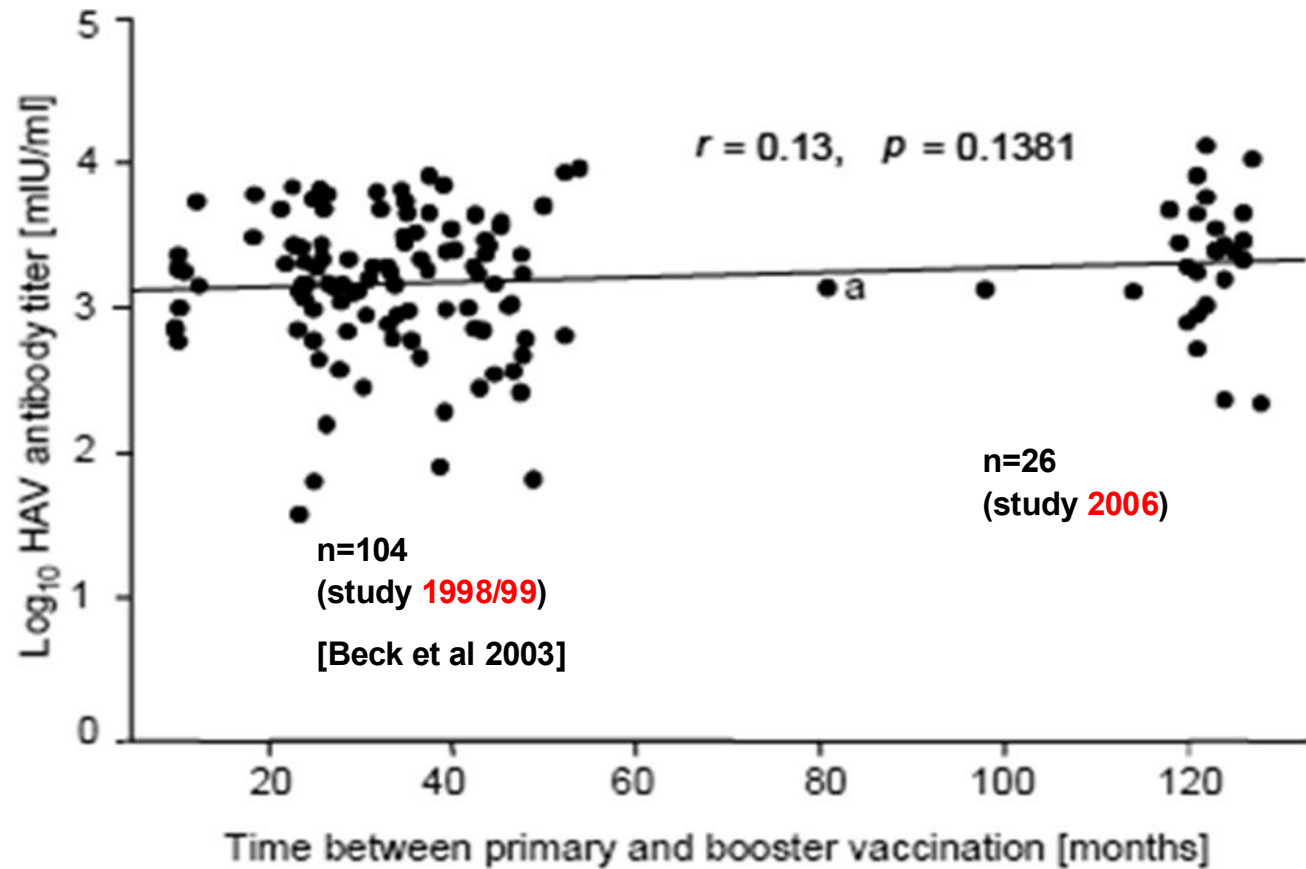
Landry P et al. Vaccine 2001;19:399-402

Beck BR et al. Clin Infect Dis 2003;37:e126-8

Iwarson S et al. J Trav Med 2004;11:120-1

Hatz C et al. Clin Vaccine Immunol 2011;18:885-7

Scatterplot of anti-HAV mIU/mL (log concentrations) after booster vs time (9 – 128 months)



[Hatz C et al. Clin Vaccine Immunol 2011; 18: 885-7]

Single-dose post-exposure prophylaxis & outbreak control

Hepatitis A Vaccine versus Immune Globulin for Postexposure Prophylaxis

RCT (1 : 1 vs anti-HAV Immune Globulin) in Kazakhstan:

