

Current issues in global influenza pandemic preparedness

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Outline

1. The current pandemic threat
 - how is a pandemic influenza virus generated?
 - will avian H5N1 become pandemic in humans?
2. Global influenza surveillance
 - the role of WHO
 - barriers to effective surveillance
3. Global pandemic response
 - impact of International Health Regulations
 - outbreak prevention and control



How is a pandemic influenza virus generated?



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Influenza A viruses

- Natural hosts of all subtypes are aquatic birds:
 - subclinical infection of GI epithelium
 - virus excreted
- Some H5 and H7 subtypes are highly pathogenic, others have low pathogenicity (H6, H9) in poultry
- A few subtypes established in mammals
- New viruses emerge by:
 - mutation
 - reassortment of segmented genome when two viruses infect one cell



Origin of previous pandemic influenza A viruses

Pandemic	Subtype	Origin	Pathogenicity
1918	H1N1	Avian - mutation?	High?
1957	H2N2	Avian/human reassortment	Low
1968	H3N2	Avian/human reassortment	Low

H1N1 and H3N2 are still circulating as adapted human viruses



Species tropism and virulence factors (1)

- Specificity of HA for host sialic acid receptors:

Species	Tissue	SA α -2,3 Gal	SA α -2,6 Gal
duck	GIT	+	-
pig	RT	+	+
human	RT	-	+



Species tropism and virulence factors (1)

- Specificity of HA for host sialic acid receptors:

Species	Tissue	SA α -2,3 Gal	SA α -2,6 Gal
duck	GIT	+	-
chicken, quail	GIT, RT	+	+
pig	RT	+	+
human	upper RT	-	+
	lower RT	+	+



Species tropism and virulence factors (2)

- HA cleavage (required for viral replication):
 - cleaved by proteases restricted to RT and GIT in poultry
 - multiple basic amino acids at cleavage site enable systemic infection
 - Reduced induction of host IFN- α/β
 - Excessive induction of some other host cytokines, activation of apoptotic pathways
 - Increased resistance to host IFN- α/β and TNF- α
- **Generation of pandemic virus requires several mutations**



Will avian H5N1 become pandemic in humans?



