



# **U.S. Pandemic Preparedness Medical Countermeasures Program: Development, Stockpiling, & Infrastructure Building**

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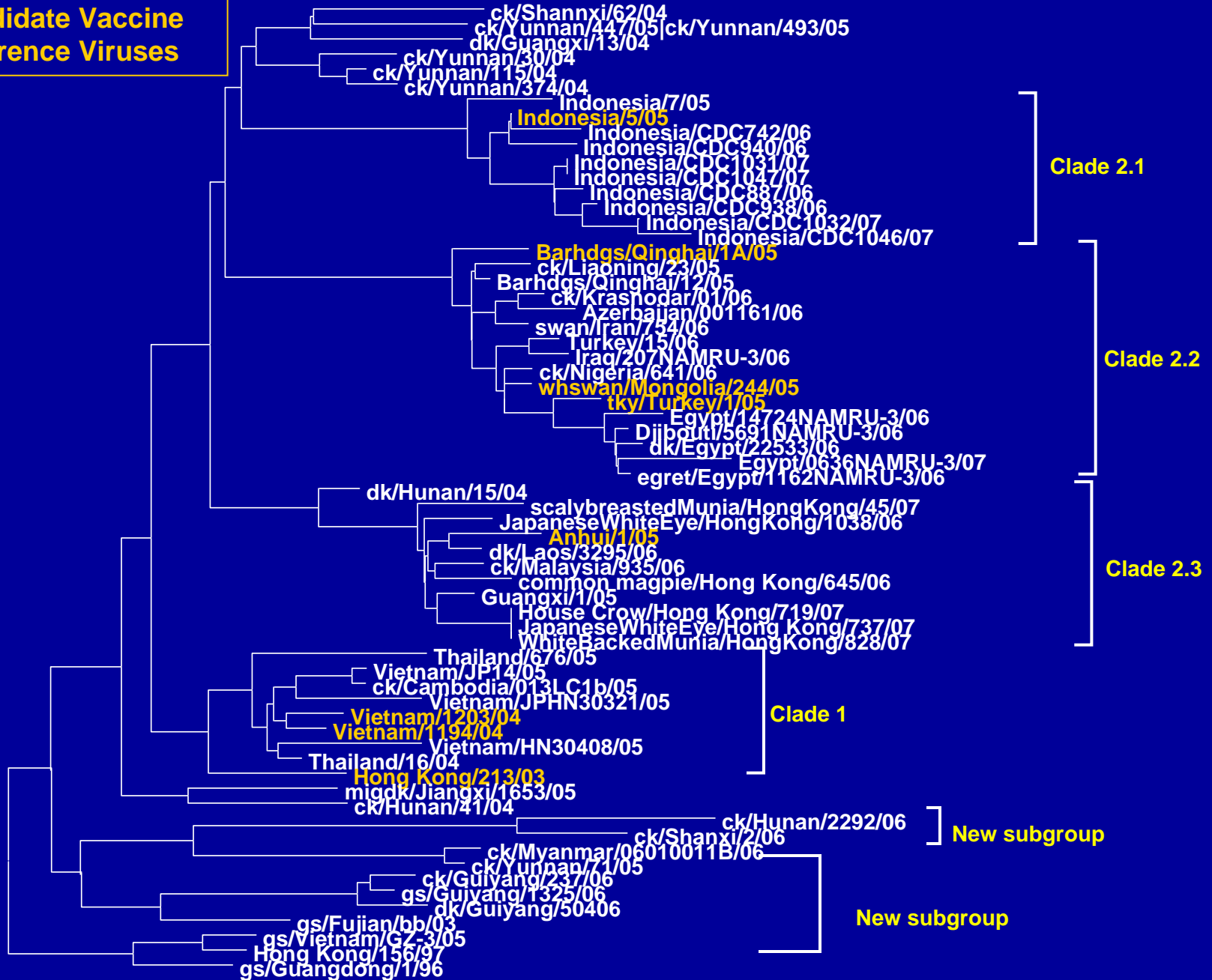


# U.S. Pandemic Influenza Preparedness: Convergence of Events

- 2004
  - Re-emergence of H5N1 virus in birds of Thailand and Vietnam
  - Seasonal influenza vaccine crisis in U.S. for 2004-05 flu season
- 2005
  - Poor immunogenicity of H5N1 vaccine candidate in clinical trials
  - Relatedness of 1918 pandemic influenza virus strain to avian H5N1 viruses
  - Emergence of new strains and drug resistant strains of H5N1 viruses
  - Limited global & U.S. influenza vaccine manufacturing surge capacity
  - Hurricane Katrina

# Evolution of the H5N1 Hemagglutinin Gene

Candidate Vaccine  
Reference Viruses



# Situation Update: H5N1 Avian Influenza

- **Outbreaks in wild birds and domestic poultry**
- **Infection of some mammalian species**
- **Continued viral evolution**
- **Sporadic human cases – as of 2/1/08**
  - 357 human cases
  - 225 deaths (63%)
  - Most cases in children and young adults
- **Rare transmission between family members**

