

## Supplementary Appendix

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

Supplement to: de Jong MD, Thanh TT, Khanh TH, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005;353:2667-72.

**Supplementary appendix***GenBank accession numbers of N1 sequences of influenza H5N1 isolates*

<b>Patient</b>	<b>Virus isolate</b>	<b>Accession number</b>
1	A/Vietnam/CL2009/2005	DQ250165
2	A/Vietnam/CL119/2005	DQ250164
3	A/Vietnam/CL100/2004	DQ250162
5	A/Vietnam/CL115/2005	DQ250163
6	A/Vietnam/CL01/2004	DQ250159
7	A/Vietnam/CL26/2004	DQ250160
8	A/Vietnam/CL36/2004	DQ250161

### Clinical characteristics and laboratory values on admission

Variable	Patients							
	1	2	3	4	5	6 <sup>a</sup>	7 <sup>a</sup>	8
<b>Clinical</b>								
Illness day at onset	2	6	7	6	4	8	7	6
Sex	Female	Female	Female	Female	Female	Female	Male	Male
Age (yr)	13	35	16	18	26	8	23	22
Cough	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sputum	No	Yes	No	Yes	Yes	Yes	Yes	No
Diarrhea	No	No	No	Yes	No	Yes	Yes	No
Temperature (°C)	40.3	38.5	39.7	39	40	38.5	38.7	40.2
Respiratory rate (breaths/min)	36	48	60	40	32	40	28	46
Blood pressure (mm Hg)	110/60	60/40	110/60	120/60	110/60	104/64	120/80	120/60
Pulse (beats/min)	106	110	140	120	120	110	130	120
<b>Hematology</b>								
Leucocyte count (cells per mm <sup>3</sup> )	4800	567	2040	4820	2430	1200	2100	2630
Lymphocytes (%)	12	23	29	18	18	31	18	21
Neutrophils (%)	80	71	51	79	78	55	79	75
Platelet count (cells per mm <sup>3</sup> )	183,000	137,000	105,000	98,500	80,300	117,000	102,000	78,400
<b>Blood chemistry</b>								
AST (U/liter)	45	534	426	100	39	320	110	58
ALT (U/liter)	20	467	201	60	21	354	89	42
<b>Arterial Blood</b>								
pH	NA	7.45	7.42	7.46	NA	NA	7.43	7.45
pO <sub>2</sub> (mm Hg)	NA	36	27	63	NA	NA	75	56
pCO <sub>2</sub> (mm Hg)	NA	42	38	34	NA	NA	31	31
Bicarbonate (mEq/liter)	NA	24	24	23	NA	NA	20	20
Saturation (%)	NA	45	51	NA	NA	95	90	88
<b>Microbiology</b>								
Blood culture	-	-	-	-	-	-	-	-
H5N1 RT-PCR	+ <sup>b</sup>	+	+	+	+	+	+	+
H5N1 culture	NA	+	+	-	+	+	+	+
NA 274 residue	NA	His	His	His <sup>c</sup>	His	His	His	His

<sup>a</sup> Patients 6 and 7 are identical to patients 5 and 10 in reference 2 (Tran TH *et al.* Avian influenza A (H5N1) infection in 10 patients in Vietnam. N Engl J Med 2004; 350: 1179-88); <sup>b</sup> Performed at a different laboratory; <sup>c</sup> Sequence of viral RNA extracted directly from pharyngeal swab. Normal ranges are as follows: leukocyte count, 5,500 to 15,500 per cubic millimeter; % neutrophils, 23 to 45; % lymphocytes, 35 to 65; platelet count, 250,000 to 550,000 per cubic millimeter; alanine aminotransferase (ALT) level, below 55 U per liter; aspartate aminotransferase (AST) level, below 50 U per liter; arterial blood pH, 7.35 to 7.45; arterial oxygen pressure (pO<sub>2</sub>), 70 to 100 mm Hg; arterial carbon dioxide pressure (pCO<sub>2</sub>), 35 to 45 mm Hg; arterial bicarbonate level, 19 to 25 mEq per liter. NA denotes not available, a plus sign positive, and a minus sign negative.

## Summary of clinical courses

<i>patient</i>	<i>Summary of clinical course</i>
1	See case report in main text.
2	Patient was admitted in the evening of 20 January 2005 with shock, respiratory failure, and bilateral pneumonia. On admission, she was intubated and ventilated, and treatment was started with oseltamivir, ceftriaxone and azithromycin. She died the next day shortly after receiving the second dose of oseltamivir.
3	Patient was admitted on 26 December 2004 with respiratory failure and bilateral pneumonia. On admission, she was intubated and ventilated, and treatment was started with oseltamivir, ceftriaxone and amikacin. On 3 January 2005, she developed high fever and peripheral leucocytosis (leucocyte count 21,800 cells per cubic millimeter with 90% neutrophils). Bacterial suprainfection was suspected, and antibiotics were switched to imipenem, gatifloxacin and vancomycin. Despite this, the clinical and respiratory condition continued to worsen, and she died 5 days later on 8 January. Bacteriological investigations on the day before her death revealed <i>Stenotrophomonas maltophilia</i> from broncho-alveolar lavage fluid.
4	Patient was admitted on 5 January 2005 with bilateral pneumonia. On admission, treatment was started with oseltamivir, ceftriaxone and azithromycin. Supplemental oxygen was given by nasal cannula during the first 3 days of admission, but on the fourth day of admission she was intubated and ventilated because of progressive respiratory failure. On the 9 <sup>th</sup> day of admission (13 January, the day that resistant H5N1 virus was isolated from her throat), her temperature rose and her leucocyte count had increased to 18,000 cells per cubic millimeter with 90% neutrophils. Antibiotics were switched to imipenem and gatifloxacin but her respiratory and clinical condition continued to deteriorate. Bacterial culture of broncho-alveolar lavage fluid obtained 3 days later was negative. She died on the 15 <sup>th</sup> day of admission (19 January 2005).
5	Patient was admitted on 18 January 2005 with right-sided pneumonia. On admission, treatment was started with oseltamivir, ceftriaxone and azithromycin. She did not require supplemental oxygen. The patient's temperature normalized within 3 days, and her respiratory condition improved gradually. She was discharged after 10 days on January 28.
6	Patient was admitted on 23 January 2004 with right-sided pneumonia. On admission, treatment was started with oseltamivir, ceftriaxone, amikacin, and vancomycin. She received supplemental oxygen by continuous positive airway pressure, which could be discontinued after 6 days. Antibiotic treatment was stopped after 14 days. She was discharged on 17 February 2004.
7	Patient was admitted on 3 February 2004 with bilateral pneumonia. On admission, treatment was started with oseltamivir, ceftriaxone and amikacin. Supplemental oxygen was given by nasal cannula. The patient's clinical condition improved gradually. Antibiotic treatment was stopped after 13 days, and supplemental oxygen could be discontinued after 15 days. The patient was discharged on 1 March 2004.
8	Patient was admitted on 6 February 2004 with left-sided pneumonia. On admission, treatment was started with oseltamivir, ceftriaxone and vancomycin. Supplemental oxygen was given by oxygen mask. After 6 days, antibiotics were switched to imipenem and vancomycin because of increasing fever. Bacterial cultures of blood and sputum obtained on the same day were negative. The patient's clinical condition slowly improved but on 27 February he developed recurrent left-sided pneumothoraces. On 15 March, he was transferred to a pulmonary referral hospital for further management of pneumothorax. He was discharged from this hospital one month later.