

Summary of neuraminidase (NA) amino acid substitutions assessed for their effects on inhibition by NA inhibitors (NAIs) among avian influenza viruses of Group 1 (N1, N4, N5, N8 subtypes) and Group 2 (N2, N3, N6, N7, N9 subtypes) NAs.

NA subtype	Amino acid substitution ^a	N2 numbering ^b	Susceptibility assessed by NA inhibition assays (IC ₅₀ fold change) ^c				Source of viruses/selection with ^d	References
			Oseltamivir	Zanamivir	Peramivir	Laninamivir		
Group 1								
H5N1	V96A	116	RI (11–18)	RI (10–63)	NI (4)	? ^e	Sur	(1, 2)
	I97T	117	RI (19)	RI (12)	?	?	Sur	(3)
	I117T ^f	117	NI (1)	NI (1)	NI (1)	NI (1)	Sur	(4)
	I97V	117	NI (5–9)	NI (2–4)	?	?	RG; Sur	(3, 5, 6)
	E99A	119	RI (10–35)	HRI (51–1254)	NI (7)	?	RG	(5, 7)
	E99D	119	RI (87)	HRI (132)	HRI (1436)	?	RG	(7)
	E99G	119	NI (3–6)	HRI (438–1485)	RI/HRI (12–164)	?	RG; in vitro/Zan	(7, 8)
	Q116L	136	RI (26)	HRI (350)	?	?	In vivo/Zan	(9)
	V129A	149	NI (4)	NI (8)	?	?	Sur	(10)
	D179G	198	RI (32)	RI (44)	NI (4)	?	RG; in vitro/Zan	(8)
	I203M	222	RI (13-36)	NI (1-3)	NI (1)	?	RG; in vitro/Zan; Sur	(8, 11)
	I203V	222	NI (2-7)	NI (1-2)	NI (1)	?	RG; in vitro/Zan; Sur	(8, 11)
	S227N	246	NI/RI (6-24)	NI (2-6)	?	?	Sur	(1, 11)
	S247N ^f	246	NI (6)	NI (1)	NI (4)	NI (2)	Sur	(4)
	H255Y	274	RI/HRI (44–2502)	NI (1–3)	RI/HRI (23–533)	NI (6)	Sur; Clin/Ose; RG; in vitro/Zan	(5, 7, 8, 12, 13)
	N275S	294	RI/HRI (12–138)	NI/RI (1–27)	NI/RI/HRI (1–130)	?	Clin/Ose; RG	(5, 7, 12, 14)
	N295D ^f	294	NI (1)	NI (4)	NI (2)	NI (2)	Sur	(4)
	N295S ^f	294	RI (14)	NI (4)	NI (6)	NI (3)	Sur	(4)
	K412T	432	NI (9)	RI (12)	NI (5)	?	Sur; in vitro	(15)
	T438I ^f	439	NI (1–8)	RI/HRI (17–98)	NI/RI (6–23)	?	RG, Sur	(9, 16)
	T438N ^f	439	NI (2)	RI (12)	NI (2)	NI (2)	Sur	(4)
	I97V+I294V	117+314	RI (16)	NI (1)	NI (1)	?	Sur	(2)
	E99A+H255Y	119+274	HRI (1530)	RI (50)	HRI (2686)	?	RG	(7)
	E99D+H255Y	119+274	HRI (160)	RI (65)	HRI (1629)	?	RG	(7)
	E99G+H255Y	119+274	HRI (801)	RI (76)	HRI (>7692)	?	RG	(7)
	I203L+ S227N	222+246	RI (14)	NI (1)	NI (5)	?	Sur; in vitro	(15)
	I203M+H255Y	222+274	HRI (8024)	NI (3)	HRI (3340)	?	RG; in vitro/Zan	(8)
	I203V+H255Y	222+274	HRI (1925)	NI (2)	HRI (2106)	?	RG; in vitro/Zan	(8)
	N295S+T438N ^f	294+439	HRI (51–74)	HRI (76–86)	HRI (73–90)	RI (16-19)	Sur	(4)
	K130N+I203L+S227N	150+222+246	RI (77)	NI (1)	?	?	Sur	(1)

