Vaccine Experiences and Lessons from the Past

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Inactivated Influenza Vaccines for Influenza Pandemics and Pandemic Threats of the Past

1957	Influenza A (H2N2), “Asian”
1968	Influenza A (H3N2), “Hong Kong”
1976	Influenza A (H1N1), “Swine”
1978	Influenza A (H1N1), “Russian”

Relationship of CCA and µg HA for Influenza A/NJ (H1N1) and A/USSR (H1N1) Inactivated Vaccines

CCA	µg HA A/NJ	µg HA A/USSR
100-200	13-24	10-19
200-400	29-58	43-45
400-600	-	61
600-800	61-119	59

Reactogenicity Summary

Asian vaccine (all whole virus)

- Increasing dose causes increasing reactions with "severe" reactions in up to 15%

Hong Kong vaccine (purified whole)

- Low reactogenicity but increasing dose causes increasing reactions

Comparative Reactogenicity after Conventional and Zonal Centrifuged WV Vaccine

(Peck, JAMA, 206:2277, 1968)

Vaccine	No.	Local ≥ 3 x 4 cm	Fever	Malaise/Chills
Conventional	454	29%	2.2%	18%
Zonal	777	4.9%	0.9%	5.6%

Vaccine was 300 CCA A/H2N2 and 300 CCA B/Md given SC

Immunogenicity Summary for Asian (A/H2N2) and Hong Kong (A/H3N2) Vaccines

- Increasing dose increases antibody responses
- Two doses ≥ 4 weeks apart increased antibody responses (Asian >HK; younger > older)
- Priming (based on response to one dose) was the major determinant of increased responses

Dose Response for Asian (A/H2N2) Inactivated Vaccine among Young Adults (Hilleman, JAMA, 166:1134, 1958)

	GMT[1] After	
Dose (CCA)	1 Dose	2 Doses
125	8	10
250	12	20
500	27	38
750	18	84
1000	30	47

[1]HAI

Serum HAI Responses to One and Two 200 CCA Doses of Inactivated Asian (A/H2N2) Vaccine

(Bayne, AJMS, Sept, 1958)

Group	N	% Ab Rise
1 dose	29	55
2 doses 2 weeks apart	21	57
2 doses 4 weeks apart	12	92

Serum HAI Responses to One 200 CCA Dose of Inactivated Asian (A/H2N2) Vaccine According to Age

(Bayne, AJMS, Sept, 1958)

Age	N	No. ≥ 32
17-20	5	1
21-30	16	0
31-40	8	0
41-50	26	7
51-60	20	3
61-70	12	2

≥40 years = born before 1918

Summary Comments on Asian (H2N2) Vaccine Experience by Gordon Meiklejohn (ARRD, 83:175, 1961)

- HAI antibody increased as dose increased (25-400 CCA)
- 100 CCA with IFA is comparable to 400 CCA aqueous
- Two doses with second $\geq$4 weeks later appeared optimal (with and without adjuvant)

Serum Antibody Responses of Healthy Adults to Inactivated A/H3N2 Whole Virus Vaccine

(Knight, et al., Bull WHO, 45:767, 1971)

	% ≥4 Fold Rise		GMT	
Dose (CCA)	HI	Nt	HI	Nt
137	46	80	14	16
332	60	93	21	22
535	76	93	29	25
1265	80	100	36	60

[1]HI No. = 50-58, Nt No. = 15

Serum HAI Antibody Responses After 1 and 2 Doses of Inactivated A/H3N2 Vaccine in Young Adults

Vaccination	400 CCA, SC, 0 and 2 wks	
GMT (log_2)	Pre	<1
	% Rise/GMT 2 wks	100/6.7
	% Rise (2 to 4)/GMT 4 wks	30/7.3

Lessons Learned from the A/H2N2 and A/H3N2 Vaccine Experience

- Increase in purity reduces reactogenicity
- Increasing the dose will increase the antibody response
- Two doses a month apart may increase the antibody response
- Priming is probably a major factor for increasing antibody responses to one dose
- Use of an adjuvant can decrease the antigen needed for a response similar to aqueous vaccine

Evaluations in Clinical Trials of A/New Jersey (H1N1) and A/USSR (H1N1) Inactivated Vaccines in 1976 and 1978

Variables

- Vaccine Manufacturer
  - 2 WV (MN/CL and MSD)
  - 2 SV (PD and Wyeth)
- Dose (CCA and μg HA)
- Schedule (1 or 2 doses)
- Age (children, adults, elderly)

Measurements

- Vaccine characteristics
  - CCA, HA, protein, endotoxin, mass
- Reactogenicity
- Serum antibody responses

Reactogenicity Summary

A/New Jersey (SV and WV)

- Split virus vaccines less reactogenic than whole
- Increasing dose causes increasing reactogenicity
- Reactions greater among children than adults

