Inactivated Influenza Vaccine by the Intranasal Route

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Rationale for Optimizing Influenza Vaccine Responses in Respiratory Secretions

- Increase the level of protection provided by IM vaccination
- Broaden the protection (via IgA antibody) to antigenic variants

Features of the Mucosal Immune System

- The mucosal immune system is relatively distinct from the systemic immune system
- The predominant immunoglobulin secreted into mucosal secretions is IgA (dimeric and polymeric)
- For nasopharyngeal secretions, the predominant Ig is IgA; in airways of the lower respiratory tract, it is IgG
- Optimal/maximal induction of a mucosal immune response requires antigen administration by the mucosal route

Mucosal Immunizations Reported to Induce Responses to Inactivated Influenza Vaccines in Respiratory Secretions

(and to provide systemic responses in many instances)

Approach	Increase in: R[1]	Increase in: H[2]
Products		
Whole virus	❄	❄
Subunits	❄	❄
VLPs	❄	
Peptides	❄	
M2e	❄	
Increased dosage	❄	❄
Repeated doses	❄	❄
Adjuvants/immunoenhancers		
CT, LT & mutants	❄	❄
Virosomes/liposomes	❄	❄
Proteosomes (w OMP)	❄	❄
Alpha Interferon	❄	?
Surfactant-like	❄	
ISS	❄	
MPL	❄	
QS21, QS7	❄	
Many others	❄	

[1]R = Rodents
[2]H = Humans

Increased Dosage Intranasally

Dose-response of Trivalent Inactivated Influenza Vaccine Given IN and IM to Healthy Adults

(Atmar, et al., Vaccine 2007, 25:5363)

Subjects:	18-40 years, healthy
	No vaccine in past three years
Vaccine:	Sanofi Pasteur, 15, 30, 60 micrograms of each HA (45, 90, 180 micrograms total)
Design:	All given IM and IN administration
	0.5 ml vaccine or placebo
Evaluations:	Reactogenicity
	Immunogenicity
	Serum HAI and neut
	NS EIA H1 and H3 IgA and IgG

Summary Reactogenicity

- All combinations well tolerated
- Significantly greater than placebo for IN
  - Bad taste ($p < .001$)
  - Mild nasal discomfort ($p = .03$)
- Significantly greater than placebo for IM
  - Arm soreness ($p < .001$)
  - Increased arm soreness with increased dosage ($p = .02$)
  - Malaise ($p = .03$)
  - Myalgias ($p < .01$)

Serum Antibody Responses to Trivalent Vaccine Intramuscularly

		Fold Increase in Neut Ab[1]	
IM Dosage (μg)	N	H3	H1
15	21	6.3	15
30	19	6.1	24
60	20	9.5	48
120	20	14.0	72

[1]Dose-response = linear regression tests = $p < 0.5$ for each

Antibody Responses in Nasal Secretions to Trivalent Vaccine Intranasally

		% IgA Increase			% IgG Increase			
IN Dosage (µg)	No.[1]	H1	H3	Either	No.[1]	H1	H3	Either
0[2]	28	7	4	11	21	29	14	33
15[3]	16	13	6	13	10	20	0	20
30[3]	12	17	0	17	9	22	11	22
60[3]	15	33	20	40[4]	10	50	10	50

[1]No. with satisfactory secretions for tests
[2]All received 15 – 120 micrograms IM of each antigen
[3]About ½ also received the same dosage IM
[4]Greater than % in IM vaccinees, $p < .05$

Summary

- Improvement in inactivated influenza vaccines is needed, particularly for the elderly. Mucosal immunization is one option for improving influenza vaccines.
- Mucosal IgA antibody, the predominant antibody in upper respiratory tract secretions, can increase the protection against influenza provided by systemic IgG antibody and may convey greater heterotypic and heterosubtypic immunity to humans
- Immunization via the respiratory route appears necessary for optimizing IgA antibody responses. Increased dosage, number of doses and mucosal adjuvants can increase responses
- One adjuvanted preparation, “FluInsure” is being developed for use in humans; one preparation, virosomes with LT, was discontinued. A large number of adjuvant options have been described for enhancing immune responses and protection in animal models.