N4	H274Y	274	HRI (318)	NI (2)	HRI (115)	NI (5)	in vitro; RG	(17, 18)
	E276D	276	RI (11)	HRI (249)	RI (18)	RI (81)	in vitro; RG/Zan	(17, 18)
	R292K	292	HRI (52862135)	HRI (465)	HRI (30252)	HRI (293)	in vitro; RG	(17, 18)
	I428L	427	RI (19)	RI (76)	NI (9)	RI (21)	in vitro; RG/Zan	(17, 18)
N5	E116V	119	RI (59)	HRI (737)	RI (64)	HRI (386)	in vitro; RG/Ose	(17, 18)
	N143I	147	NI (1)	RI (31)	NI (3)	NI (1)	in vitro; RG/Zan	(17, 18)
	H271Y	274	HRI (1082)	NI (3)	HRI (312)	NI (2)	in vitro; RG	(17, 18)
	R289K	292	HRI (964)	NI (4)	HRI (284)	NI (3)	in vitro; RG	(17, 18)
	L87I+E116V	91+119	RI (43)	HRI (556)	RI (87)	HRI (274)	in vitro; RG/Ose	(17, 18)
N8	E117V	119	RI (30)	HRI (255)	HRI (130)	?	RG	(19)
	Q134K	136	NI (1)	HRI (263)	HRI (185)	HRI (550)	in vitro; RG/Zan	(17, 18)
	G145V	147	NI (2)	RI (25)	NI (5)	RI (22)	in vitro; RG/Zan	(17, 18)
	H273Y	274	HRI (202–425)	NI (1–2)	HRI (103–244)	NI (3)	in vitro; RG	(17–19)
	R291K	292	HRI (50636336)	RI (93)	HRI (8540)	HRI (152)	in vitro; RG	(17, 18)
	N293S	294	RI (62–79)	NI (3)	RI (15)	?	RG, Sur	(19, 20)
Group 2								
N2	E119A	119	NI (9)	HRI (100–600)	NI (1)	?	in vitro/Zan	(21, 22)
	E119D	119	NI (4–5)	HRI (323– 500)	RI (33)	?	in ovo; in vitro/Zan	(21–23)
	E119G	119	RI (2–87)	HRI (71–700)	NI (2)	?	in vivo; in vitro/Zan	(21, 22, 24)
	E119V	119	RI (48)	NI (3)	NI (1)	?	RG	(19)
	H274Y	274	NI (1)	NI (5)	NI (2)	?	RG	(19)
	R292K	292	HRI (1268– >2900)	NI/RI (4– 26)	RI (43–100)	?	in vivo, in ovo; in vitro/Zan; RG	(19–23, 25, 26)
	N294S	294	NI (3)	RI (14)	NI (1)	?	RG	(19)
N3	E119G	119	RI (25)	HRI (523)	RI (14)	RI (24)	in vitro; RG/Zan	(18, 27)
	H276Y	274	HRI (12229)	NI (2)	NI (1)	NI (0.5)	in vitro; RG	(18, 27)
	R293K	292	HRI (17960)	RI (23)	RI (41)	NI (2)	in vitro; RG/Ose	(18, 27)
N6	E119D	119	NI (2)	HRI (249)	RI (31)	HRI (370)	in vitro; RG/Zan	(18, 27)
	E119V	119	RI (75)	NI (4)	NI (4)	?	RG	(19)
	A247V	246	NI (3)	RI (17)	NI (5)	RI (14)	in vitro; RG/Zan	(18, 27)
	H275Y	274	RI (13)	NI (3)	NI (3)	?	RG	(19)
	R293K	292	HRI (15068)	RI/HRI (46)	HRI (844)	HRI (126)	in vitro; RG/Ose	(18, 27)
	N295S	294	NI (1)	RI (18)	NI (3)	?	RG	(19)
	R372K	371	RI (23)	RI (53)	RI (12)	RI (95)	in vitro; RG/Zan	(18, 27)
N7	E118D	119	NI (3)	HRI (101)	NI (1)	RI (60)	in vitro; RG/Zan	(18, 27)
	E118G	119	NI (1)	RI (67)	NI (1)	RI (42)	in vitro; RG/Zan	(18, 27)