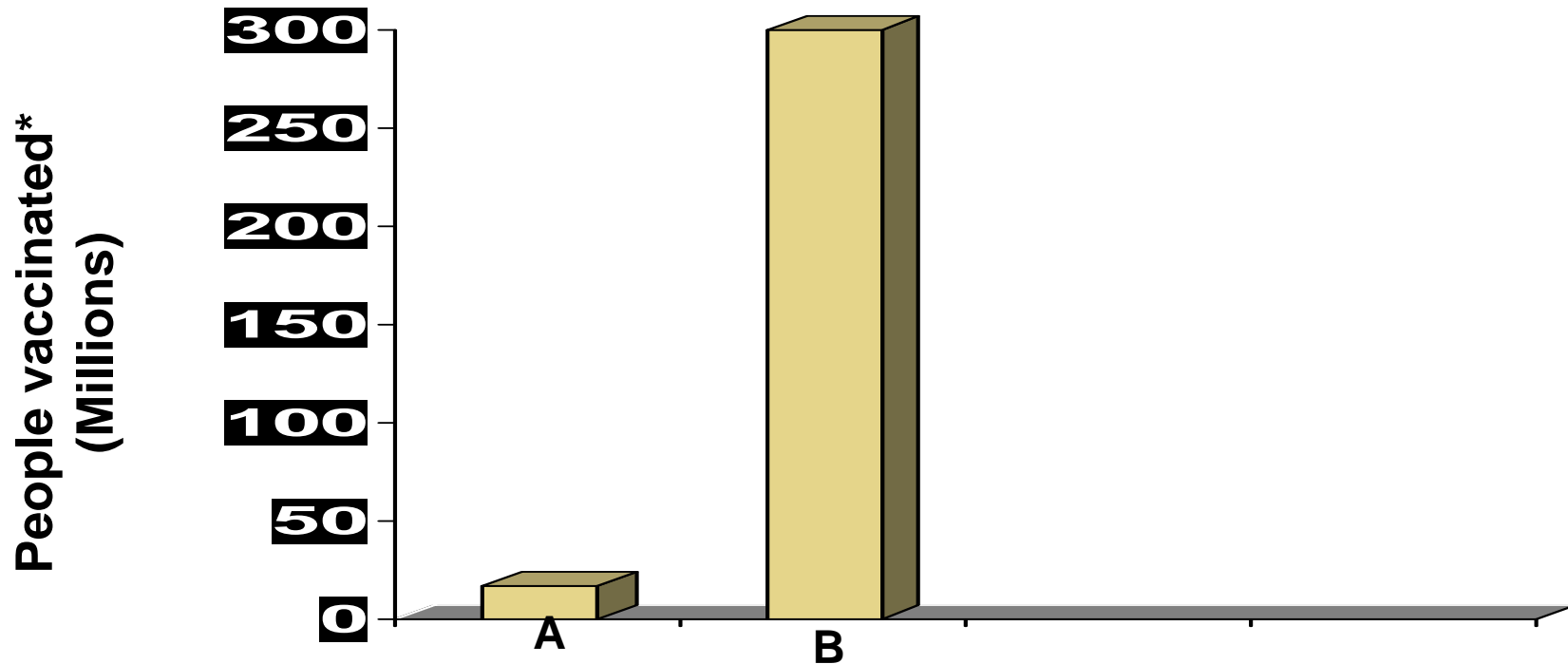


# Transitioning Influenza Vaccine Production Technology





# Estimated Annual Domestic Pandemic Influenza Vaccine Production: Capacity and Need --2005 projections

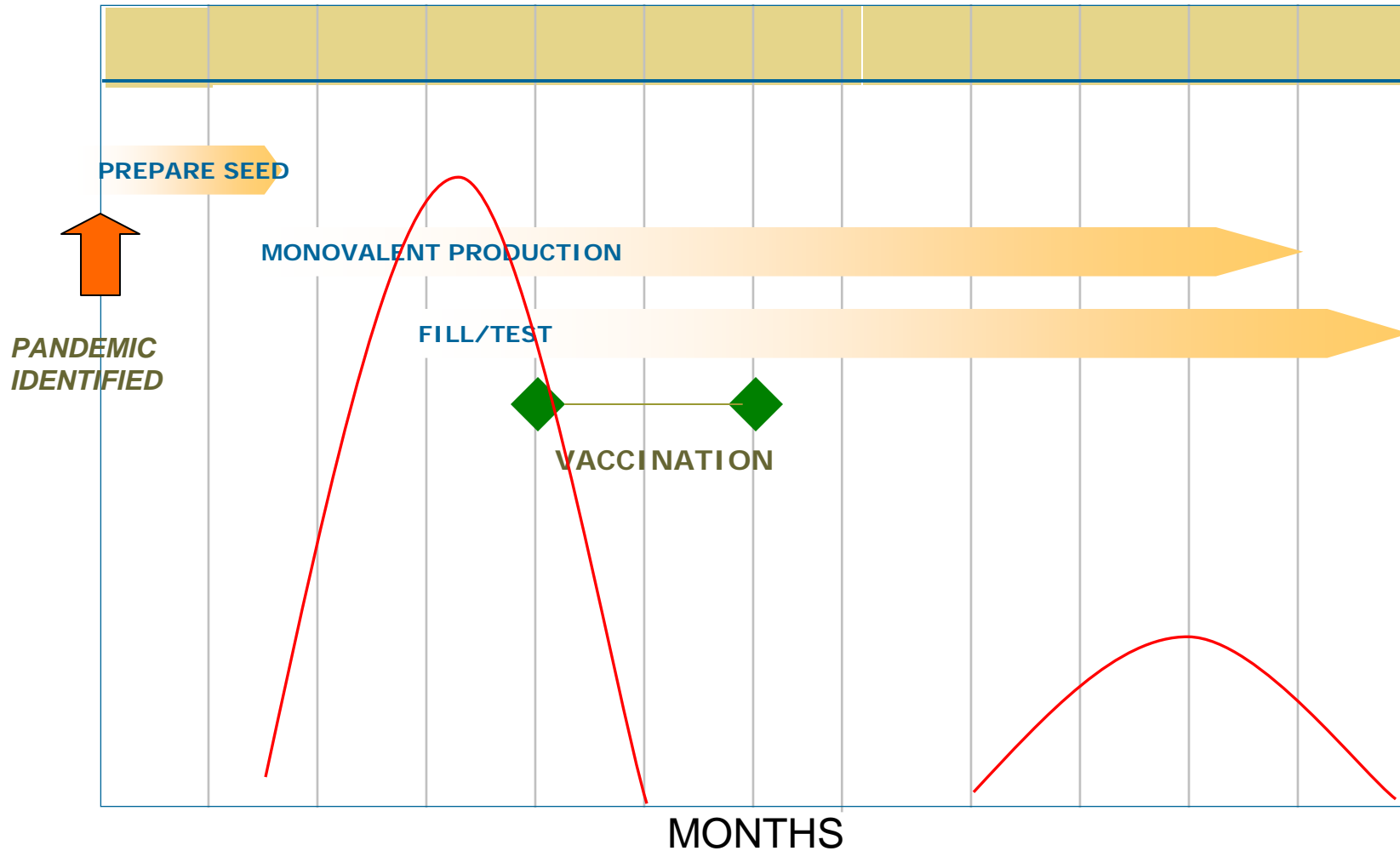


**A: Annual domestic capacity - 2005**

**B: National need**

\*Assumes 2 doses/person, 90 ug/dose

# Timing of Pandemic Vaccine Availability



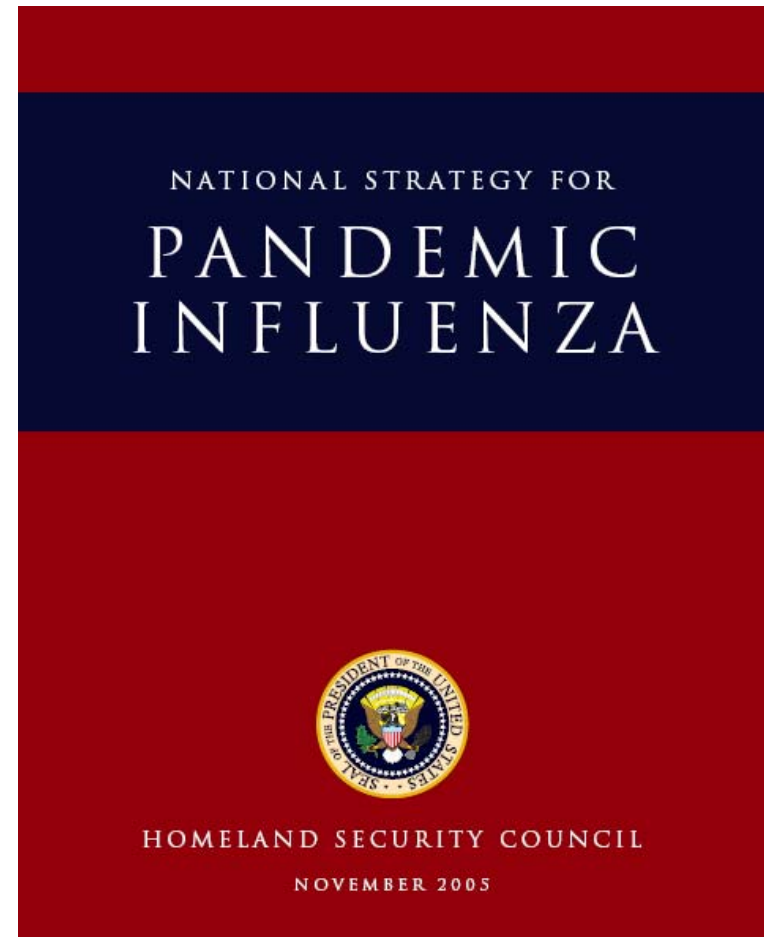


# (When) Will the Pandemic Hit?



# National Strategy for Pandemic Influenza

- **Preparedness and Communication**
- **Surveillance and Detection**
- **Response and Containment**
- **Shared responsibility** is key to for successful preparedness and response
- **Stakeholders** include federal, state, local governments, industry, communities, and individual citizens

