



AI/PI UPDATE

September 2007
Defense Health Board

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Force Health Protection & Readiness



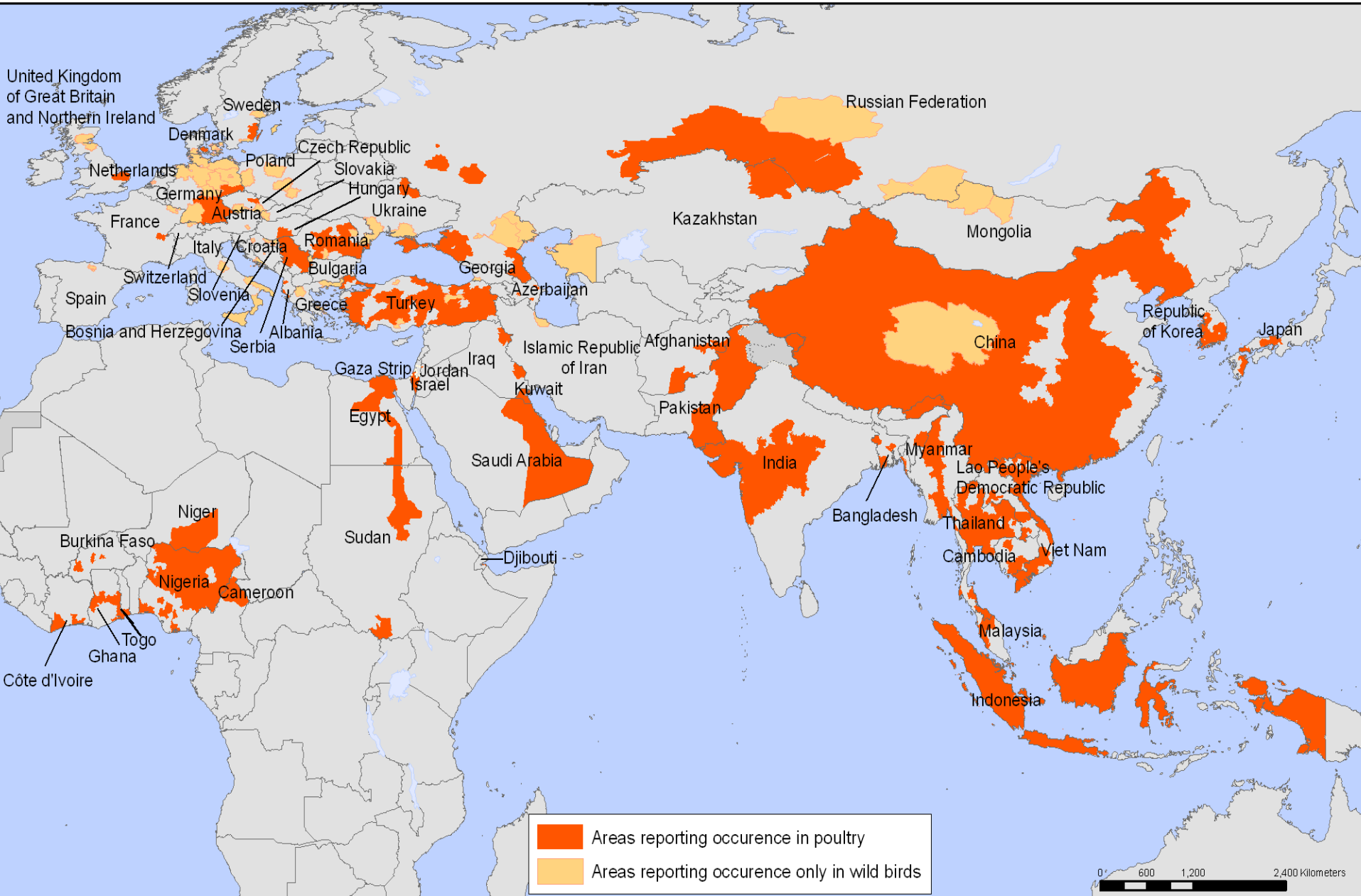
H5N1 Avian Influenza

- Virus continues to mutate
 - Persistence in wild and domestic bird population since at least 1987 is both worrisome and reassuring
 - Now four distinct strains causing human disease (2 clades, 3 subclades)
 - Indonesian subclade 2.1 with highest mortality (80%), largest number of cases, smallest geographic distribution
 - Strain affecting Europe, Africa, Middle East with lowest mortality (30%), next to highest number of cases, largest geographic location – coincides with majority of deployed forces