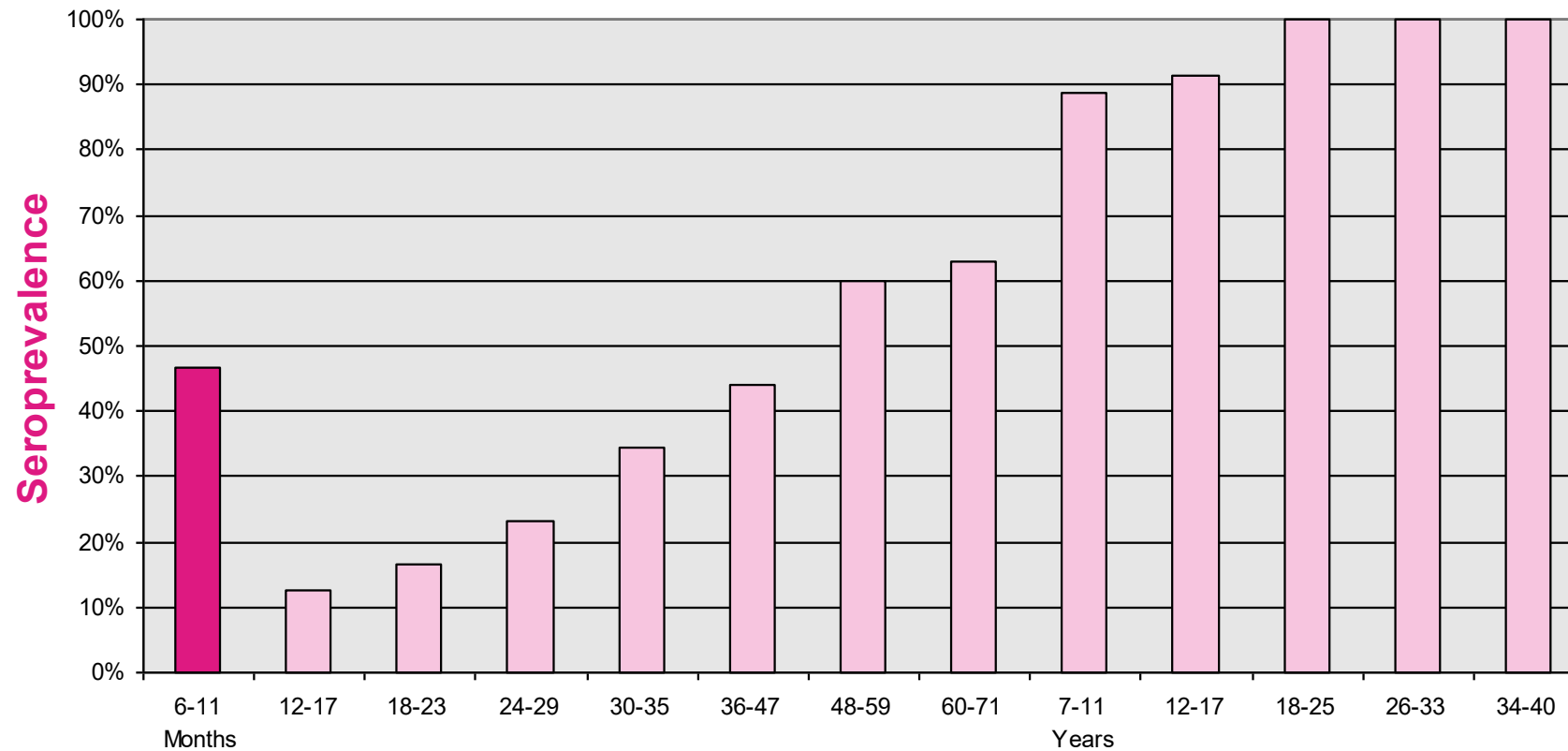
n= 1090 seroneg. subjects (2-40 yrs (mean 12 yrs)) received 1 dose hepatitis A vaccine (VAQTA) or immune globulin within 14 days after exposure to patients with hepatitis A.

Follow-up for 15 - 56 days : Symptomatic HAV infection in 25/568 vaccinees (4.4%)
and in 17/522 contacts receiving immune globulin (3.3%)

FACIT: Administration of 1 dose of vaccine within 2 weeks after exposure equally effective as immune globuline to protect against clinical hepatitis A

[Victor JC et al. NEJM 2007; 357: 1685-94]

Hepatitis A seroepidemiology in Leon, Nicaragua, 2003 (n=496)

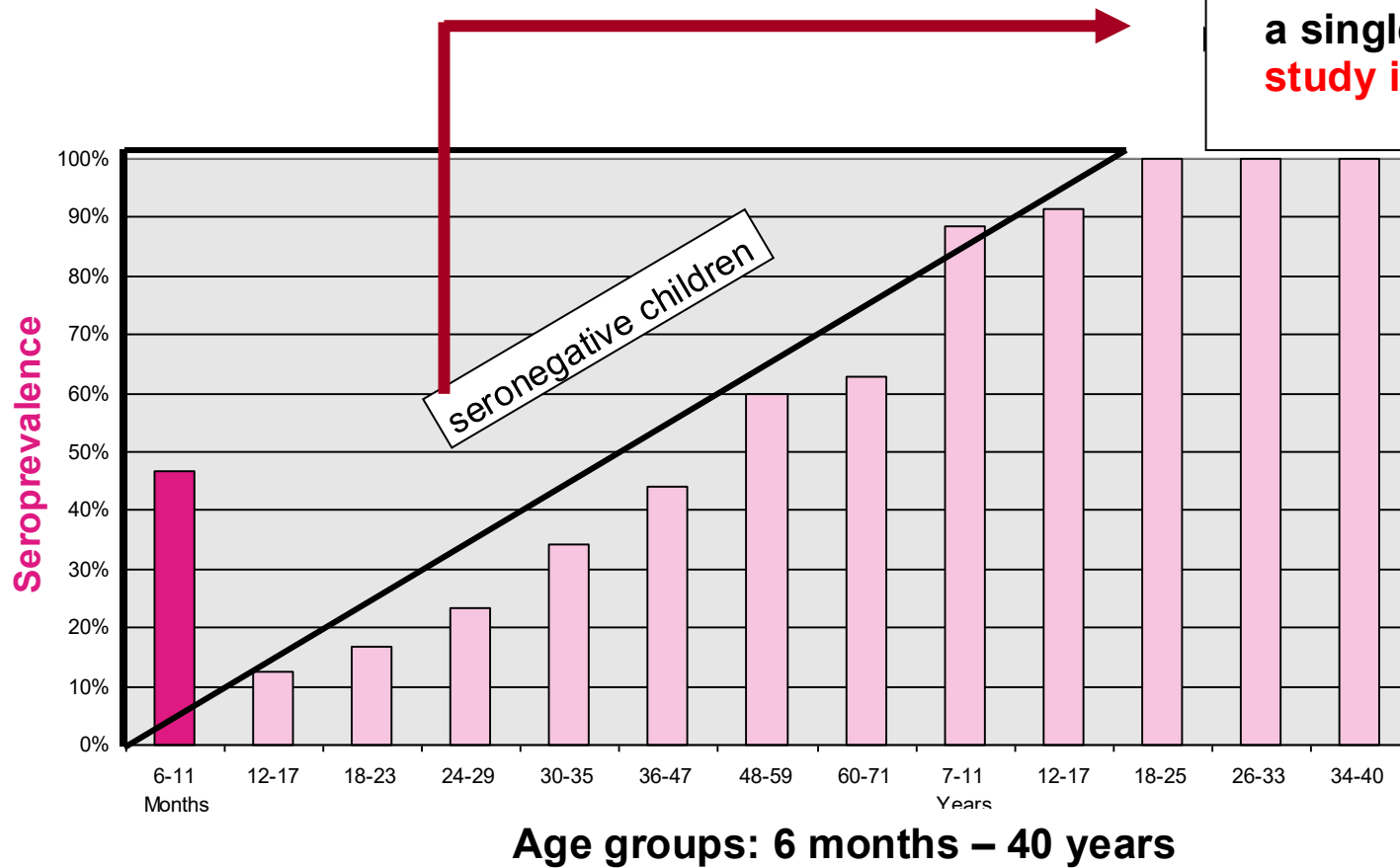


Age groups: 6 months – 40 years

[Mayorga O et al. PLoSOne 2014; 9(2): e87643]

