

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008;358:261-73.

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**Supplementary Materials: Update on Avian Influenza A (H5N1) Virus Infection in Humans**

Writing Committee of the Second World Health Organization (WHO) Consultation on Clinical Aspects of Human Infection with Avian Influenza A(H5N1) Virus

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# Update on Avian Influenza A (H5N1) Virus Infections in Humans

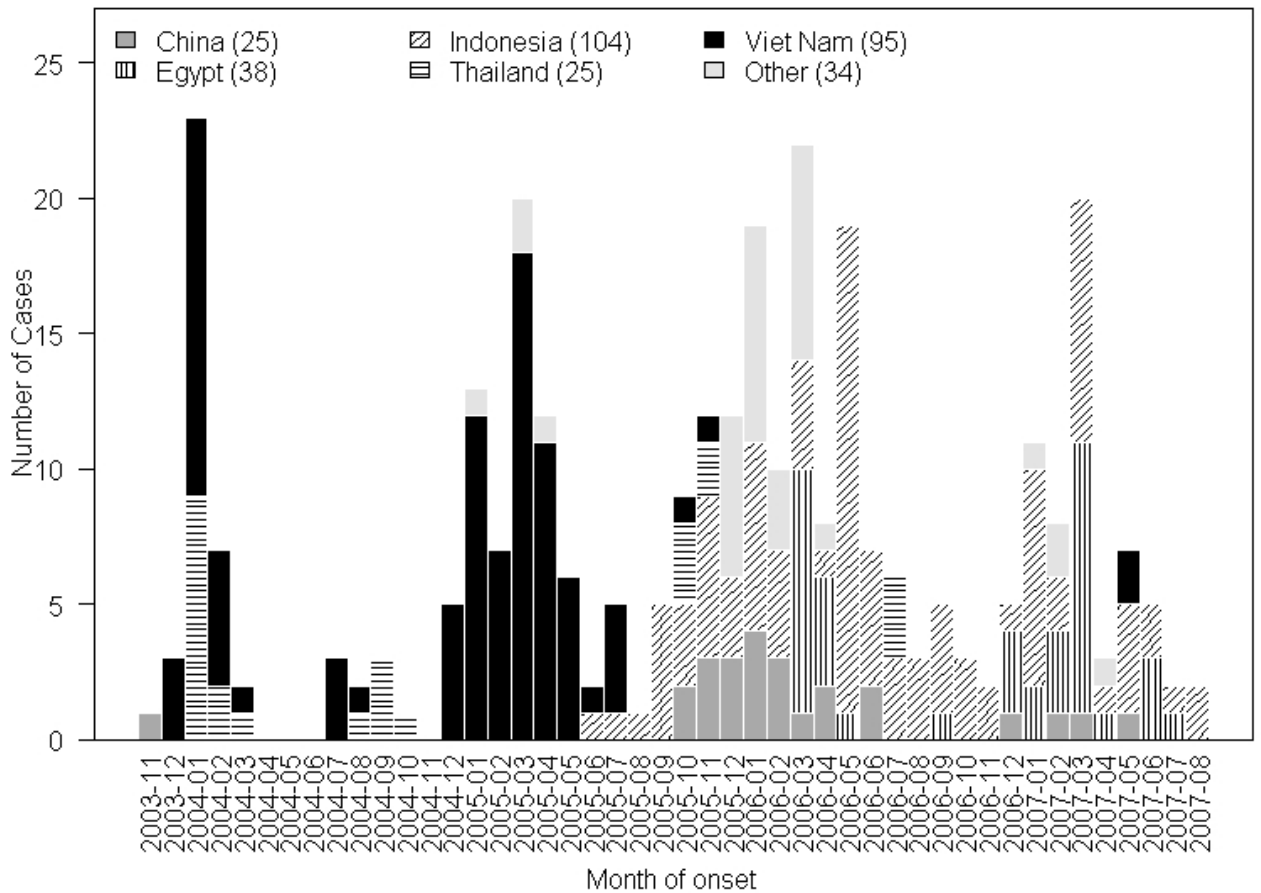
## Supplementary Figures 1 and 2

The total number of laboratory confirmed influenza A(H5N1) virus-infected persons reported to WHO by month from December, 2003 to September, 2007. Cases in several countries with larger numbers of affected persons are indicated separately. Cases have occurred year-round but increased numbers have been seen during December - May in temporal association with increased outbreaks in poultry(1).

