



Different H5N1 Vaccines: Clinical Studies

**5th WHO Meeting on Evaluation of
Pandemic Influenza Prototype Vaccines in Clinical Trials
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Overview

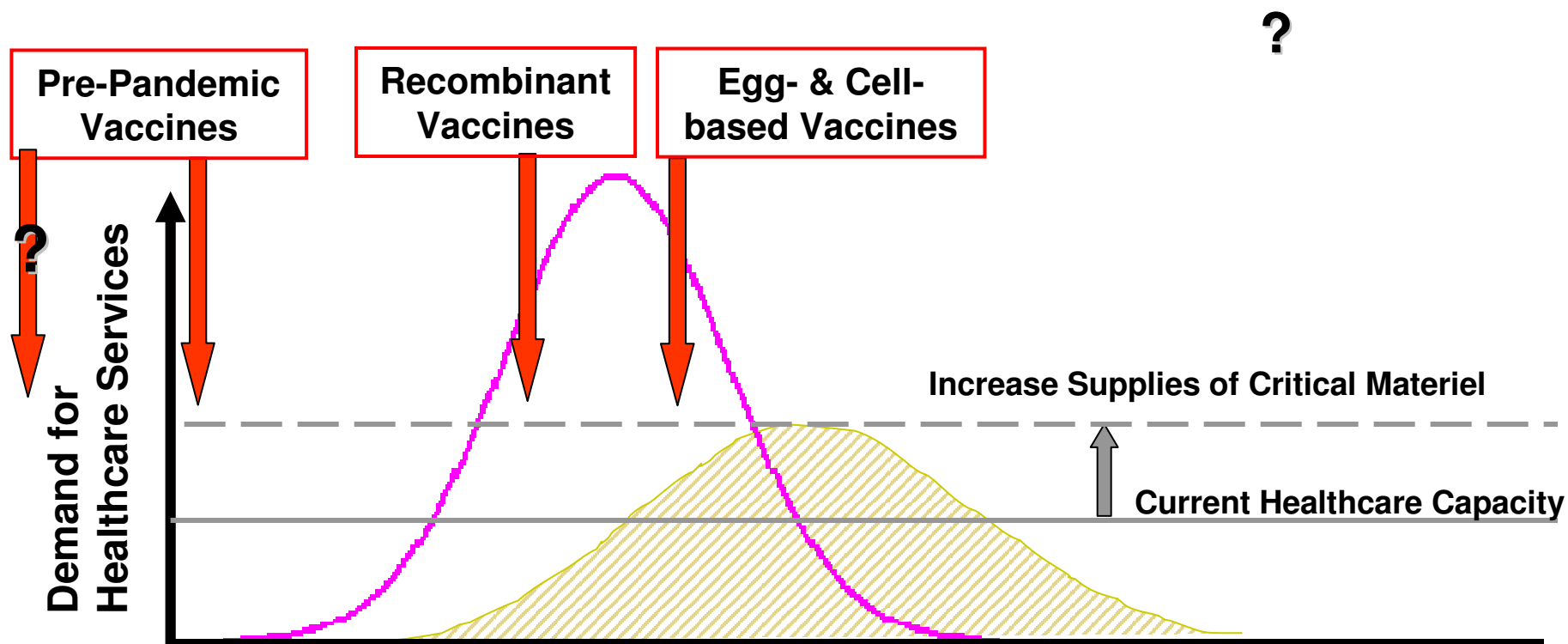
- Mix-N-Match H5N1 Vaccine Antigen-Adjuvant Study
- Cell-based H5N1 Vaccine Studies
- Whole Virion – Split Vaccine Study
- Pre-pandemic Vaccines: Large study



Pandemic Influenza Medical Countermeasure Supply-Demand Gap Closure

Reduce Demand: Pre-Pandemic Vaccines, Community Mitigation, Antivirals, Vaccines, Masks

Increase Capacity: Ventilators, Oxygen, Antivirals, Pandemic Vaccines, Masks





Vaccines: Advanced Development

- **Four Projects** (9 contracts - \$1.43 B; 3 intl. grants - \$25 M)

Projects	Contract Awards	Industry Partners	Expected Results
Cell-based	\$1.3 B	sanofi pasteur Novartis GlaxoSmithKline MedImmune Solvay DynPort/Baxter	Contracts awarded 2005 – 2006 Expand domestic flu vaccine mfg. Provide 400+ M doses pandemic vaccine by 2011
Antigen-sparing	\$146 M	Novartis GlaxoSmithKline Intercell (IOMAI)	Contracts awarded 2007 Reduce amount of vaccine antigen needed BARDA Mix-N-Match Studies
Intl. in-country PI vaccine development	\$25 M	Vietnam WHO	Grants awarded 2006-08 Facilitate pan flu vaccine mfg in developing countries
Next Generation: Recombinant	Open RFP	Contract awards expected in FY09	Diversify flu vaccine mfg. Reduce mfg. time

