Influenza Vaccination by Oral Tablet is Protective and Induces a Unique Mucosal B Cell Immune Response

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Abstract

Background: Room temperature stable oral vaccines delivered by tablet offer several advantages over injection-based vaccines, including ease of distribution and administration. Oral vaccination is also advantageous because it induces a strong mucosal response, which is thought to be critical for preventing future infections. Here we present recent results from a phase 2 clinical challenge study comparing efficacy of an oral recombinant adenovirus-based vaccine expressing hemagglutinin (rAd-HA) from A/California/04/09 to that of a commercial injectable quadrivalent (QIV) influenza vaccine.

Study Design & Methods

Methods: In this 2016-2017 clinical trial (NCT02918006), subjects were immunized with either oral VXA-A1.1 (rAd-HA), QIV, or placebo and then challenged 90-120 days post-immunization with a wildtype influenza A H1 virus to measure vaccine efficacy.

- **A single dose administration of one of the following:**
  - Arm 1: VXA-A1.1 oral vaccine [1x10^{11} IU±0.5 log] + placebo IM injection (n=60 + 12 extra)
  - Arm 2: QIV injection + oral placebo tablet (n=60 + 12 extra)
  - Arm 3: Placebo IM injection + oral placebo tablet (n=30 + 6 extra)
- **Subjects with baseline HAI titers ≤10**
- **Challenge at single time point post randomization at Day 90**
- **Primary endpoint: Number and % of subjects protected against homologous A strain influenza virus by VXA-A1.1 compared to QIV and placebo**

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Results

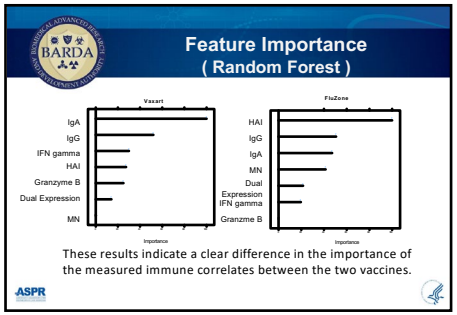
Vaxart's oral influenza vaccine showed a reduction in illness compared to placebo as well as equivalent vaccine efficacy when compared to quadrivalent intramuscular vaccination.

Groups	Vaxart Oral Tablet	Commercial QIV Injection	Placebo
Illness*	29.3% (18.1-42.7%)	35.2% (22.7-49.4%)	48.4% (30.2-66.9%)

*Illness defined as shedding plus flu-like symptoms based on FluPro data questionnaire

While the rate of HAI (hemagglutinin inhibition) seroconversion was elevated in individuals immunized with QIV; individuals immunized with Vaxart's oral vaccine seroconverted at a lower frequency, indicating that the mechanism of protection is not only associated with HAI.

Groups	Vaxart Oral Tablet	Commercial QIV Injection	Placebo
HAI-Seroconversions	35% (22.5-48.1%)	83% (70.7-92.1%)	0% (0-11.2%)

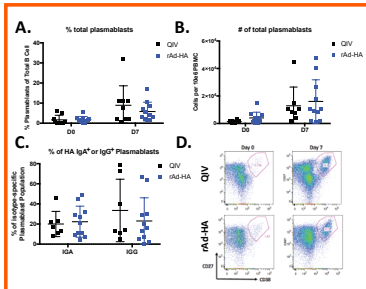


Protection against infection amongst Vaxart's immunized subjects was more strongly correlated with IgA ASC counts indicating a role for IgA plasmablasts in driving protection.

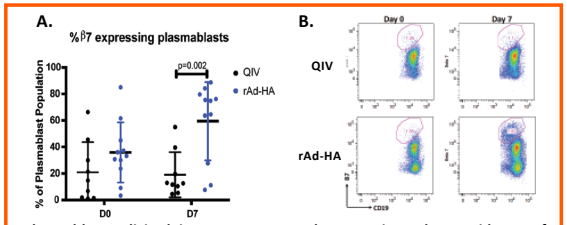
Vaccine	Illness		Mean		Median	
	Status	#	Day 1	Day 8	Day 1	Day 8
VXA-A1.1	No	41	2	104	0	62
	Yes	17	3	22	0	14
Fluzone	No	35	2	346	0	262
	Yes	19	1	247	0	129
Placebo	No	16	3	6	1	1
	Yes	15	3	15	0	1

IgG and IgA ELIspot assays were conducted using PBMCs collected at Day 1 and Day 8 post-immunization. While, the range of IgA ASC in QIV immunized subjects were greater, there was no specific correlation with IgA ASC and protection, unlike that observed in Vaxart-immunized subjects.

Role of IgA and Mucosal B Responses in Conferring Protection



Phenotyping of activated B cells in response to rAd-HA and QIV vaccines. **(A)** Quantitation of the percentage of plasmablasts (CD19$^+$CD38$^+$CD27$^+$IgM$^-$) in individuals immunized with either rAd-HA or QIV at Day 0 and Day 7 post-immunization (n: QIV = 9; rAd-HA =11). **(B)** Number of plasmablasts in individuals immunized with either rAd-HA or QIV at Day 0 and Day 7 post-immunization. **(C)** Percentage of IgA$^+$ or IgG$^+$ plasmablasts within the plasmablast compartment in individuals immunized with either rAd-HA or QIV **(D)** Representative FACS dot plot of plasmablasts (CD19$^+$CD38$^+$CD27$^+$IgM$^-$)



Plasmablasts elicited in response to rAd-HA vaccines show evidence of mucosal homing. **(A)** Quantitation of the percentage of plasmablasts (CD19$^+$CD38$^+$CD27$^+$IgM$^-$) expressing β7 in individuals immunized with either rAd-HA or QIV at Day 0 and Day 7 post-immunization (n: QIV = 9; rAd-HA =11). Statistical significance determined using Student's T test where p = 0.002. **(B)** Representative FACS dot plot of β7 expression on CD19 (collected from PBMCs) expressing B cells at Day 0 and Day 7 post-immunization.

Conclusion

Vaxart's oral influenza tablet vaccine protected against influenza infection as well as or better than the injectable quadrivalent vaccine. However, the mechanism of protection appears to be unique to the route of immunization. Vaxart's platform allows for homing of influenza-specific B cells to sites of infection which may provide more effective mechanisms of protection. Taken together, these results suggest that an oral influenza vaccine can generate a robust, tissue-specific protective response comparable to intramuscular influenza vaccination.