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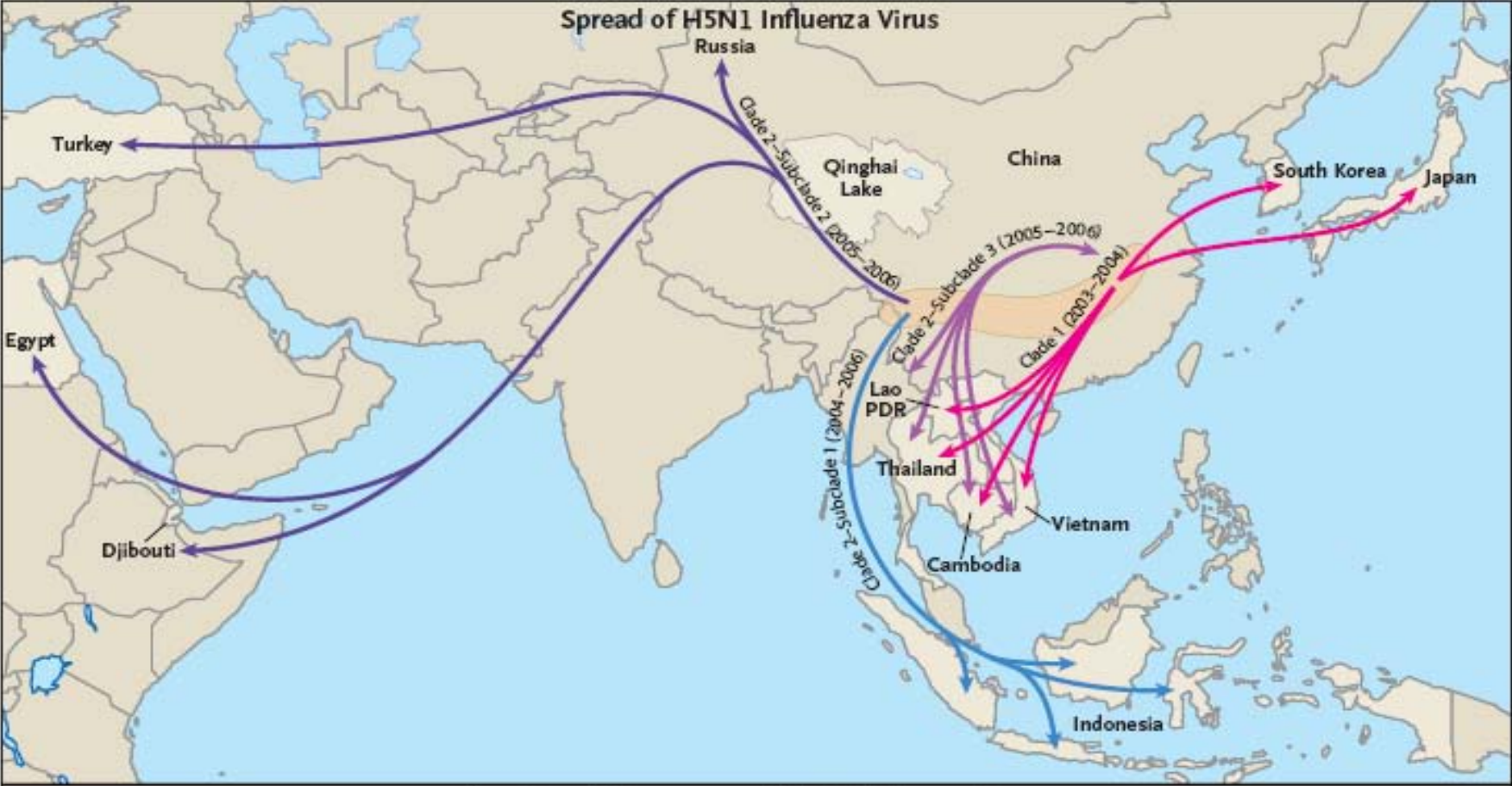


Characteristics of a pandemic influenza virus

- It spreads easily from person to person
- It causes severe disease
- People are not protected by their existing immunity to other influenza viruses
- It spreads globally



