

Summary of neuraminidase (NA) amino acid substitutions assessed for their effects on inhibition by neuraminidase inhibitors (NAIs)

Amino Acid Substitutions in the NA Protein

The table below includes details regarding amino acid substitutions in the NA protein of seasonal and zoonotic viruses whose effects were assessed in enzymatic assays using clinical isolates, laboratory strains, reverse-genetics derived viruses, or recombinant NA proteins. These substitutions may arise as a result of exposure to NAIs (oseltamivir, zanamivir, peramivir, laninamivir) or in instances unrelated to drug exposure (e.g., selection of NA mutants during isolation/propagation in cell cultures).

The amino acid substitution H275Y in N1 subtype (corresponding to H274Y in N2 numbering; reference numbering system in the table) is shown in bold font because it is a known molecular marker of clinically relevant resistance to oseltamivir. This was established for pre-2009 A(H1N1) viruses, but available evidence indicates that this substitution in other N1 containing viruses (e.g., A(H5N1) and A(H1N1)pdm09) can also confer oseltamivir-resistance and, possibly, to peramivir. Clinical significance of other substitutions has not been demonstrated. Moreover, some substitutions are found infrequently or have resulted from virus isolation and propagation in cell culture. Viruses carrying substitutions that confer reduced or highly reduced inhibition in NA inhibition assays may require additional analysis at WHO Influenza Collaborating Centres (WHO CC).

Virologic Surveillance and Criteria for Reduced/Highly Reduced Inhibition

Phenotypic cell culture-based assays should not be used to assess susceptibility of viruses to NAIs, as they cannot reliably predict the antiviral effect of these compounds on virus replication in a human host. Therefore, a functional NA inhibition assay is used as a surrogate phenotypic assay, which determines the effect of antiviral on NA enzymatic activity. The generated IC_{50} value (half maximal inhibitory concentration of NAI) often varies depending on the assay used (e.g., fluorescent versus chemiluminescent).

For virologic surveillance, IC_{50} values are used to calculate a fold increase compared to wild-type or subtype- or clade-specific median IC_{50} values. To harmonise reporting, arbitrary threshold increases (fold-changes) in IC_{50} values were introduced by the WHO antiviral working group (AVWG). The relationship between RI/HRI and reduced susceptibility has not been established, and therefore NA inhibition assay data should be interpreted with caution.

- Normal Inhibition (NI): <10-fold IC_{50} change for Influenza A viruses, <5-fold IC_{50} change for Influenza B viruses
- Reduced Inhibition (RI): 10-100-fold IC_{50} change for Influenza A viruses, 5-50-fold IC_{50} change for Influenza B viruses
- Highly Reduced Inhibition (HRI): >100-fold IC_{50} change for Influenza A viruses, >50-fold IC_{50} change for Influenza B viruses

How to use this table for global virologic surveillance:

- Use IC_{50} fold-changes to compare results across laboratories
- Assign NI, RI, or HRI designations as described above
- Use the latest version of this table, updated annually by the WHO-AVWG

Type/subtype <i>Comments</i>	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		
Type A								
A(H1N1)pdm09	S110F	110	NI/RI (9.8–10.5)	RI (17–18)	? ^e	?	Sur	(1, 2)
	I117R	117	NI (1)	RI (10)	?	?	Sur	(3)
	E119A	119	NI/RI (6.3–17)	RI (17–90)	NI/RI (7–12)	RI (82)	Sur; RG	(4-6)
	E119D	119	RI (25–94)	HRI (583–2731)	HRI (104–402)	HRI (649–702)	Clin/Zan; RG	(5, 7, 8)
	E119G	119	NI (1–7)	HRI (113–1306)	RI/HRI (51–167)	HRI (112–327)	RG; Clin/Zan	(5, 8-10)
	E119V	119	RI (60)	HRI (571)	RI (25)	?	RG	(9)
	Q136H	136	NI (1)	NI (1)	NI (1)	NI (1)	Sur	(107)
<i>Cell culture- selected</i>	Q136K	136	NI (0.5-1)	RI/HRI (86–749)	HRI (143)	RI (42–45)	Sur; RG; in vitro	(4, 6, 11, 12)
<i>Cell culture- selected</i>	Q136R	136	NI (1)	HRI (200)	HRI (234)	RI (33)	Sur	(13)
	R152K	152	RI (18–43)	NI/RI (4–12)	NI (4–7)	RI (16)	RG	(5, 8)
	D199E	198	RI (16–26)	NI (7–8)	NI (3)	NI (3)	Sur; RG	(8, 14)
	D199G	198	RI (17)	NI (6)	NI (2)	NI (2)	Sur; in vitro; RG	(4, 9)
	D199V	198	NI (2)	NI (1)	NI (1)	NI (1)	Sur	(107)
	D199Y	198	RI (37)	RI (28)	NI (4)	NI (7)	Clin/Sur	(15)
	I223K	222	RI (12–39)	NI (5–6)	NI (1–4)	NI (4)	Clin/Sur; RG	(14, 16, 17)
	I223L	222	RI (11)	NI (2)	NI (1)	NI (1)	Clin/Sur	(18)
	I223M	222	RI (12)	NI (2)	NI (2)	NI (1)	Clin/Sur	(18)
	I223R	222	RI (13–58)	NI/RI (8–12)	NI/RI (5–11)	NI (2–5)	Clin/No; Clin/Ose/Zan; RG; Clin/Sur	(14, 16, 18-22)
	I223T	222	NI/RI (9–15)	NI (3)	NI (2)	NI (2)	Clin/Sur	(6, 14)
	I223V	222	NI (3–6)	NI (1–2)	NI (1–2)	NI (1)	RG; Clin/Sur	(4, 9, 23)
	S247G	246	RI (11-15)	NI (1)	NI (1-1.3)	NI (1-1.1)	Clin/Sur	(6, 14)
	S247N	246	NI (2.7–8)	NI (2–5)	NI (1–3)	NI (3)	Clin/Sur	(23-25)
	S247R	246	RI (36–37)	RI (51–54)	RI/HRI (94–115)	RI/HRI (90–122)	Clin/No	(3)
	H275Y	274	HRI (221–2846)	NI (0.5–6)	RI/HRI (50–751)	NI (0.8–4.9)	Clin/Ose; Clin/Sur; in vitro	(6, 26-35)
	R293K	292	RI (33)	NI (4)	NI (8)	?	RG	(5)
	N295S	294	RI/HRI (64–208)	NI (2–9)	NI/RI (3–12)	NI (3)	RG	(4, 5, 9, 13)

