Session 8: Overview of Evidence including GRADE Tables

Hepatitis A Working Group
Prof. D. Shouval
On behalf of SAGE HepA Working Group

Countries Using HepA Vaccine in National Immunization Schedule, 2010

No *(182 countries or 94%)*

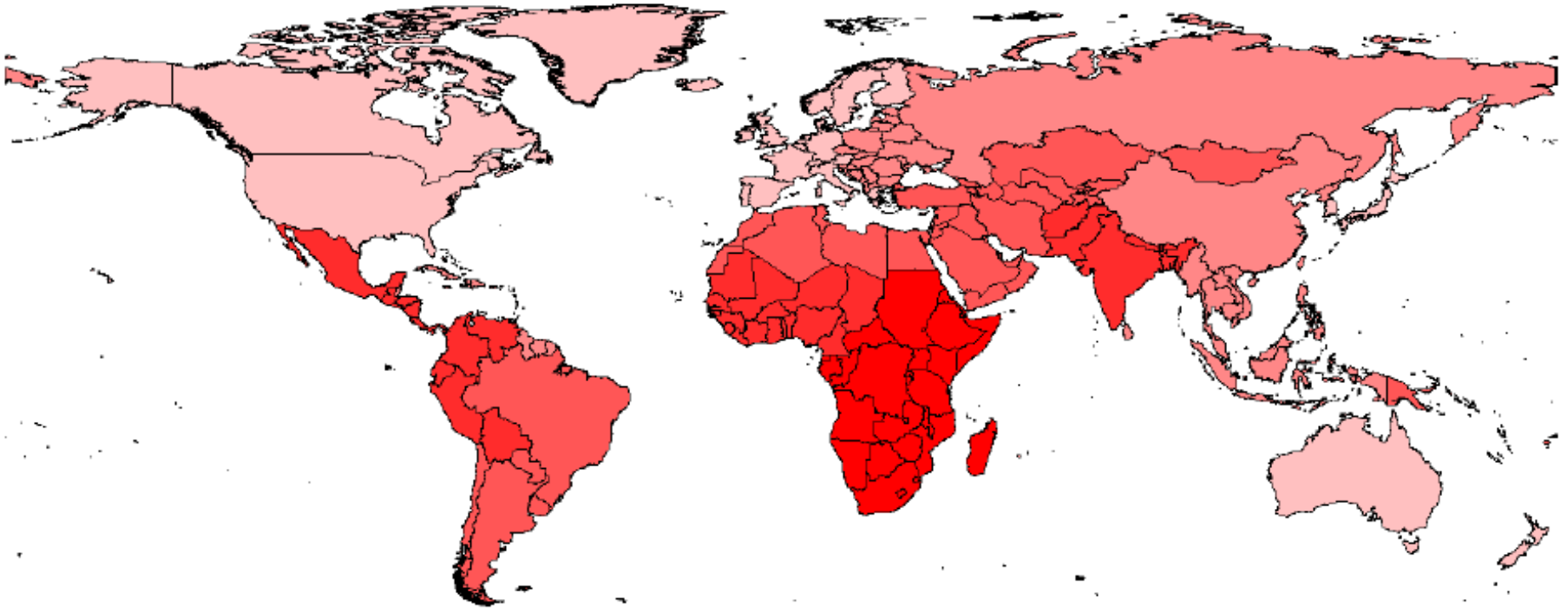
Yes (11 countries or 6% -Argentina, Bahrain, China, Greece, Israel, and Kazakhstan, Panama, Qatar, Saudi Arabia, Uruguay, USA