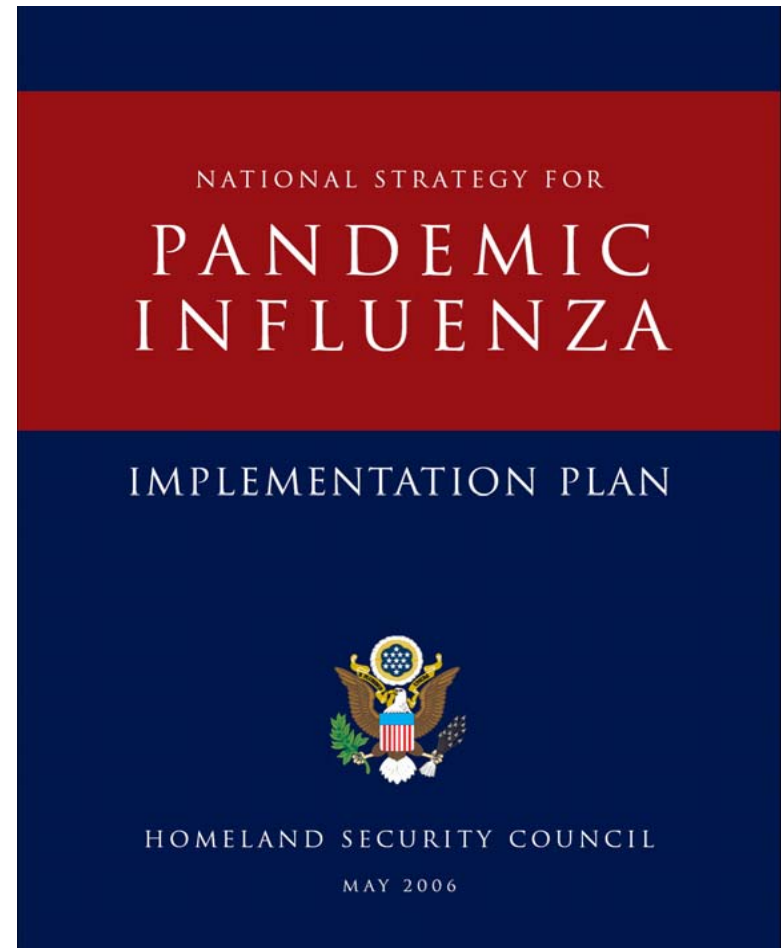


Nov. 2005

# National Pandemic Influenza Implementation Plan

- **Maintain a constitutional government and sustain social and economic order**
- **Attempt to slow the influenza pandemic reaching the U.S.**
- **Reduce disease, suffering, and death**
- **Keep community services working**
- **Reduce the danger to our economy and society**

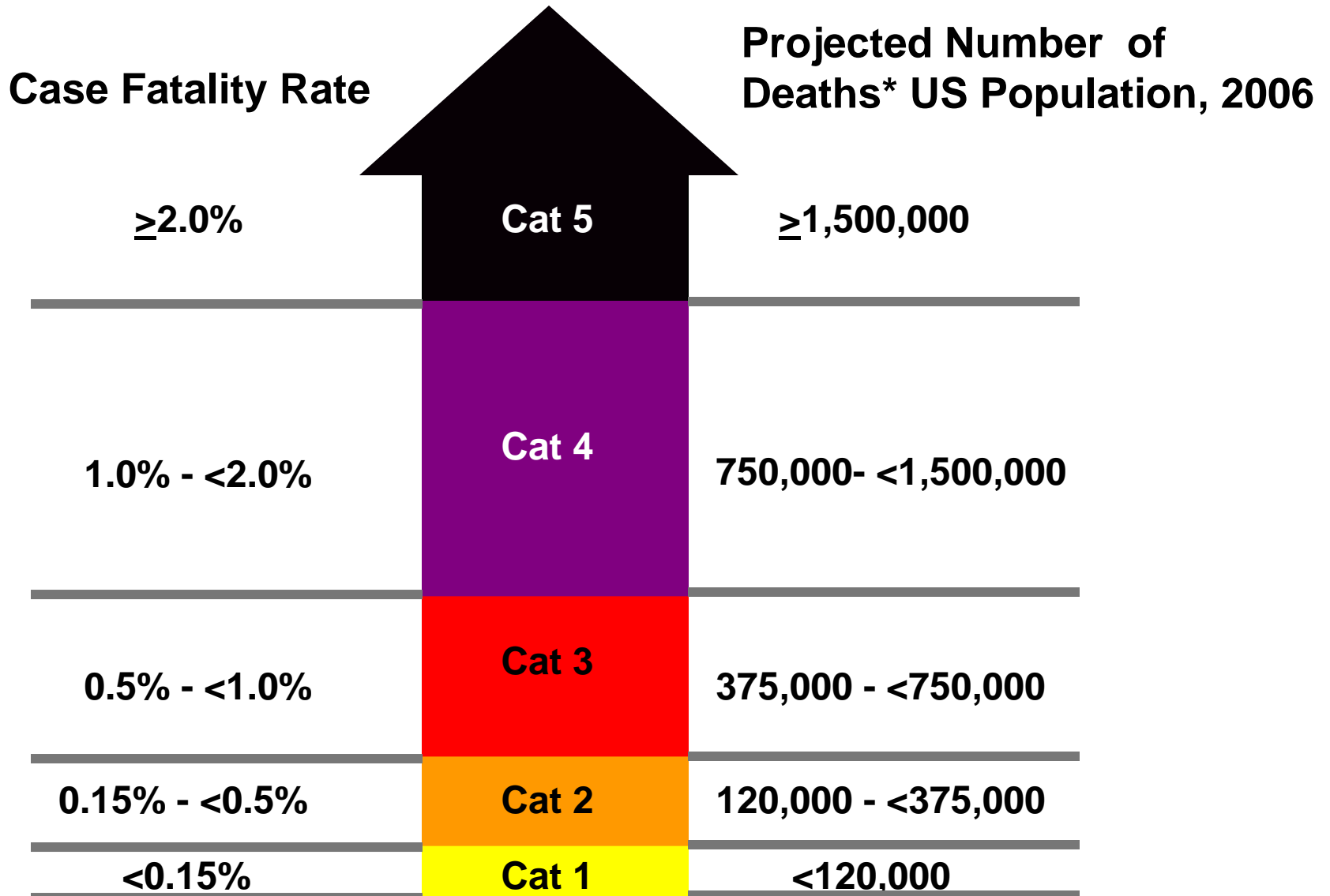
May 2006



# Planning Assumptions

	Moderate (1957-like)	Severe (1918-like)
<b>Illness</b>	<b>90 million (30%)</b>	<b>90 million (30%)</b>
<b>Outpatient medical care</b>	<b>45 million (50%)</b>	<b>45 million (50%)</b>
<b>Hospitalization</b>	<b>865,000</b>	<b>9,900,000</b>
<b>ICU care</b>	<b>128,750</b>	<b>1,485,000</b>
<b>Mechanical ventilation</b>	<b>64,875</b>	<b>745,500</b>
<b>Deaths</b>	<b>209,000</b>	<b>1,903,000</b>

# Pandemic Severity Index



# Doctrine of Shared Responsibility



**"Any community that fails to prepare with the expectation that the federal government will come to the rescue will be tragically wrong."**