	I427T	427	RI (37)	RI (41)	NI (6)	RI (11)	Sur	(15)
	I436N	436	RI (31)	RI (71)	RI (20)	RI (19)	RG	(36)
	P458T	459	HRI (280)	HRI (808)	HRI (148)	HRI (211)	RG	(8)
	H275Y+I436N	274+436	HRI (4811)	RI (36)	HRI (10460)	RI (22)	RG	(36)
<i>Some IC₅₀s were given for mixed virus populations; to be assessed using recombinant NA</i>	D199N+H275Y	198+274	HRI (318–744)	NI (2–3)	HRI (108)	?	Sur; Clin/Ose	(33, 37)
	G147R+H275Y	147+274	HRI (2649)	NI (5)	HRI (1427)	NI (1)	Clin/Lan+Per	(3)
	E119A+H275Y	119+274	HRI (1173)	RI (56)	NI (3)	?	RG	(5)
	E119D+H275Y	119+274	HRI (790–3381)	HRI (136–903)	HRI (5958–33333)	HRI (366)	RG	(5, 7)
	E119G+H275Y	119+274	HRI (225–2483)	HRI (225–1546)	HRI (3333–93433)	HRI (650)	Clin/ Zan; Sur; RG	(5, 10)
	I223V+S247N	222+246	RI (11–16)	NI (3)	NI (4)	NI (3)	Clin/Sur	(23, 38)
	I223K+H275Y	222+274	HRI (>10822)	RI (11)	HRI (5343)	RI (11)	Sur; in vitro	(29)
	I223R+H275Y	222+274	HRI (>9100)	RI (22–27)	HRI (>7500)	RI (17)	Clin/Ose; RG	(17, 21, 29)
	I223V+H275Y	222+274	HRI (1733)	NI (2)	HRI (1331)	?	Clin/Ose; RG	(9, 39)
	S247N+H275Y	246+274	HRI (5880)	NI (5)	HRI (334)	?	Sur	(24)
	Q313R+I427T	313+427	RI (10–43)	NI/RI (3–20)	NI (4)	?	Sur	(27, 40)
A(H1N1)	E119V	119	RI/HRI (15–1727)	HRI (136–2144)	HRI (5050)	?	RG	(41, 42)
<i>Host cell selected in both studies; not found in clinical specimens</i>	Q136K	136	NI (1)	RI/HRI (36–327)	RI (75–80)	?	Sur	(27, 43)
<i>This result is virus specific</i>	Y155H	155	HRI (123)	HRI (555)	?	?	Sur	(44)
	I223M	222	NI (8)	NI (1)	NI (1)	?	RG; in vitro/Zan	(45)
	I223V	222	NI (3)	NI (2)	NI (1)	?	RG; in vitro/Zan	(45)
	S247G	246	NI (5)	NI (1)	?	?	Sur	(46)
	H275Y	274	HRI (321–2597)	NI (1–2)	HRI (111–1095)	?	Sur; RG	(27, 42, 46, 47)
	R293K	292	NI (1)	RI (18)	?	?	RG	(42)
	N295S	294	RI/HRI (40–197)	NI (1–5)	RI (12)	?	RG	(41, 42)
	I117V+E119V	117+119	NI (7)	HRI (391)	?	?	RG	(42)
	I117M+E119V	117+119	RI (20)	HRI (181)	?	?	RG	(42)