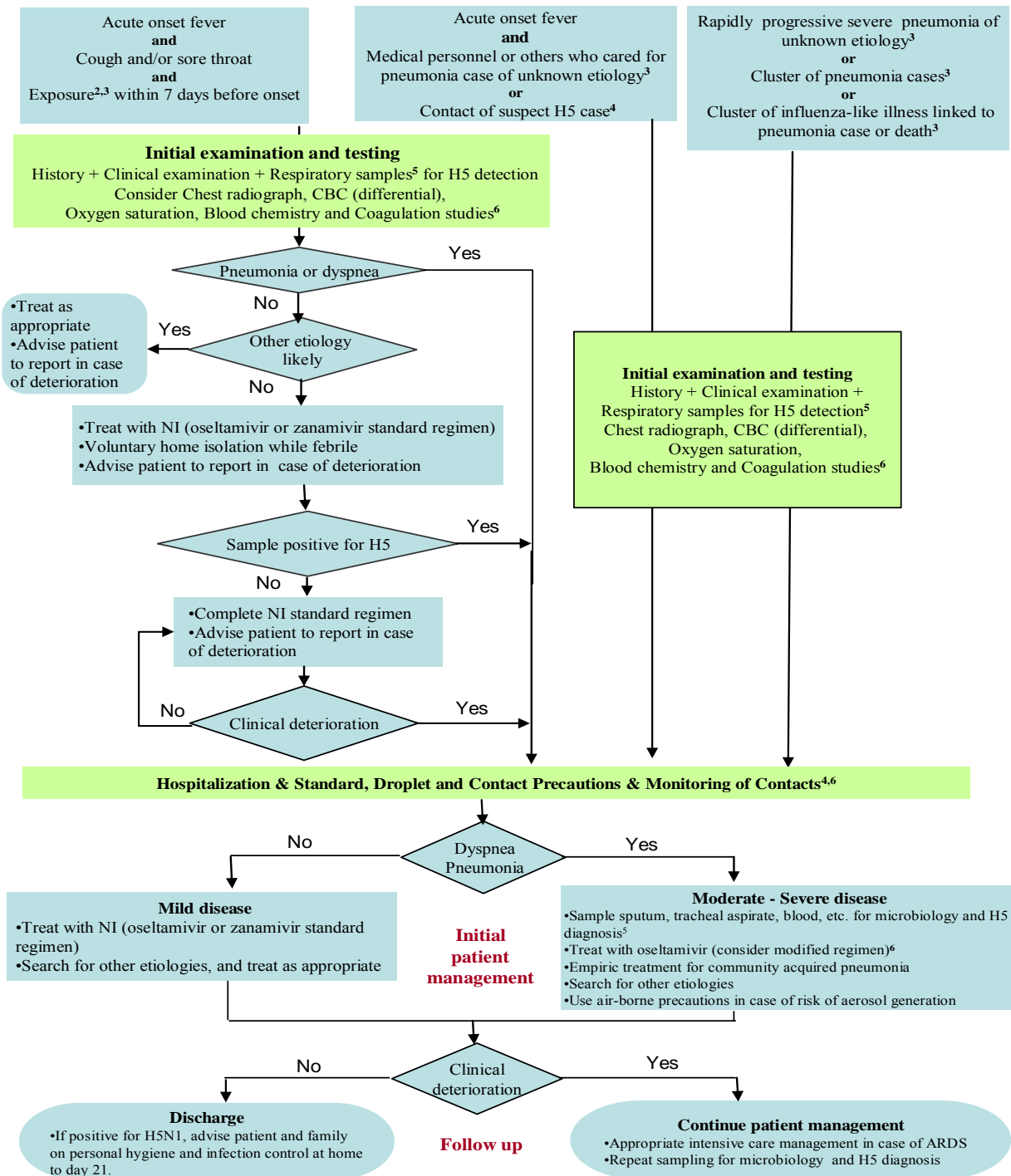
See the WHO web site for updated information:

[http://www.who.int/csr/disease/avian\\_influenza/country/en/index.html](http://www.who.int/csr/disease/avian_influenza/country/en/index.html)

**Number of Confirmed Human H5N1 Cases  
by month of onset as of 2007-08-24**



## Clinical management algorithm (in areas with H5N1 virus infection)<sup>1</sup>



## Notes to Figure 2:

1. This suggested evaluation and management algorithm applies to areas with A(H5N1) virus infection in poultry, other animals, or humans during the current pandemic alert period. It should be considered as general basic guidance and adapted according to local circumstances and new information.
2. Exposure history to animals (chickens, other poultry, or other animals ) or their environment includes the following:
  - Handled, played with, de-feathered, slaughtered, butchered, prepared, cleaned cages, shared living space, handled/used dropping as fertilizers,
  - Visited live bird /wet market,
  - Hunting, contact with wild birds,
  - Occupational exposure to animals and /or animal products (slaughterer, farm worker, factory worker, poultry seller, veterinarian, culler, laboratory worker),
  - Consumption of raw or undercooked poultry products (e.g. meat, eggs, blood, liver).