Spread of H5N1 Influenza virus



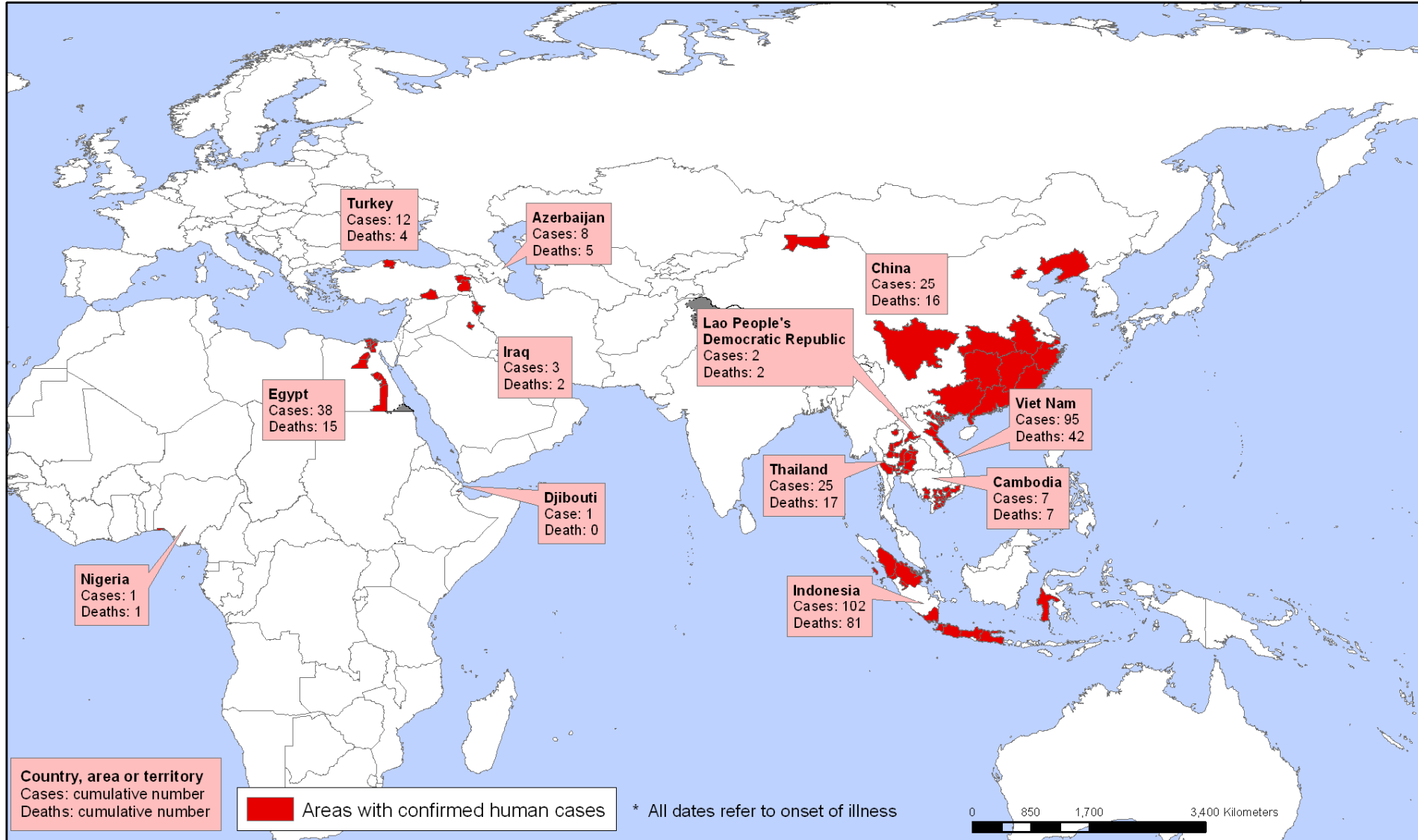
*From Webster & Govorkova
NEJM (November 2006)*

Properties of avian H5N1

- Shed by sub-clinically infected ducks
- 80-100% mortality in domestic poultry
- Probably originated in Guangdong province <1996, now antigenically divergent into multiple clades and subclades
- A million infected animals for every infected human
- ~60% mortality in humans
- Transmission to humans by close contact with infected birds
- Several family clusters but human-to-human transmission not yet confirmed



Areas with confirmed human cases of H5N1 avian influenza since 2003 *



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Data Source: WHO / Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS) World Health Organization

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Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) (WHO 25 July)

Country	2003-2005		2006		2007		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	0	0	8	5	0	0	8	5
Cambodia	4	4	2	2	1	1	7	7
China	9	6	13	8	3	2	25	16
Djibouti	0	0	1	0	0	0	1	0
Egypt	0	0	18	10	20	5	38	15
Indonesia	20	13	55	45	27	23	102	81
Iraq	0	0	3	2	0	0	3	2
Laos	0	0	0	0	2	2	2	2
Nigeria	0	0	0	0	1	1	1	1
Thailand	22	14	3	3	0	0	25	17
Turkey	0	0	12	4	0	0	12	4
Viet Nam	93	42	0	0	2	0	95	42
Total	148	79	115	79	56	34	319	192



Will H5N1 become pandemic for humans?

WHO Alert Phase 3: a novel influenza virus is causing sporadic human cases, but is poorly adapted to humans.

