

# Clinical presentations and management of H7N9



11-1-2017

# Content

- Background
- Clinical manifestations
- Clinical management

# First human case of H7N9 confirmed in 2013 in China

ORIGINAL ARTICLE

## Human Infection with a Novel Avian-Origin Influenza A (H7N9) Virus

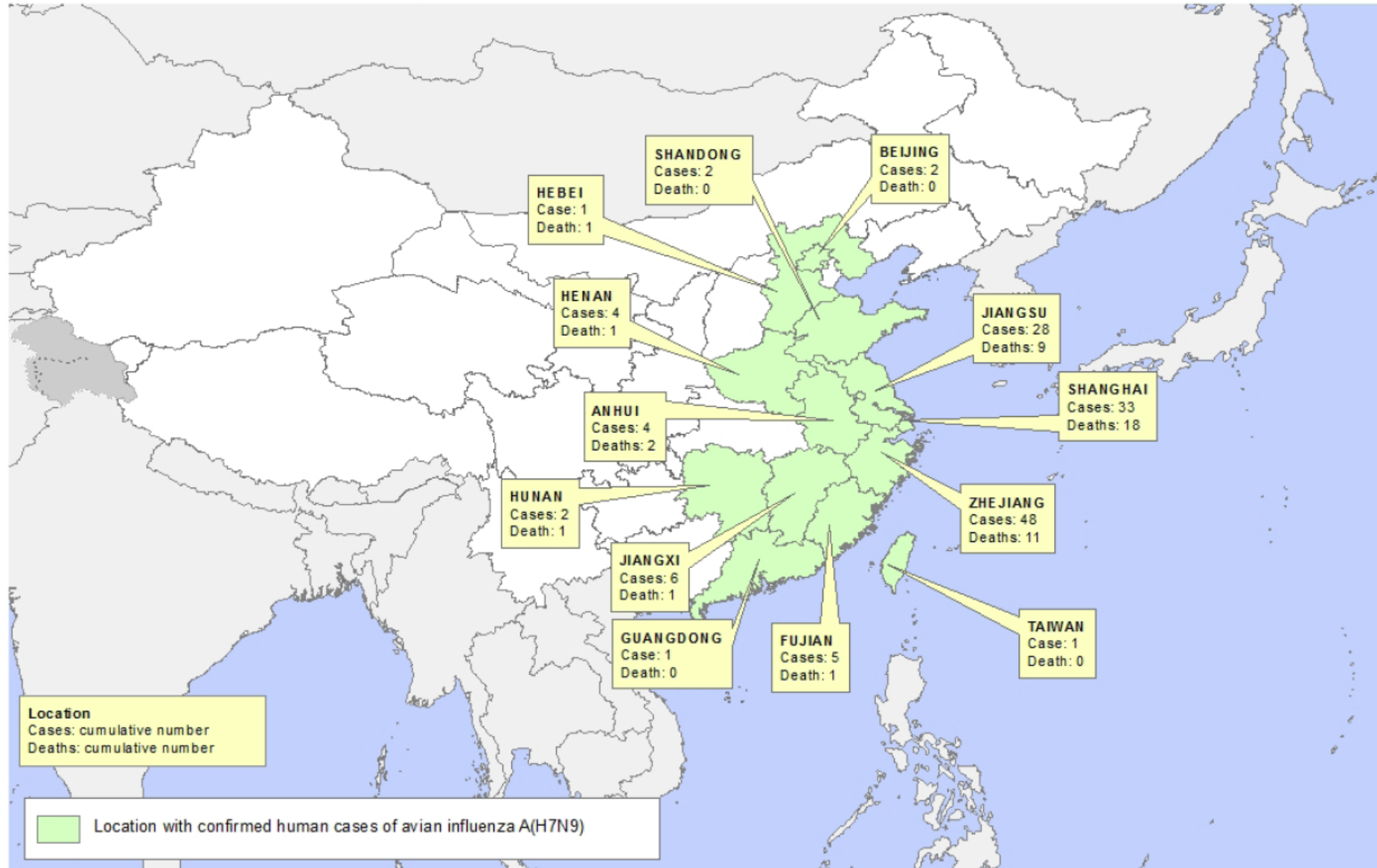
**Table 1.** Demographic, Epidemiologic, and Virologic Characteristics and Complications, Treatment, and Clinical Outcomes of Three Patients Infected with Avian-Origin Influenza A (H7N9) Virus.\*

Characteristic	Patient 1	Patient 2	Patient 3
Age (yr)	87	27	35
Sex	Male	Male	Female
Occupation	Retired	Butcher	Housewife
Underlying conditions	COPD, hypertension	Hepatitis B	Depression, hepatitis B, obesity
Area of origin	Shanghai	Shanghai	Anhui
Exposure to chicken market in past 7 days	No	Yes	Yes
Date of illness onset	February 18, 2013	February 27, 2013	March 13, 2013
Date of admission	February 25, 2013	March 4, 2013	March 19, 2013
Admission to ICU	None	March 6, 2013	March 20, 2013
Date of specimen collection	February 26, 2013	March 5, 2013	March 20, 2013
Date of laboratory confirmation of virus	March 30, 2013	March 30, 2013	March 30, 2013
Viral isolation	A/Shanghai/1/2013 (H7N9)	A/Shanghai/2/2013 (H7N9)	A/Anhui/1/2013 (H7N9)
<b>Complications</b>			
Septic shock	No	No	Yes
ARDS	Yes	Yes	Yes
Acute renal damage	No	No	Yes
Encephalopathy	Yes	No	Yes
Rhabdomyolysis	No	Yes	Yes
Secondary infections	No	Yes†	Yes†
Oxygen therapy	Mask‡	Mechanical ventilation	Mechanical ventilation
Extracorporeal membrane oxygenation	No	No	Yes
Continuous renal-replacement therapy	No	No	Yes
Antibiotic therapy	Imipenem, moxifloxacin, and vancomycin	Cefoperazone-sulbactam, levofloxacin, and linezolid	Imipenem and vancomycin
Antiviral agent§	Oseltamivir (started on day 7)	Oseltamivir and amantadine (started on day 7)	Oseltamivir (started on day 8)
Glucocorticoid therapy	Yes	Yes	Yes
Intravenous immune globulin therapy	Yes	Yes	Yes
Length of stay in hospital	6 days	6 days	19 days
Date of death	March 4, 2013	March 10, 2013	April 9, 2013