HHS Secretary Mike Leavitt

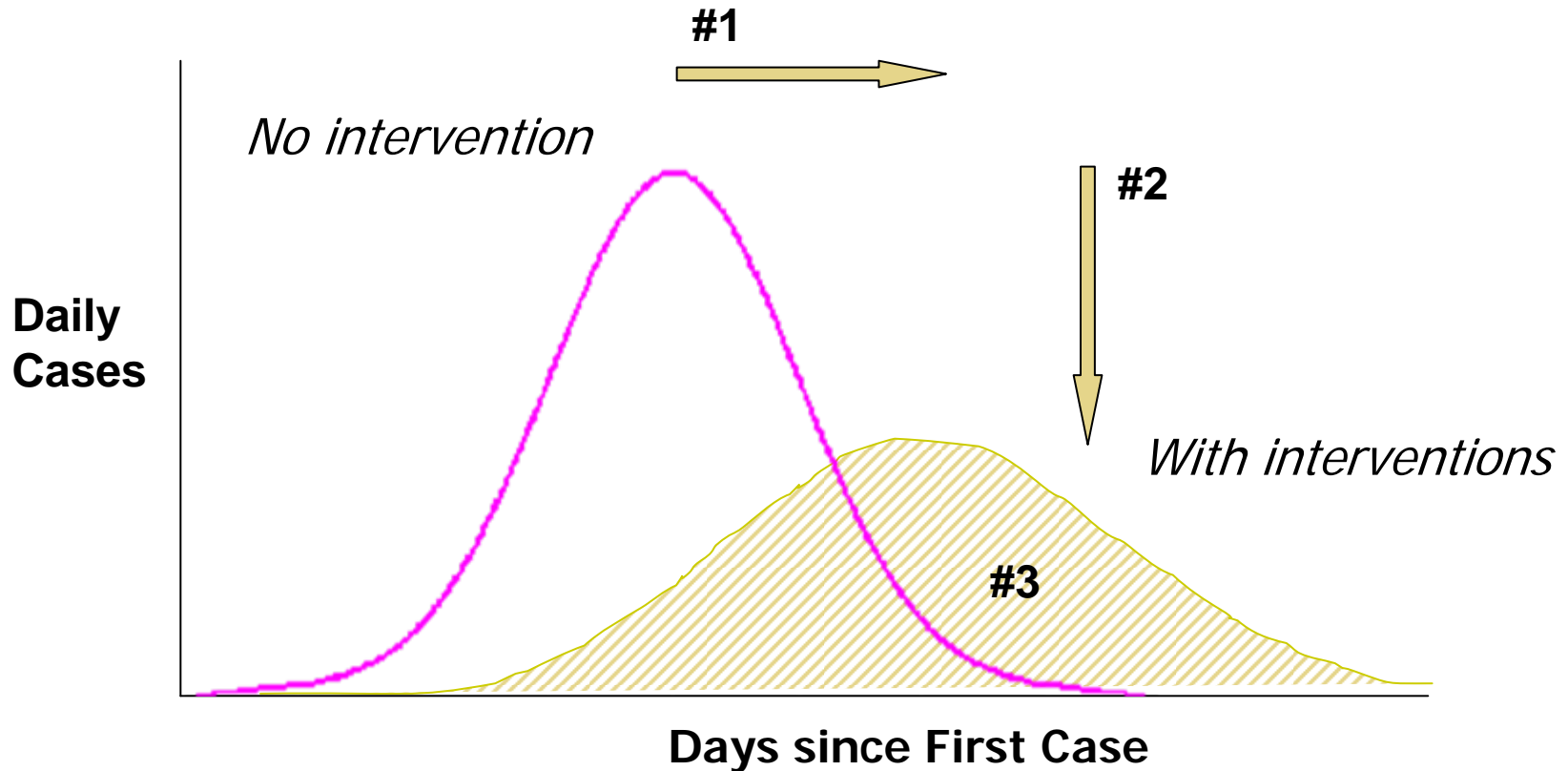
Washington Post

February 25, 2006



# Setting Expectations and Defining Success: Potential Impact of Community Mitigation

1. Delay and flatten outbreak peak
2. Reduce peak burden on healthcare system
3. Reduce number of cases



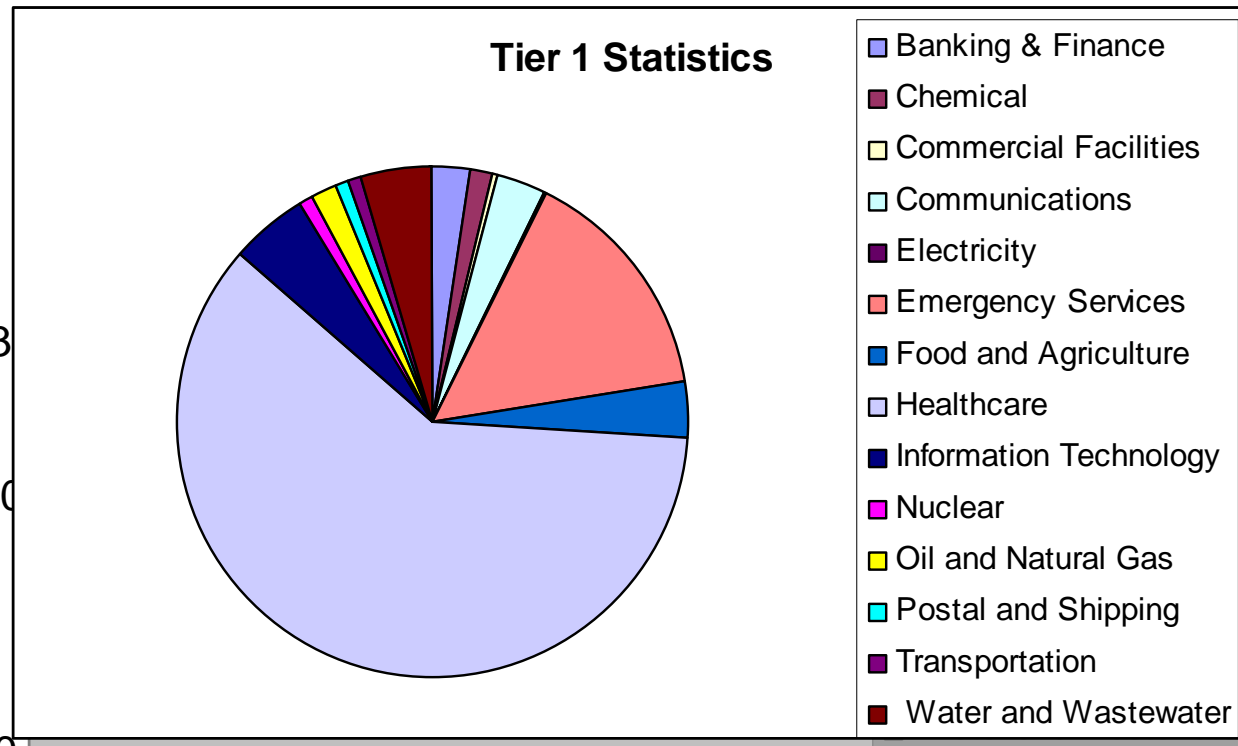
# **PRIORITIZATION: Who Goes First?**

- **To reduce morbidity, mortality and risk of complications**
- **To reduce occupational risk of infection**
- **To reduce risk of transmission to vulnerable persons**
- **To maximize vaccine effectiveness**
- **To protect persons working to delay entry of pandemic into US**
- **To protect persons providing pandemic response services**
- **To protect persons who maintain national and homeland security**
- **To protect persons providing essential economic services**
- **To protect children**
- **To protect persons providing essential community and government services**