	I117V+H275Y	117+274	HRI (683)	NI (1)	?	?	RG	(42)
	I117M+H275Y	117+274	HRI (395)	NI (1)	?	?	RG	(42)
	I117V+N295S	117+294	RI (60)	NI (1)	?	?	RG	(42)
	I117M+N295S	117+294	RI (52)	NI (4)	?	?	RG	(42)
	E119V+H275Y	119+274	RI (21)	HRI (132)	?	?	RG	(42)
<i>Both changes were host cell selected</i>	Q136K+D151E	136+151	NI (1)	RI (25)	RI (18)	?	Sur	(27)
<i>Q136K was host cell selected</i>	Q136K+H275Y	136+274	HRI (198)	RI (15)	HRI (1805)	?	Sur	(27)
<i>D151E/N was host cell selected</i>	D151E/N+H275Y	151+274	HRI (231–799)	NI (1–3)	RI/HRI (80–718)	?	Sur	(27)
<i>D151G was host cell selected</i>	D151G+H275Y	151+274	HRI (1189)	RI (14)	HRI (1161)	?	Sur	(27)
	I223M+H275Y	222+274	HRI (1943)	NI (1)	HRI (400)	?	RG; in vitro/Zan	(45)
	I223V+H275Y	222+274	HRI (584–971)	NI (1–2)	HRI (893)	?	RG; in vitro/Zan	(42, 45)
	I223V+N295S	222+294	RI (97)	NI (2)	?	?	RG	(42)
	R293K+H275Y	292+274	HRI (207)	NI (1)	?	?	RG	(42)
	N295S+H275Y	294+274	HRI (108)	NI (1)	?	?	RG	(42)
	S334N+H275Y	336+274	HRI (415)	NI (1)	?	?	RG	(42)
	I117V+N295S+H275Y	117+294+274	HRI (336)	RI (12)	?	?	RG	(42)
	I117M+N295S+H275Y	117+294+274	HRI (121)	RI (11)	?	?	RG	(42)
<i>Q136K+D151N were host cell selected</i>	Q136K+D151N+H275Y	136+151+274	HRI (356)	NI (4)	HRI (2300)	?	Sur	(27)
	I223V+N295S+H275Y	222+294+274	HRI (300)	RI (13)	?	?	RG	(42)
A(H5N1)	V96A	116	RI (11–18)	RI (10–63)	NI (4)	?	Sur	(48, 49)
	V116A ^f	116	NI (3)	RI (14–22)	NI/RI (6–12)	NI (3–6)	RecNA	(50)
	V116I ^f	116	NI (1)	NI (2)	NI (1)	NI (1)	RecNA	(50)
	I97T	117	RI (19)	RI (12)	?	?	Sur	(51)
	I117T ^f	117	NI (1)	NI (1)	NI (1)	NI (1)	Sur	(52)
	I97V	117	NI (5–9)	NI (2–4)	?	?	RG; Sur	(51, 53, 54)
	E99A	119	RI (10–35)	RI/HRI (51–1254)	NI (7)	?	RG	(5, 53)
	E99D	119	RI (87)	HRI (132)	HRI (1436)	?	RG	(5)
	E99G	119	NI (3–6)	HRI (438–1485)	RI/HRI (12–164)	?	RG; in vitro/Zan	(5, 45)
	E119D ^f	119	RI (18–22)	HRI (6281–8072)	HRI (1957–3213)	HRI (1488–2735)	RecNA	(50)

	Q116L	136	RI (26)	HRI (350)	?	?	In vivo/Zan	(55)
	V129A	149	NI (4)	NI (8)	?	?	Sur	(56)
	R152G ^f	152	RI (13–16)	HRI (1273–1754)	HRI (810–1515)	HRI (619–1433)	RecNA	(50)
	D179G	198	RI (32)	RI (44)	NI (4)	?	RG; in vitro/Zan	(45)
	I203M	222	RI (13–36)	NI (1–3)	NI (1)	?	RG; in vitro/Zan; Sur	(45, 57)
	I203V	222	NI (2–7)	NI (1–2)	NI (1)	?	RG; in vitro/Zan; Sur	(45, 57)
	I223T ^f	222	NI (3)	NI (3–4)	NI (3–4)	NI (2)	RecNA	(50)
	S227N	246	NI/RI (6–24)	NI (2–6)	?	?	Sur	(57, 58)
	S247N ^f	246	NI (5–7)	NI (1–2)	NI (4)	NI (2)	Sur; RecNA	(50,52)
	H255Y	274	RI/HRI (44–2502)	NI (1–3)	RI/HRI (23–533)	NI (6)	Sur; Clin/Ose; RG; in vitro/Zan	(5, 45, 53, 59, 60)
	H275Y ^f	274	HRI (159–184)	NI (1–2)	HRI (1064–1724)	NI (3)	RecNA	(50)
	N275S	294	RI/HRI (12–138)	NI/RI (1–27)	NI/RI/HRI (1–130)	?	Clin/Ose; RG	(5, 53, 59, 61)
	N295D ^f	294	NI (1)	NI (4)	NI (2)	NI (2)	Sur	(52)
	N295S ^f	294	RI (14)	NI (4)	NI (6)	NI (3)	Sur	(52)
	I427T ^f	427	NI (6–7)	RI (75–90)	RI (16–23)	RI (15–25)	RecNA	(50)
	K412T	432	NI (9)	RI (12)	NI (5)	?	Sur; in vitro	(62)
	K432R ^f	432	NI (1)	NI (1)	NI (1)	NI (1)	Sur	(50)
	T438I ^f	439	NI (1–8)	RI/HRI (17–119)	NI/RI (6–26)	RI (24–33)	RG, Sur, RecNA	(50, 57)
	T438N ^f	439	NI (2)	RI (12)	NI (2)	NI (2)	Sur	(52)
	S439G ^f	440	NI (2)	NI (6–8)	NI (2–3)	NI (1)	Sur	(50)
	I97V+I294V	117+314	RI (16)	NI (1)	NI (1)	?	Sur	(49)
	E99A+H255Y	119+274	HRI (1530)	RI (50)	HRI (2686)	?	RG	(5)
	E99D+H255Y	119+274	HRI (160)	RI (65)	HRI (1629)	?	RG	(5)
	E99G+H255Y	119+274	HRI (801)	RI (76)	HRI (>7692)	?	RG	(5)
	I203L+ S227N	222+246	RI (14)	NI (1)	NI (5)	?	Sur; in vitro	(62)
	I203M+H255Y	222+274	HRI (8024)	NI (3)	HRI (3340)	?	RG; in vitro/Zan	(45)
	I203V+H255Y	222+274	HRI (1925)	NI (2)	HRI (2106)	?	RG; in vitro/Zan	(45)
	N295S+T438N ^f	294+439	RI (51–74)	RI (76–86)	RI (73–90)	RI (16–19)	Sur	(52)
	K130N+I203L+S227N	150+222+246	RI (77)	NI (1)	?	?	Sur	(48)
A(H3N2)	E119D	119	NI (2)	RI (32)	NI (2)	?	RG	(63)
	E119I	119	HRI (208)	RI (17)	NI (3)	?	Clin/Ose; in vitro	(64)