# Geographical location

Oct 2013

Confirmed human cases of avian influenza A(H7N9) reported to WHO

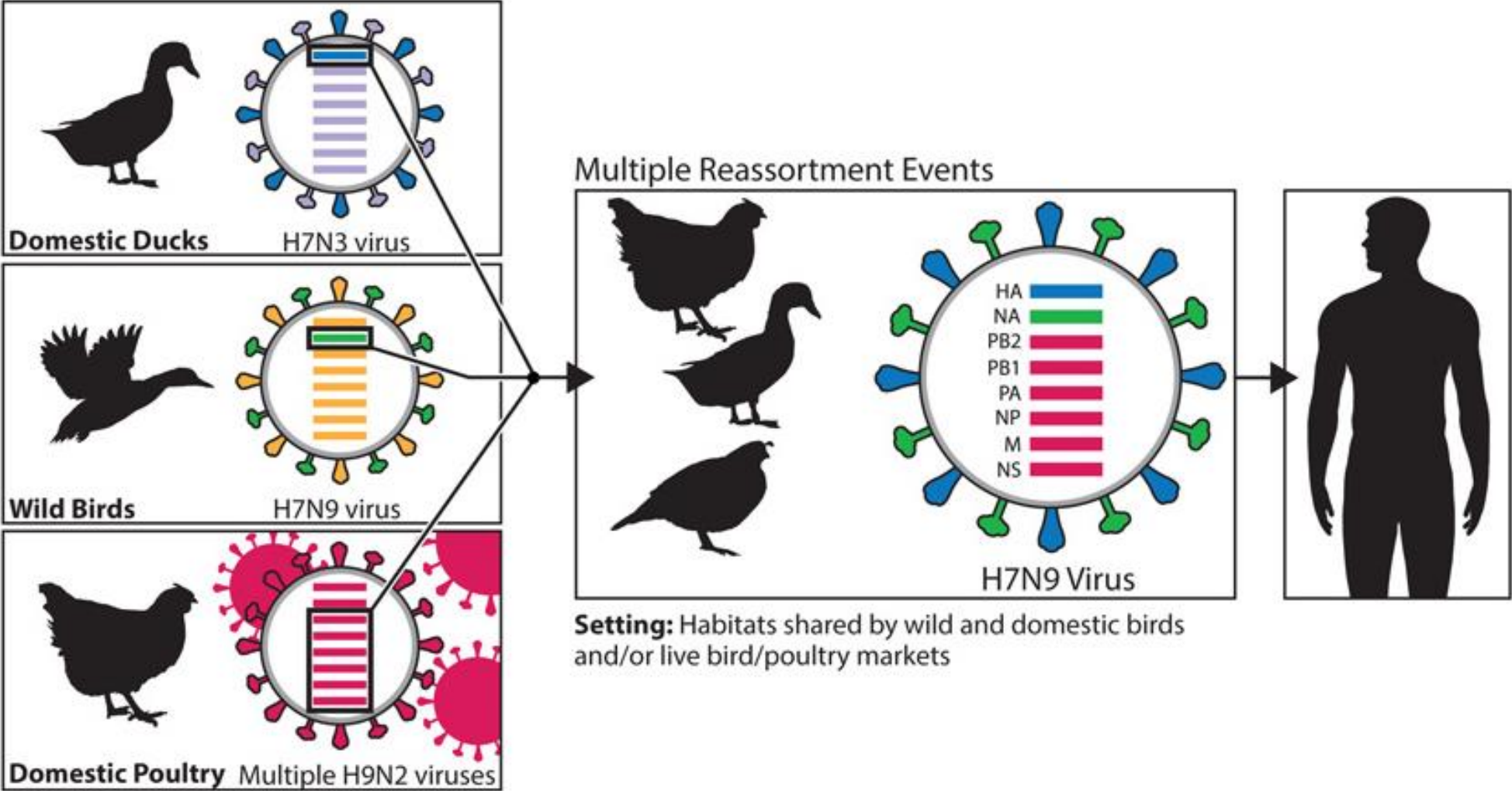


Data as of 25 October 2013, 8:00 GMT+1  
Source: WHO/GIP

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or borders. Dotted and dashed lines on maps represent approximate border lines for which there may not be full agreement.  
©WHO 2013. All rights reserved.