Source: WHO/IVB database, 193 WHO Member States.
27 October 2011

Estimated burden of HAV-related disease, 1990 and 2005

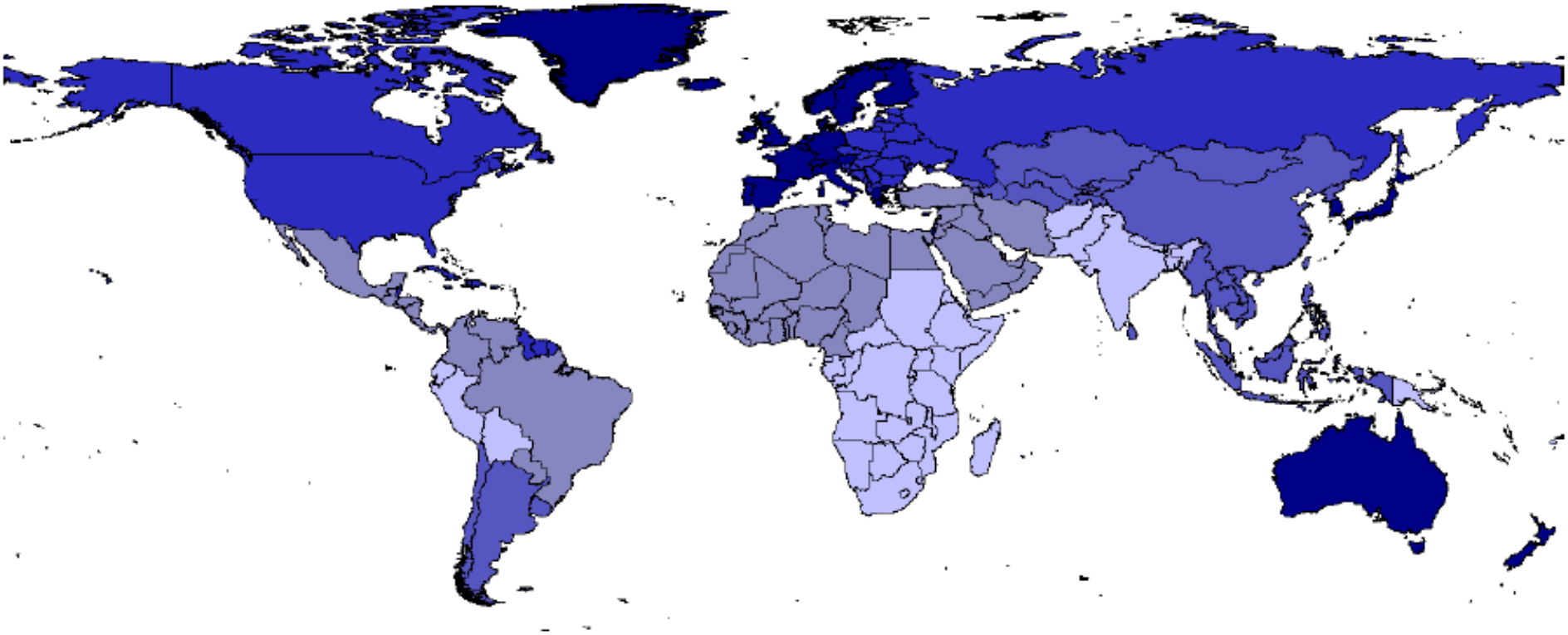
- Annual incidence declined from 2.1%/year in 1990 to 1.9%/year in 2005
- HAV infected 115 million people in 1990 and 119 million in 2005
- Resulted in 24.7M symptomatic illnesses and 29,000 deaths in 1990 and 31M symptomatic illnesses and 34,000 deaths in 2005
- Burden is increasing as incidence declines

Figure 9. Estimated child immunity rate. Darker shades indicate a higher exposure rate.



*Anti-HAV age 10-14: high > 90%, high-medium 75-89%, medium 60-74%, low-medium 40-59%, low <20%

Figure 10. Estimated adult susceptibility rate. Darker shades indicate a greater proportion of at-risk adults.



*Anti-HAV age 35-44: high >40%, medium 20-39%, low-medium 10-19%, low 1-9%, very low =0%

Developments since 2000 Position Paper

- Changing epidemiology: shift from high to intermediate endemicity
- Evidence for HepA public health benefit
- Strengthened immunization systems
- Evidence for post-exposure efficacy, long-term protection, and population impact
- Increased supply of HepA with price reduction
- Mandate for comprehensive hepatitis prevention and control (WHA63.18)
- Publication of "The immunological basis for immunization series: module 18: hepatitis A" in 2011

Process of Data Collection on Single Dose use of inactivated hepatitis A vaccine

- Data from previously conducted systematic reviews and meta-analysis (reference scan for studies on 1-dose schedules with regard to long-term protective effects)
- Additional information on flexible dose issues, i.e. single dose HepA and long-term protection
    1. Correspondence to vaccine manufacturer associations (IFPMA and DCVMN)
    2. Correspondence to Argentinean MOH (only MS with universal 1-dose HepA)
    3. Contacts suggested by replies from #1