Serological cohort study to assess protective effectiveness of single-dose HAV vaccination

2003 Hepatitis A seroepidemiology in Leon, Nicaragua
(n=496: infants, children & adults)

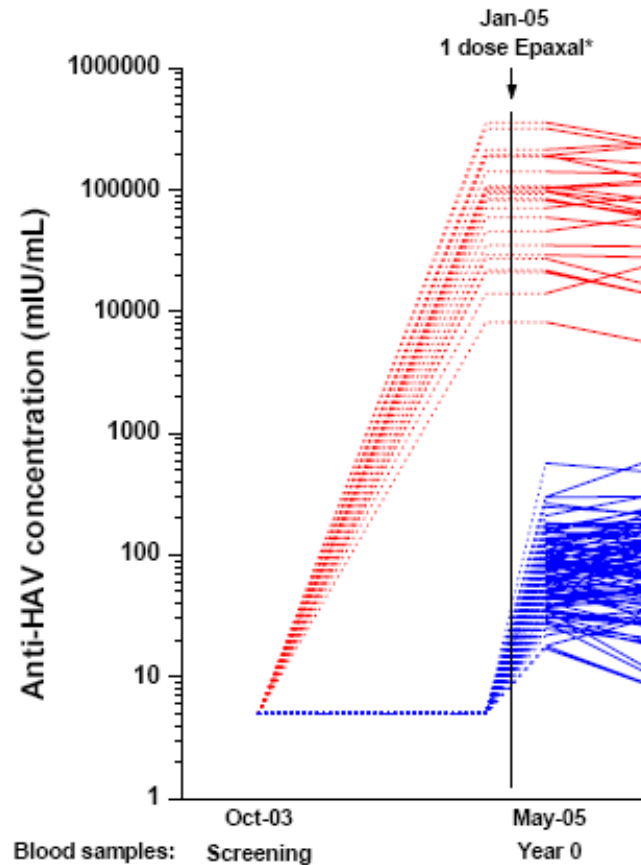


Opportunity to start with n=130 HAV seronegative, 2-17 year old children a single-dose protective **observational study in 2005** using Epaxal® 0.5 mL

[Mayorga O et al. J Infect Dis 2016; 214: 1498-506]

Serological cohort study (2005-2012) to assess protective effectiveness of single-dose HAV vaccination

Anti-HAV IgG antibody concentrations 2003 - 2005



2003: **N=130** HAV seronegative,
2 - 17 year old children

N=25 excluded
as **HAV infected**
between
2003 and 2005

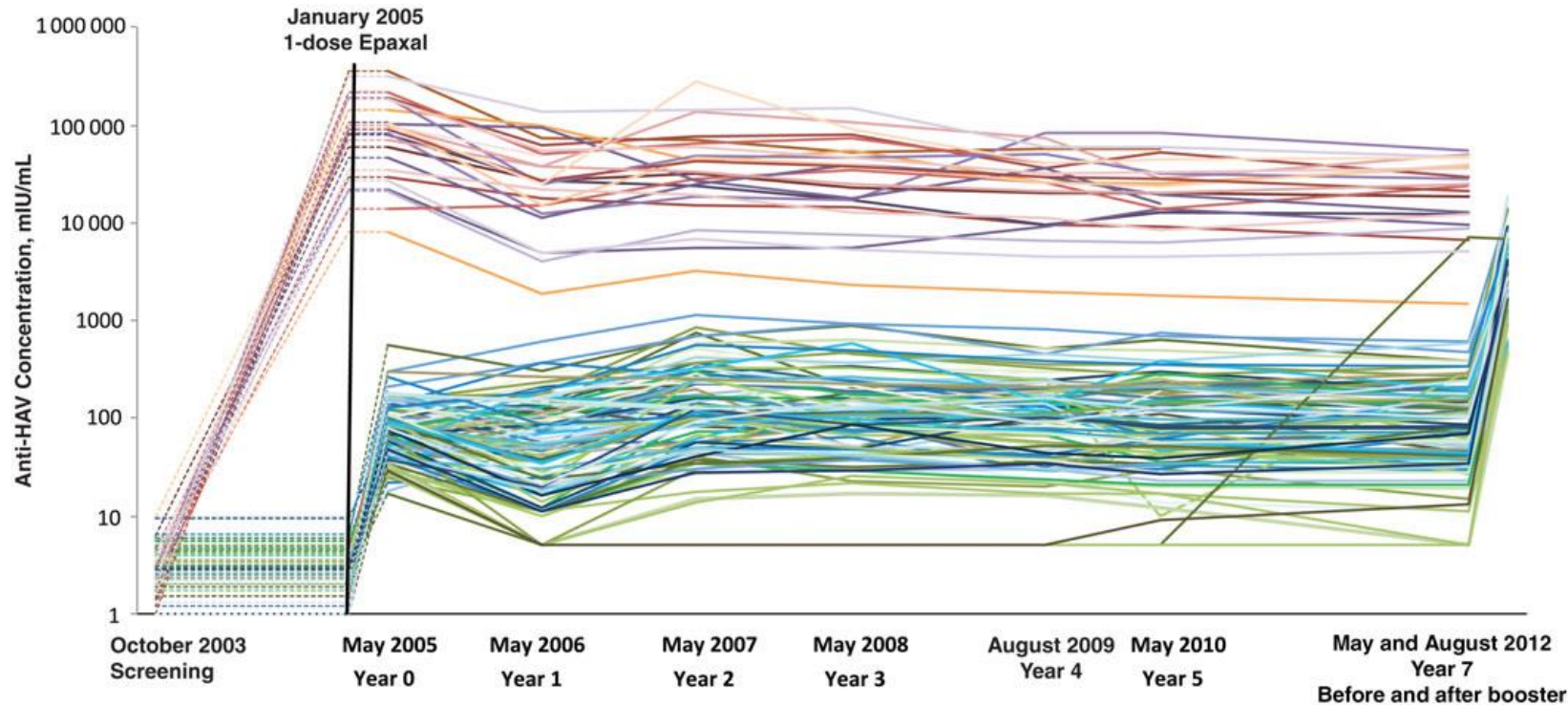
2005: **N=105** non-infected
children single dose
of HAV vaccine