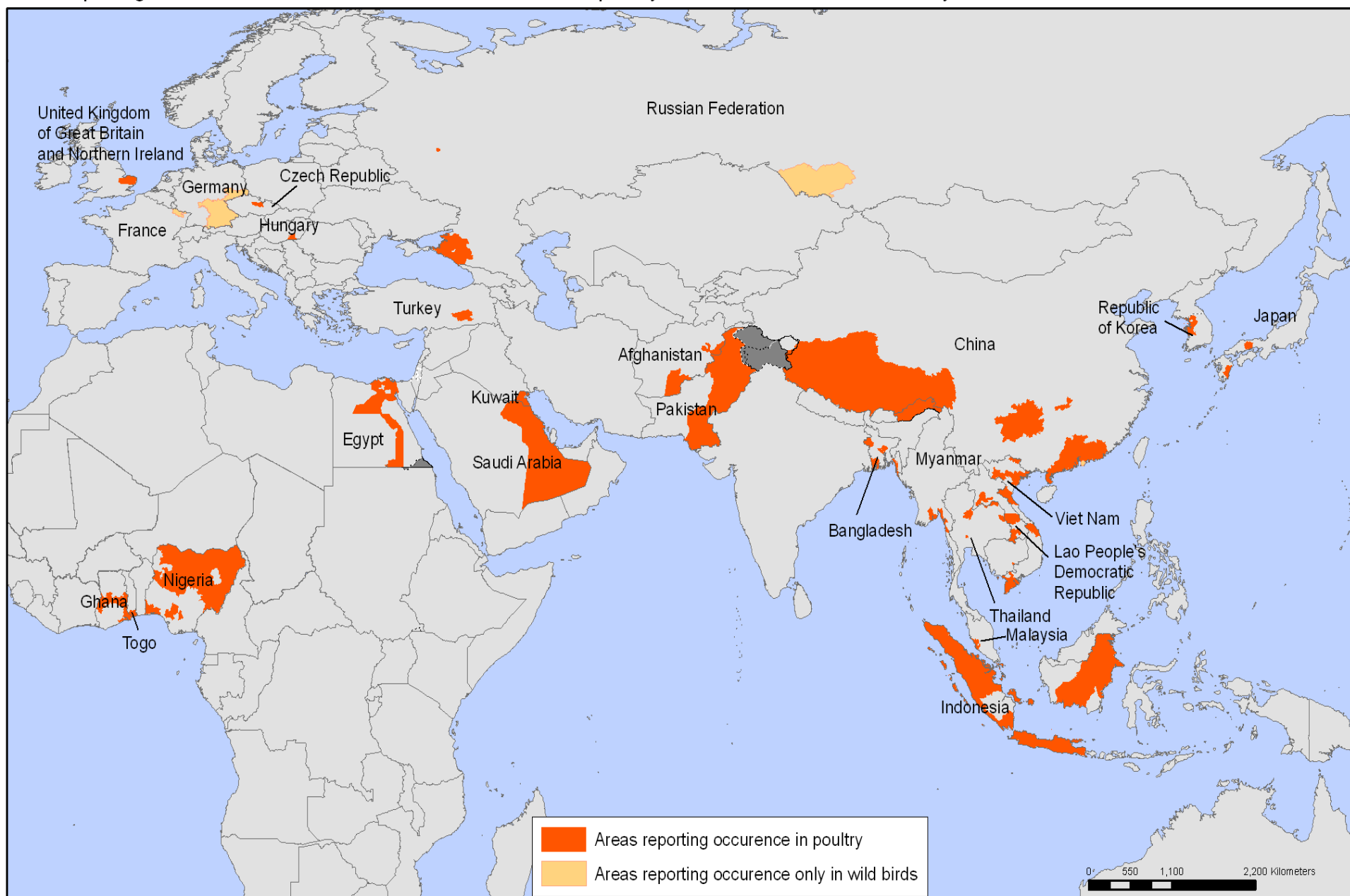


H5N1 Avian Influenza

- Geographic spread consistent with domestic and wild bird distribution
- No significant change in human-to-human transmission – sporadic cases continue
- Birds remain the primary host
 - Cats, dogs and other mammals have developed disease without effective transmission
 - No evidence of transmission to humans other than via avian or human routes