# Identifying critical employee groups: The most critical among the critical infrastructure

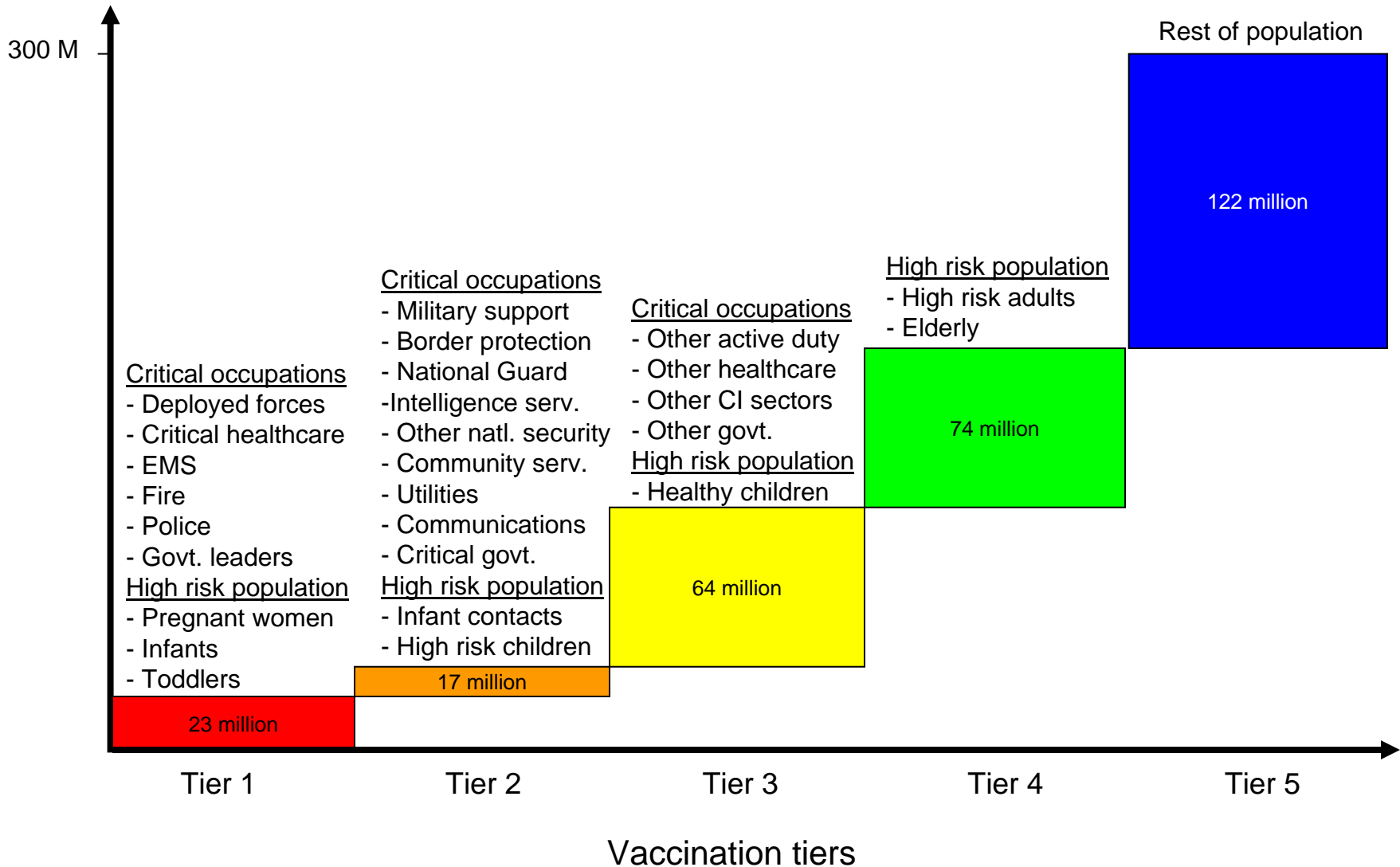
## Employees: Tier 1 Only

- **Banking & Finance:** 417,000
- **Chemical:** 161,309
- **Commercial Facilities:** 42,000
- **Communications:** 396,097
- **Electricity:** 50,000
- **Emergency Services:** 1,997,583
- **Food and Agriculture:** 500,000
- **Healthcare:** 6,999,725
- **Information Technology:** 692,800
- **Nuclear:** 86,000
- **Oil and Natural Gas:** 223,934
- **Postal and Shipping:** 115,344
- **Transportation:** 100,185
- **Water and Wastewater:** 608,000



**Total: 12,398,977**

# Pandemic Vaccination Allocation Framework for a Severe Pandemic



# Current and Proposed Antiviral Drug Use Strategies

<b>Population</b>	<b>Antiviral drug strategy</b>	<b>Est. number of regimens (millions)</b>
<b>Containment</b>	<b>Rx, Px</b>	<b>6</b>
<b>Ill persons</b>	<b>Rx</b>	<b>75</b>
Front-line healthcare and emergency service workers	Outbreak Px	86
Other healthcare workers	PEP	17
Household contacts of cases	PEP	88
Unique/specialized CI workers	Outbreak Px	2
Immunocompromised persons	PEP	2
Outbreak control in closed settings	PEP	5

Rx = Treatment; Px = Prophylaxis; PEP = Post-exposure prophylaxis

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# The Critical Role of Communications

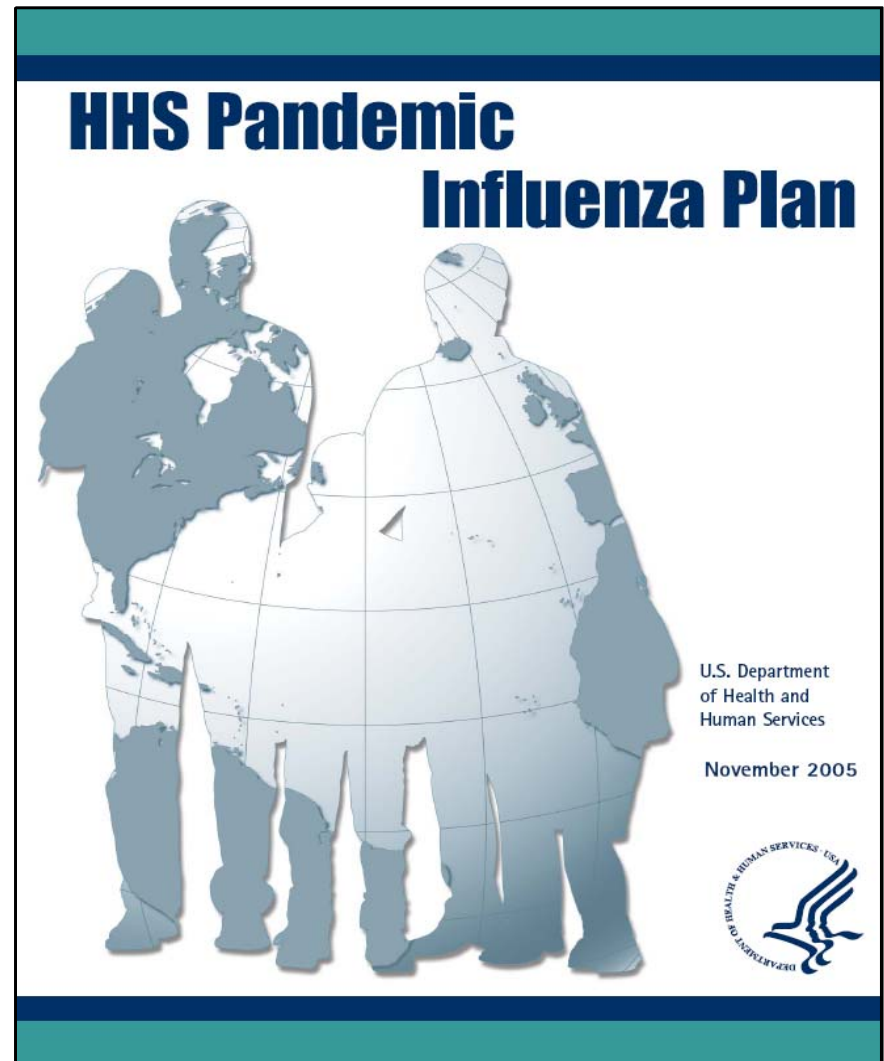


[www.pandemicflu.gov](http://www.pandemicflu.gov)

# HHS Pandemic Influenza Plan

- Vaccine
- Antiviral Drugs
- Diagnostics
- State and Local Planning
- Surveillance
- Healthcare Planning
- Infection Control
  - ❖ Community and Healthcare
- International Collaboration
- Communications

November 2005



# U.S. Pan Flu MCM Strategic Current & Possible New Goals

- **Vaccines**

- **Goal #1:** Establish and maintain a dynamic pre-pandemic influenza vaccine stockpile available for 20 M persons (2 doses/person) *or more persons depending on vaccine mfg. capacity & results of dose-sparing adjuvant studies and prime-boost immunization studies: H5N1 vaccine stockpiles*
- **Goal #2:** Provide pandemic vaccine to all U.S. citizens within 6 months of a pandemic declaration: pandemic vaccine (600 M doses)

- **Antivirals**

- **Goal #1:** Provide influenza antiviral drug stockpiles for pandemic treatment of 25% of U.S. population (75 M treatment courses) *and federal share pf antivirals for outbreak prophylactic usage as a community mitigation measure*
- **Goal #2:** Provide influenza antiviral drug stockpiles for strategic limited containment at onset of pandemic (6 M treatment courses)

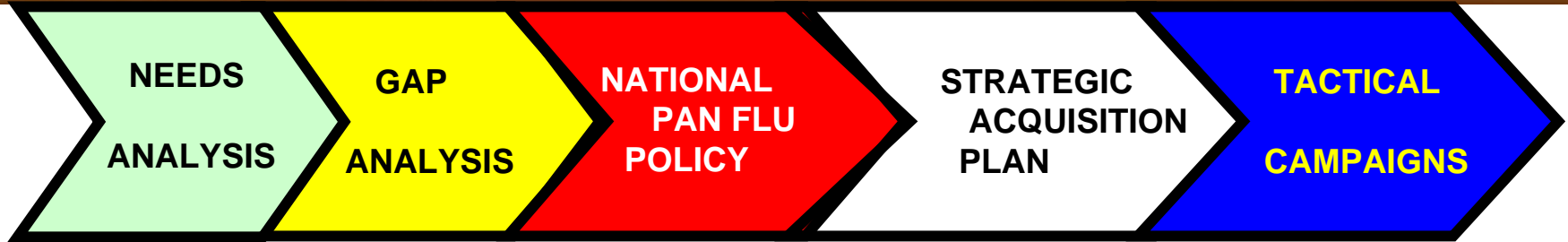
- **Diagnostics**

- **Goal #1:** Develop new high-throughput laboratory, point-of-care (POC), and home detection influenza diagnostics for pandemic influenza virus detection