- Likely that several mutations are required
 - Risk is higher than ever before
 - Social and economic consequences potentially severe
- Low probability event, but high impact



Global influenza surveillance: the role of WHO



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WHO Global Influenza Surveillance Network (GISN)

Monitors circulating viruses to identify novel antigenic variants and to recommend strains for Northern and Southern hemisphere seasonal vaccines (A/H1N1, A/H3N2, B)

- 118 National Influenza Centres in 89 countries (3 in Australia)
- 10 H5 Reference Laboratories in 7 countries
- 4 WHO Collaborating Centres for Influenza:
London, Atlanta, **Melbourne** and Tokyo (+ Memphis)
- 3 key national reference laboratories:
NIBSC (UK), FDA (USA) and **TGA (Australia)**

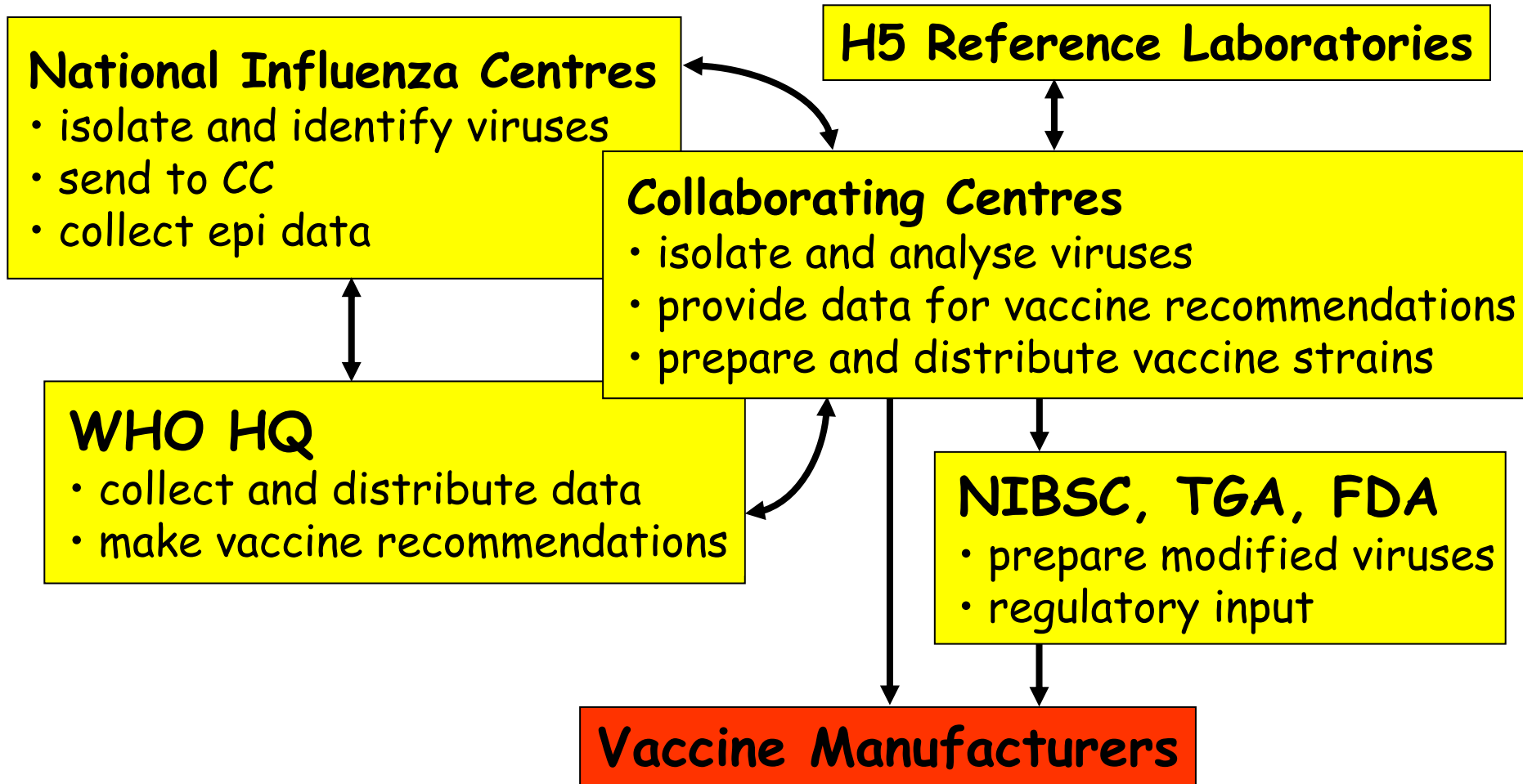


The WHO Collaborating Centre in Melbourne

- 1951:** Established as WHO Regional Influenza Centre, based at Commonwealth Serum Laboratories (now CSL Limited)
- 1992:** Designated as WHO Collaborating Centre for Influenza
- 2005:** Enhanced Commonwealth funding announced
- 2006:** Management of Centre transferred to Victorian Infectious Diseases Reference Laboratory (VIDRL)
- 2008:** Centre will move to new BSL2/BSL3 laboratories at VIDRL



WHO Global Influenza Surveillance Network (GISN)



A specimen is submitted to a WHO CC:

- What influenza subtype is it?
- Is it different from known circulating influenza strains in antigens (HA, NA) or genetic sequence?
- Is it detected by current diagnostic tests?
- Would immunity to previous viruses or vaccines be protective?
- Is it sensitive to antiviral drugs?
- Is it readily transmitted to or between humans?
- What is its geographical spread?



Pandemic influenza risk assessment by WHO depends on:

- Early access to specimens and viruses from around world
- High level of specific technical expertise and infrastructure
- Comparison with data obtained with other influenza viruses from many countries and over many years