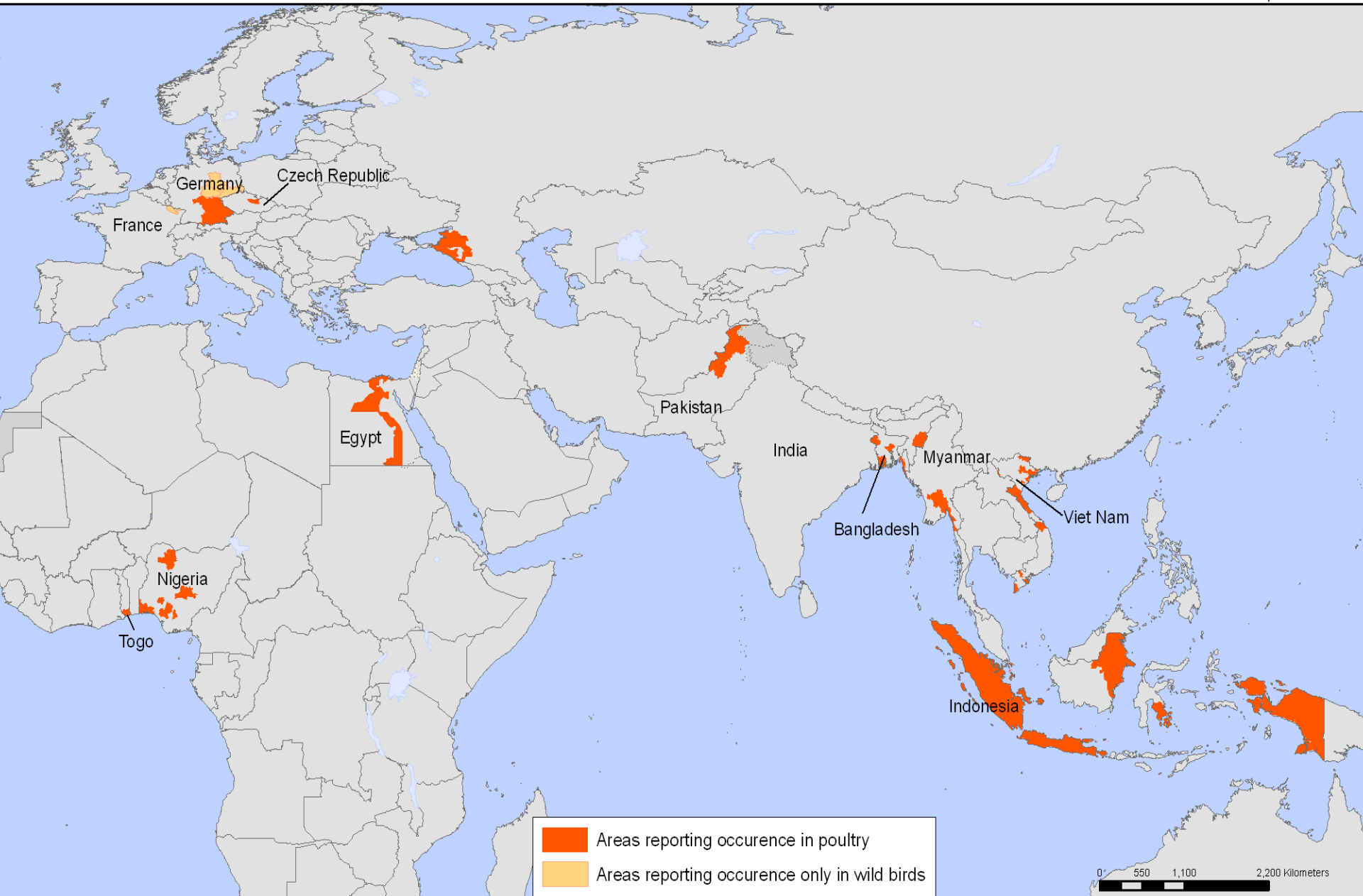
Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds between January and June 2007





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Data Source: World Organisation for Animal Health (OIE) and national governments
Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS) World Health Organization



 Areas reporting occurrence in poultry
 Areas reporting occurrence only in wild birds