- **Other Countermeasures**

- **Goal #1:** Develop and acquire other MCMs including syringes/needles, masks/respirators, ventilators, antibiotics, & other supplies

# BARDA Strategic Acquisition Plan for Pandemic Influenza Medical Countermeasures

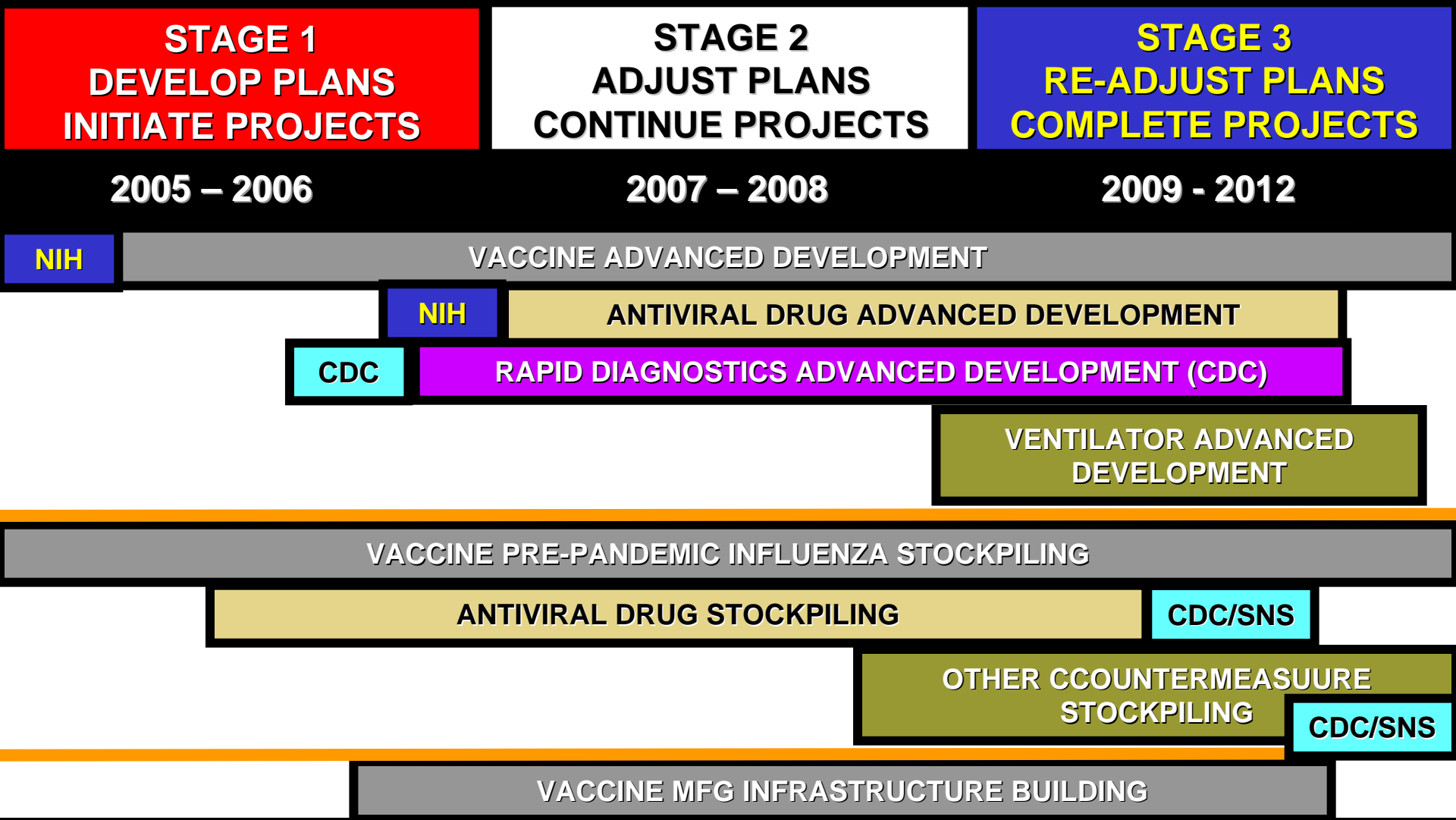


- Pandemic MCM needs identified (e.g. ventilators)
- Gap analyses of MCM need performed on industrial capacities & government stockpiles
- U.S. pandemic influenza strategy sets policy and goals
- Acquisition recommendations, guidance, & plans developed & provided (e.g. shared responsibilities)
- Tactical approach executed
  - MCM advanced development
  - MCM stockpile purchases (e.g. federal subsidies)
  - Infrastructure mfg. capacity building (e.g. retrofitting facilities)
  - Warm base operations
  - Misc. (e.g. futures contracts, liability relief, recommendation changes)

# U.S. Pan Flu MCM Program Principles

- **Utilize integrated approach using HHS- and USG-wide resources including senior HHS executive steering committee having biweekly meetings.**
- **Prioritize advanced product development of influenza MCMs towards U.S. licensure using following guidance:**
  - Targeted products (modernized mfg. process, broader specificity, longer lasting, easier delivery)
  - Multiple candidates with programmed attrition
  - Performance-based funding
  - Contractor commitments to U.S.-based mfg. surge capacities
  - BARDA oversight: Monthly reporting/meetings & quarterly on-site visits.
- **Establish & maintain pre-pandemic influenza vaccine & antiviral stockpiles using the following guidance:**
  - Stockpile composition and strain selection determined by HHS-wide process.
  - Licensed product or using licensed product mfg. processes and mfg. sites (vaccine)
  - Stored as bulk vaccine at mfg. site and final antiviral products at SNS with BARDA delivery inspections and annual audits
  - Formulated & filled when safety & immunogenicity data from clinical trials are available
- **Expand domestic MCM mfg. surge capacities to circumvent global border closures.**