A/USSR (SV and WV)

- Both split and WV vaccines exhibited low reactogenicity (dose range 7-60 μg)

Systemic Reactogenicity Among Children After Whole and Split Inactivated A/New Jersey (H1N1) Vaccines

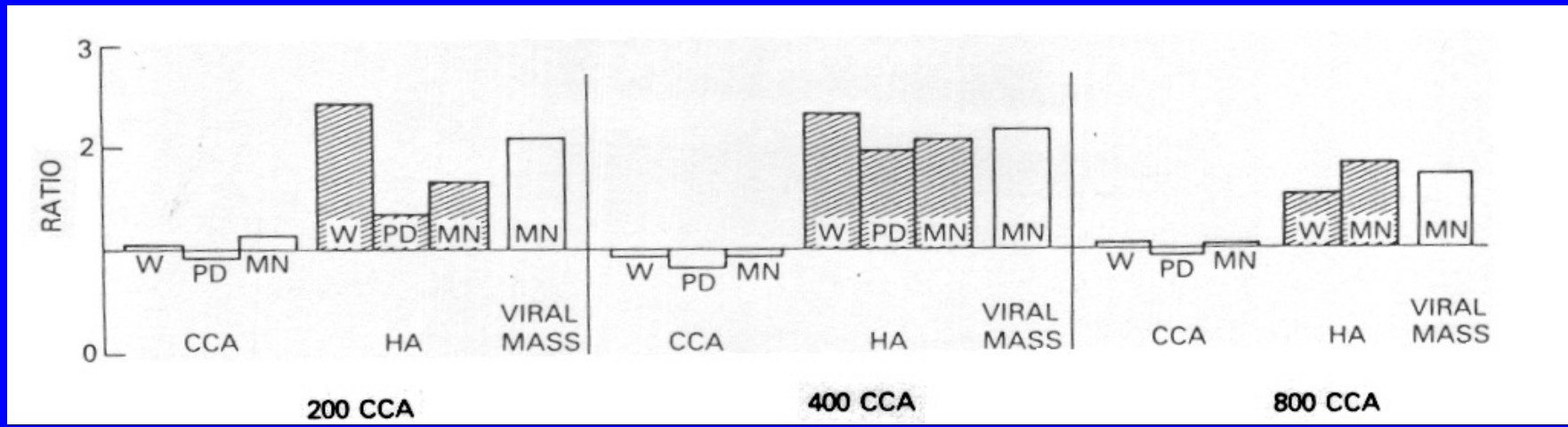
(from Ennis and Wright, JID, Vol. 136 Suppl, 1977)

Vaccine/CCA		Endo[1]	HA[2]	R.I.[3] 3-5 Yrs	R.I.[3] 6-10 Yrs
Wyeth	50			.13	
	100	≤.001	12	.24	.36
MN	50			.55	
	100	.003	~7	.52	.68
MSD	100	<.001	11	.47	1.28

[1]Endotoxin, µg/.5 ml

[2]HA µg/.5 ml

[3]Reaction index, mean score for fever, headache, malaise, abdominal symptoms; RI >0.6 considered significant


RATIO
3
2
0
W
PD
MN
W
PD
MN
MN
CCA
HA
VIRAL MASS
200 CCA
400 CCA
800 CCA

Comparison of Reactogenicity for A/New Jersey (H1N1) and A/USSR (H1N1) Inactivated Influenza Virus Vaccines

(LaMontagne, RID, 5:723, 1983; Parkman, JID, 136:S722, 1977)

		~200 CCA		~400 CCA		~800 CCA	
Vaccine		HA[1]	RI[2]	HA[1]	RI[2]	HA[1]	RI[2]
Wyeth	NJ	24	.47	40	.30	90	.28
	USSR	16	.26	61	.39		
MN/CL	NJ	13	.44	29	.27	61	.58
	USSR	19	.34			59	.31
MSD	NJ	22	.49	58	.90		
	USSR	12	.21	45	.34		

[1]Micrograms

[2]Mean systemic reaction score (fever, HA, malaise, GI)

Immunogenicity for A/New Jersey (H1N1) and A/USSR (H1N1) Vaccines

- Increasing dose increases antibody responses
- Two doses 4 weeks apart increased antibody responses among unprimed (children and young adults)
- Priming was the major determinant of increased responses
- Whole virus vaccines appeared more immunogenic than split vaccines partly from increased dose
- In unprimed, a single high dose was often as immunogenic as 2 smaller doses
- Serum HAI titers decreased 2-4 fold by 6 months past vaccination

Serum HAI Responses to 1 and 2 Doses of A/New Jersey (H1N1) among Unprimed Adults (17-24 Years) after A/New Jersey Inactivated Vaccine

(Parkman, et al., JID, 136:722, 1977)