# Genetic Evolution of H7N9 Virus in China, 2013



## Estimating the Distribution of the Incubation Periods of Human Avian Influenza A(H7N9) Virus Infections

**Table 2.**

Published Estimates of the Incubation Periods of Human Avian Influenza A(H7N9) Virus Infections, 2013–2014

First Author, Year (Reference No.)	No. of Patients Analyzed	Method	Incubation Period, days			
			Mean	95% CI	Median	Range
Current study	229	Parametric	3.4	3.3, 3.6		
Wu, 2014 <sup>(21)</sup>	NA <sup>a</sup>	Parametric	3.4	2.2, 5.0		
Yu, 2014 <sup>(3)</sup>	NA <sup>a</sup>	Parametric	3.3	1.4, 5.7		
Cowling, 2013 <sup>(4)</sup>	32	Parametric	3.1	2.6, 3.6		
Gao, 2013 <sup>(9)</sup>	62	Midpoint			5.0	2–8
Gong, 2014 <sup>(7)</sup>	30	Midpoint			2.0	
Sun, 2014 <sup>(8)</sup>	16 <sup>b</sup>	Midpoint			2.5 <sup>b</sup>	
	30 <sup>c</sup>				4.0 <sup>c</sup>	
Li, 2014 <sup>(5)</sup>	23	Midpoint			6.0	1–10
Huang, 2014 <sup>(6)</sup>	22	Midpoint			7.5	2–12.5

# Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

- 111 patients with laboratory-confirmed avian-origin influenza A (H7N9) infection through May 10, 2013

**Table 1. Demographic and Epidemiologic Characteristics of 111 Patients Infected with H7N9 Virus in China.**

Characteristic	Value
<b>Age</b>	
Median (range) — yr	61 (3–88)
<b>Subgroup — no. (%)</b>	
0–4 yr	1 (0.9)
5–14 yr	1 (0.9)
15–49 yr	28 (25.2)
50–64 yr	34 (30.6)
≥65 yr	47 (42.3)
Female sex — no. (%)	35 (31.5)
<b>Coexisting condition — no. (%)</b>	
Any	68 (61.3)
Hypertension	51 (45.9)
Diabetes	18 (16.2)
Coronary heart disease	11 (9.9)
Immunosuppression*	10 (9.0)
Chronic obstructive pulmonary disease	8 (7.2)
Cancer†	6 (5.4)
Cerebrovascular disease	4 (3.6)
Hepatitis B infection‡	4 (3.6)
Chronic renal disease	2 (1.8)
Pregnancy	2 (1.8)
Current smoker — no. (%)	27 (24.3)
<b>Exposure to live poultry</b>	
In previous 14 days — no. (%)	62 (55.9)
Median incubation time since exposure (interquartile range) — days	5 (2–8)
Hospitalization — no. (%)	109 (98.2)

# Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

**Table 2. Clinical Characteristics and Selected Laboratory Abnormalities of 111 Patients Infected with H7N9 Virus \***

Characteristic	Value
<b>Fever</b>	
Any — no. (%)	111 (100.0)
Maximal temperature — °C	39.2±0.8
Subgroup — no. (%)	
37.3–38.0°C	11 (9.9)
38.1–39.0°C	43 (38.7)
>39.0°C	57 (51.4)
Fatigue — no. (%)	40 (36.0)
Conjunctivitis — no. (%)	0
Cough — no. (%)	100 (90.1)
Sputum production — no. (%)	62 (55.9)
Hemoptysis — no. (%)	27 (24.3)
Shortness of breath — no. (%)	62 (55.9)
Diarrhea or vomiting — no. (%)	15 (13.5)

<b>White cells</b>	
Median — per mm <sup>3</sup>	4450
Interquartile range — per mm <sup>3</sup>	2900–6230
Subgroup — no. (%)	
>10,000 per mm <sup>3</sup>	5 (4.5)
<4000 per mm <sup>3</sup>	51 (45.9)
<b>Lymphocytes — per mm<sup>3</sup></b>	
Median	460
Interquartile range	320–700
Lymphocytopenia — no. (%)	98 (88.3)
Hemoglobin — g/dl	12.9±3.1
<b>Platelets — per mm<sup>3</sup></b>	
Median	115,500
Interquartile range	82,000–149,500
Thrombocytopenia — no. (%)	81 (73.0)
C-reactive protein >10 mg/liter — no. (%)	85 (76.6)
Procalcitonin >0.5 ng/ml — no. (%)	28 (37.3)
Aspartate aminotransferase >40 U/liter — no. (%)	73 (65.8)
Creatinine >133 μmol/liter (1.5 mg/dl) — no. (%)	10 (9.0)
Lactate dehydrogenase >250 U/liter — no. (%)	91 (82.0)
Creatine kinase >200 U/liter — no. (%)	49 (44.1)
Myoglobin >80 μg/ml — no. (%)	16 (55.2)
<b>PaO<sub>2</sub>:FiO<sub>2</sub></b>	
Median	144.0
Interquartile range	107.1–226.9
Potassium — mmol/liter	3.8±0.5
Sodium — mmol/liter	136.8±6.0
D-dimer >0.5 mg/liter — no. (%)	47 (90.4)
<b>Chest radiologic findings — no. (%)</b>	
Involvement of both lungs	60 (54.1)
Ground-glass opacity	62 (55.9)
Consolidation	99 (89.2)



# Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

**Table 3. Complications, Treatment, and Clinical Outcomes in 111 Patients Infected with H7N9 Virus.\***

Variable	Value <i>no. of patients (%)</i>
<b>Complications</b>	
Pneumonia	108 (97.3)
Acute respiratory distress syndrome	79 (71.2)
Shock	29 (26.1)
Acute kidney injury	18 (16.2)
Rhabdomyolysis	11 (9.9)
<b>Treatment</b>	
Bacteria isolation from culture	29 (26.1)
Administration of oseltamivir or peramivir	108 (97.3)
Timing from onset of illness to administration of antiviral therapy	
0–2 days	11 (9.9)
3–5 days	32 (28.8)
≥6 days	65 (58.6)
Oxygen therapy	111 (100)
Mechanical ventilation	
Noninvasive	31 (27.9)
Invasive	65 (58.6)
Admission to an intensive care unit	85 (76.6)
Extracorporeal membrane oxygenation	20 (18.0)
Continuous renal-replacement therapy	29 (26.1)
Artificial-liver-support-system therapy*	17 (15.3)
Antibiotics	79 (71.2)
Antifungal drugs	1 (0.9)
Glucocorticoids	69 (62.2)
Intravenous immune globulin	59 (53.2)