- Universal influenza vaccines – NIH grants early development



H5N1 Vaccine Stockpile Inventory: 2008

H5N1 Vaccine Strain	Clade	2004	2005	2006	2007	2008	Totals
A/VTN/1203/04	1	0.23	2.86	0.79		1.16	5.04
A/Indo/05/05	2.1			6.25	2.25	0.041	8.54
A/BHG/QL/1A/05	2.2				6.32		6.32
A/Anhui/1/05	2.3				2.56		2.56
Totals Ag-Along Formulation (90 ug/dose)		0.2 M	2.9 M	7.0 M	11.1 M	1.2	22.5* M
Adjuvant	AS03					5.2	5.2 M
Totals Oil-in-Water Adjuvant Formulation (7.5 ug/dose)		2.7 M	34.3 M	84 M	133.2 M	14.4 M	268 M

* Adjusted for usage and potency



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Mix-N-Match H5N1 Vaccine Antigen – Adjuvant Study

- **STRATEGIC GOAL:** Expand the supply of pre-pandemic and pandemic influenza vaccines available at onset and during an influenza pandemic by optimization of antigen content using available adjuvants
- **SPECIFIC AIM:** Determine whether stockpiled H5N1 vaccine antigens manufactured by one company can be used safely and effectively with adjuvants from other manufacturers during an influenza pandemic under Emergency Usage Authorization.



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Mix-N-Match Plan: Products

- Conduct a series of laboratory, animal, and clinical studies
 - Physicochemical analyses (GSK, Novartis)
 - Murine immunogenicity studies (SRI)
 - Rabbit toxicology studies (SRI)
 - Phase I clinical study: dosage-ranging study for safety, immunogenicity, & cross-reactivity (NIH)
 - Ferret challenge studies (CDC)
 - Phase 2 clinical study: single dosage study

Adjuvant (Oil-in Water Emulsions)	H5N1 A/Indonesia/05/2005 (Egg-based inactivated split antigen)
ASO3 GSK	sanofi pasteur
MF59 Novartis	sanofi pasteur



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MnM Animal Immunogenicity Studies

Murine Immunogenicity Studies with H5N1 vaccine with Adjuvants

- Healthy adult mice housed at SRI were immunized i.m. as admixture with two doses (1 ug HA/dose) of an antigen/liquid adjuvant mixture
- Animals were bled at day 0, 21, and 42 days post-immunization
- Antibody titers (HI & MN) were determined by SRI
- **RESULTS: All mixtures were immunogenic at comparable HAI and MN antibody levels.**



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MnM Rabbit Toxicology Studies

Rabbit Toxicology Studies with H5N1 vaccine with Adjuvants

- Toxicology studies were conducted for each antigen/adjuvant mixture in concert with IND held by NIH
- Healthy adult rabbits housed at SRI were immunized i.m. as admixture of two doses at highest antigen dosage (15 ug HA/dose) of an antigen/liquid adjuvant mixture or antigen alone i.m.
- Animals were bled at day 0, 21, and 42 days post-immunization
- Antibody titers (HI & MN) were determined by SRI
- Immunized animals were observed daily and sacrificed at 56 days p.i. for organ/tissue pathology by SRI
- **RESULTS: All animals tolerated vaccinations without localized or systemic adverse events and no histopathological damage. HAI and MN antibody titers were comparable for all mixtures..**



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MnM Phase 1 Clinical Study

- **Randomized, Double-Blinded, Controlled, Phase I, Study of the Safety, Reactogenicity, and Immunogenicity of Intramuscular Inactivated Influenza A/H5N1 Vaccine Given Alone or with Adjuvants (MF59 or AS03) in Healthy Adults**
- **Six cohorts (N= 480 total; 60-80/cohort) among 8 clinical centers**
 - H5N1 antigen alone
 - AS03 + H5N1 antigen
 - MF59 + H5N1 antigen
- **5 and 15 ug HA/dose antigens formulated as admixtures with equal volumes of adjuvants**
- **One or two doses**
- **Immunization schedule: 0 d, 28 d**
- **Blood schedule: 0d, 28 d, 56 d, 180 d**
- **Clinical sample assays (SRI): HAI & MN assays (HRBC)**
- **Expected start date: April 2009**



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Cell-based H5N1 Vaccine Studies

- **Determine whether there are differences in the safety, immunogenicity, cross-reactivity, and prime-boost profiles of egg- and cell-based inactivated split H5N1 vaccines derived from the same clinical isolate**



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Whole Virion - Split H5N1 Vaccine Studies

- **Determine whether there are differences in the safety, immunogenicity, cross-reactivity, and prime-boost profiles of egg-based inactivated whole virion and split H5N1 vaccines formulated with aluminum hydroxide, oil-in-water adjuvant emulsion, or without adjuvant**



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Large Scale H5N1 Vaccine/Oil-in-Water Adjuvant Studies

- Determine the safety, immunogenicity, cross-reactivity, and prime-boost profiles of egg-based inactivated split H5N1 vaccines formulated with oil-in-water adjuvant emulsions in large clinical study (N=40-60k) representing different risk groups