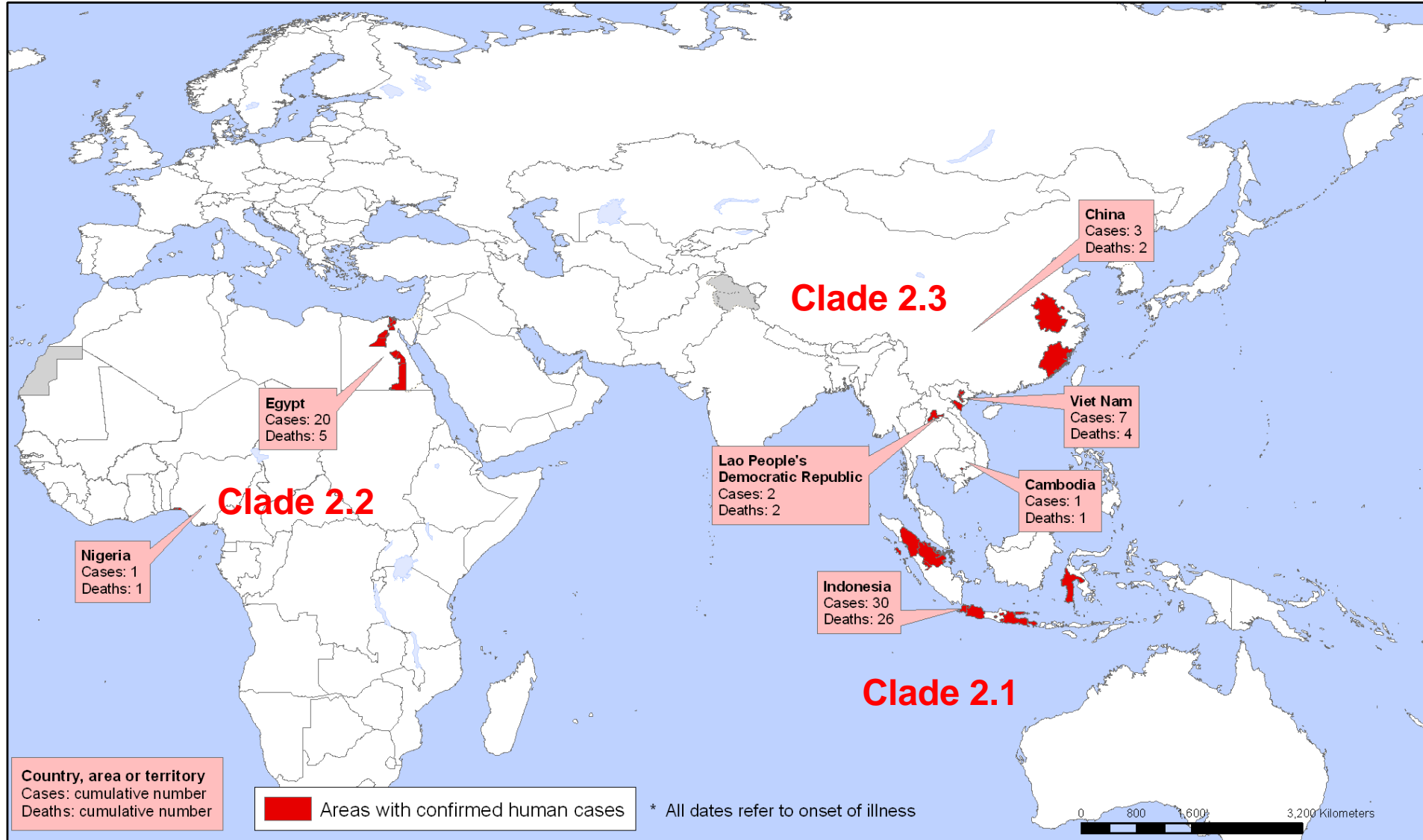
0 550 1,100 2,200 Kilometers



H5N1 Avian Influenza Clades Causing Human Infections Since 2003

H5N1 clade	Cases	Deaths	Countries
Clade 1	125	66	Cambodia, China, Thailand, Vietnam
Clade 2.1	106	85	Indonesia
Clade 2.2	63	27	Azerbaijan, Djibouti, Egypt, Iraq, Nigeria, Turkey
Clade 2.3	27	18	China, Laos, Vietnam
Total	321	196	

Areas with confirmed human cases of H5N1 avian influenza since 1 January 2007 *





Sample Sharing Issues

- Indonesia demanding guaranteed access to benefits stemming from samples
 - Threatens existing Global Influenza Surveillance Network
 - Ongoing negotiations
 - Currently engaged in limited sample sharing
 - Recent events questioning GOI transparency
 - Recent denial of previously confirmed limited human-to-human transmission



What's New Potpourri

- WHO recently changed its criteria for diagnosis of cases by in-country labs
 - Improved real time reporting of positive cases
- 7 Seroprevalence Studies
 - Studies in Vietnam, Thailand, Cambodia, Russia all with negative findings
 - Only one with + results: 4/2000 poultry workers in Korea all without clinical disease
- Two required mutations identified for transition from avian to human binding site affinity
 - Despite change, not able to sustain transmission