	E119V	119	RI/HRI (18–2057)	NI (1–7)	NI (1–3)	NI (1–4)	Sur; Clin/Ose, Clin/Ose+Zan; in vitro; RG	(6, 41, 47, 63–70)
<i>Host cell selected, not found in clinical specimens</i>	Q136K	136	NI (1–7)	RI/HRI (11–132)	NI (3–9)	NI (2)	Sur; Clin, Clin/Ose+Zan	(22, 35, 69, 71)
	N142S	142	HRI (595)	HRI (244)	RI (40)	RI (53)	Clin/Sur	(22)
<i>Cell culture-selected</i>	D151A	151	NI (2–3)	RI (29–43)	RI (10)	NI (7)	Sur	(22, 46)
<i>Cell culture-selected</i>	D151E	151	RI (11)	NI (2)	?	?	RG	(72)
<i>Cell culture-selected</i>	D151G	151	NI (1)	HRI (>1500)	?	?	RG	(73)
	I222L	222	NI (9)	NI (2)	?	?	RG	(74)
	R224K	224	HRI (>4000)	RI (>50)	?	?	RG	(72)
	N245Y	245	RI (15)	NI (5)	NI (2)	NI (1)	Sur	(18)
	Del 245–248 ^g	245–248	HRI (157–222)	NI/RI (3–21)	NI (1)	NI (1)	Clin/Ose	(69, 75, 76)
	A246V	246	NI (1.9)	RI (10.2)	?	?	Clin/Sur	(6)
	Del 247–250 ^g	247–250	HRI (235)	RI (17)	NI (5)	NI (1)	Sur/recNA	(76)
	K249E	249	RI (10–15)	NI (4–6)	NI (1–3)	NI (1–3)	Sur	(3, 6)
	E276D	276	RI (15)	HRI (160)	?	?	RG	(72)
	R292K	292	HRI (>10 000)	NI/RI/HRI (3–134)	RI/HRI (14–719)	NI (2–3)	Clin/Ose, Clin/Ose+Zan, Clin/Ose+Per; in vitro/Zan; RG; Clin/Sur	(13, 22, 41, 46, 63, 65, 69, 72, 77–79)
	N294S	294	HRI (300–1879)	NI (8)	NI (1)	?	Clin/Ose; RG	(41, 79)
<i>Increased NA K_{ms} for MUNANA substrate^h</i>	N329K ⁱ	329	NI/RI (5–21)	NI/RI (3–12)	?	?	Sur	(14, 80, 81)
<i>Increased NA K_{ms} for MUNANA substrate^h</i>	N329R ⁱ	329	RI (13)	NI (8)	?	?	Sur	(81)
<i>Increased NA K_{ms} for MUNANA substrate^h</i>	S331R ⁱ	331	NI/RI (5–77)	NI/RI (3–30)	?	?	Sur	(14, 80, 81)
<i>Increased NA K_{ms} for MUNANA substrate^h</i>	S334R	334	NI (<2) ^j	NI (<2) ^j	?	?	Sur	(81)
	R371K	371	RI (45)	RI (15)	?	?	RG	(72)