## Clinical outcome

Death	30 (27.0)
Cause of death	
Refractory hypoxemia	22 (73.3)
Shock	1 (3.3)
Acute heart failure	2 (6.7)
Secondary bacterial or fungal infection	3 (10)
Arrhythmia	2 (6.7)
Discharge from hospital†	49 (44.1)

# Epidemiological, clinical and viral characteristics of fatal cases of human avian influenza A (H7N9) virus in Zhejiang Province, China

Table 2 Epidemiological features of 30 survivors and 10 deaths infected with human avian influenza A (H7N9) virus from Zhejiang Province, China.

	Characteristics	Survivors (N = 30)	Deaths (N = 10)	p value	
Personal information	Age (0~)	0 (0.00%)	0 (0.00%)		
	Age (21~)	6 (20.00%)	1 (10.00%)		
	Age (41~)	13 (43.33%)	0 (0.00%)		
	Age (61~)	11 (36.67%)	7 (70.00%)		
	Age (81–100)	0 (0.00%)	2 (20.00%)		
	Average Age (Yr) (*)	55.87	68.00	0.021 (*)	
	Sex (Male)	17 (56.67%)	8 (80.00%)	0.187	
	Sex (Female)	13 (43.33%)	2 (20.00%)		
	Race (Han race)	30 (100.00%)	10 (100.00%)	1.00	
	Socio-economic status	Education (<high school)	95.45% (21/22)	100% (8/8)	1.00 (Fisher)
Family income/Year (RMB)		17954.55	21428.57	0.390	
BMI (Body mass index kg/m <sup>2</sup> )		25.12	21.20	0.071	
Personal nutrition	Smoking rate (*)	33.33% (10/30)	70.00% (7/10)	0.04 (*)	
	Smoking years	27.50	27.14	0.801	
Personal habits	Smoking volume/Day	9.8	15	0.059	
	Drinking rate	23.33% (7/30)	30.00 (3/10)	0.69 (Fisher)	
Basic health conditions	Chronic coexisting illness-No. (%) (*)	17 (56.67%)	9 (90.00%)	0.05 (*)	
	One disease	5 (29.41%)	2 (22.22%)		
	Two diseases	8 (47.06%)	4 (44.44%)		
	Three disease or above	4 (23.53%)	3 (33.33%)		
	Chronic lung diseases (*)	3 (10.00%)	5 (50.00%)	0.015 (*)	
	Immuno-suppressive disorders (*)	0 (0.00%)	4 (40.00%)	0.002 (*) (Fisher)	
	Pregnancy	1 (3.33%)	0 (0.00%)	0.76	
	Living condition	The average residential population	3.31	3.40	0.892
Living floor		2.33	3.10	0.198	
Infection of Area	Rural area	12 (40.00%)	3 (30.00%)	0.26	
	Exposure condition	70.00% (21/30)	80.00 (8/10)	0.28	
Exposure condition	Poultry in neighbourhood (<1 km)	50.00% (15/30)	50.00 (5/10)	1.000	
	Breeding birds in home	20.00% (6/30)	30.00 (3/10)	0.512	
	Contacting with poultry in home	46.67% (14/30)	50.00 (5/10)	0.855	
	Catching and killing poultry	13.33% (4/30)	40.00% (4/10)	0.068	
	Eating birds	53.33% (16/30)	50.00 (5/10)	0.855	
	Eating times in a week	1.40	1.33	0.873	
	Exposing to live poultry market	53.33% (16/30)	50.00 (5/10)	0.855	
	No of visits to live poultry market/week	4.70	2.33	0.124	
	Drug administration	Anti-allergic drug history	6.67% (2/30)	0.00% (0/10)	1.00 (Fisher)
		Chronic drug treatment history (*)	33.33% (10/30)	70.00% (7/10)	0.042 (*)

Note: An analysis of variance (F test) was applied to weigh the quantity data statistically. Chi-square ( $\chi^2$ ) test was applied to compare the distribution of the different variables of qualitative measurements. Fisher's exact test was used in the analysis of contingency tables when the sample sizes were small.