# BARDA Strategic Pan Flu MCM Acquisition Plans





# BARDA Integrated Program Portfolio Approach

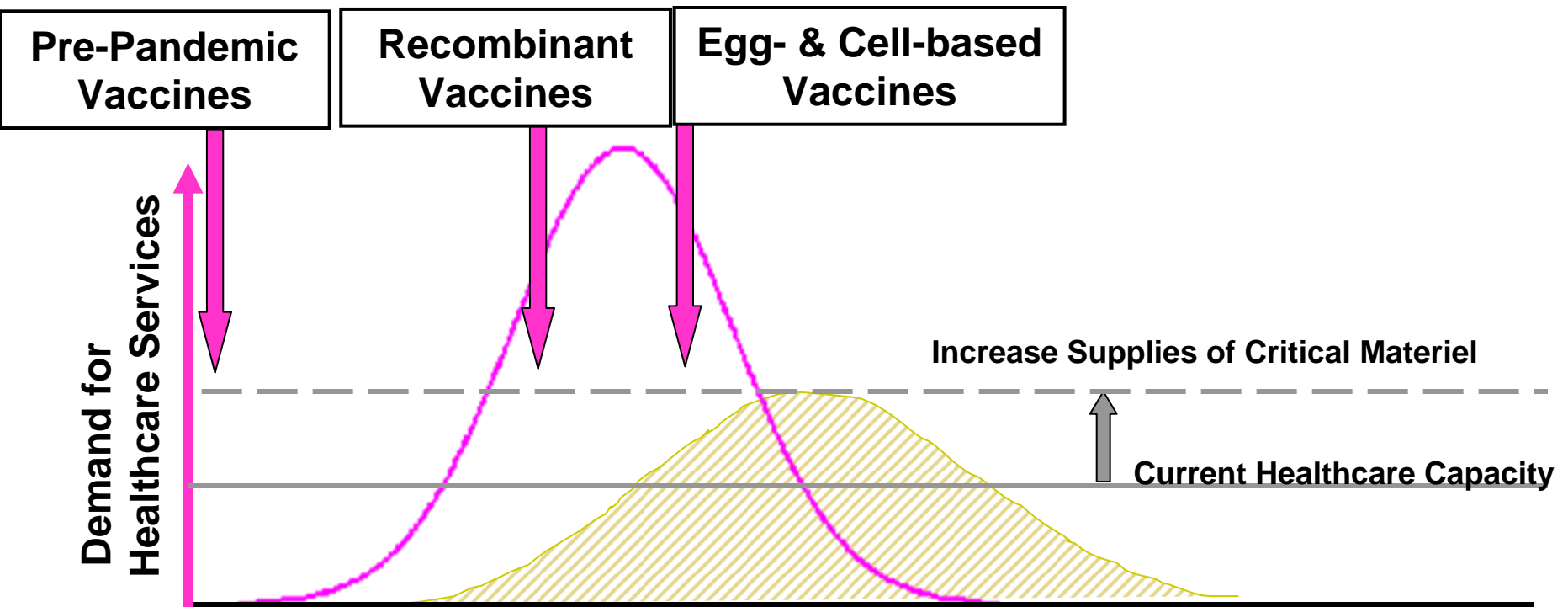
<b>27 contracts &amp;            2 grants            totaling \$3.5 B</b>	<b>Vaccines</b>	<b>Antivirals</b>	<b>Diagnostics/            Respiratory            Devices</b>
<b>Advanced            Development</b>	Cell-based Antigen-sparing Next Generation Recombinant	Peramivir	<u><b>Diagnostics</b></u> Point of Care Clinical Lab <u><b>Ventilators</b></u> Next Generation
<b>Stockpile            Acquisitions</b>	H5N1 Pre-Pandemic Vaccine Stockpiles	<u>Tamiflu &amp; Relenza</u> Federal Stockpiles State Stockpiles	Masks & Respirators
<b>Infrastructure            Building</b>	Retrofit Existing Mfg Facilities Build New Cell- based Mfg Facilities Egg-based Supply		

# Pre-pandemic and Pandemic Influenza Vaccines

- **Pre-pandemic vaccine**
  - Vaccine against viruses with “pandemic potential”
  - Produced during gaps in annual vaccine production
  - Match with pandemic strain and efficacy unknown
- **Pandemic vaccine**
  - Vaccine against the specific pandemic virus
  - Can only be produced once the pandemic occurs
  - Limited U.S. based vaccine production capacity

# MCM Gap Closure Between Supply and Demand

- Reduce Demand — **Pre-pandemic Vaccines**, Community Mitigation, Antivirals, Vaccines, Masks
- Increase Capacity—Ventilators, Oxygen, Antivirals, **Pandemic Vaccines**, Masks



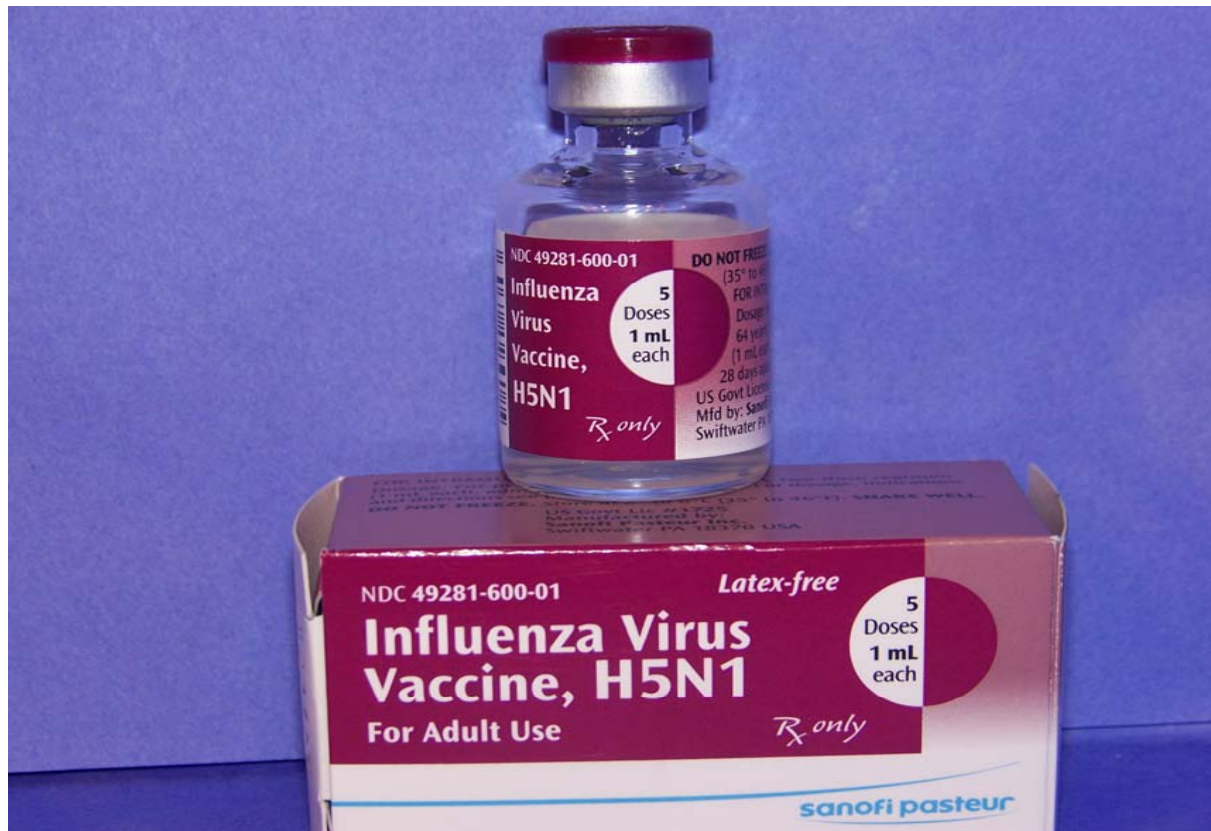
# Vaccines: Advanced Development

- **Five Projects** (10 contracts - \$1.5 B; 2 intl. grants - \$11 M)

Projects	Contract Awards	Industry Partners	Expected Results
Cell-based	\$1.3 B	sanofi pasteur Novartis GlaxoSmithKline MedImmune Solvay DynPort/Baxter	Expand domestic flu vaccine mfg. Provide 475 M doses pandemic vaccine by 2011
Antigen-sparing	\$133 M	Novartis GlaxoSmithKline IOMAI	Reduce amount of vaccine antigen needed  <b>BARDA Mix-N-Match Studies</b>
Next Generation: Recombinant	RFP Oct. 07	Contract awards expected in FY08	Diversify flu vaccine mfg. Reduce mfg. time
Egg-based Supply	\$43 M	sanofi pasteur	Provide year-round egg supply for flu vaccine mfg Provide clinical study vaccines

# Vaccines: Advanced Development

- H5N1 vaccine – first avian influenza vaccine for humans licensed (Apr. 2007) & #1 medical breakthrough in 2007 (Time, Dec. 2007)



# Pre-Pandemic Vaccine Stockpile: Challenges

- Virus antigenic drift
- Vaccine product stability over time
- Optimal vaccine product formulation
- Multiple vaccine products & manufacturers
- Vaccination strategy



# Vaccines: Stockpile Acquisitions

- **Four Projects** (6 contracts, \$925 M)
- **First H5N1 vaccine** licensed (Apr. '07) to sanofi pasteur.