<i>T148I was host cell selected</i>	E119V+T148I	119+148	HRI (>6000)	HRI (>800)	HRI (>110)	HRI (>250)	Sur; in vitro; RG	(68)
	E119V+I222L	119+222	HRI (1571)	NI (5)	?	?	RG	(74)
	E119V+I222V	119+222	HRI (293–2286)	NI (2)	NI (7)	?	Clin/Ose	(67, 82)
	E119V + Q136K	119+136	HRI (325)	HRI (220)	HRI (101)	?	Clin/Ose+Zan	(69)
	E119V + Del 247-250 ^g	119+245-248	?	?	?	?	Clin/Ose+Zan	(69)
	I222T+S331R	222+331	RI (12–31)	NI (3–7)	NI (2)	NI (3–4)	Sur/Clin	(22)
	Q391K+K249E	391+249	RI (87)	RI (32)	RI (16)	NI (9)	Sur	(3)
A(H1N1)v	S247N	246	NI (2–4)	NI (2)	NI (3)	NI (3)	Sur	(111)
	I427V	427	RI (17)	NI (1)	NI (1)	NI (1)	Sur	(111)
A(H3N2)v	S245N	245	NI (1)	NI (1)	NI (1)	NI (1)	Sur; RG	(83)
	S247P	247	RI (42–46)	RI/HRI (94–266)	NI (2)	NI (9)	Sur; RG	(111, 83)
	S245N+S247P	245+247	RI (31–40)	RI/HRI (66–235)	NI (1–2)	NI (7–9)	Sur; RG	(35, 83)
A(H7N9)	E115A	119	RI (19)	HRI (228)	RI (20)	RI (62)	In vitro; recNA	(84)
	E115D	119	RI (14)	HRI (1436)	HRI (411)	HRI (383)	In vitro; recNA	(84)
	E115G	119	NI (2)	HRI (419)	RI (48)	HRI (124)	In vitro; recNA	(84)
	E115V	119	RI/HRI (84–169)	NI (6–9)	NI (1–2)	NI (2–5)	Sur; P-p; in vitro; recNA; RG	(84–86)
	Q132K	136	NI (1)	HRI (702)	HRI (131)	HRI (313)	In vitro; recNA	(84)
	R148K	152	NI (1)	NI (5)	NI (3)	RI (16)	In vitro; recNA	(84)
	I219K	222	RI (32–46)	NI/RI (8–17)	NI/RI (6–11)	RI (13–27)	In vitro; recNA; Sur; P-p	(84, 85)
	I219L	222	NI (5)	NI (2)	NI (1)	NI (2)	RG	(86)
	I219R	222	RI/HRI (37–143)	RI (12–38)	RI (12–44)	RI (14–63)	In vitro; recNA; Sur; P-p	(84, 85)
	T244P	247	RI (27)	RI (69)	NI (4)	NI (9)	In vitro; recNA	(84)
	H271Y	274	HRI (105)	NI (2)	NI (9)	NI (2)	In vitro; Sur	(84)
	E273D	276	RI (13)	HRI (427)	RI (25)	RI (90)	In vitro; recNA	(84)
	R289K	292	HRI (>4600)	RI (11–67)	HRI (405–2487)	RI (16–35)	In vitro; recNA; Sur; P-p	(84, 85, 87, 88)
	N291S	294	NI (2)	RI (10)	NI (1)	NI (3)	In vitro; recNA	(84)
	R367K	371	RI (70)	RI (64)	RI (29)	RI (19)	In vitro; recNA	(84)
	E115V+I219L	119+222	HRI (306)	NI (8)	NI (2)	NI (4)	RG	(86)

Type B								
<i>Not found in clinical specimen</i>	H101L	103	NI (2–3)	RI (30–34)	HRI (688–791)	NI/RI (4–5)	Sur; RG	(89)
	G104E	106	HRI (87)	HRI (1220)	HRI (17724)	HRI (701)	Sur	(3)
	E105K	107	NI/RI (4–10)	NI/RI (1–42)	RI/HRI (6–681)	NI/RI (1–12)	Clin/No; RG	(90, 91)
	G108E	110	NI/RI/HRI (4.9–215)	NI/RI/HRI (4.9–4493)	HRI (55)	NI /HRI (3–7310)	Sur; Clin/Ose; RG	(89)
	E117A	119	HRI (>300–3171)	HRI (>560–12538)	HRI (>1598–13780)	HRI (421–2163)	Sur; RG	(91–94)
	E117D	119	HRI (>300)	HRI (>560)	HRI (>1598)	?	RG	(92)
	E117G	119	RI/HRI (6–53)	RI/HRI (33–4612)	HRI (>1598–>10000)	HRI (423–855)	In vitro; RG	(91, 92, 95)
	E117V	119	HRI (300)	NI (2)	HRI (531)	?	RG	(92)
	H134N	136	NI (3–4)	HRI (121–212)	HRI (100–131)	RI/HRI (49–240)	Sur; Clin/No; RG	(3, 96, 97)
	H134Q	136	NI (3)	RI (6)	?	?	Sur	(1)
	H134Y	136	NI (4)	NI (1)	HRI (76)	NI (2)	Sur	(3)
	Q138R	140	NI (1)	RI (15)	RI (41)	RI (7)	Sur; in vitro	(98)
	P139S	141	RI/HRI (10–68)	NI/RI/HRI (2–160)	RI/HRI (12–>9091)	NI/RI/HRI (3–142)	Sur; in vitro; RG	(91, 98)
	G140R	142	RI/HRI (9–184)	NI/RI/HRI (1–1037)	RI/HRI (12–9091)	NI/RI/HRI (2–1197)	Sur; in vitro; RG	(91, 98)
	Y142H	144	NI (2)	NI (1)	RI (6)	NI (1)	Sur	(13)
	G145E	147	NI (1)	NI (1)	RI (14)	NI (1)	Sur	(22)
	G145R	147	NI (2–3)	NI/RI (3–9)	RI (5–6)	NI (1–3)	Sur	(18)
<i>Not found in clinical specimen</i>	T146I	148	NI (2)	NI (1)	HRI (145)	NI (1)	Sur	(22)
<i>Not found in clinical specimen</i>	T146K	148	NI/RI (1–34)	NI/RI/HRI (3–192)	HRI (187–21893)	NI/RI (1–6)	Sur; RG	(89)
<i>Not found in clinical specimen</i>	T146P	148	NI/RI (2–8)	NI/RI (4–11)	HRI (128–3338)	NI (3)	Sur; RG	(89)
	R150K	152	HRI (60–252)	NI/RI/HRI (5–1000)	HRI (214–2869)	HRI (473)	Clin; Clin/Zan; RG; Sur	(2, 47, 72, 92, 97, 99–101)
	N151S	153	NI (1)	RI (7)	?	?	Sur	(14)
	K152M	154	RI (5.4)	NI (1)	NI (1)	NI (1)	Sur	(22)
	K152N	154	RI (6)	NI (2)	NI (1)	NI (2)	Sur	(3)
	N169S	170	NI (2)	NI (1)	NI (1)	NI (1)	RG	(89)
	D197E	198	RI (12–26)	NI/RI (3–7)	RI (16–18)	?	Clin/No; Sur; RG	(44, 94, 102)
<i>Not found in clinical specimen</i>	D197G	198	NI (3)	RI (5.4)	?	?	Sur	(22)
	D197N	198	NI/RI (4–10)	NI/RI (3–17)	RI (5.4–24)	NI (2–3)	Clin/No; Clin/Ose; Sur	(3, 46, 47, 66, 103)