Exposure to a confirmed, probable, or suspected A(H5N1) patient. Recommend empiric NI treatment pending confirmation of an alternative diagnosis. Note that initial manifestations of H5N1 illness may be nonspecific or atypical (e.g. fever with or without diarrhoea).

See WHO web site for details of case investigation:

*WHO guidelines for investigation of human cases of avian influenza A(H5N1)*

[http://www.who.int/csr/resources/publications/influenza/WHO\\_CDS\\_EPR\\_GIP\\_2006\\_4/en/index.html](http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_4/en/index.html)

3. For those presenting with illness in non-A(H5N1)-affected areas, consider travel history to an outbreak area or contact with an ill traveller returning from an A(H5N1)-affected area within 7 days before onset of illness, as well as the exposures to sick or dead birds.
4. Anyone who is contact of a confirmed, probable, or, depending on public health resources, suspect case should be actively monitored for illness for a minimum of 7 days after the last exposure.

See WHO guidelines for NI post-exposure prophylaxis:

*WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus*

[http://www.who.int/csr/disease/avian\\_influenza/guidelines/pharmamanagement/en/index.html](http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html)

5. Viral RNA detection is method of choice for initial diagnosis. Collect nose and throat swabs and, if available, tracheal secretions for detection of H5 and influenza A RNA by nucleic acid amplification testing (reverse transcriptase-polymerase chain reaction). Throat swabs are currently the highest yield upper respiratory tract specimen for detecting A(H5N1) virus. Nasal swabs with nasal secretions or nasopharyngeal aspirates or swabs are appropriate specimens for detecting human influenza A and B and therefore useful if the influenza is not due to A(H5N1). Collection of multiple specimens over several days may increase diagnostic yield. **Use appropriate precautions when collecting clinical specimens.**

See WHO web site for details of sampling:

*Collecting, preserving and shipping specimens for the diagnosis of avian influenza A(H5N1) virus infection. Guide for field operations*

[http://www.who.int/csr/resources/publications/surveillance/WHO\\_CDS\\_EPR\\_ARO\\_2006\\_1/en/](http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_ARO_2006_1/en/)

6. Pending the results of H5N1 diagnostic testing and depending on available resources, voluntary home isolation while on empiric antiviral therapy may be a reasonable alternative for contacts with mild illness.

See WHO web site for updated advice regarding A(H5N1) case management:

*Clinical management of human infection with avian influenza A(H5N1) virus*

[http://www.who.int/csr/disease/avian\\_influenza/guidelines/clinicalmanage07/en/index.html](http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage07/en/index.html)

See WHO web site for guidance regarding infection control:

*Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care*

[http://www.who.int/csr/resources/publications/WHO\\_CD\\_EPR\\_2007\\_6/en/index.html](http://www.who.int/csr/resources/publications/WHO_CD_EPR_2007_6/en/index.html)

Abbreviations: NI, neuraminidase inhibitors

**Supplementary Table 1. Frequencies of A(H5N1) infection in various risk populations, 2004-7.**

<b>Location (Reference)</b>	<b>Years</b>	<b>Groups</b>	<b>Sampling methods</b>	<b>No. sampled for A(H5N1)</b>	<b>No. (%) positive for A(H5N1)</b>	<b>Comment</b>
Cambodia (2)	2005	Villagers $\leq$ 1 km of fatal human A(H5N1) infection in area with poultry outbreaks	Serology (MN, WB)	351	0	High frequency of direct poultry contact in cohort.
Cambodia(3)	2005-6	Close contacts (relatives, HCWs, villagers) of A(H5N1) patients	Clinical, RT-PCR, serology (MN)	80	0	
China (4)	2005	Close contacts of 2 cases	Clinical	191	NA	No illnesses during 10 days of observation.
Thailand (5)	2004	Healthcare workers with exposure to H5N1 patient	Clinical, serology (MN, WB)	25	0	Exposed HCWs had unprotected contact for 2 days with case.
		Healthcare workers with no known exposure contact		24	0	