N=9 children lost
to follow-up/contact

2012: **N=96** children
receiving booster
vaccination (7.5 yrs
after 1st dose)

Single-Dose Hepatitis A Immunization: 7.5-Year Observational Pilot Study in Nicaraguan Children to Assess Protective Effectiveness and Humoral Immune Memory Response

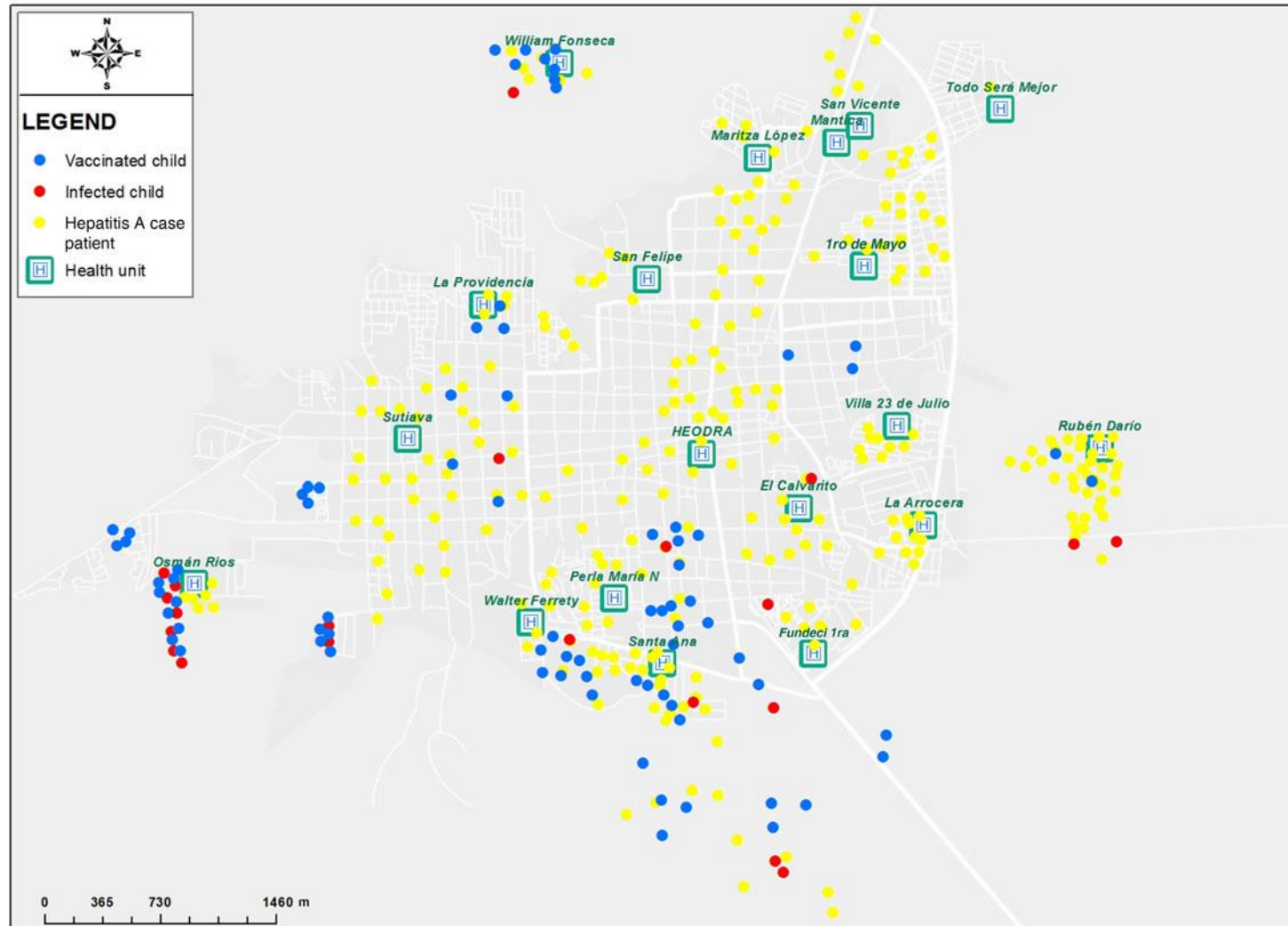
[Mayorga O et al. J Infect Dis 2016; 214: 1498-506]



- Based on the **≥15% annual infection risk**, an **estimated 60% of the n=105 vaccinated children** were **exposed to HAV encounters** during follow-up.
- No child presented with hepatitis symptoms.
- One serological breakthrough infection represents an estimated **protective effectiveness of 98.3%** (95% CI, 87.9–99.8).

