Hepatitis A Vaccine versus Immune Globulin for Postexposure Prophylaxis

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Immune Globulin

- For over 50 years, IG was the only product for postexposure prophylaxis.
- Shown to be >85% efficacious.
- Several problems:
  - Duration of protection limited
  - Interference with live attenuated vaccines
  - Not globally available / supply limitations
  - Acceptability (painful injections and perceived safety concerns)
  - Evidence that does not control outbreaks
  - Expensive

Hepatitis A Vaccines – accumulating evidence

- Long incubation period of virus (15-50 days)
- Rapid immune response
- Phase III trial – no cases starting in 3rd week postvaccination
- Animal model challenge studies
- Open label trial (versus untreated control) in Italy indicated efficacy of ~80% against infection

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.
- In absence of studies directly comparing vaccine with immune globulin, Advisory Committee on Immunization Practices continues to recommend immune globulin for postexposure prophylaxis in the US.

Almaty, Kazakhstan: ~1.2 million residents

Hepatitis A occurs year round, but outbreaks involving large numbers of children occur annually in the fall and winter.

>95% of cases are hospitalized.

Primary Objective

To compare 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 Participants

- Household or daycare contacts of index cases
- 2 to 40 years of age
- Exposed to index case within 2 weeks after index case symptom onset
- No history of hepatitis A or receipt of hepatitis A vaccine or IG (within past 6 months)
- No medical diagnosis of liver disease
- No contraindications to receipt of vaccine or IG

Interventions

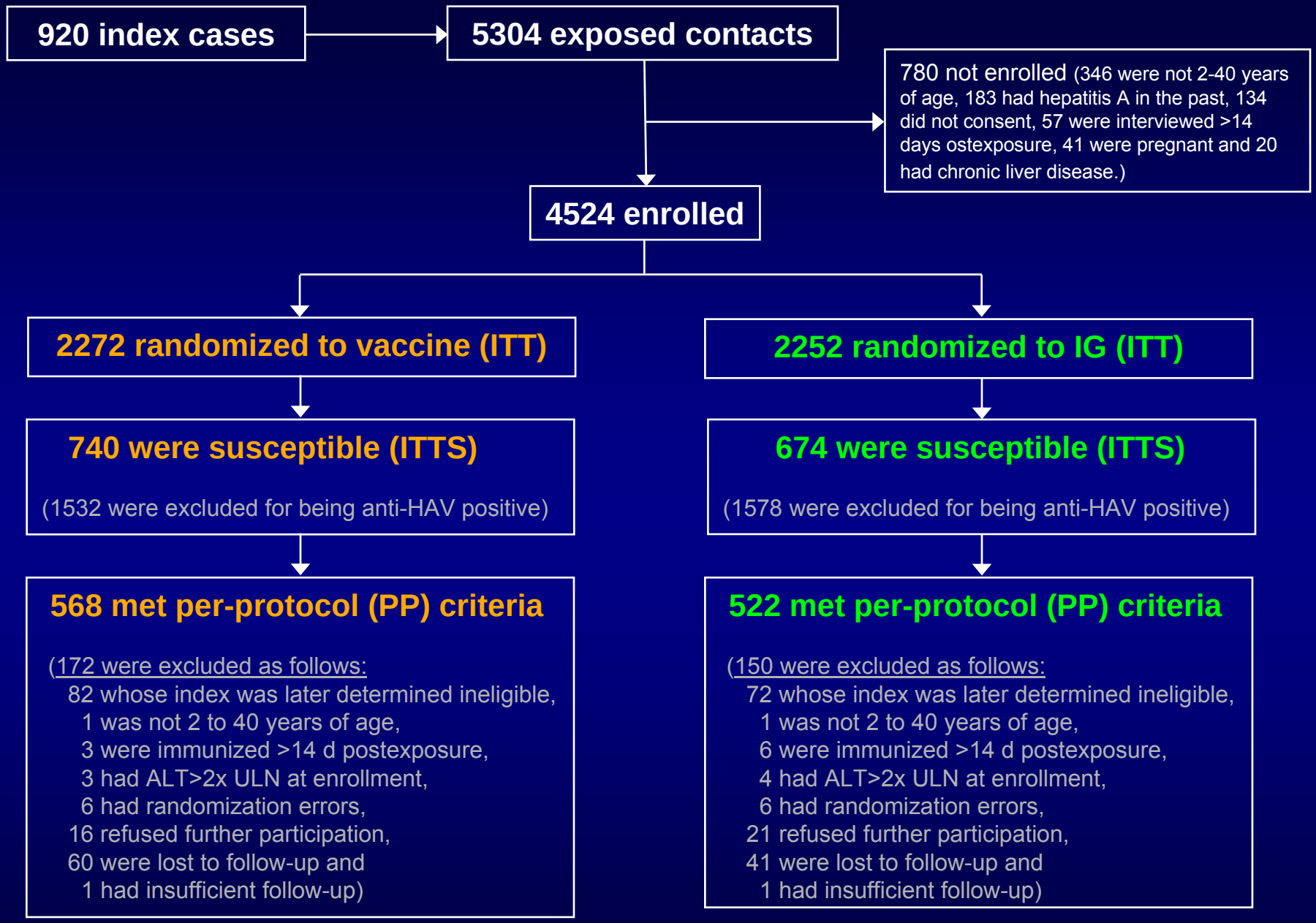
- Hepatitis A vaccine (VAQTA®, Merck & Co., Inc.) at age-appropriate licensed dose for pre-exposure protection
- Immune globulin (Massachusetts Biological Laboratories) at 0.02 mL/kg
- Both interventions administered intramuscularly in the deltoid