Abbreviations: FPMA: Int Federation of Pharmaceutical Manufacturers Association

DCVMN Developing Countries Vaccine Manufacturers Network

Responses to requests for data

Letter to	Reply	Comment
IFMPA (reply no 1)	Sent confidential data, which were not included in grading (SPR after 3 years post-primary dose, Argentina).	Not included for GRADING since confidentiality and longer-term data available from Argentina.
IFMPA (reply no 2)	Poster on dynamic transmission of hep A including one dose scenario	Not included for GRADING since modelling data only and assumption on waning rate questionable.
IFMPA (reply no 3)	- Did not send data on single dose, since indicated that vaccine licensed as 2-dose regimen only; indicated that there are no long-term efficacy data following single dose. -Forwarded reference to published manuscripts (Werzberger et al. 1992, Nalind 1995, Hornick et al 2001, Averhoff et al 2001). - It was commented that only a very small number of persons who received one dose during a study might not have been exposed during natural hepatitis A in the meanwhile. - Primary author of a study indicated that there are a number of individuals who were not exposed to hepatitis A after single dose since hepatitis A infection dropped after the study. Indicated the possibility of obtaining serology from these individuals.	
IFMPA (reply no 4)	-Forwarded reference to published manuscripts (Beck et al. 2003, Hatz et al. 2011, Mayorga Perez et al. 2003). - Mentioned that study protocols of Nicaraguan cohort included two dose immunization for all subjects and that it was decided to discontinue study because the doses used are not the standard doses and that it was no longer relevant to prolong this study and every volunteer received a booster dose. - Provided link to public available presentation with data and highlighted the potential of taking blood before revaccination which would provide a 7 year interval post-primary dose.	Published references and public available meeting presentation from independent researcher included for GRADING:
DCVMN (reply no 5)	- Indicated no data available on single dose.	
Ministry of Health, Argentina	- Preliminary data were sent in confidentiality (but agreed to be used for SAGE) and used for grading (4-5 year seroprotection in Argentinean children). - Forwarded reference to published manuscript (Vizzotti et al. 2008)	Included for GRADING.

Results

- 16 data sources identified reporting evidence of 1-dose administration of inactivated HepA with follow-up times >12 months after immunization
- Those with longest follow-up (4-10.6 years) used for grading the evidence (8 studies)
- Outcomes considered: HAV incidence, fulminant hepatitis incidence, sero-protection rate (SPR) and geometric mean titre (GMT)

GRADE TABLE 1

Authors: Wiersma S, Ott J

Does single dose of inactivated hepatitis A vaccine provide long-term protection against HAV-related disease and fulminant hepatitis A?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 observational	2
	Factors decreasing Confidence	Limitation in study design	Serious[1]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious[2]	0
		Publication bias	None serious	0
	Factors increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is very limited.**
	Conclusion			**Two to three years after a single dose inactivated hepatitis A vaccine program there is evidence for a decrease in both, hepatitis A incidence[3] and fulminant hepatitis A[4] among hepatitis A cases.**

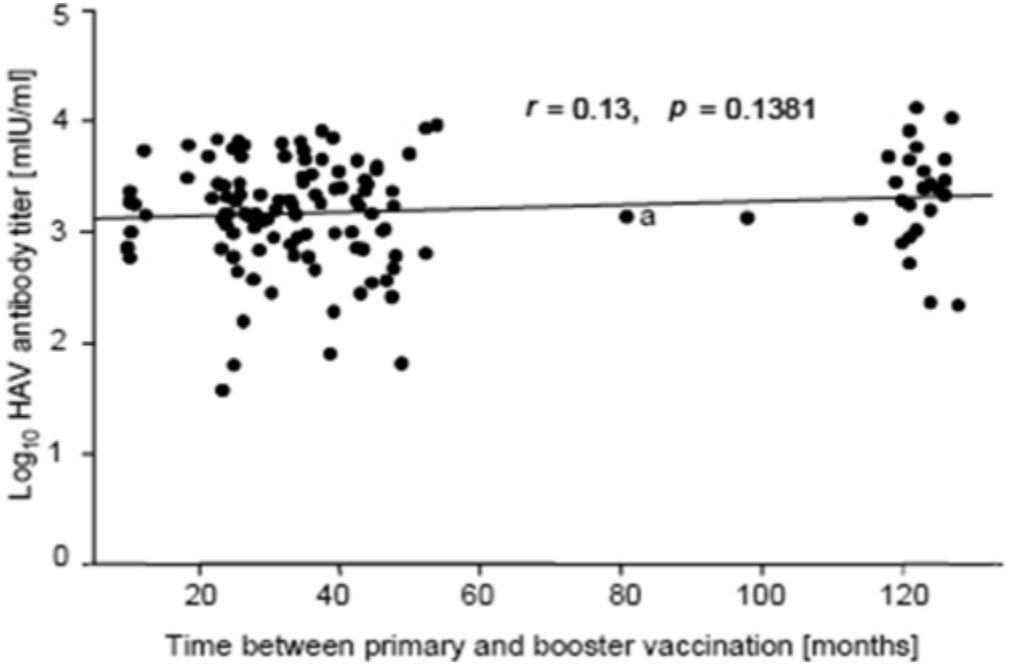
GRADE TABLE 2

Authors: Wiersma S, Ott J

Is there evidence for long-term sero-protection achieved by single dose vaccination with inactivated hepatitis A vaccine, as measured by GMT of anti-HAV and seroprotection rate (SPR)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		6 observational[1]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Non serious[2]	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on sero-protection is limited.**
	Conclusion			**There is evidence for 10.6 year sero-protection achieved by single dose vaccination of inactivated hepatitis A vaccines (GMT of 24 (95% CI: 14-41))[3], SPRs ranging from 53.8-95.1%, depending on follow-up time.**