Anti-hepatitis A virus (HAV) antibody concentrations during 2003–2012 in **n=105 vaccinated and noninfected** (green and blue lines) and **n=25 infected** (orange and violet lines) children

Map of the community of León with the places of residence for the community HAV (IgM pos.) clinical cases observed from 2006 to 2010



Community control group:

N=557 jaundiced subjects attended screening from May 2006 – March 2010

N=316 (57%) Hep A positive (yellow circles)

Study participants:

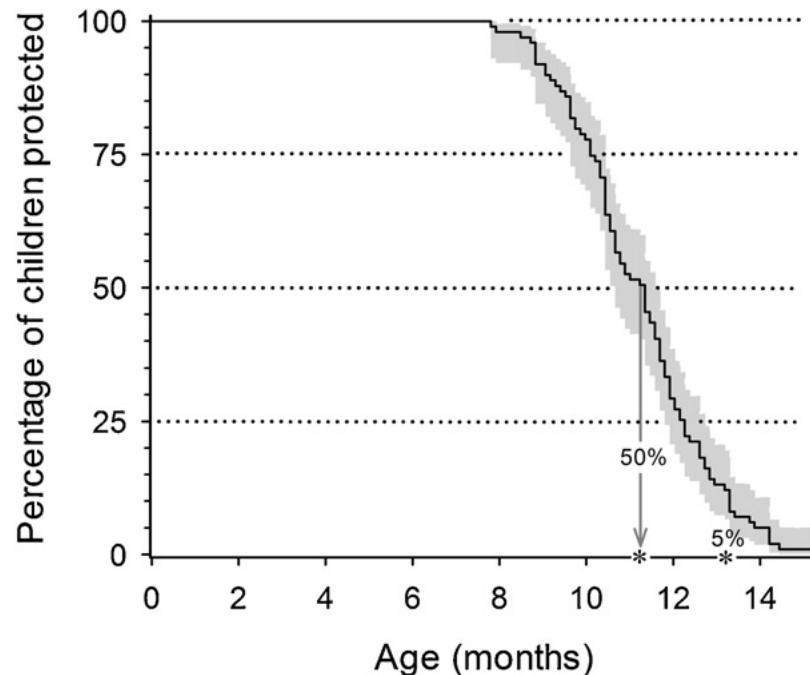
Acutely infected (red circles)

Non-infected (blue circles)

Optimal age for pediatric single-dose UMV

Waning of maternally acquired anti-HAV antibodies

N= 99 infants aged 7 months, Nicaragua, **1999** (cord blood GMC: 8,392 mIU/mL)



Proportion of children with maternally acquired anti-HAV antibody concentration above 10 mIU/ml (gray area: 95% CI)

Prediction: 50% and **95% of Nicaraguan children will have lost passive immunity by the age of 11.1 (95% CI: 10.7–11.5) and 13.2 (13.1–13.6) months.**

[Brinkhof MWG et al. Vaccine 2013; 31: 1490–5]

10 year persistence of hepatitis A vaccine induced seropositivity in infants and young children ... by **maternal antibody status**

Anti-HAV levels after 2 doses (age 6 & 12 months) of hepatitis A vaccine in Alaska infants, by maternal HAV status and follow-up period

Maternal Anti-HAV status	1 Month after Dose 2		3 Years of Age		5 Years of Age		7 Years Of Age		10 Years Of Age	
	N	GMC	N	GMC	N.	GMC	N.	GMC	N.	GMC
Negative	40	1,177	38	214	35	103	33	63	31	51
Pos. Natural	17	300	19	72	18	51	15	37	9.	25
Pos. Vaccine	16	1,523	17	194	15.	84	16	57	13.	33

- **Seropositivity persisted** for 10 years between 90% and 100%, regardless of the original presence of maternal antibodies, but **lower antibody levels**
- **Vaccine-induced maternal anti-HAV** antibodies have **no influence**

[Sharapov UM et al Hepatology. 2012; 56: 516–22].

Argentina 2005 - 2011: more evidence re single-dose

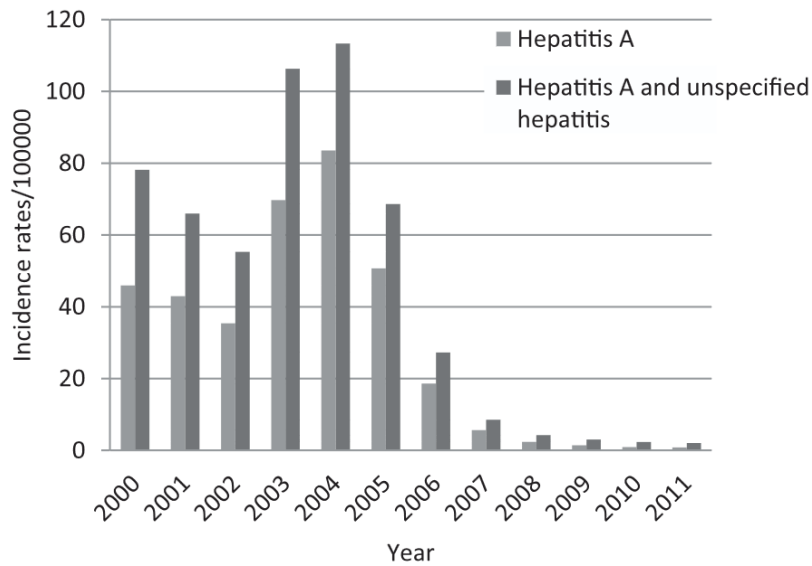
First long-term Immunogenicity follow-ups of 1 or 2 doses of hepatitis A vaccine

Persistence of immunity from 1 year of age after one or two doses of hepatitis A vaccine in Argentinian toddlers (June 2007 – Dec 2010):