China (6)	2006	Wet poultry market workers	Serology (MN)	110	1 (0.1%)	
Thailand (7)	2005-6	Adults with CAP admitted to ICU	TA for RT-PCR, virus culture; serology (MN, IF)	115	0	18 (16%) met Thai clinical-epidemiologic criteria for probable A(H5N1) disease. Respiratory pathogen found in 58%, including 8 (7%) with influenza A(H3N2)
Nigeria(8)	2006	Poultry market workers	Serology (MN)	295	0	Exposed poultry workers had a median of 14 days to suspected or confirmed A(H5N1)-infected poultry
Multiple (9)	2003-6	ARD in returning US travelers from A(H5N1) affected areas or their contacts	RT-PCR, serology (MN)	41	0	25/59 (42%), including 2 of 4 who died, were positive for influenza A(H3N2). 27/59 (46%) patients met CDC criteria for suspected A(H5N1) case, but none had direct poultry contact

**Abbreviations:** MN, microneutralization; WB, Western blot; HAI, hemagglutination-inhibition; CAP, community-acquired pneumonia; TA, tracheal aspirate; RT-PCR, reverse-transcriptase- polymerase chain reaction; HCW, health care workers; ILI, influenza-like illness; ARD, acute respiratory disease

**Supplementary Table 2. Sensitivity of commercial rapid antigen testing in human A(H5N1) infections.** Diagnostic yield depends heavily on the quality and type of specimen, conditions of sample transport and storage, and duration of illness.

<b>Location (Reference)</b>	<b>Specimen type</b>	<b>No. patients tested</b>	<b>Sensitivity</b>	<b>Comment</b>
Hong Kong, 1997 (10)	Nasopharyngeal aspirates	7	86 %	The relatively high sensitivity of antigen testing in nasopharyngeal aspirates is notable but requires confirmation.
Thailand [T Chotpitayasunondh, unpublished observations]	Nasopharyngeal swabs	18	28 %	
Vietnam [M de Jong, unpublished observations]	Throat swabs	14	21 %	
Turkey (11)	Nasopharyngeal swabs	8	0 %	
Indonesia (12)	Nose, throat swabs	8	0 %	
<b>Total since 2004</b>	Respiratory	48	17 %	

**Supplementary Table 3. Representative antiviral agents of clinical investigative interest with activity against A/H5N1 viruses in animal models.**

<b>Agent (Reference)</b>	<b>Target</b>	<b>Route of administration</b>	<b>Activity in animal model of A/H5N1 (type)</b>	<b>Status of human testing</b>	<b>Comment</b>
Peramivir(13-15)	Neuraminidase	IV, IM	Yes (mouse, ferret)	Phase 2 in seasonal influenza	Prolonged human plasma T1/2elim
Zanamivir(16;17)	Neuraminidase	IV	Yes (macaque)	Phase 2a	Highly active and well-tolerated in experimental human influenza
T-705(18)	RNA polymerase	PO	Yes (mouse)	Phase 1	Phase 2 in seasonal influenza anticipated this season
DAS181(19;20)	HA receptor	Topical	Yes (ferret)	Phase 1 (pending)	
Antibody(21-24)	HA, other virus proteins	IV	Yes (mouse)	Convalescent plasma used in several A/H5N1 patients.	Several murine and human monoclonals active in animals.

Ribavirin(25)	RNA polymerase	PO, IV	Yes (mouse)	Used in several A(H5N1) patients	Combinations of oseltamivir and ribavirin show enhanced antiviral and survival benefits in murine models of A(H5N1) virus infection
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**Supplementary Table 4. Representative immunogenicity studies of candidate inactivated H5N1 vaccines with or without adjuvants**