	D197Y	198	RI/HRI (15-57)	RI (14)	HRI (168)	?	Sur; RG	(94, 104)
	A200T	201	RI (6-48)	NI/RI (3-23)	RI (67-85)	NI/RI (4-27)	Sur; RG	(15, 35, 89)
	I221L	222	HRI (70-121)	RI (7-41)	RI (39-56)	?	Clin/Ose	(105, 106)
	I221N	222	RI/HRI (36-219)	RI (6-14)	HRI (136-956)	?	RG	(106)
	I221T	222	RI (5-18)	NI (2-4)	RI (15-43)	NI (<3)	Clin/No; Sur; RG	(31, 44, 94, 103, 107, 108)
	I221V	222	NI (2)	NI (2)	RI (6)	NI (3)	Sur	(3)
	G243D	244	RI (23)	HRI (257)	?	?	Sur	(18)
	G243S	244	RI (19)	RI (22)	HRI (58)	NI (3)	Clin/Sur	(18)
	A245G	246	NI (2)	NI (1)	RI (14)	NI (0-1)	Sur	(109)
	A245T	246	RI (9-24)	RI/HRI (39-205)	RI (5-10)	NI/RI (3-5)	Sur	(15, 31)
	S246P	247	NI (2)	RI (40)	?	?	Sur	(2)
	G247D	248	NI (4)	NI (4)	NI (2)	NI (2)	RG	(89)
	H273Q	274	NI (0.03)	NI (3)	NI (0.23)	NI (1)	Sur	(107)
	H273Y	274	NI/RI (2-12)	NI (1)	RI/HRI (15-13434)	NI (1)	Sur; RG	(3, 33, 46, 94)
	R292K	292	HRI (>300)	RI (29)	HRI (502)	?	RG	(92)
	N294S	294	RI (8-61)	NI/RI (1-18)	RI (17-58)	?	Clin/No; RG	(94, 97, 106, 110)
	K360E ⁱ	358-359 ^k	NI (2)	NI (2)	HRI (165)	NI (<3)	Sur	(31)
	I361V	358	NI (2)	NI (1)	NI (1)	NI (1)	RG	(89)
	R374K	371	HRI (101-407)	RI/HRI (29-145)	HRI (352)	?	Sur; RG	(46, 94)
	A395E	392	RI (5)	NI (1)	RI (5.5)	NI (<3)	Sur	(31)
	L396H	393	NI (3)	RI (11)	?	?	Sur	(15)
	G407S	404	NI (4)	RI (7)	?	?	Clin/Ose; Sur	(103)
	D432G	429	NI (1)	NI (1-3)	RI/HRI (41-148)	NI (1-3)	Sur; RG	(31, 89)
	D432N	429	NI (1)	NI (1)	RI (8)	NI (1)	Sur	(15)
	H439P	439	NI/RI (1-6)	NI/RI (4-13)	HRI (56-120)	NI (2-4)	Sur; RG	(89)
	H439R	439	NI (1)	RI (5-10)	RI (20-23)	NI (2)	Sur; RG	(89)
	M464T	464	NI (1)	NI (1)	RI (8)	NI (1)	Sur	(15)
	T106I+P165L	108+166	NI (4)	RI (14)	?	?	Sur	(3)
	G140R+N144K	142+146	NI (6)	RI (10)	HRI (257)	?	Sur	(33)
	Y142H+G145R	144+147	NI (?)	NI (?)	HRI (487)	NI (<3)	Sur	(31)
	T146P+N169S	148+170	RI (31-44)	HRI (225-573)	HRI (7158-10074)	HRI (86-280)	Sur; RG	(89)
	K186R+I262T	187+263	NI (3)	RI (17)	?	?	Sur	(3)
	G247D+I361V	248+358	NI/RI (2-6)	NI/RI (3-6)	NI/RI (4-46)	NI (1-3)	Sur;RG	(89)

^aNumbering is based on the neuraminidase subtype for type A viruses and the neuraminidase of type B viruses.