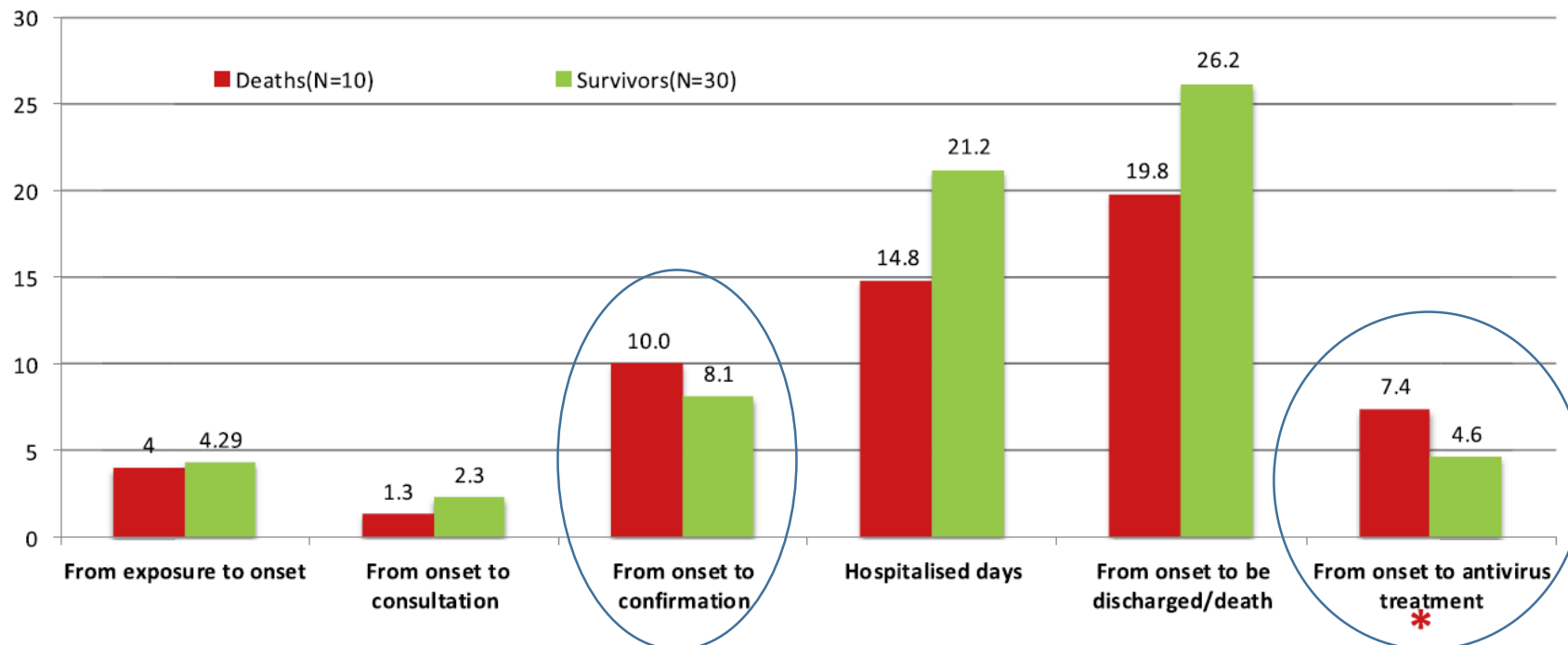
Note: \* The difference is being significant between the two groups ( $p < 0.05$ ).

Epidemiological features associated with mortality:

- Increasing age
- smoking
- underlying medical background
- chronic drug treatment history

# Epidemiological, clinical and viral characteristics of fatal cases of human avian influenza A (H7N9) virus in Zhejiang Province, China

Mean days



**Figure 5** Median days of from exposure to onset (of appearance of initial symptoms), onset to consultation, onset to confirmation, days of hospitalisation, onset to be discharged/death, onset to antiviral treatment, of 30 survivors and 10 deaths infected with H7N9 avian influenza from Zhejiang Province, China. Note: \* denotes that the difference is statistically significant ( $p < 0.05$ ).