	E118V	119	RI (55)	NI (1)	NI (2)	NI (0.5)	in vitro; RG/Ose	(18, 27)
	R151W	152	RI (14)	RI (11)	NI (1)	NI (4)	in vitro; RG/Ose	(18, 27)
	H274Y	274	RI (17)	NI (2)	NI (2)	NI (1)	in vitro; RG	(18, 27)
	E276D	276	NI (7)	RI (26)	NI (5)	NI (3)	in vitro; RG/Zan	(18, 27)
	R292K	292	HRI (44326)	RI (21)	HRI (415)	RI (11)	in vitro; RG/Ose	(18, 27)
	D293N	293	RI (14)	RI (57)	NI (5)	RI (31)	in vitro; RG/Zan	(18, 27)
	S110N+E119D	111+119	NI (4)	HRI (116)	NI (1)	RI (79)	in vitro; RG/Zan	(18, 27)
	I275T+E276D	275+276	NI (6)	RI (14)	NI (5)	NI (0.4)	in vitro; RG/Zan	(18, 27)
H7N9	E115A	119	RI (19)	HRI (228)	RI (20)	RI (62)	in vitro; recNA	(28)
	E115D	119	RI (14)	HRI (1436)	HRI (411)	HRI (383)	in vitro; recNA	(28)
	E115G	119	NI (2)	HRI (419)	RI (48)	HRI (124)	in vitro; recNA	(28)
	E115V	119	RI/HRI (84–169)	NI (6–9)	NI (1–2)	NI (2–5)	Sur; P-p; in vitro; recNA; RG	(28–30)
	Q132K	136	NI (1)	HRI (702)	HRI (131)	HRI (313)	in vitro; recNA	(28)
	R148K	152	NI (1)	NI (5)	NI (3)	RI (16)	in vitro; recNA	(28)
	I219K	222	RI (32–46)	NI/RI (8–17)	NI/RI (6–11)	RI (13–27)	in vitro; recNA; Sur; P-p	(28, 29)
	I219L	222	NI (5)	NI (2)	NI (1)	NI (2)	RG	(30)
	I219R	222	RI/HRI (37–143)	RI (12–38)	RI (12–44)	RI (14–63)	In vitro; recNA; sur; P-p	(28, 29)
	T244P	247	RI (27)	RI (69)	NI (4)	NI (9)	in vitro; recNA	(28)
	H271Y	274	HRI (105)	NI (2)	NI (9)	NI (2)	in vitro; Sur	(28)
	E273D	276	RI (13)	HRI (427)	RI (25)	RI (90)	in vitro; recNA	(28)
	R289K	292	HRI (>4600)	RI (11–67)	HRI (405–2487)	RI (16–35)	in vitro; recNA; Sur; P-p	(28, 29, 31, 32)
	N291S	294	NI (2)	RI (10)	NI (1)	NI (3)	in vitro; recNA	(28)
	R367K	371	RI (70)	RI (64)	RI (29)	RI (19)	in vitro; recNA	(28)
	E115V+I219L	119+222	HRI (306)	NI (8)	NI (2)	NI (4)	RG	(30)
N9	<i>E120V</i>	119	RI (50)	NI (3)	NI (1)	NI (3)	in vitro; RG/Ose	(18, 27)
	<i>Q137K</i>	136	NI (0.5)	HRI (121)	RI (54)	RI (63)	in vitro; RG/Zan	(18, 27)
	<i>R153K</i>	152	NI (2)	RI (10)	?	?	RG	(30)
	<i>I224M</i>	222	RI (18)	NI (4)	NI (4)	NI (1)	in vitro; RG/Ose	(18, 27)
	<i>A248T</i>	246	NI (6)	RI (25)	NI (7)	NI (2)	in vitro; RG/Zan	(18, 27)
	<i>H276Y</i>	274	RI (80–90)	NI (2–3)	RI (11)	NI (2)	in vitro; RG	(18, 27, 33)
	<i>R294K</i>	292	HRI (10000–68891)	RI (32–51)	HRI (2068)	RI (35)	in vitro; RG/Ose	(18, 27, 33)

^a Numbering is based on the neuraminidase subtype of influenza A viruses.

^b Equivalent N2 numbering is based on an alignment of neuraminidases from A/turkey/Turkey/1/2005 (H5N1), A/goose/Taiwan/01031/2015 (H5N2), A/turkey/Minnesota/916/80 (H7N3), A/environment/South Korea/W140/2006 (H10N4), A/aquatic bird/Korea/W69/2005 (H6N5), A/environment/South Korea/W20/2005 (H4N6), A/chicken/Jiangxi/02.05 YGYXG023-P/2015 (H5N6), A/duck/Germany/62-4/81 (H7N7), A/environment/Korea/W468/2014 (H5N8), A/scarlet ibis/Germany/AR44-L01279/2015 (H5N8), and A/duck/Memphis/546/74 (H11N9 – N9 numbers shown in *italics*) influenza viruses.

^c Assessed by NA inhibition (NI) assays: chemiluminescent (NA-Star), fluorescent (MUNANA) and/or colorimetric (fetuin). NAI results are shown according to the referenced studies: NI, normal inhibition; **RI**, reduced inhibition; **HRI**, highly reduced inhibition as defined in (34). Fold-changes in IC₅₀ (half maximal inhibitory concentration) relative to wild-type viruses or subtype- or clade-specific median IC₅₀s, are shown in parentheses.

^d Clin, clinical detection; Ose, oseltamivir used; Zan, zanamivir used; P-p, Plaque purification; RG, reverse genetics; recNA, recombinant NA; Sur, surveillance studies.

^e ? signifies that the NAI(s) indicated were not studied.

^f Equivalent N1 numbering is based on an alignment of neuraminidase from A/bald eagle/Florida/W22-134-OP/2022 (H5N1) clade 2.3.4.4b influenza virus that does not carry a 20 amino acid deletion in the neuraminidase stalk region.

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