^bEquivalent N2 numbering is based on an alignment of neuraminidases from A/Brisbane/59/2007 [H1N1], A/California/7/2009 [H1N1pdm09], A/turkey/Turkey/1/2005 [H5N1], A/Singapore/1/57 [H2N2], A/Aichi/2/68 [H3N2], A/Perth/16/2009 [H3N2], A/Hong Kong/1074/97 [H9N2], A/Anhui/1/2013 [H7N9], B/Brisbane/60/2008 [B/Vic lineage], B/Bangladesh/3333/2007 [B/Yam lineage].

^cAssessed by NA inhibition (NI) assays: chemiluminescent (NA-Star), fluorescent (MUNANA) and/or colorimetric (fetuin). NAI phenotype is shown according to the referenced studies: NI, normal inhibition; **RI**, reduced inhibition; **HRI**, highly reduced inhibition as defined in (112). Fold-changes in IC₅₀ (half maximal inhibitory concentration) relative to wild-type virus or type/subtype-specific median IC₅₀s, are shown in parentheses. For type A viruses: <10-fold - NI; 10-100-fold - RI; >100-fold - HRI. For type B viruses: <5-fold - NI; 5-50-fold - RI; >50-fold - HRI (102).

^dClin, clinical detection; No, no NAI used; Ose, oseltamivir used; Zan, zanamivir used; P-p, Plaque purification; RG, reverse genetics; recNA: Recombinant NA; Sur, Surveillance studies; Lan, laninamivir used; Per, peramivir used. The most common amino acid substitutions associated with **HRI** by oseltamivir and peramivir which have been associated with clinical resistance are shown in bold text.

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

^fEquivalent 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.

^gDel signifies deletion of the amino acids indicated.

^hThe positive charge on the amino acid sidechain causes higher NA K_ms for the MUNANA substrate resulting in higher IC₅₀ values and therefore fold-changes relative to wild-type virus or type/subtype-specific median IC₅₀s.

ⁱShows NI in current NA background.

^jSome viruses lacked sufficient neuraminidase activity to allow IC₅₀ determination.

^kPrecise N2 numbering cannot be given because the NA of influenza B carries an insertion in the alignment compared to the NA of H3N2.

References

1. Huang W, Cheng Y, Li X, Tan M, Wei H, Zhao X, Xiao N, Dong J, Wang D. 2018. Neuraminidase inhibitor susceptibility profile of human influenza viruses during the 2016-2017 influenza season in Mainland China. *J Infect Chemother* 24:729-733.
2. Lackenby A, Besselaar TG, Daniels RS, Fry A, Gregory V, Gubareva LV, Huang W, Hurt AC, Leang SK, Lee RTC, Lo J, Lollis L, Maurer-Stroh S, Odagiri T, Pereyaslov D, Takashita E, Wang D, Zhang W, Meijer A. 2018. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors and status of novel antivirals, 2016-2017. *Antiviral Res* 157:38-46.
3. Gubareva LV, Besselaar TG, Daniels RS, Fry A, Gregory V, Huang W, Hurt AC, Jorquera PA, Lackenby A, Leang SK, Lo J, Pereyaslov D, Rebelo-de-Andrade H, Siqueira MM, Takashita E, Odagiri T, Wang D, Zhang W, Meijer A. 2017. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2015-2016. *Antiviral Res* 146:12-20.
4. Samson M, Abed Y, Desrochers FM, Hamilton S, Luttick A, Tucker SP, Pryor MJ, Boivin G. 2014. Characterization of drug-resistant influenza virus A(H1N1) and A(H3N2) variants selected in vitro with laninamivir. *Antimicrob Agents Chemother* 58:5220-8.
5. Baek YH, Song MS, Lee EY, Kim YI, Kim EH, Park SJ, Park KJ, Kwon HI, Pascua PN, Lim GJ, Kim S, Yoon SW, Kim MH, Webby RJ, Choi YK. 2015. Profiling and characterization of influenza virus N1 strains potentially resistant to multiple neuraminidase inhibitors. *J Virol* 89:287-99.
6. Hussain S, Meijer A, Govorkova EA, Dapat C, Gubareva LV, Barr IG, Brown SK, Daniels RS, Fujisaki S, Galiano M, Huang W, Kondor RJ, Lackenby A, Lewis N, Lo J, Nguyen HT, Patel MC, Pereyaslov D, Rattigan A, Samaan M, Wang D, Webby RJ, Yen HL, Zhang W, Takashita E. 2025. Global update on the susceptibilities of influenza viruses to neuraminidase inhibitors and the cap-dependent endonuclease inhibitor baloxavir, 2020-2023. *Antiviral Res* 241:106217.
7. L'Huillier AG, Abed Y, Petty TJ, Cordey S, Thomas Y, Bouhy X, Schibler M, Simon A, Chalandon Y, van Delden C, Zdobnov E, Boquete-Suter P, Boivin G, Kaiser L. 2015. E119D Neuraminidase Mutation Conferring Pan-Resistance to Neuraminidase Inhibitors in an A(H1N1)pdm09 Isolate From a Stem-Cell Transplant Recipient. *J Infect Dis* 212:1726-1734.
8. Lloren KKS, Kwon JJ, Choi WS, Jeong JH, Ahn SJ, Choi YK, Baek YH, Song MS. 2019. In Vitro and In Vivo Characterization of Novel Neuraminidase Substitutions in Influenza A(H1N1)pdm09 Virus Identified Using Laninamivir-Mediated In Vitro Selection. *J Virol* 93.
9. Pizzorno A, Bouhy X, Abed Y, Boivin G. 2011. Generation and characterization of recombinant pandemic influenza A(H1N1) viruses resistant to neuraminidase inhibitors. *J Infect Dis* 203:25-31.
10. Tamura D, DeBiasi RL, Okomo-Adhiambo M, Mishin VP, Campbell AP, Loechele B, Wiedermann BL, Fry AM, Gubareva LV. 2015. Emergence of Multidrug-Resistant Influenza A(H1N1)pdm09 Virus Variants in an Immunocompromised Child Treated With Oseltamivir and Zanamivir. *J Infect Dis* 212:1209-1213.
11. Kaminski MM, Ohnemus A, Staeheli P, Rubbenstroth D. 2013. Pandemic 2009 H1N1 influenza A virus carrying a Q136K mutation in the neuraminidase gene is resistant to zanamivir but exhibits reduced fitness in the guinea pig transmission model. *J Virol* 87:1912-5.
12. Pizzorno A, Abed Y, Rheame C, Bouhy X, Boivin G. 2013. Evaluation of recombinant 2009 pandemic influenza A (H1N1) viruses harboring zanamivir resistance mutations in mice and ferrets. *Antimicrob Agents Chemother* 57:1784-9.

