Segment	Type (SUBTYPE)	NB of isolates	Position (H3 and N2 numbering)	Wild	Mutant	Antiviral resistance				High patho-genicity	Hum. adapt.	Ref.
						Neuraminidase inhibitors			Adam.			
						Ose.	Zan.	Per.				
NA	A(N2), B	12	119	E	V	X						38, 40, 42, 43
NA	A(N2), B	1	119	E	A	X	X					42, 43
NA	A(N2), B	3	119	E	G		X					42, 43
NA	A(N2), B	7	119	E	D		X	X				42, 43
NA	A(N1)	415	274	H	Y	X		X				34-38, 41, 43, 44
NA	A(N1,N2)	0	294	N	S	X						33
NA	A(N2), B	2	292	R	K	X	X	X				39, 42, 43
NA	B	0	152	R	K	X	X	X				36-38, 42, 43
NA	B	3	198	D	N/E	X	X					38, 43, 44
NA	B	1	222	I	T	X	X					44
NA	A(N2)	6	222	I	V	X	X					44
M2	A	20	26	L	F				X			46
M2	A	130	27	V	A				X			45, 46
M2	A	8	30	A	T				X			18, 46
M2	A	1433	31	S	N				X			18, 45, 46
M2	A	0	34	G	E				X			46
HA	A	2030	HA cleavage site		≥ 5 R or K					+++		24, 25
NP	A	92	319	N	K						++	31
PB2	A	3181	627	E	K						++	29
PB2	A	177	701	D	N						++	29, 30, 31
NS1	A	97	92	D	E					+ (M)	+	27, 26
NS1	A	1240	80-84	XXXXX	-					+ (M)	+	27
PB1-F2	A	1416	66	N	S					++		28

Table 1: List of mutations used to compute antiviral resistance and putative human adaptation. Ose.: Oseltamivir. Zan.: Zanamivir. Per.: Peramivir. Adam.: Adamantanes. Hum. adapt.: Human adaptation. Ref.; bibliographic reference number. High pathogenicity: could contribute, alone or in association with other mutations, to a higher pathogenicity in avians and/or mammals. +++: high level of confidence; ++: medium level of confidence; +: low level of confidence, or in correlation with other mutations; (M): mammals only.

17. Hay A.J., Zambon M.C., Wolstenholme A.J., Skehel J.J. and Smith M.H. (1986) Molecular basis of resistance of influenza A viruses to amantadine. *J Antimicrob Chemother* **18** Suppl B,19-29.
18. Belshe R.B., Smith M.H., Hall C.B., Betts R. and Hay A.J. (1988) Genetic basis of resistance to rimantadine emerging during treatment of influenza virus infection. *J Virol* **62**(5), 1508-1512.
19. Cox N.J., Kawaoka Y. (1998), Orthomyxoviruses: influenza. In: Collier L., Balows A., Sussman M., eds. *Topley & Wilson's Microbiology and Microbial Infections,* Vol **1**. Virology. London: Arnold, 385-433.
20. Gabriel G., Abram M., Keiner B., Wagner R.*, et al.* (2007) Differential polymerase activity in avian and mammalian cells determines host range of influenza virus. *J Virol* **81**(17), 9601-9604.
21. Basler C.F. and Aguilar P.V. (2008) Progress in identifying virulence determinants of the 1918 H1N1 and the Southeast Asian H5N1 influenza A viruses. *Antiviral Res* **79**(3), 166-178.
22. Ferraris O. and Lina B. (2008) Mutations of neuraminidase implicated in neuraminidase inhibitors resistance. *Journal of Clinical Virology*, **41**, 13-19.
23. Korteweg C. and Gu J. (2008) Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. *Am J Pathol* **172**(5),1155-1170.
24. Hulse D.J., Webster R.G., Russell R.J. and Perez D.R. (2004) Molecular determinants within the surface proteins involved in the pathogenicity of H5N1 influenza viruses in chickens. *J Virol* **78**(18) 9954-9964.
25. Steinhauer D.A. (1999) Role of hemagglutinin cleavage for the pathogenicity of influenza virus. *Virology* **258**(1) 1-20.
26. Seo S.H., Hoffmann E., Webster R.G. (2002) Lethal H5N1 influenza viruses escape host anti-viral cytokine responses. *Nat Med* **8**(9) 950-954.
27. Long J.X., Peng D.X., Liu Y.L., Wu Y.T. and Liu X.F. (2008). Virulence of H5N1 avian influenza virus enhanced by a 15-nucleotide deletion in the viral nonstructural gene. *Virus Genes* **36**(3) 471-478.
28. Conenello G.M., Zamarin D., Perrone L.A., Tumpey T. and Palese P. (2007) A single mutation in the PB1-F2 of H5N1 (HK/97) and 1918 influenza A viruses contributes to increased virulence. *PLoS Pathog* **3**(10) 1414-1421.
29. Le Q.M., Sakai-Tagawa Y., Ozawa M., Ito M., Kawaoka Y. (2009) Selection of H5N1 influenza virus PB2 during replication in humans. *J Virol* **83**(10) 5278-5281.
30. Li Z., Chen H., Jiao P., Deng G. *et al.* (2005) Molecular basis of replication of duck H5N1 influenza viruses in a mammalian mouse model. *J Virol* **79**(18) 12058-12064.
31. Gabriel G., Dauber B. Wolff T., Planz O. *et al.* (2005) The viral polymerase mediates adaptation of an avian influenza virus to a mammalian host. *Proc Natl Acad Sci USA* **102**(51) 18590-18595.
32. ViralZone (2009). http://www.viralzone.ch.
33. Abed Y., Nehmé B., Baz M., Boivin G. (2008) Activity of the neuraminidase inhibitor A-315675 against oseltamivir-resistant influenza neuraminidases of N1 and N2 subtypes. *Antiviral Res*. **77**(2),163-166.
34. Gubareva L.V., Kaiser L., Matrosovich M.N., Soo-Hoo Y., Hayden F.G. (2001) Selection of influenza virus mutants in experimentally infected volunteers treated with oseltamivir*. J. Infect. Dis*. **183**, 523–531.
35. Gubareva L.V., Webster R.G., Hayden F.G. (2001) Comparison of the activities of zanamivir, oseltamivir, and RWJ-270201 against clinical isolates of influenza virus and neuraminidase inhibitor-resistant variants. *Antimicrob. Agents Chemother*. **45**, 3403–3408.