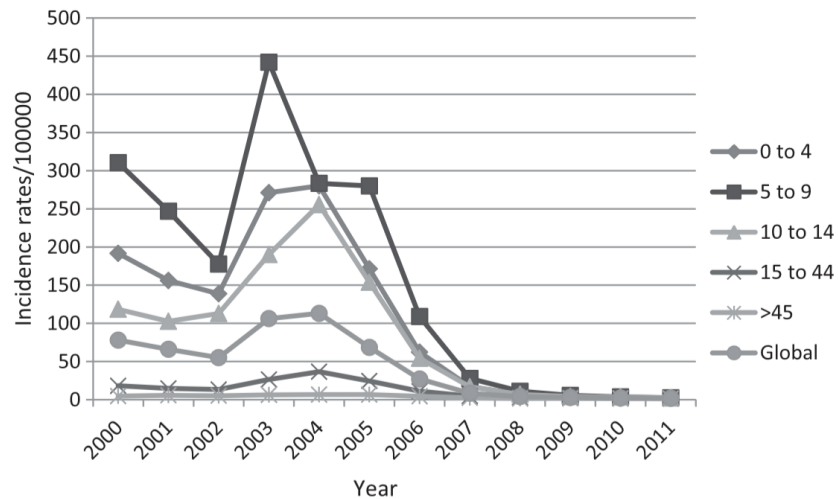
Study Groups	Anti-HAV antibody response	Follow-up period	
		1 year	3 Years
1 Dose N= 365	Seroprotection (%)	98.6%	99.7%
	GMC (mIU/mL)	209.7	170.2
2 Doses N= 94	Seroprotection (%)	99.1	100%
	GMC (mIU/mL)	1,434	872.9

Seroprotection : ≥ 10 mIU/mL

[Espul C et al. Hepat Med Evidence Res 2012; 4: 53–60]

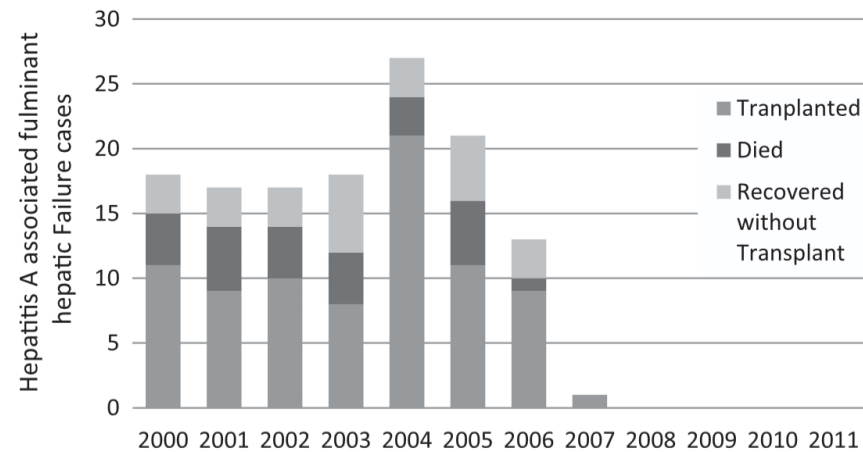


National hepatitis A incidence rates (per 100,000 inhabitants)



Yearly hepatitis A and unspecific hepatitis incidence rates by age group (per 100,000)

Impact of the 1-dose immunization strategy against hepatitis A in Argentina on disease burden 2005 ---> 2011



Hepatitis A associated yearly pediatric fulminant hepatic failure and liver transplantation cases

[Vizzotti C et al. Pediatr Infect Dis J 2014; 33: 84–88]

WHO 2012 position re single-dose vaccine schedule

In **2012** still only **Argentina** used nation-wide **1 dose-UMV** (+ China with live-att. vaccines) + **Eight further countries** had (since 1999) implemented nation-wide **2 dose-UMVs**

WHO recommends that vaccination against HAV be integrated into the national immunization schedule for children aged ≥ 1 year
[using the licensed 2-dose schedule]

... if indicated on the basis of incidence of acute hepatitis A,
... if change in the endemicity from high to intermediate,
... and with consideration of cost-effectiveness.

Regarding **single-dose** hepatitis A vaccination **WHO suggested in 2012:**

*“National immunization programmes **may consider** inclusion of **single-dose** inactivated hepatitis A vaccines in immunization schedules.”*

Further single-dose data emerging 2012 – 2022

Longterm follow-ups, projections & cost-effectiveness studies

Single-dose programs in **Argentina** and **Brazil** lowered, with >95% coverage **national morbidities** within 2-3 years **by 88%** and **86%** [Vizzotti 2014, Souto 2019]

Several studies published on single-dose longterm **8-12 years** immune protection for **Panama** and **Argentina**, with model predictions of up to **30 years** [Juliao 2021, Ureña 2016, Espul 2020]

Only few modeling studies so far using well-founded assumptions (derived from real data) and including potential impact of immune memory, as e.g. for **Mexico**:

- Routine vaccination of toddlers against HAV would be **cost-effective** in Mexico using a single-dose strategy [Curran 2016]

SAGE Immunization Working Group on hepatitis A vaccines – March 2022

Summarizing **single-dose findings** published **2012 – 2021**:

- UMGs ---> hepatitis A incidence decreased in all age groups by 59% to 99%
- Single dose schedules were more cost-effective than 2 dose schedules
- No difference versus two dose schedules re clinical case incidence and sero-protection.
- Booster studies of individuals receiving one dose live-attenuated vaccine showed up to 17 years later a strong anamnestic immune memory response, even in HAV seronegative individuals
- The impact of single dose programs (inact. & live vacc.) is marked on HAV epidemiology.
- Major gap in evidence was the lack of direct comparisons of single vs two dose inactivated HAV vaccine regimens over the long-term (> 7 - 10 years)

FACIT: Increasing evidence of the impact of single infant vaccine programs to reduce burden of HAV and confer long-lasting immunity

WHO 2022 recommendations re double/single-dose schedule

WHO recommends that **vaccination** against hepatitis A virus **be introduced into national immunization** schedules for individuals **aged ≥ 12 months**, if indicated on the basis of: (i) an **increasing trend over time of acute hepatitis A disease**, including severe disease, among older children, adolescents or adults; (ii) **changes in the endemicity from high to intermediate**; and (iii) considerations of **cost-effectiveness**.

- *“For **children**, inactivated hepatitis A vaccines **can be given as a single- or 2-dose schedule** ... starting from age ≥ 12 months”*
- *“Data on vaccine effectiveness ... (etc) ... indicate that an **off-label, single-dose schedule is equivalent to the two-dose schedule in children**, in addition to being less costly and easier to implement”*
- *“For **adults aged >40 years**, vaccination with inactivated vaccines using the 2-dose schedule is preferred since there is **insufficient evidence** on the immunogenicity and long-term protection from a single dose in this age group”.*
- *“In **outbreak situations**, single-dose hepatitis A vaccination is recommended”*

Interesting new single-dose data since 2021/22.