- Rapid sharing of viruses, reagents and data with other CCs



Issues in pandemic influenza risk assessment

- Lack of awareness of avian and other influenza
- Poor integration of animal and human health authorities
- Lack of diagnostic and other capabilities in many countries
- Lack of participation in WHO surveillance network
- Cost and regulatory barriers to shipping of viruses
- Political issues in virus sharing



Issues in virus sharing

Indonesia has stopped sending viruses to WHO until developing countries can share in benefits that currently flow to industrialised countries:

- information and data
- biological materials related to influenza
- **affordable, accessible diagnostics, drugs and vaccines for pandemic preparedness**
- capacity building in diagnosis and virus analyses
- involvement in research undertaken with their viruses



WHO's response to Indonesia's position on virus sharing (WHA 60.28, May 2007)

- Recognises need for equitable sharing of benefits
- Developing new arrangements for virus sharing and new terms of reference for GISN laboratories
- Working on ways to:
 - increase seasonal vaccine use and production capacity
 - increase surveillance capacity in developing countries
 - build and finance H5N1 vaccine stockpiles
 - ensure equitable distribution of vaccines in pandemic
 - increase R&D on novel vaccine technologies



Global pandemic response: impact of the International Health Regulations (2005)



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WHO International Health Regulations (2005)

- Came into force on 15 June 2007
- Binding legal framework to prevent and respond to international spread of disease while avoiding unnecessary interference with international travel and trade
- States are obliged to undertake surveillance and to report public health events of international concern
- **Human influenza caused by a new subtype must be notified**
- WHO is mandated to assess, assist and intervene