Neuraminidase Resistance

- Two new mutations (in vitro) identified
 - Oseltamivir no longer alone
 - Potential Oseltamivir, Zanamivir and Peramivir resistance Clade 2.1
 - Specific mutation is rare
 - Zanamivir resistant hemagglutinin mutants easier to generate



DoD Activities- Recently Published Guidance and Policy

- Antiviral guidance
 - Guidance for use is based on variable supply and disease severity
 - Uses National Pandemic Severity Categories
 - Reinforces need for early and consistent implementation of non-pharmacologic mitigation measures
 - Introduces a post-exposure prophylaxis strategy



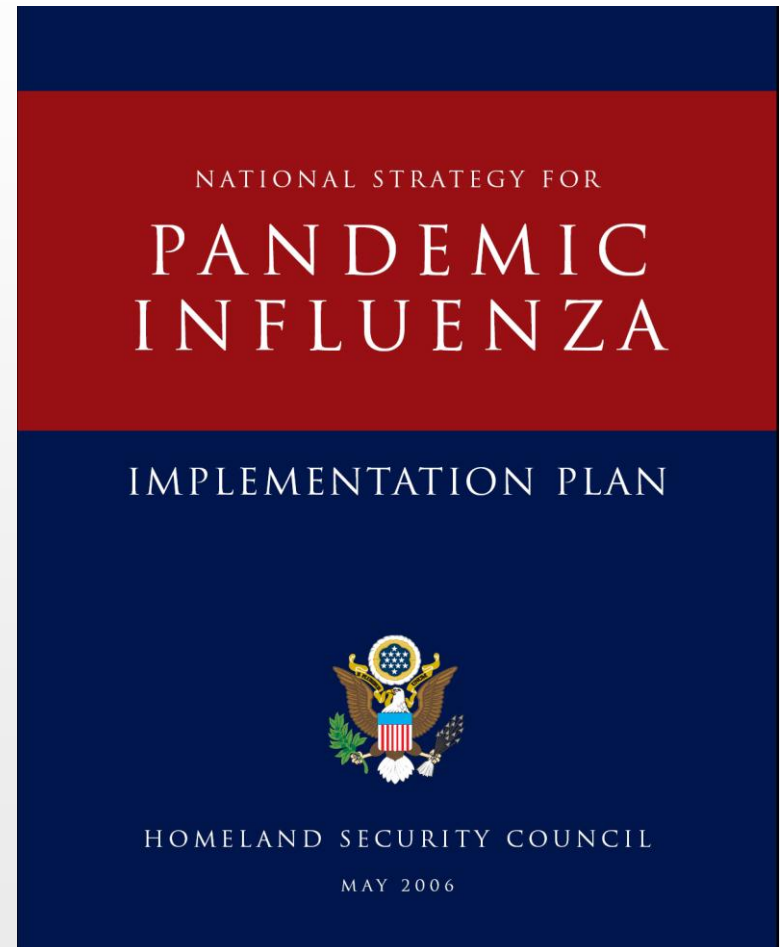
Vaccine





Current Pre-Pandemic Vaccine Targets

- HHS: Establish and maintain stockpiles of pre-pandemic vaccines adequate to immunize 20 million persons against influenza strains that present a pandemic threat
- DoD: Establish stockpiles of H5N1 vaccine and other influenza subtypes determined to represent a pandemic threat adequate to immunize 1.35 million persons





Current Status of National Pre-Pandemic Vaccine Stockpiling

- Includes 14.85 million doses of H5N1 vaccines
 - DoD portion 1.2 million doses
 - Vaccines produced in 2004-07
 - Products from 3 manufacturers
 - Products use different reference strains reflecting the evolution of H5N1 viruses in birds and humans
 - One product licensed
 - Most of HHS stockpile stored by manufacturers in bulk
 - Most of DoD stockpile in vials – pursuing shelf life extension
- Additional vaccine contracts being completed for 2007-08
 - Will include vaccine to new H5N1 virus strains



Current Strategies for Use of Civilian Stockpile of Pre-Pandemic Vaccine

- Vaccination of laboratory personnel who work with H5N1 and pandemic response personnel is ongoing (using licensed vaccine under a CDC IND)
- Vaccination of defined target groups when a pandemic is imminent
 - 2 doses per vaccine recipient
 - Level of protection depends on similarity between vaccine and pandemic viruses