Vaccine	Doses	% >1:40	GMT
Wyeth	1	21	10
8 µg HA	2	52	39
MN	1	44	22
12 µg HA	2	83	72
MSD	1	56	42
28 µg HA	2	94	125
MSD	1	91	82
118 µg HA			

Wyeth = split virus; MN, MSD = whole virus

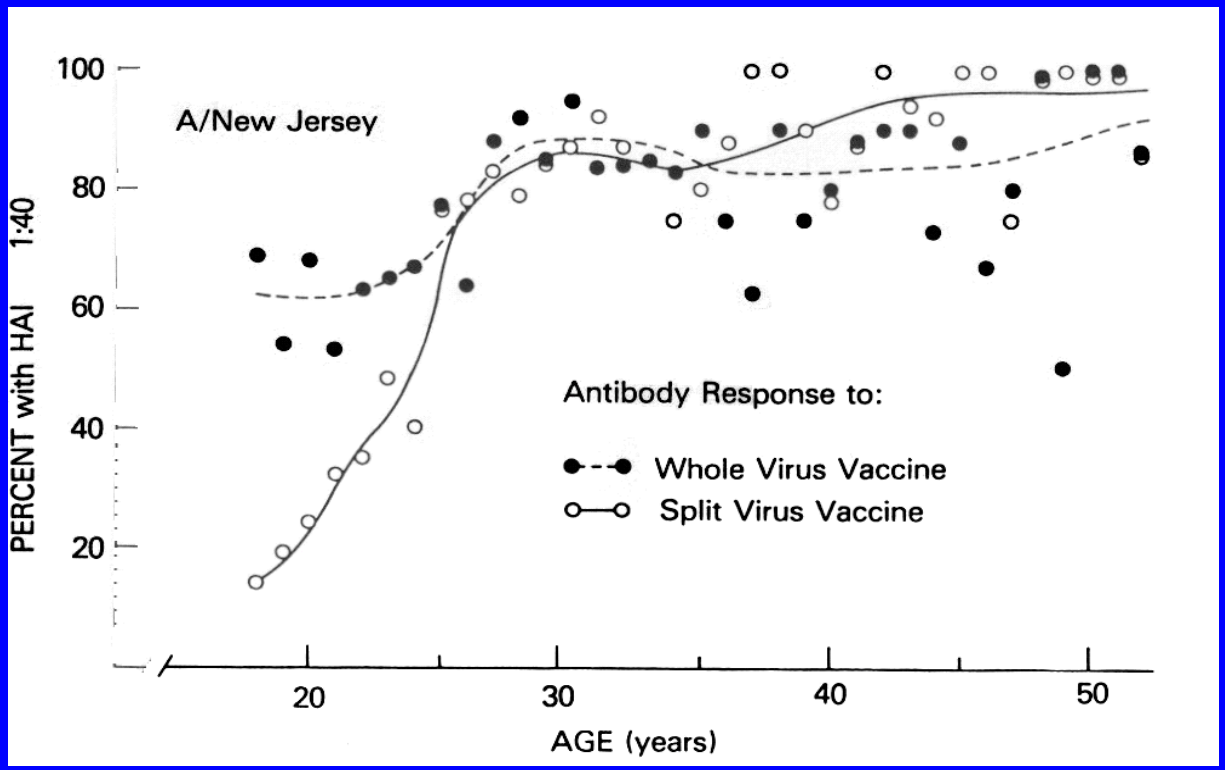
Serum HAI Responses to A/New Jersey (H1N1) among Primed Adults (>25 Years) after Inactivated Vaccine by HA Dose

(Parkman, et al., JID, 136:722, 1977)

Vaccine	HA*	% >1:40	GMT
Wyeth	8	75	112
	23	90	205
	65	93	329
MN	12	85	75
	26	88	117
	51	95	185
MSD	28	92	161
	60	91	211
	118	93	218

*Micrograms

Wyeth = split virus; MN, MSD = whole virus


A/New Jersey
PERCENT with HAI 1:40
100
80
60
40
20
20
30
40
50
AGE (years)
Antibody Response to:
Whole Virus Vaccine
Split Virus Vaccine

Serum HAI Antibody to A/New Jersey (H1N1) Virus among Persons ≥50 Years after Bivalent A/NJ, A/Victoria Vaccine[1]

(Cate, et al., JID, 136:518, 1977)

Vaccines	CCA/HA	% >1:40		GMT	
		Pre	Post	Pre	Post
MN	200/13	70	98	48	164
MSD	200/22	81	98	74	191
MN	400/29	77	100	55	232
MSD	400/58	64	98	46	246

[1]Both vaccines whole virus

Serum HAI Responses to Inactivated A/USSR (H1N1) Vaccines among Seronegative Young Adults: %≥1:40

(Wright, et al., RID, 5:758, 1983)