Projects	Contracts	Industry Partners	Current Results
H5N1 Vaccine 2004	\$21M	sanofi pasteur	Provide 0.47 M doses @ 90 ug/dose of pre-pandemic stockpile (H5N1 Clade 1)
H5N1 Vaccine 2005	\$243 M	sanofi pasteur Novartis	Provide 8.0 M doses @ 90 ug/dose of pre-pandemic stockpile (H5N1 Clade 1)
H5N1 Vaccine 2006	\$241 M	sanofi pasteur Novartis GlaxoSmithKline	Provide 4.9 M doses @ 90 ug/dose of pre-pandemic stockpile (H5N1 Subclade 2.1)
H5N1 Vaccine 2007	\$420 M	sanofi pasteur Novartis GlaxoSmithKline	Provide 11.2 M doses of pre-pandemic stockpile (H5N1 clade 2)



# U.S. H5N1 Vaccine Stockpiles 2007

H5N1 Vaccine Strain	Clade	2004	2005	2006	2007	Totals
A/VTN/1203/04	1	0.45	7.05	0.91		8.41
A/Indo/05/05	2.1			6.44	2.25	8.69
A/BHG/QL/1A/05*	2.2				6.42	6.42
A/Anhui/1/05	2.3				2.51	2.51
Totals (90 ug/dose)		0.45 M	7.05 M	7.35 M	11.18 M	26.03 M
Totals w/adjuvants 7.5 ug/dose		5.4 M	84.6 M	88.2 M	134.2 M	312 M

^ doses represented as 90 ug HA/dose antigen alone

\* A/Bar-headed Goose/Quinghai Lake/1A/05

# Pre-Pandemic Vaccine Stockpile



# Vaccines: Infrastructure Building

- **Three Projects** (3 contracts - \$175.5 M)

<b>Projects</b>	<b>Funding</b>	<b>Industry Partners</b>	<b>Expected Results</b>
Egg-based Supply	\$43 M	sanofi pasteur Contract awarded in 2004	Provide secure year-round egg supply for flu vaccine mfg Provide clinical study vaccines
Retrofit existing mfg. facilities	\$132.5 M new RFP in FY08 for pilot & fill-finish facilities	sanofi pasteur MedImmune Contracts awarded in 2007	Increase domestic flu vaccine capacity to produce 100+ M doses of egg-based pandemic flu vaccine & warm-base operations
Build new cell-based vaccine facilities	RFP expected in FY08	Contract awards expected in FY08	Build domestic cell-based flu vaccine mfg. Capacity to support 475 M pandemic dose level

# Vaccines: Infrastructure Building

- Secure, year-round egg supply for domestic flu vaccine manufacturing completed 2006



# Vaccines: Infrastructure Building

- sanofi pasteur – new egg-based flu vaccine manufacturing facility completed 2007





# Vaccines: Infrastructure Building

- **Novartis – new cell-based flu vaccine manufacturing facility started 2007**



# Antivirals: Advanced Development

- **One Project** (1 contract - \$102.6 M)

Projects	Contract	Industry Partner	Expected Results
New influenza antiviral drugs	\$102.7 M	BioCryst	Expand & diversify flu antivirals Develop <b>peramivir</b> for I.M./I.V. administration towards U.S. licensure by 2011

**Peramivir is a neuraminidase inhibitor with a cyclopentane derivative structure -- not an analog of sialic acid**





# Antivirals: Stockpile Acquisitions

- **Two Projects** (4 contracts - \$924 M)

Projects	Contracts	Industry Partners	Current Results
Federal pan flu antivirals stockpiles	\$754 M	Roche GlaxoSmithKline	50 M treatment courses of flu antivirals purchased for federal stockpile for pandemic containment & treatment (50 M treatment courses stockpile goal)
State pan flu antivirals stockpiles	\$170 M	Roche GlaxoSmithKline	19.3 M treatment courses of federally-subsidized purchases of flu antivirals by States and other entities (31 M treatment courses stockpile goal)



# Diagnostics: Advanced Development

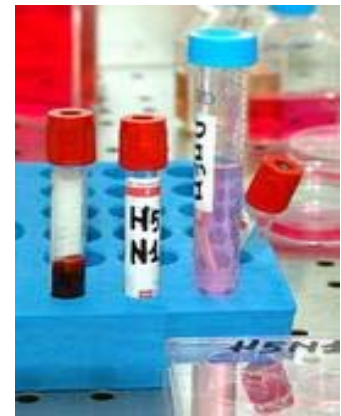
- **Two Projects** (4 contracts - \$40.6 M with CDC)

<b>Projects</b>	<b>Contacts</b>	<b>Industry Partners</b>	<b>Expected Results</b>
POC flu diagnostics	\$15 M (\$41 M)	Nanogen MesoScale Cepheid IQuum	Facilitate development of point of care diagnostics towards U.S.-licensure for detection of pandemic flu viruses within 30 min.
Clinical lab diagnostics	RFP Oct. '07	Contract awards expected in FY08	Facilitate development of high throughput clinical laboratory diagnostics towards U.S.-licensure for detection of pandemic flu viruses

# Point of Care Influenza Diagnostics

## GOAL

- Facilitate development of 30 minute point-of-care diagnostics towards U.S.-approval for detection of pandemic flu viruses
  - Detect and differentiate influenza A H5N1 from seasonal influenza
- Dec. '06: Contracts awarded
  - Cepheid: GeneXPert<sup>®</sup> Flu Assay (**Terminated Aug. '07**)
  - Iquum: LAIT<sup>™</sup> -- Lab-in-a-Tube (**Terminated May '07**)
  - MesoScale: Multi-Array<sup>™</sup> Detection
  - Nanogen: Point of care immunoassay system



# Other MCMs & Materials: Gaps and Responsibilities

<b>MCMs &amp; Materials for PI &amp; All Hazards</b>	<b>I</b>	<b>B</b>	<b>H</b>	<b>S</b>	<b>F</b>
<b>Antiviral drugs for prophylactic usage in household contacts of infected persons</b>					
<b>Syringes and Needles for vaccines</b>					
<b>N95 respirators</b>					
<b>Surgical Masks</b>					
<b>Ventilators and Associated Equipment</b>					
<b>Medical Oxygen</b>					
<b>IV Antibiotics</b>					
<b>Mortuary Supplies – body bags</b>					

**I – Individual; B – Business; H – Healthcare; S – State; F – Federal**

# Pandemic Influenza Summary

- Robust and comprehensive portfolio approach to developing and acquiring a broad array of medical countermeasures (vaccines, antivirals, and diagnostics)
  - HHS awarded 27 contracts totaling \$3.5 B since Dec. 2005 for Stage 1 of the medical countermeasure program
  - HHS initiated Stage 2 initiatives in Sept. '07 for advanced development of next generation recombinant vaccines, expansion & management of vaccine and antiviral stockpiles, & domestic vaccine infrastructure building
- Cooperative effort leveraging resources from throughout HHS (NIH, CDC, FDA, OS & ASPR), USG, States and Industry
- Develop, acquire, & build domestic capacity for other countermeasures including syringes, masks, ventilators, etc.

# PI MCM Preparedness Next Steps in 2008

- **Vaccines**
  - Continue advanced development of vaccines
  - Continue expansion of pre-pandemic vaccine stockpile
  - Expand domestic manufacturing surge capacity
  - Stockpile syringes/needles
- **Antivirals**
  - Complete State AV stockpiles for treatment in 2008
  - Determine shared responsibilities for in outbreak antiviral prophylactic usage
  - Continue & expand advanced development of antivirals
- **Diagnostics**
  - Facilitate development of home influenza virus detection devices
- **Other Countermeasures**
  - Develop guidance for masks & respirators
  - Determine shared responsibilities
  - Develop next generation ventilators warm base mfg., & add to SNS stockpile & materials



# U.S. Pan Flu MCM Program Future

- **Complete the mission on each program and project (“Finish the end game”) aligned with doctrine of shared responsibility**
- **Determine whether stockpiling of re-pandemic vaccines in people s safe, effective, and feasible**
- **Develop cross-cutting MCMs using platform technologies, broad spectrum drugs, and others that may afford expanded domestic manufacturing surge capacity rather than stockpiling**
- **Innovate MCM technological breakthroughs using PAHPA**
- **Model Pan Flu MCM stockpiling & stockpiling ideas including people periodically with other key agencies**