HAV-AB after booster dose of inactivated hepA vaccine, as a function of time between first and booster dose



Hatz et al. 2011

TABLE 2. Geometric mean concentrations of anti-HAV antibodies by booster interval[a]

Booster interval (mo)	Subjects	Visit	No. of subjects	GMC (mIU/ml)	95% CIs	Fold increase
9–29	All	Prebooster	45	16	10, 24	NA
		Postbooster	45	1,397	1,009, 1,934	90
	Age <50 yr	Prebooster	35	19	12, 29	NA
		Postbooster	35	1,528	1,090, 2,142	82
	Age ≥50 yr	Prebooster	10	9	3, 23	NA
		Postbooster	10	1,022	404, 25,887	120
30–41	All	Prebooster	32	23	14, 37	NA
		Postbooster	32	1,687	1,147, 2,481	75
	Age <50 yr	Prebooster	26	26	16, 44	NA
		Postbooster	26	1,825	1,233, 2,701	70
	Age ≥50 yr	Prebooster	6	12	3, 44	NA
		Postbooster	6	1,199	362, 3,978	99
42–54	All	Prebooster	27	11	6, 18	NA
		Postbooster	27	1,262	829, 1,920	120
	Age <50 yr	Prebooster	23	10	6, 17	NA
		Postbooster	23	1,185	781, 1,798	123
	Age ≥50 yr	Prebooster	4	18	4, 86	NA
		Postbooster	4	1,812	417, 7,867	103
98–128	All	Prebooster	26	24	14, 41	NA
		Postbooster	26	2,115	1,379, 3,245	89
	Age <50 yr	Prebooster	16	34	17, 65	NA
		Postbooster	16	2,117	1,284, 3,489	63
	Age ≥50 yr	Prebooster	10	14	5, 37	NA
		Postbooster	10	2,113	835, 5,349	155
9–128 (all subjects)	All	Prebooster	130	17	13, 22	NA
		Postbooster	130	1,557	1,285, 1,886	91
	Age <50 yr	Prebooster	100	19	15, 25	NA
		Postbooster	100	1,590	1,301, 1,943	83
	Age ≥50 yr	Prebooster	30	12	7, 20	NA
		Postbooster	30	1,451	863, 2,439	123

[a] Geometric mean concentrations (GMCs), including 95% confidence intervals (CIs), were calculated from logarithmically transformed titer values. NA, not applicable.

Hatz et al. 2011

References

Beck BR, Hatz C, Brönnimann R, Herzog C. Successful booster antibody response up to 54 months after single primary vaccination with virosome-formulated, aluminum-free hepatitis A vaccine. Clinical Infectious Diseases 2003; 37: 126-8.

Cervio G, Trentadue J, D`Agostino D et al. Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program. Hepatic Medicine: Evidence and Research 2011; 3:99-106.

Hatz C, Ploeg van der R, Beck BR, Frösner G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis A vaccine delayed up to 11 years. Clinical and vaccine immunology 2011, 18: 885-7.

Herzog C. Epaxal ®- Alluminium free. Presentation and personal communication at the "SAGE hepatitis A working groupd meeting". 2010, Buenos Aires, Argentina.

Iwarson S, Lindh M, Widerström L. Excellent booster response 4 to 8 years after a single primary dose of an inactivated hepatitis A vaccine. J travel Med 2004; 11: 120-1.

Sabanin IuV, Rikhter W, Kuzin SN. [Assessment of effectiveness and immunogenicity of hepatitis A vaccination in servicemen of Internal Forces of Ministry of Internal Affairs of Russia]. [Article in Russian]. Zh Mikrobiol Epidmeiol Immunobiol 2010;1:35-9

Vacchino MN. Incidence of hepatitis A in Argentina after vaccination. J Viral Hep 2008; 15 (suppl 2); 47-50.

Vizzotti C. Seroprevalence of hepatitis A antibodies four years after a single dose vaccination strategy in Argentinean children. Ministry of Health Argentina. Personal communication, January 2012.