DoD Activities — Pre-Pandemic Vaccine Policy

- Pre-Pandemic Vaccine Use
 - Offer FDA approved vaccine to lab personnel and response teams with direct contact with High Path H5N1
 - Establishes tracking, effectiveness and adverse event monitoring
 - With imminent onset of pandemic designates JS with NORTHCOM as COCOM synchronizer to determine priorities based on risk, ability to receive two doses and critical role



National and DoD Strategy May Change

- If production can be substantially increased
 - Added/expanded facilities – long term
 - Non-egg based production – intermediate
 - Adjuvanted vaccine – short term
- If there is a better vaccine
 - Universal vaccine
 - Improved cross protection



H5N1 Vaccine Studies

- Split virion and whole cell vaccines
- Adjuvants (alum, MF59, AS)
- Intradermal vs. IM vaccination
- Mix and Match Adjuvant Study
- Data on cross immunogenicity between clades and subclades



Immunogenicity of Whole Cell Clade 1 H5N1 Vaccine Across Clades

Results of Phase 1/2 study of Baxter vero-derived whole cell A/Vietnam/1203/2004 (H5N1) vaccine, 7.5 ug unadjuvanted, in persons aged 18-44, who received doses on day 0 and 21*

Day	Number (%) with microneutralization titer $\geq 1:20$	
	A/Vietnam/1203/2004	A/Indonesia/05/2005
0	0/42 (0%)	0/42 (0%)
21	17/42 (40.5%)	10/42 (23.8%)
42	32/42 (76.2%)	19/42 (45.2%)

Notes:

- 1) Microneutralization test not standardized; titer $\geq 1:20$ may not correlate with protection
- 2) Other manufacturers also have evaluated cross-immunogenicity (e.g., GSK AS adjuvanted vaccine)

*WHO meeting on H5N1 vaccines, February 2007



Immune Priming and Cross- Immunogenicity After a Booster Dose

Stephenson I, J Infect Dis, 2005

- Subjects received 2 doses (21 day interval) of plain or MF59 adjuvanted Dk/Sing/97 (H5N3)
- 16 months later, 26 subjects received a third dose of the same vaccine



Immune Priming and Cross-Immunogenicity After a Booster Dose

Stephenson I, J Infect Dis, 2005

Test antigen, # doses	% with ≥ 4 -fold rise HAI titer	
	MF59	Plain
Dk/Sing/97 (H5N3) 2 doses 3 doses	64% 100%	0 18%
HK/213/03 (H5N1) 2 doses 3 doses	14% 100%	9% 27%
VN/1203/04 (H5N1) 2 doses 3 doses	9% 27%	0 0
Thai/16/04 (H5N1) 2 doses 3 doses	14% 71%	0 0



Booster Immune Response Following Priming with an Antigenic Variant

(Goji, IDSA 2006, Abstract LB-4)

- 37 persons vaccinated in 1998 with 2 doses of 90 ug unadjuvanted A/HK/156/1997 (H5N1)
- Vaccinated 8 years later with 1 dose, 90 ug unadjuvanted
- A/VN/1203/2004 (H5N1)
- Antibody responses compared with H5 naïve subjects who received a single 90 ug dose of the latter vaccine

Group	4-fold rise	HAI titer $\geq 1:40$
Primed	68%	70%
Unprimed	23%	24%



Adjuvanted Clade 1 Vaccine Safety and Efficacy Data

Leroux-Roels et al. Lancet Aug 18, 2007

- Design
 - Observer blind randomized trial
 - 2 doses inactivated split A/Vietnam/1194/2004 vaccine
 - Doses administered 21 days apart
 - N= 400 (eight groups of 50 aged 18-60)
 - 4 antigen doses (3.8, 7.5, 15, 30 ug)
 - Vaccine with and without adjuvant