Source of report, year (Reference)	Target population	Vaccine type	Route	Vaccine dose (ug of HA)	Seroconversion ( $\geq$ 4-fold increase) or responses to specific titer for vaccine virus (percent of subjects)	GMT titer change (fold change vs baseline)	Comment
Treanor, 2001 (26)	Healthy adults (N=146)	Recombinant HA, insect cells, non-adjuvanted H5 from A/HongKong/156/97 and A/HongKong/483/97	IM X 2 (Days 0, 21-42)	0 25 40 90 + 10 90	MN $\geq$ 1:80 4% 17% 28% 33% 52%		Dose-related antibody responses to recombinant H5 antigen. Highest dose group (90 ug) showed an increase in MN titer after 1 dose in 17% of subjects.
Nicholson, 2001 (27)	Healthy adults, 18-40 yrs (N=65)	Surface antigen, egg-grown, with or without MF-59 A/duck/Singapore/97 (H5N3)	IM X 2 (days 0, 21)	7.5 / 7.5 + MF59 15 / 15 + MF59 30 / 30 + MF59	MN 10%/80% 18%/100% 36%/100%	SRH 1.0/23 3.1/19 2.4/18	Frequency of MN seroconversion to clade 0 A/Hong Kong/156/97 was 9% without adjuvant and 93% with MF-59. Low frequency of seroconversions to clade 1

								viruses (0-14%) after 2 doses. (28)
Treanor, 2006 (29)	Healthy adults, 18-64 yrs (N=451)	Split virus (rg), egg-grown, formalin-inactivated, non-adjuvanted A/VN/1203/04	IM X 2 (Days 0, 21)	0 7.5 15 45 90	HAI 0 13% 24% 41% 57%	MN $\geq$ 1:20 0 25% 32% 57% 70%	HAI 1.0 1.3 2.0 3.2 5.4	Dose-related antibody responses. Boosting of antibody responses with 3 <sup>rd</sup> dose at 6 months.
Treanor, 2007*	Elderly, healthy adults, 65-87 yrs (N=259)	Split virus (rg), egg-grown, formalin-inactivated, non-adjuvanted A/VN/1203/04	IM X 2 (Days 0, 28)	0 45 90	MN 2% 21% 35%	HAI $\geq$ 1:40 4% 35% 46%	HAI 6.7 16.7 26.2	Antibody responses generally comparable to those in younger adults.

Bernstein, 2007*	Healthy adults, 18-64 yrs (N=378)	Split virus (rg), egg-grown, formalin-inactivated, non-adjuvanted or with alum (AL(OH) <sub>3</sub> ) or MF-59 A/VN/1203/04	IM X 2 (Days 0, 28)	0 7.5 + alum 7.5 + MF59 15/ 15 + alum 15 + MF-59 30/ 30 + alum 45	HAI ≥ 1:40 0% 3% 23% 24%/ 7% 63% 18%/ 14% 24%	MN ≥ 1:40 4% 14% 37% 26%/ 18% 81% 28%/ 24% 48%		Benefit from addition of MF-59 but not alum adjuvant. Two doses of 15 ug + MF-59 induced MN ≥ 1:40 in 81% of subjects. Antibody titers decreased significantly by 6 months.
Leroux-Roels, 2007 (30)	Healthy adults, 18-60 yrs (N=394)	Split virus (rg), egg-grown, inactivated, with or without AS03 adjuvant, A/VN/1194/04(NIBRG-14)	IM X (Days 0, 21)	3.8 / 3.8 +ASO3 7.5 / 7.5 +ASO3 15 / 15 +ASO3 30 / 30 +ASO3	HAI 4% / 82% 16% / 90% 35% / 96% 41% / 85%	MN 22% / 86% 37% / 86% 53% / 86% 65% / 98%	HAI 1.2 / 27.9 1.7 / 38.1 2.8 / 60.5 3.9 / 36.4	All CHMP criteria met by 2 doses of 3.8ug + ASO3 but by none of non-adjuvanted doses. Cross-reactive responses to clade 2.1 virus in 77% at 3.8 ug dose of AS03-adjuvanted vaccine.