36. Gubareva L.V., Nedyalkova M.S., Novikov D.V., Murti K.G., Hoffmann E., Hayden F.G. (2002) A release-competent influenza A virus mutant lacking the coding capacity for the neuraminidase active site. *J. Gen. Virol.* **8**, 2683–2692.
37. Gubareva L.V., Webster R.G., Hayden F.G. (2002) Detection of influenza virus resistance to neuraminidase inhibitors by an enzyme inhibition assay. *Antiviral Res*. **53**, 47–61.
38. Gubareva L.V. (2004) Molecular mechanisms of influenza virus resistance to neuraminidase inhibitors. *Virus Res*. **103**(1-2), 199-203.
39. Carr J., Ives J., Kelly, L., et al. (2002) Influenza virus carrying neuraminidase with reduced sensitivity to oseltamivir carboxylate has altered properties in vitro and is compromised for infectivity and replicative ability in vivo. *Antiviral Res*. **54**, 79–88.
40. Ives J., Carr J., Roberts N.A., Tai C.Y., Mendel D.B., Kelly L., Lambkin R., Oxford J.(2000) An oseltamivir treatment selected influenza A/Wuhan/359/95 virus with a E119V mutation in the neuraminidase gene has reduced infectivity in vivo. *J. Clin. Virol*. **18**, 251–269.
41. Ives J.A., Carr J.A., Mendel D.B., et al. (2002) The H274Y mutation in the influenza A/H1N1 neuraminidase active site folowing oseltamivir phosphate treatment leave virus severely compromised both in vitro and in vivo*. Antiviral Res*. **55**, 307–317.
42. Jackson D., Barclay W., Zürcher T. (2005) Characterization of recombinant influenza B viruses with key neuraminidase inhibitor resistance mutations. *J Antimicrob Chemother*. **55**(2), 162-169.
43. Mishin V.P., Hayden F.G., Gubareva L.V. (2005) Susceptibilities of antiviral-resistant influenza viruses to novel neuraminidase inhibitors. *Antimicrob Agents Chemother*. **49**(11), 4515-4520.
44. Monto A.S., McKimm-Breschkin J.L., Macken C., Hampson A.W., Hay A., Klimov A., Tashiro M., Webster R.G., Aymard M., Hayden F.G., Zambon M. (2006) Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of their use. *Antimicrob Agents Chemother*. **50**(7), 2395-2402.
45. Ilyushina N.A., Govorkova E.A., Webster R.G. (2005) Detection of amantadine-resistant variants among avian influenza viruses isolated in North America and Asia. *Virology*. **341**(1), 102-106.
46. Abed Y., Goyette N., Boivin G. (2005) Generation and characterization of recombinant influenza A (H1N1) viruses harboring amantadine resistance mutations. *Antimicrob Agents Chemother*. **49**(2), 556-559.