# Temporal distribution of H7N9 cases since 2013

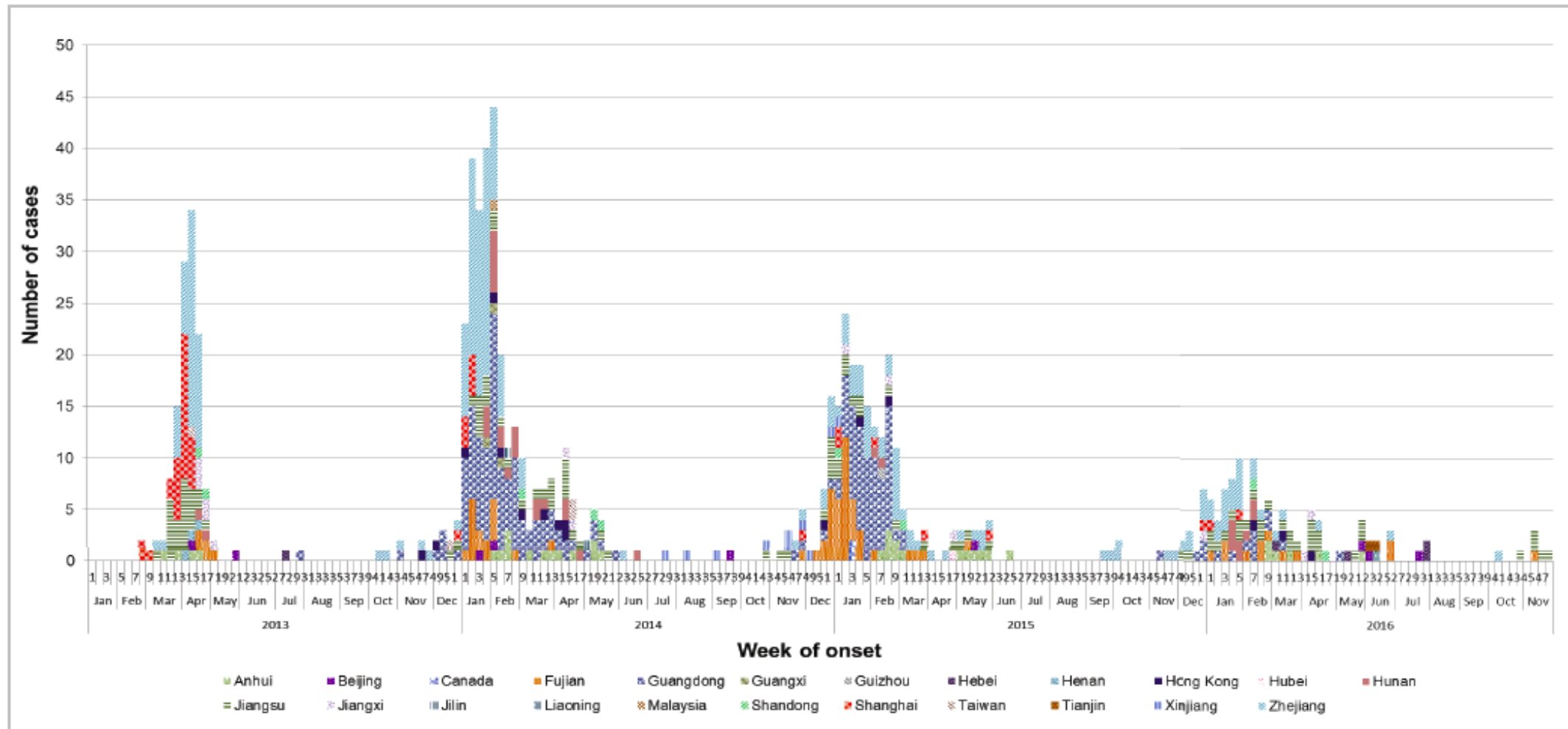


Figure 1 - Weekly number of confirmed human H7N9 cases by place of confirmation and onset date since 2013. (Remark: The onset date of 12 cases remained unknown. The case in Macau confirmed on December 14, 2016 was asymptomatic.)

# Geographical distribution of H7N9 cases in China



# History

- M/70 retired manual worker
- Lives with wife
- Chronic smoker
- Past medical history
  - CVA with mild right hemiparesis
  - Hyperlipidaemia
- Presenting symptoms
  - Developed **fever, cough with sputum, shortness of breath, vomiting and diarrhea**
  - Recent travel to “China” but no poultry exposure history/visit to wet market
- Attended UCH AED and admitted to isolation ward (for suspected TB)
- Empirically started Augmentin and doxycycline

Specimen :- Sputum

AFB Smear :-

No acid alcohol fast bacilli seen

Mycobacterium tuberculosis complex DNA Not Detected

# Sputum for flu PCR

Influenza A virus RNA	Detected
Influenza A virus subtype H1 RNA	Not Detected
Influenza A virus subtype H3 RNA	Not Detected
Influenza A virus subtype H5 RNA	Not Detected
Influenza A virus subtype H7 RNA	Detected
Influenza B virus RNA	Not Detected

Infection control comment:

This is a notifiable disease, please report through NDORS.



# Nasopharyngeal swab

Specimen :- Nasopharyngeal swab

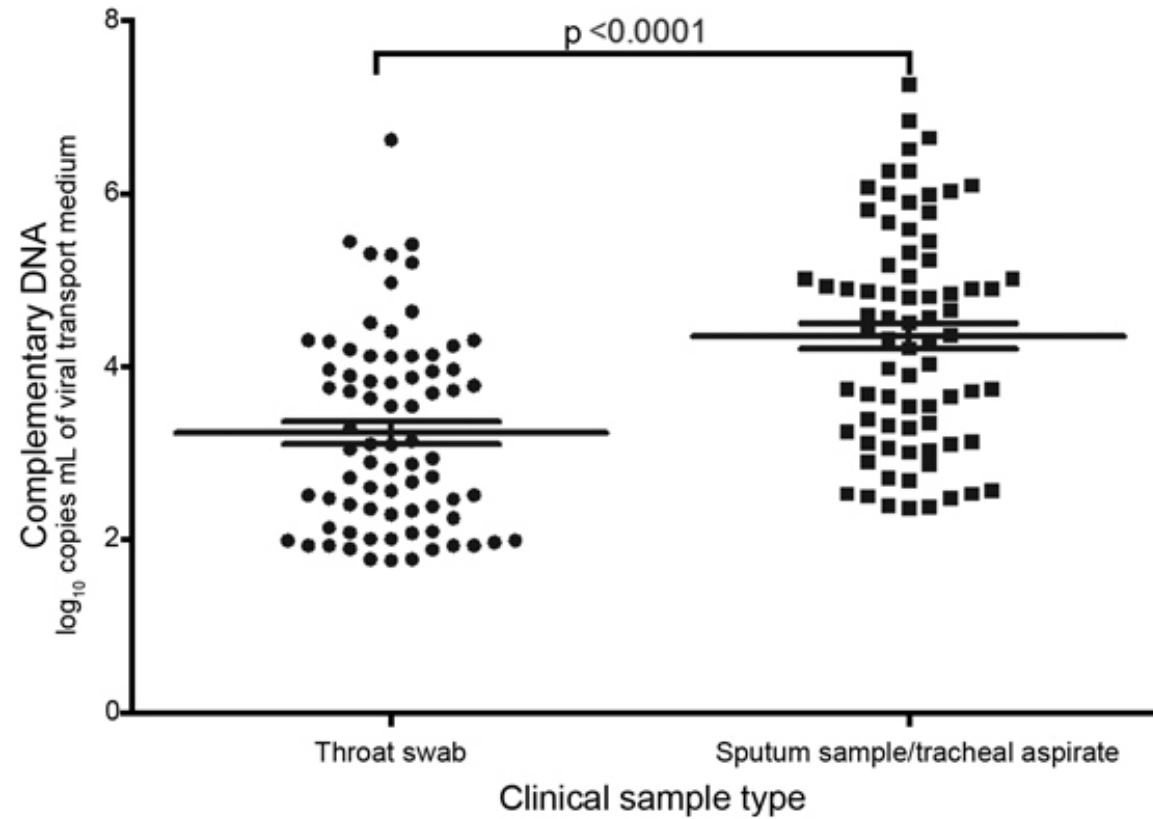
Influenza A direct antigen	Negative
Influenza B direct antigen	Negative

Limitation of rapid antigen test: A positive result cannot distinguish influenza A subtype; a negative result does not exclude influenza virus infection.