Keitel, 2007*	Healthy adults, 18-49 yrs (N=570)	Split virus (rg), egg-grown, formalin-inactivated, with or without alum (Al(OH) <sub>3</sub> ) A/VN/1203/04	IM X 2 (days 0, 28)	3.75/3.75 + alum 7.5 / 7.5 + alum 15 / 15 + alum 45 / 45 + alum	HAI 4%/ 2% 0%/ 14% 13%/ 14% 25%/ 33%	HAI 5.7/ 5/4 5.3/ 7.7 8.5/ 8.1 12.0/14.8	No significant effect of adding alum, except at 7.5ug HA dose level.
Bresson, 2006 (31)	Healthy adults, 18-40 yrs (N=300)	Split virus (rg), egg-grown, formalin-inactivated, with or without alum (Al(OH) <sub>3</sub> ) A/VN/1194/04(NIBRG-14)	IM X 2	7.5 / 7.5 + alum 15 / 15 + alum 30 / 30 + alum	HAI MN ≥ 1:20 43% / 28% 20% / 16% 44% / 44% 22% / 18% 52% / 67% 27% / 41%	HAI 4.9 / 2.6 4.5 / 4.3 6.7 / 11.6	Effect of alum adjuvant evident only at 30 ug HA dose. Cross-reacting Nt antibody to clade 2.2 (32-39%) > 2.1 (4-5%) viruses with or without alum*.
Tashiro, 2007*	Healthy adults, 20-39 yrs (N=120)	Whole virus (rg), egg-grown, formalin-inactivated, with alum A/VN/1194/04(NIBRG-14)	IM X 2 (day 0, 21)  SC X 2	1.75 + alum 5.0 + alum 15 + alum  1.75 + alum 5.0 + alum 15 + alum	MN 43% 71% 96%  50% 72% 84%	MN 3.1 7.2 10.6  3.3 5.6 10.4	Single 15 ug dose induced seroconversion in 62%. Evidence for heterologous antibody reactivity to clade 2 viruses. SC route associated with higher local reactogenicity and no greater immunogenicity.

Hehme, 2007*	Healthy adults, 18-60 yrs (N=371)	Whole virus (rg), egg-grown, with or without alum (Al(OH) <sub>3</sub> ) A/VN/1194/04(NIBRG-14)	IM X 2 (days 0, 21)	3.8 / 3.8 + alum 7.5 / 7.5 + alum 15 / 15 + alum 27 / 27 + alum	HAI 51% / 69% 57% / 62% 70% / 72% 72% / 92%	HAI 5.7 / 12.2 7.9 / 10.2 10.7 / 14.3 14.7 / 30.5	All 3 CHMP criteria met by 2 doses of 15ug + alum or of 27 ug without adjuvant
Lin, 2006 (32)	Healthy adults, 18-60 yrs (N=120)	Whole virus (rg), egg-grown, formalin-inactivated, with alum A/VN/1194/04(NIBRG-14) (Sinovec)	IM X 2 (Day 0, 28)	0 1.25 + alum 2.5 + alum 5.0 + alum 10 + alum	HAI MN ≥ 1:20 0 4% 13% 48% 21% 50% 33% 96% 78% 96%	HAI 1.0 2.7 2.7 4.9 11.5	All 3 CHMP criteria met by 2 doses of 10ug + alum at day 42.
Kistner, 2007*	Healthy adults, 18-45 yrs (N=270)	Whole virus without genetic modification, Vero cells, formalin-inactivated, with or without alum (Al(OH) <sub>3</sub> ) A/VN/1203/04	IM X 2 (days 0, 21)	3.75 + alum 7.5 / 7.5 + alum 15 / 15 + alum 30 + alum	Nt ≥ 1:20 NT/ 69% 76%/ 64% 71%/ 61% NT/ 66%	MN NT / 4.4 5.3 / 4.0 5.7 / 3.9 NT / 4.6	Higher antibody titers observed without alum. Cross-reactive MN titers ≥ 1:20 to A/Indonesia/05/2005 in 45% of non-adjuvanted 7.5 ug dose group.

**Abbreviations:** rg, reverse genetics; HAI, hemagglutination-inhibition; MN, micro-neutralization; GMT, geometric mean titer

**Notes: Serology data are those reported at 3-4 weeks after second vaccine dose.**

\*Presented at 3<sup>rd</sup> WHO meeting on evaluation of pandemic influenza prototype vaccines in clinical trials, 15-16 February, WHO, Geneva. See WHO web site for details: [http://www.who.int/vaccine\\_research/diseases/influenza/meeting\\_150207/en/index.html](http://www.who.int/vaccine_research/diseases/influenza/meeting_150207/en/index.html)

CHMP criteria: The criteria for immunogenicity of seasonal influenza vaccines elaborated by the European Union Committee for Medicinal Products on the basis of HAI antibody assays and defined by ratio of GMT pre/post immunization > 2.5; seropositivity (HAI titer  $\geq$ 1:32) in >70% of subjects; and seroconversion (four-fold titer rise or significant increase from negative pre immunization) in >40% of subject



# **WORLD HEALTH ORGANIZATION**

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**The Second WHO Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus Meeting, 19-21 March, 2007 Antalya Turkey**

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