Study Design

- 1:1 randomization *within* households or daycare center classrooms
- Participants blinded to intervention
- Study physicians administering interventions (unblinded) were different from those conducting follow-up (blinded)
- Weekly follow-up for 8 weeks postexposure

Primary Endpoint

1. Positive for IgM anti-HAV
2. A serum ALT level at least 2x the upper limit of normal during an episode of illness with no other obvious cause;
3. jaundice; pale stool; dark urine; abdominal pain/upper right quadrant pain; nausea; vomiting; loss of appetite; malaise; or an axillary temperature of 37.5°C or higher with no other obvious cause.
4. Illness onset between 2 and 8 weeks postexposure.


920 index cases
5304 exposed contacts
780 not enrolled (346 were not 2-40 years of age, 183 had hepatitis A in the past, 134 did not consent, 57 were interviewed >14 days ostexposure, 41 were pregnant and 20 had chronic liver disease.)
4524 enrolled
2272 randomized to vaccine (ITT)
2252 randomized to IG (ITT)
740 were susceptible (ITTS)
(1532 were excluded for being anti-HAV positive)
674 were susceptible (ITTS)
(1578 were excluded for being anti-HAV positive)
568 met per-protocol (PP) criteria
(172 were excluded as follows:
82 whose index was later determined ineligible,
1 was not 2 to 40 years of age,
3 were immunized >14 d postexposure,
3 had ALT>2x ULN at enrollment,
6 had randomization errors,
16 refused further participation,
60 were lost to follow-up and
1 had insufficient follow-up)
522 met per-protocol (PP) criteria
(150 were excluded as follows:
72 whose index was later determined ineligible,
1 was not 2 to 40 years of age,
6 were immunized >14 d postexposure,
4 had ALT>2x ULN at enrollment,
6 had randomization errors,
21 refused further participation,
41 were lost to follow-up and
1 had insufficient follow-up)

Characteristics of Contacts in Per-Protocol Dataset

N=1090	Vaccine n=568		IG n=522	
	Freq	**Percent**	**Freq**	**Percent**
Sex				
Female	297	52%	289	55%
Contact Type				
Household	470	83%	437	84%
Age (years) of:				
Index Case	12 ± 9		12 ± 9	
Contact	11 ± 8		13 ± 9	
Day of immunization	10 ± 2		10 ± 2	

Characteristics of Primary Endpoints

Characteristics of cases of hepatitis A meeting the primary case definition among contacts. n=44.