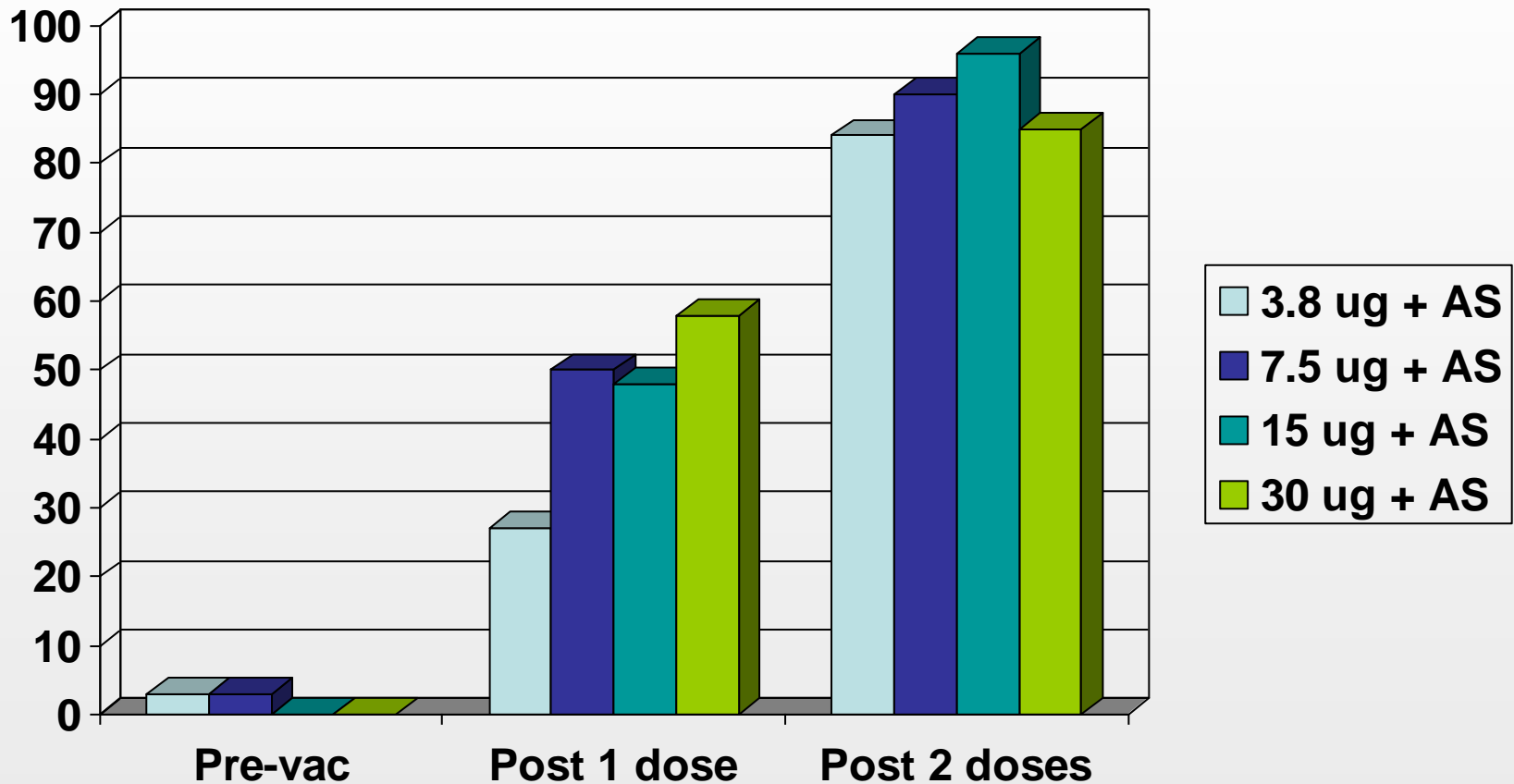
Demographics

	Total	3.8ug n=50	3.8 adj n=51	7.5ug n=50	7.5 adj n=50	15ug n=50	15 adj n=50	30ug n=50	30 adj n=49
Age Yrs									
Mean	34.3	33.7	35.3	33.0	34.4	35.1	33.9	35.3	33.6
Gender %									
Female	54	54	71	50	44	50	60	54	51
Ethnicity %									
White	100	100	100	96	100	100	100	100	100
African	<1	0	0	2	0	0	0	0	0
Asian	<1	0	0	2	0	0	0	0	0

Extracted from Leroux-Roels et al. Lancet Aug 18, 2007



Immune Response to Adjuvanted (AS) H5N1 Vaccine, A/VN/1194/2004



Derived from Hehme, GSK, presentation at WHO, Geneva, 2/15-16/07



HI Antibody Response to Homologous Vaccine Strain Non-Adjuvanted Vaccine

	3.8 ug	7.5 ug	15 ug	30 ug
Prime +21 d				
Seroprotection titer >1:40	0%	8%	20%	29%
Boost + 21 d				
Seroprotection titer >1:40	4%	16%	35%	43%

Extracted from Leroux-Roels et al. Lancet Aug 18, 2007



HI Antibody Response to Homologous Vaccine Strain Adjuvanted Vaccine

	3.8 ug + ad	7.5 ug+ad	15 ug+ad	30 ug+ad
Prime +21d				
Seroprotection titer >1:40	26%	50%	49%	58%
Boost + 21d				
Seroprotection titer >1:40	84%	90%	96%	85%

