

Vaccine Experiences and Lessons from the Past

Robert B. Couch, M.D.
Baylor College of Medicine
Houston, Texas, U.S.A.



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

<u>CCA</u>	<u>μg HA A/NJ</u>	<u>μg HA A/USSR</u>
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)

<u>Vaccine</u>	<u>No.</u>	<u>Local $\geq 3 \times 4$ cm</u>	<u>Fever</u>	<u>Malaise/Chills</u>
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)

<u>Dose (CCA)</u>	<u>GMT¹ After</u>	
	<u>1 Dose</u>	<u>2 Doses</u>
125	8	10
250	12	20
500	27	38
750	18	84
1000	30	47

¹HAI

**Serum HAI Responses to
One and Two 200 CCA Doses of
Inactivated Asian (A/H2N2) Vaccine
(Bayne, AJMS, Sept, 1958)**

<u>Group</u>	<u>N</u>	<u>% Ab Rise</u>
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)

<u>Age</u>	<u>N</u>	<u>No. ≥ 32</u>
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 ≥ 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)

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

¹HI 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)

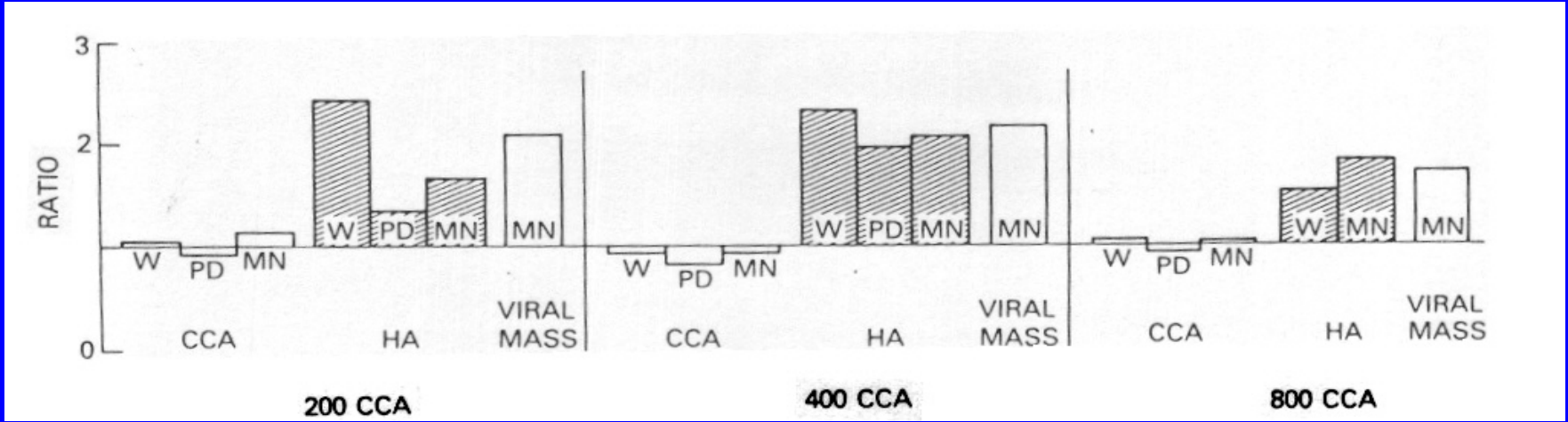
R.I.³

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

¹Endotoxin, µg/.5 ml

²HA µg/.5 ml

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



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)

<u>Vaccine</u>	<u>~200 CCA</u>		<u>~400 CCA</u>		<u>~800 CCA</u>	
	<u>HA¹</u>	<u>RI²</u>	<u>HA¹</u>	<u>RI²</u>	<u>HA¹</u>	<u>RI²</u>
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		

¹Micrograms

²Mean 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)

<u>Vaccine</u>	<u>Doses</u>	<u>% >1:40</u>	<u>GMT</u>
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			