## Nucleic acid testing

Specimen Type:	Nasopharyngeal swab
Adenovirus DNA	Not detected
Parainfluenza virus 1 RNA	Not detected
Parainfluenza virus 2 RNA	Not detected
Parainfluenza virus 3 RNA	Not detected
Parainfluenza virus 4 RNA	Not detected
Respiratory syncytial virus RNA	Not detected
Influenza A virus RNA	Not detected
Influenza B virus RNA	Not detected
Influenza C virus RNA	Not detected
Enterovirus / Rhinovirus RNA	Not detected

# Rapid Diagnostic Tests for Identifying Avian Influenza A(H7N9) Virus in Clinical Samples





- Isolate the patient in AIIR
- Continue Augmentin/doxycycline and oseltamivir
- Closely monitor clinical conditions and vital sign
  - Desaturation on the night after transferal to HAIDC
  - Consulted ICU for close monitoring (may require intubation and ventilator support) → suggested management in isolation ward

# Association between the Severity of Influenza A(H7N9) Virus Infections and Length of the Incubation Period

Factors	Risk of Death <sup>1</sup> OR (95% CI)	Risk of Death <sup>1</sup> OR (95% CI)
<b>Continuous incubation period using resampling method</b>	<b>All patients</b>	<b>Patients with exact exposure dates</b>
Incubation period <sup>2</sup> (continuous)	1.70 (1.47–1.97)	1.57 (1.25–1.99)
Age in years	1.04 (1.02–1.05)	1.03 (1.01–1.04)
Sex (male vs female)	0.95 (0.58–1.55)	1.08 (0.56–2.24)
Location		
Capital cities	1.00	1.00
Non-capital cities	1.06 (0.59–1.83)	1.52 (0.68–3.42)
Rural areas	1.02 (0.58–1.75)	1.42 (0.56–3.18)
Underlying conditions	1.03 (0.57–1.78)	1.04 (0.47–2.38)
<b>Incubation period split into tertiles</b>	<b>All patients</b>	<b>Patients with exact exposure dates</b>
Incubation period <sup>2</sup>		
- below 1st tertile (shortest) <sup>3</sup> (reference group)	1.00	1.00
- between 1st and 2nd tertile <sup>3</sup>	3.53 (2.02–6.21)	4.80 (2.16–9.73)
- above 2nd tertile (longest) <sup>3</sup>	3.90 (2.30–7.40)	7.42 (3.34–16.25)
Age in years	1.03 (1.02–1.05)	1.03 (1.01–1.05)
Sex (male vs female)	1.03 (0.61–1.69)	1.02 (0.55–1.95)
Location		
Capital cities	1.00	1.00
Non-capital cities	1.37 (0.79–2.32)	1.57 (0.71–3.66)
Rural areas	1.25 (0.75–2.16)	1.41 (0.67–3.10)
Underlying conditions	0.96 (0.55–1.67)	1.21 (0.58–2.49)

# Association between the Severity of Influenza A(H7N9) Virus Infections and Length of the Incubation Period

**Table 4. Age stratified analysis of association between risk of death and estimated incubation period, sex, location and underlying condition.**

Cases	Risk of Death <sup>1</sup> OR (95% CI)	
	0–59 years old	≥60 years old
All cases (n = 395)	60/129 <sup>2</sup>	113/93 <sup>2</sup>
Incubation period <sup>1</sup>	1.35 (1.06–1.70)	2.13 (1.73–2.67)
Cases with exact exposure dates (n = 203)	41/57 <sup>2</sup>	60/45 <sup>2</sup>
Incubation period <sup>1</sup>	1.51 (1.10–2.03)	2.23 (1.49–3.43)

# To exclude other concomitant causes of chest infection

Clinical Diagnosis / Chest infection	
<b>Nucleic acid testing</b>	
Specimen Type:	Sputum
Adenovirus DNA	Not detected
Parainfluenza virus 1 RNA	Not detected
Parainfluenza virus 2 RNA	Not detected
Parainfluenza virus 3 RNA	Not detected
Parainfluenza virus 4 RNA	Not detected
Respiratory syncytial virus RNA	Not detected
Influenza A virus RNA	Detected
Influenza B virus RNA	Not detected
Influenza C virus RNA	Not detected
Influenza A virus subtype H1 RNA	Not detected
Influenza A virus subtype H3 RNA	Not detected
Influenza A virus subtype H7 RNA	Detected
Influenza A virus subtype N9 RNA	Detected
Enterovirus / Rhinovirus RNA	Not detected