Global pandemic response: outbreak prevention and control



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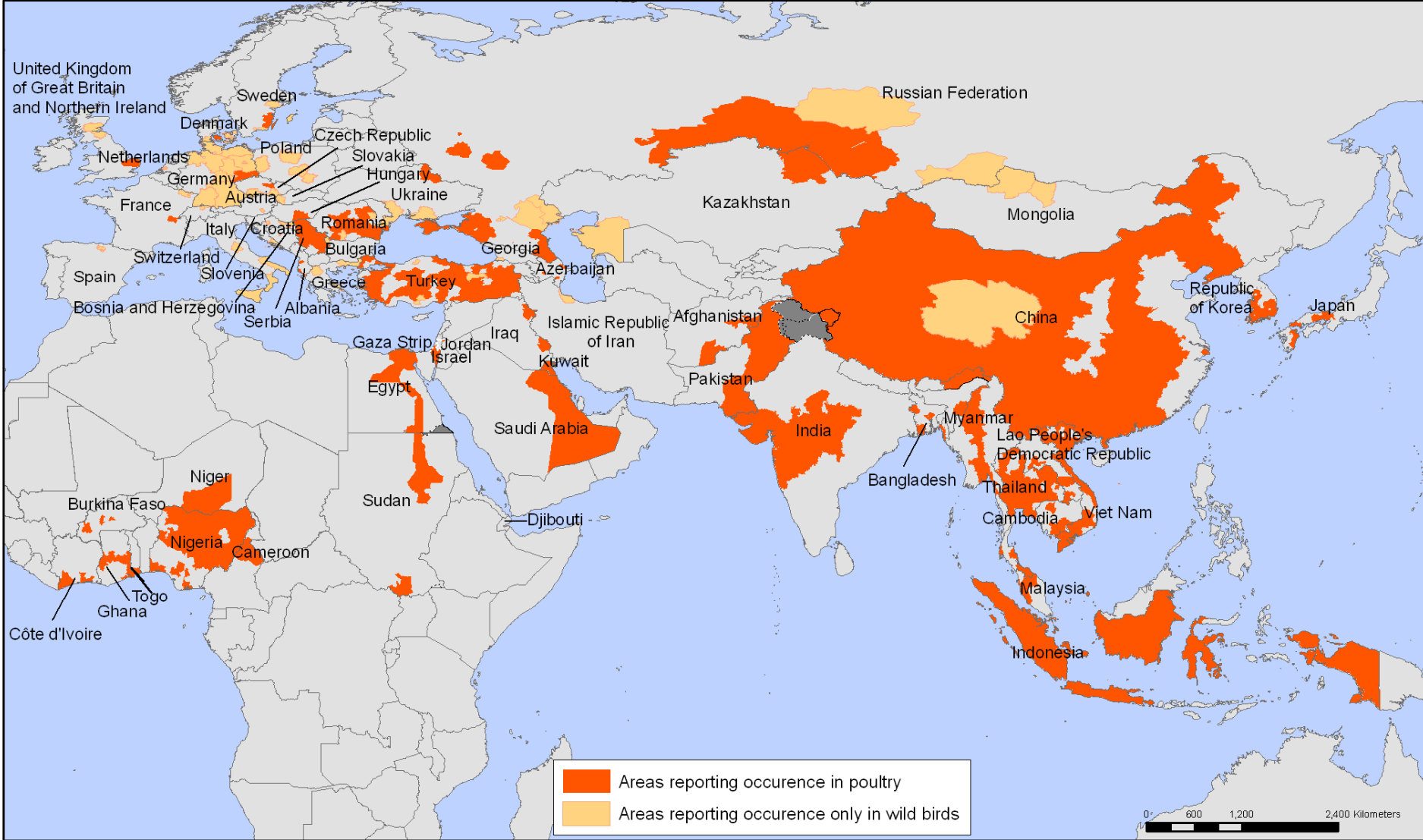
Factors favouring spread of avian H5N1

- Backyard flocks with mixing of chickens and ducks
- Unregulated live poultry markets
- Poultry as main protein source
- Poor local recognition and control, lack of compensation
- Traditional practices in food preparation
- Use of poultry products as fertilizer and animal feed
- Cross-border trade in poultry, poultry products and wildlife
- Cockfighting
- Migratory birds



Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds since 2003

Status as of 6 August 2007
 Latest available update



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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

Available means to prevent and control outbreaks

Avian influenza

- vaccination
- regulation of farming practices, trade, transport
- public awareness
- culling (with compensation)

Human influenza

- vaccination
- antivirals (especially neuraminidase inhibitors)
- quarantine
- social controls
- border control
- coordination within and between countries



Conclusions

- **Generation of a pandemic virus may occur infrequently but both the opportunity and the global risks are now high.**
- **WHO is the only organisation with the mandate and networks to attempt global pandemic control.**
- **The practical and political barriers to effective prevention and control remain very high, especially in the countries at greatest risk.**



Thank you



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