Antibody persistence:

- Espul **2026**/Argentina, 1-dose, age 1-2 y, 15 yrs FU--> SP: 100% + modelling: 40 yrs seroprotection
- Scobie **2024**/Alaska, 2-dose, age 12-15 months, 23 yrs FU--> SP: 86% & maternal antibodies still a negative factor

Immune memory:

- De Brito **2023**/Brazil, 1-dose, age 1y, 7-8 yrs FU--> SP: 64% & CMI response in 34% of seroneg. kids
- Febriani **2026**/Canada, 1-dose, age 12/19 months, 3 yrs FU--> SP: 40%/77%--> challenge: 96-98% booster response

Efficacy/effectiveness/impact:

- Im **2020**/S.Korea, 1-dose, young adults (army), 4 yrs FU--> 78% effectiveness re incidence
- Sun **2020**/China, 1-dose live, age 18-22 months, 8-9 yrs FU--> SP: 75%
- Lopatukhina **2024**/Tyva Republic (Russia), age 3-18 yrs, 1-dose UMV, in 3 yrs high incidence --> zero

‘Natural booster’ ... an unsolved, controversial issue

Issue relevant for the single-dose strategy, as **sometimes it is claimed that single-dose strategy might only work because of the natural boosting phenomenon**, an effect which seems to exist regarding live-attenuated vaccines

WHO 2022 SAGE: ***“It was not possible to estimate to what extent observed effectiveness and immunogenicity were influenced by the boosting effect of natural infection”***

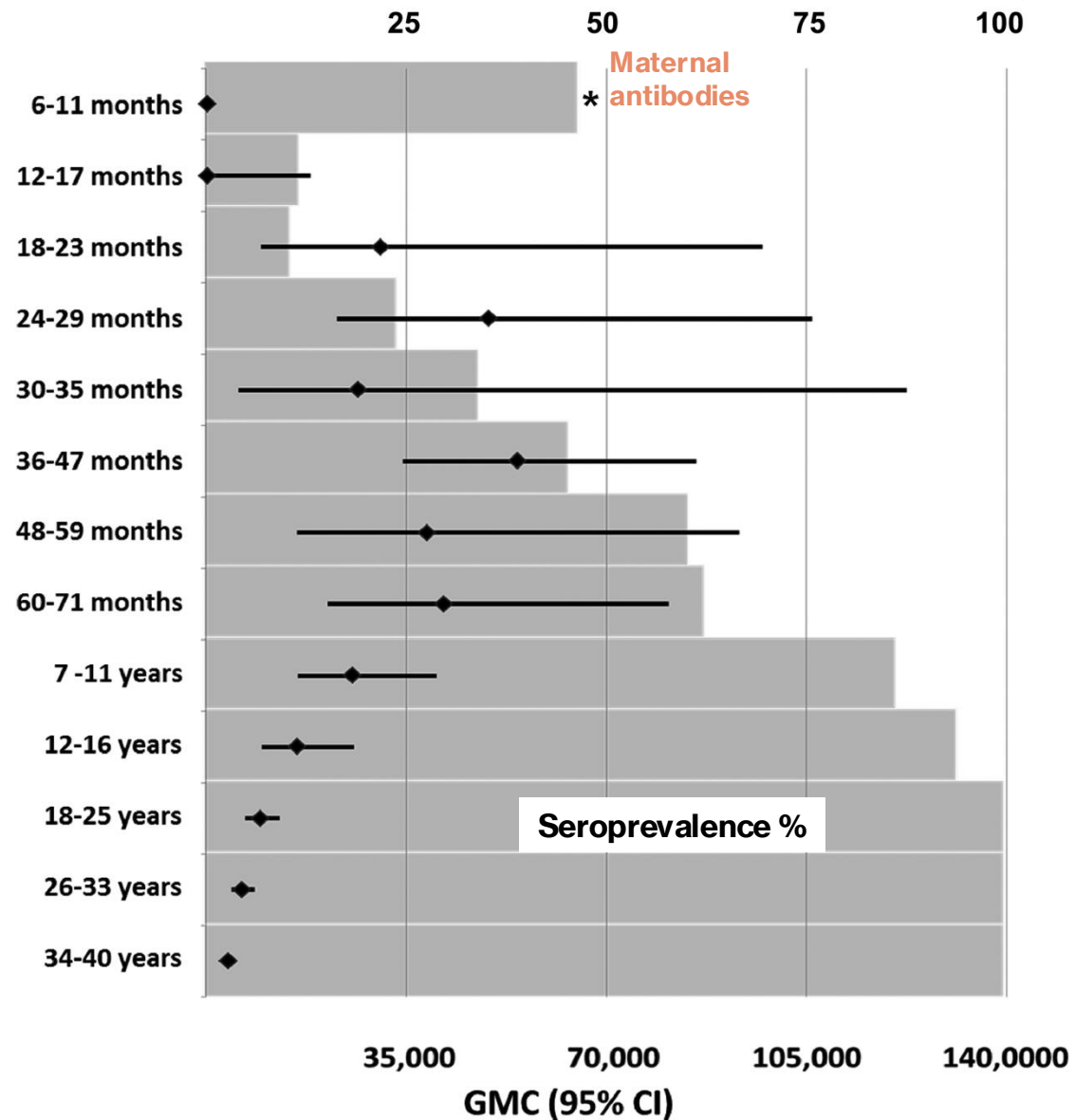
The experience from nearly 20 years clinical research on hepatitis A (vaccines, disease, epidemiology) in Europe and Nicaragua let me to conclude:

No hard & consistent evidence for natural booster effect in vaccinees having received non-live HAV vaccine !