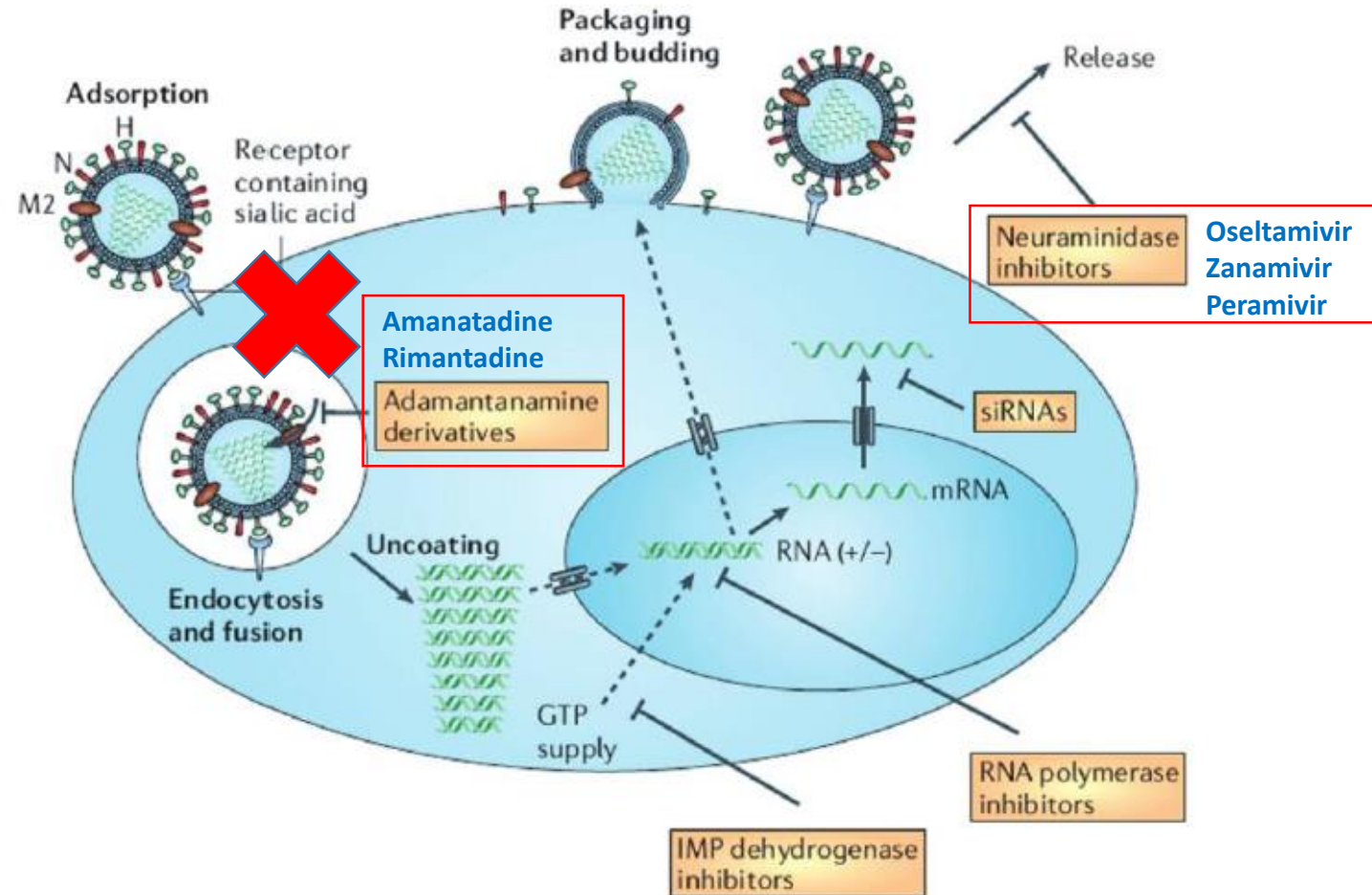
Virus isolation is not routinely performed. Please contact PHL5B if clinically indicated.  
Tel: 2319 8239 Fax: 2319 5989

This report supplements a previous report of the same laboratory number issued on 29/12/2016.

Novel influenza A virus infection is a notifiable disease.

- **Urine for Legionella and Pneumococcal Ag negative**
- **Sputum for AFB smear and TB PCR negative**
- **NPA for Mycoplasma PCR negative**
- **Sputum culture : commensals only**
- **Blood culture and urine culture negative**

# Life cycle of influenza virus





醫院管理局  
HOSPITAL  
AUTHORITY

## HA Central Committee on Infectious Diseases and Emergency Response (CCIDER)

Subject  
Interim Guidance on Clinical Management of Human  
Infection due to Avian Influenza A (H7N9)

Ref No.	CCIDER-AI-H7-002(V1)
Issue Date	30 April 2013
Review Date	30 April 2015
Approved by	CCIDER
Page	Page 2 of 3

### Table of Contents

<u>Section</u>	<u>Page</u>
1. Purpose.....	3
2. Scope.....	3
3. Heightened awareness and case detection.....	3
4. Infection control measures.....	3
5. Investigations.....	3
6. Treatment.....	4
6.1. Antiviral therapy.....	4
6.2. Antibiotics: Start empiric antibiotics to cover bacterial causes of community acquired pneumonia and secondary bacterial infections.....	4
6.3. Management of complications.....	4
6.4. Steroid and immunomodulators.....	4





醫院管理局  
HOSPITAL  
AUTHORITY

**HA Central Committee on Infectious Disease and  
Emergency Responses (CCIDER)**

**Interim Recommendation on Antiviral Therapy for  
Human Infection due to Avian Influenza A (H7N9)**

Ref No.	CCIDER-AI-H7-001
Issue Date	4 Jan 2017
Review Date	14 Jan 2018
Approved by	CCIDER
Page	Page 2 of 15

**Table of Contents**

<u>Section</u>		<u>Page</u>
1	Title.....	3
2	Purpose.....	3
3	Scope.....	3
4	Background Information.....	3
5	Recommended antiviral agents.....	3
	5.1 Oseltamivir (proprietary name: Tamiflu®).....	3
	5.2 Zanamivir (proprietary name: Relenza®).....	5
	5.3 Intravenous neuraminidase inhibitors.....	5
	5.4 Post-exposure antiviral chemoprophylaxis / presumptive antiviral treatment.....	7
<u>Table</u>		
1	Dosage adjustment of oseltamivir for renal impairment.....	11
2	Once-Daily Dose Regimens of IV Peramivir for Adults, Children and Individuals with Renal Impairment <sup>1</sup> .....	12
3	Parameters to be monitored in patients receiving peramivir.....	13
4	Initial Dose Amounts and Twice Daily Maintenance Dose Regimens of IV Zanamivir for Subjects with Renal Impairment.....	14
5	Contact management for cases of influenza A (H7N9).....	15