Extracted from Leroux-Roels et al. Lancet Aug 18, 2007



Results

- All eight vaccine formulations had a good safety profile with no serious adverse events reported
- Adjuvanted vaccine induced more injection-site and general symptoms
 - Most mild to moderate and all transient
- Adjuvanted formulations significantly more immunogenic at all doses



In Praise of Ferrets





Ferret Data Adjuvanted Vaccine

- Immunization with low dose adjuvanted split H5N1 vaccine protects ferrets against homologous and heterologous challenges
 - Ferrets immunized with a A/Vietnam/1194/2004 adjuvanted vaccine
 - Challenge with Clade 1 A/Vietnam/1194/2004 and Clade 2.1 A/Indonesia/5/2005





Homologous Challenge Protection Day 5 Post-challenge

	Dead	Alive	% Survival
Unadjuvanted Vaccine	4	1	20
Adjuvant alone	6	0	0
Vaccine-AS (0.6 ug)	2	4	67
Vaccine-AS (1.7 ug)	1	4	80
Vaccine-AS (5 ug)	0	5	100
Vaccine-AS (15 ug)	0	6	100



Heterologous Challenge Protection Day 5 Post-challenge

	Dead	Alive	% Survival
Unadjuvanted Vaccine	6	0	0
Adjuvant alone	6	0	0
Vaccine-AS (1.7 ug)	1	5	83
Vaccine-AS (3.8 ug)	0	0	100
Vaccine-AS (7.5 ug)	0	5	100
Vaccine-AS (15 ug)	0	6	100



Summary of H5N1 Pre-Pandemic Vaccine Studies

- Adjuvants increase immunogenicity and cross-immunogenicity of H5N1 vaccines
- A single dose of GSK AS adjuvanted H5N1 vaccine could protect ~1/2 vaccine recipients
- Priming with 1 or 2 vaccine doses leads to a booster response to a subsequent dose of the same or a different H5N1 vaccine
- Pending studies
 - “Mix-and-match” GSK AS adjuvant with other companies’ influenza antigen
 - Further trials of cross-immunogenicity and of priming

If you
are sick,



**STAY
HOME!**



**PANDEMIC
INFLUENZA
EXERCISE
IN PROGRESS**



ARE YOU READY?

Beat the flu...



**PRACTICE
SOCIAL
DISTANCING!**





Exercise Purpose

To ensure P&R's preparedness to continue mission essential operations, with a diminished force, and to safeguard its staff during a pandemic influenza health crisis.

The exercise was designed to:

- Assess overall preparedness to handle a pandemic influenza
- Identify vulnerabilities in plans, policies and procedures
- Identify strengths that could be expanded/exported
- Capture lessons learned to help frame policies for use in the field and to share best practices/lessons learned with other Federal agencies
- Identify Way Forward for improvement



Exercise Goals

Assess:

- ✓ Ability to work at home
 - IT connectivity/server capacity
- ✓ Capability of Communication Systems
 - 1-800 Call-In Number
 - Telephone Trees
- ✓ Ability to socially distance at work
- ✓ Ability to execute a sample of mission essential functions with a diminished workforce
 - Flow of order of succession
 - Delegation of authorities
- ✓ Ability to muster using web based tool

All goals accomplished!



Exercise Accomplishments

- At endstate, the overall readiness rating at P&R was 96%.
 - Total number of participants: 1506
 - Total number of on-site employees: 1201 (81%)
 - Total number of teleworkers: 251 (17%)
 - Total number of incapacitations: 54 (3%)
- Telework Practice Helps
 - First day of exercise: 32 Force Net IT Help Desk Calls
 - Second day: 14 Force Net IT Help Desk CallsInput from satellite organizations reflects similar statistics



Leadership Decisions

- Continue with readiness preparations to resolve identified vulnerabilities
 - PI Way Forward should be incorporated in P&R COOP plan
 - Future exercises should:
 - More fully stress IT capabilities when working from home
 - Include more contractors
 - Assess impact of PI on Pentagon parking and food service
 - Test OSD and interagency integration
- Consideration of appointment of a full time P&R Emergency Preparedness Program Manager to oversee preparation and exercise for COOP, Pandemic and other crises



Next update

- Expanded PI exercise results
- Policy adjustment after increase in antiviral stockpile
- Pre-pandemic vaccine
 - Acquisition plans
 - More data
- Vaccine modeling results

**She's coming to
your next meeting...**



AP / Said Abu el-Einein

**PRACTICE
SOCIAL
DISTANCING!**



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Any Questions?

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