		Dose (μg HA)	
Age (yrs)	Vaccine/No. Doses	7	20
13-25	SV/1	21	62
	SV/2	54	77
	WV/1	32	63
	WV/2	72	85

SV = split vaccine, WV = whole virus vaccine

Serum HAI Responses to Inactivated A/USSR (H1N1) Vaccines Among Young and Older Adults

(Cate, et al., RID, 5:737, 1983)

	% ≥1:40 After 1 Dose		% ≥1:40 after 2 Doses	
Vaccine*/Dose/ug HA	Young	Older	Young	Older
S/7	38	82	83	88
W/7	35	86	76	100
S/20	71	94	90	100
W/20	83	72	94	83

*S = split vaccine; W = whole virus vaccine

Young = 20-25 years; older = 55-88 years

Lessons Added by the N/NJ and A/USSR Vaccine Experience

- The conclusion that whole virus vaccines are more reactogenic and immunogenic than split virus vaccines may not be generalizable to all WV vaccines
- Priming is clearly a major factor for increasing antibody responses to one dose
- Among the unprimed, a single high dose is often as immunogenic as two small doses

Summary of Efficacy of A/H2N2, A/H3N2, and A/USSR (H1N1) Vaccines at First Exposure

- Efficacy for A/H2N2 vaccines was good
- Efficacy for A/H3N2 vaccines was relatively poor
- Efficacy for A/USSR vaccines appeared low for standard doses
- An increased dose appeared to correct the deficiency of A/H3N2 and A/USSR (H1N1) vaccines

Efficacy of Inactivated Influenza Virus Vaccine for Pandemic Asian (A/H2N2) Influenza (Randomized Studies)

Study Group	Dose	Infection Rate Control (%)	Efficacy (%)
Children	400 CCA x?	?	57
	20,000 HA[1]	36	67
Adults	7,000 HA[1] x 2	14.8	75
	200 or 400 CCA	3.8-16.2[2]	42-77[2]

[1]Vaccines contained alum

[2]Five studies in the military

Efficacy of Inactivated Influenza Virus Vaccine for Pandemic A/Hong Kong (H3N2) Influenza (Randomized Studies)

Study Group	Dose (CCA)	% Infection, Control	% Efficacy
Children	200 x 2	27.5	80 (Ab↑)
	400	16	~15
	7000 HA	26	27
		59	0
		~14-54	0-50
Adults	400	12.6	55
	100-1800	13	34
	300	34	24
Elderly	300	9.5	37

Note: CCA = chick cell agglutinating units; HA = hemagglutinin units

A/H2N2 versus A/H3N2 Field Trials at the Initial Epidemic: Comments of David Tyrrell (J Hyg, 68:359, 1970)

- A/H3N2 vaccines produced little protection whereas A/H2N2 had done well
- A/H3N2 vaccines appeared to induce serum HAI antibody better than the A/H2N2 vaccines
- What might account for the disparity?
  - Quality of the antibody, DT doubts
  - Anti NA antibody, DT doubts
  - Interval vaccine → challenge, 0 (H2N2) vs. 7 mos. (H3N2)
    - Fall in serum Ab, DT doubts
    - Fall in secretion Ab, DT favors
- To improve protection, DT proposed a "substantially" increased dose

Efficacy of Inactivated A/USSR (H1N1) Influenza Virus Vaccine for A/Brazil (H1N1) Illnesses

Group	Dose	ILI Rate Controls (%)	Efficacy (%)
Community[1]	7 or 20 µg x 2	10	0
College	7 µg x 2	40	23
Military	60 µg	?	86%

[1]College group, 18-30; others ≥ 45 yrs

Antibody Responses and Efficacy after Inactivated A/HK Influenza Vaccine

(Mostow and Schoenbaum, WHO Bull., 1969)

	Young Adults		Elderly	
Vaccine Dose	GMT Ab[1]	Efficacy (%)[2]	GMT Ab	Efficacy (%)
300 CCA	69	24	60	37
3000 CCA	126	71	229	58

[1]HAI

[2]Febrile resp. disease

Lesson Added by the Experience with Efficacy of A/H2N2, A/H3N2, and A/USSR (H1N1) Vaccines on First Exposures

- Efficacy for the different vaccines varied
- In contrast to the interpandemic interval, the value of standard immunologic surrogates for protection is uncertain
- Available data (although limited) suggest that the goal for design of an inactivated vaccine for pandemic influenza should be to achieve the greatest and ? broadest immune response possible

Lessons Learned Summary

- Increasing purity reduces reactogenicity
- Increasing the dose, giving two doses, or using an adjuvant increases the antibody response
- Priming is a major factor determining response to one dose
- Whole virus vaccines may not be uniformly more reactogenic than split/subunit vaccines
- Efficacy is variable and may not relate well to serum HAI antibody titers
- Available data suggest that the higher the serum antibody the greater the protection. The desired level is uncertain