Characteristic	Vaccine (n=26) Mean	Vaccine (n=26) Range	IG (n=18) Mean	IG (n=18) Range	p-value
Time of immunization postexposure	10 ± 2 days	6 - 14 days	10 ± 2 days	6 - 12 days	0.403
Time of illness onset postexposure	25 ± 4 days	17 - 33 days	24 ± 4 days	16 - 33 days	0.560
Age of case	11 ± 9 years	2 - 34 years	17 ± 12 years	5 - 40 years	0.075
Average peak ALT leval measured at time of illness	1001 ± 397 U/L	156 - 1610 U/L	725 ± 461 U/L	66 - 1500 U/L	0.040
HAV RNA+ in serum and/or stool	62%		56%		0.761
Had icteric illness	73%		61%		0.515
Had nausea, vomiting and/or abdominal pain	85%		83%		1.000

Risks of Developing Hepatitis A Among Vaccine and IG Recipients (PP)

	Risks		Relative Risk
	Vaccine (n=568)	**IG (n=522)**	
	No. (risk)	**No. (risk)**	**RR (95% CI)**
Clinical endpoints:			
Primary Any symptom plus IgM Anti-HAV+ *and* ALT≥2x ULN	**25 (4.4%)**	**17 (3.3%)**	**1.35 (0.70-2.67)**
Secondary Any symptom plus IgM Anti-HAV+ *and* ALT≥2x ULN *or* PCR+*	29 (5.1%)	19 (3.6%)	1.40 (0.76-2.64)
Icteric illness plus IgM Anti-HAV+ *and* ALT≥2x ULN *or* PCR+	18 (3.2%)	12 (2.3%)	1.38 (0.63-3.14)
Subclinical endpoints: Asymptomatic plus IgM Anti-HAV+ *and* ALT≥2x ULN *or* PCR+	20 (3.5%)	16 (3.1%)	1.15 (0.57-2.37)
Clinical + Subclinical	49 (8.6%)	35 (6.7%)	1.29 (0.82-2.05)

* Includes all primary endpoints and six clinical cases which did not meet the primary endpoint criteria.

PP = per-protocol; RR = relative risk; CI = confidence interval

*Implications for Vaccine Efficacy Based on Assumed IG Efficacy, Observed IG Failure Rate and Calculated RR Upper Bound**

Assumed IGE	SAR	VE at point estimate of RR	VE at 95% CI UB of RR
100%	∞	100%	100%
95%	65%	93%	88%
90%	**33%**	**86%**	**76%**
85%	22%	80%	64%
80%	16%	73%	52%

*based on per-protocol analysis of the primary study endpoint

Summary of Trial Results

- Efficacy of hepatitis A vaccine postexposure is quite high and similar to that of IG.
- Risk of hepatitis A for vaccine recipients was never >1.5% the risk for IG recipients.
- Some evidence that IG may attenuate clinical illness.
- No evidence that vaccine given in the second week after exposure resulted in lower clinical protection.
- Household contacts experienced the highest transmission rates.

Updated ACIP Recommendations
(abbreviated)

Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered one dose of single antigen *hepatitis A vaccine or IG* (0.02 mL/kg) as soon as possible.

Reference: MMWR 2007; 56(41): 1080-1084

Updated ACIP Recommendations (abbreviated)

Information about the relative efficacy of vaccine compared to IG postexposure is limited, and no data are available in persons aged >40 years or those with underlying medical conditions.

Therefore, decisions to use vaccine or IG should take into account patient characteristics associated with more severe manifestations of hepatitis A, including older age and chronic liver disease.

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.

Other Considerations

- Hepatitis A vaccine likely to be the only product available in many countries.
- Hepatitis A vaccine appears effective in controlling outbreaks.
- Hepatitis A vaccine offers long-term protection and will not interfere with other childhood vaccines.
- Older adults in many countries are likely already immune.
- Usefulness likely limited to areas with good surveillance/testing of cases/medical infrastructure to provide prophylaxis.

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