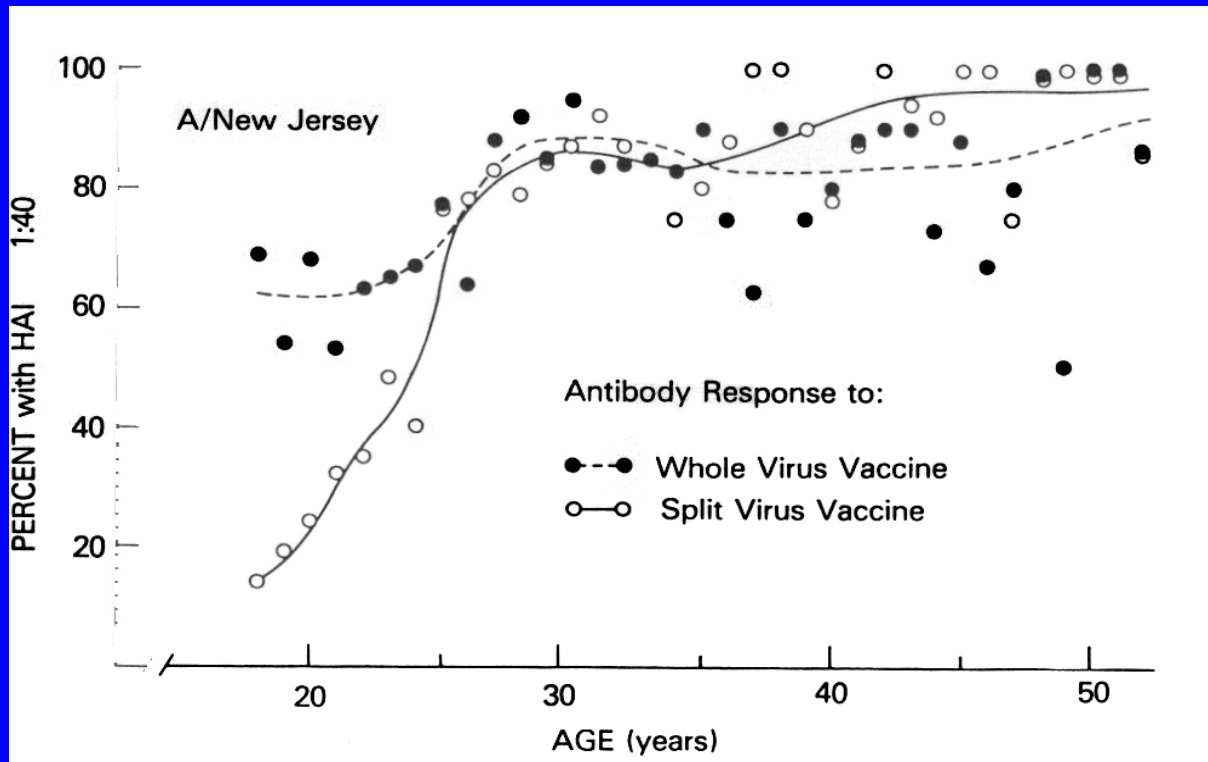
Wyeth = split virus; MN, MSD = whole virus

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)

<u>Vaccine</u>	<u>HA*</u>	<u>% >1:40</u>	<u>GMT</u>
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



**Serum HAI Antibody to A/New Jersey
 (H1N1) Virus among Persons ≥ 50 Years after
 Bivalent A/NJ, A/Victoria Vaccine¹
 (Cate, et al., JID, 136:518, 1977)**

<u>Vaccines CCA/HA</u>		<u>% >1:40</u>		<u>GMT</u>	
		<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>
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

¹Both vaccines whole virus

**Serum HAI Responses to
 Inactivated A/USSR (H1N1) Vaccines
 among Seronegative Young Adults: % \geq 1:40
 (Wright, et al., RID, 5:758, 1983)**

<u>Age (yrs)</u>	<u>Vaccine/No. Doses</u>	<u>Dose (μg HA)</u>	
		<u>7</u>	<u>20</u>
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)

<u>Vaccine*/Dose/ug HA</u>	<u>% \geq1:40 After 1 Dose</u>		<u>% \geq1:40 after 2 Doses</u>	
	<u>Young</u>	<u>Older</u>	<u>Young</u>	<u>Older</u>
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)

<u>Study Group</u>	<u>Dose</u>	<u>Infection Rate Control (%)</u>	<u>Efficacy (%)</u>
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

¹Vaccines contained alum

²Five studies in the military

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

<u>Study Group</u>	<u>Dose (CCA)</u>	<u>% Infection, Control</u>	<u>% Efficacy</u>
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

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

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

Antibody Responses and Efficacy after Inactivated A/HK Influenza Vaccine

(Mostow and Schoenbaum, WHO Bull., 1969)

<u>Vaccine Dose</u>	<u>Young Adults</u>		<u>Elderly</u>	
	<u>GMT Ab¹</u>	<u>Efficacy (%)²</u>	<u>GMT Ab</u>	<u>Efficacy (%)</u>
300 CCA	69	24	60	37
3000 CCA	126	71	229	58

¹HAI

²Febrile 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