[Herzog C et al. Human Vaccines Immunother 2021; 17(5): 1496-1519]

No boosting of natural hepatitis A immunity

[Mayorga O et al. PLoSOne 2014; 9(2): e87643]



Age-specific seroprevalence and GMCs of anti-HAV antibodies in 2003 cross-sectional population sample in Leon, Nicaragua

N= 496 subjects aged 6 months to 40 years (age group sizes: n=30-55):

- 100% seroprevalence >16 years of age
- Max. GMCs around age 3-5 years (approx. 50,000 mIU/mL)
- With age continuous decline of GMCs until age 34-40 years: 3,660 mIU/mL

FACIT: Natural immunity cannot be boosted by HAV encounters, even in hyperendemic setting

Arguments against the existence of natural boosting following vaccination with non-life vaccines

- The **1st dose** of inactivated vaccine elicits in healthy subjects a **cellular response similar to the CMI activation** observed in patients with **acute infection**.
[Melgaço JG et al. Vaccine. 2015;33: 3813–20]
- There is **no boosting of natural immunity in hepatitis A hyperendemic communities**, as shown in age-specific seroprevalence study in Nicaragua
[Mayorga O et al. PLoSOne 2014;9(2): e87643]
- Established **natural hepatitis A immunity cannot be boosted with vaccine**
[Mayorga O et al. J Infect Dis 2016; 214: 1498-506]
[Berna Biotech, unpublished 'data on file']
- **No evidence** that **natural boosting** contributed to the persistence of seroprotection **during 10 year** follow-up of **children in Alaska**
[Sharapov UM et al Hepatology. 2012; 56: 516–22].
- Many in the literature reported '**natural boosters**' are **antibody rises of barely 50-100%** and are most likely due to the fact that the consecutive sera were not tested in parallel.
[at least **two eminent researches have 'confessed' this to me**]
- The few well-documented cases (some IgM pos.) are rather related to primary vaccine failure.

**A big Thank You to all the participants and the study staff
who made all these many studies possible in Nicaragua !**



Orlando Mayorga Perez at work in 1995/96



References of quoted publications (I)

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- Mayorga O** et al. Efficacy of Virosome Hepatitis A Vaccine in Young Children in Nicaragua/Randomized Placebo-Controlled Trial. J Infect Dis **2003**; 188:671-7.
- Mayorga O** et al. Decreasing risk of hepatitis A infection in Leon, Nicaragua: evidence from cross-sectional and longitudinal seroepidemiology studies. PLoS One **2014**; 9(2): e87643.
- Mayorga O** et al. Single-dose hepatitis A immunization: 7.5-year observational pilot study in Nicaraguan children to assess protective effectiveness and humoral immune memory response. J Infect Dis **2016**; 214: 1498-506
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Wkly Epid Rec **2012**; 87(28-29): 261-76.
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Wkly Epid Rec **2022**; 97(40): 493–512.

Back-up slides

Hepatitis A seroprevalence in Leon, Nicaragua, 2003 (n=496)

Naturally acquired antibodies by age

Age	N	GMT	min	max
6-11 months	14/30	78	10	653
12-17 months	4/32	133	26	13'700
18-23 months	5/30	1'971	11	50'900
24-29 months	7/30	49'220	19'900	245'000
30-35 months	12/35	26'385	23	233'000
36-47 months	15/34	54'281	13'200	244'800
48-59 months	21/35	38'506	21	339'000
60-71 months	22/35	41'376	503	448'000
7-11 years	31/35	25'393	2'900	175'400
12-16 years	32/35	15'812	260	450'000
18-25 years	55/55	9'303	57	116'800
26-33 years	55/55	6'041	126	64'600
34-40 years	55/55	3'669	92	47'100

Non-infected, low-responding children with ≥ 1 antibody concentration of <10 mIU/mL during follow-up

Subject ID	Sex	Age yrs	2005	2006	2007	2008	2009	2010	2012 BB	2012 AB
			----- Anti-HAV Antibody Concentration (mIU/mL) -----							
074	F	3.0	28	<10	<10	<10	<10	<10	<10	561
201	M	6.0	32	<10	15	17	16	12	<10	450
224	M	5.8	66	<10	30	41	52	51	38	1825
236	F	5.9	27	<10	14	26	22	17	<10	1509
237*	F	5.6	17	<10	<10	<10	<10	<10	7106	6784
255	M	6.8	35	<10	<10	<10	<10	<10	<10	927
263	M	7.3	18	<10	<10	<10	<10	<10	lost	lost
295	M	12.9	29	<10	<10	<10	<10	ND	13	1638

BB: before booster; **AB:** after booster; **ND:** not done; * **#237:** breakthrough infection

Community control group (municipality of Leon) to document circulation of HAV in the city

All jaundiced children/adolescents presenting at any health centre were offered a free hepatitis A/B/C screening test:

Anti-HAV IgM screening (to be confirmed by HAVAB M)
Liver enzyme levels & serum bilirubin

Community
control group:

N=557 jaundiced subjects

from May 2006 – March 2010

N=316 (57%) Hep A positive

Age	Hep A pos (%)	Jaundice cases	→ % Hep A positive
1-5 yrs	94 (30%)	162 (29%)	→ 58%
6-10 yrs	176 (56%)	243 (44%)	→ 72%
11-15 yrs	38 (12%)	66 (12%)	→ 58%
16-20 yrs	8 (2%)	24 (4%)	→ 33%
>20 yrs	0 (0%)	62 (11%)	→ 0%
Total	316 (100%)	557 (100%)	→ 57%

Gaps and future research topics re single-dose hepatitis A vaccine

- Immune memory after single-dose live-attenuated vaccine
- Immune memory of single-dose inactivated vaccine beyond 20 year follow-ups
- Fractional single doses (intra/transdermal & needle-free) versus full single-dose (intramuscular) for pediatric UMV ... in order to overcome the 'relative' hepatitis A vaccine shortage
- Long-term (>30 years) surveillance of single-dose UMV impact on epidemiology
- Test for infection- versus vaccine-induced anti-HAV antibodies to allow meaningful serological monitoring of hepatitis A epidemiology