13. Meijer A, Rebelo-de-Andrade H, Correia V, Besselaar T, Drager-Dayal R, Fry A, Gregory V, Gubareva L, Kageyama T, Lackenby A, Lo J, Odagiri T, Pereyaslov D, Siqueira MM, Takashita E, Tashiro M, Wang D, Wong S, Zhang W, Daniels RS, Hurt AC. 2014. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2012-2013. *Antiviral Res* 110:31-41.
14. Takashita E, Meijer A, Lackenby A, Gubareva L, Rebelo-de-Andrade H, Besselaar T, Fry A, Gregory V, Leang SK, Huang W, Lo J, Pereyaslov D, Siqueira MM, Wang D, Mak GC, Zhang W, Daniels RS, Hurt AC, Tashiro M. 2015. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2013-2014. *Antiviral Res* 117:27-38.
15. Takashita E, Daniels RS, Fujisaki S, Gregory V, Gubareva LV, Huang W, Hurt AC, Lackenby A, Nguyen HT, Pereyaslov D, Roe M, Samaan M, Subbarao K, Tse H, Wang D, Yen HL, Zhang W, Meijer A. 2020. Global update on the susceptibilities of human influenza viruses to neuraminidase inhibitors and the cap-dependent endonuclease inhibitor baloxavir, 2017-2018. *Antiviral Res* 175:104718.
16. Huang L, Cao Y, Zhou J, Qin K, Zhu W, Zhu Y, Yang L, Wang D, Wei H, Shu Y. 2014. A conformational restriction in the influenza A virus neuraminidase binding site by R152 results in a combinational effect of I222T and H274Y on oseltamivir resistance. *Antimicrob Agents Chemother* 58:1639-45.
17. Nguyen HT, Fry AM, Loveless PA, Klimov AI, Gubareva LV. 2010. Recovery of a multidrug-resistant strain of pandemic influenza A 2009 (H1N1) virus carrying a dual H275Y/I223R mutation from a child after prolonged treatment with oseltamivir. *Clin Infect Dis* 51:983-4.
18. Govorkova EA, Takashita E, Daniels RS, Fujisaki S, Presser LD, Patel MC, Huang W, Lackenby A, Nguyen HT, Pereyaslov D, Rattigan A, Brown SK, Samaan M, Subbarao K, Wong S, Wang D, Webby RJ, Yen HL, Zhang W, Meijer A, Gubareva LV. 2022. Global update on the susceptibilities of human influenza viruses to neuraminidase inhibitors and the cap-dependent endonuclease inhibitor baloxavir, 2018-2020. *Antiviral Res* 200:105281.
19. van der Vries E, Stelma FF, Boucher CA. 2010. Emergence of a multidrug-resistant pandemic influenza A (H1N1) virus. *N Engl J Med* 363:1381-2.
20. Eshaghi A, Patel SN, Sarabia A, Higgins RR, Savchenko A, Stojios PJ, Li Y, Bastien N, Alexander DC, Low DE, Gubbay JB. 2011. Multidrug-resistant pandemic (H1N1) 2009 infection in immunocompetent child. *Emerg Infect Dis* 17:1472-4.
21. Pizzorno A, Abed Y, Bouhy X, Beaulieu E, Mallett C, Russell R, Boivin G. 2012. Impact of mutations at residue I223 of the neuraminidase protein on the resistance profile, replication level, and virulence of the 2009 pandemic influenza virus. *Antimicrob Agents Chemother* 56:1208-14.
22. Hurt AC, Besselaar TG, Daniels RS, Ermetal B, Fry A, Gubareva L, Huang W, Lackenby A, Lee RT, Lo J, Maurer-Stroh S, Nguyen HT, Pereyaslov D, Rebelo-de-Andrade H, Siqueira MM, Takashita E, Tashiro M, Tilmanis D, Wang D, Zhang W, Meijer A. 2016. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2014-2015. *Antiviral Res* 132:178-85.
23. Patel MC, Nguyen HT, Pascua PNQ, Gao R, Steel J, Kondor RJ, Gubareva LV. 2024. Multicountry Spread of Influenza A(H1N1)pdm09 Viruses with Reduced Oseltamivir Inhibition, May 2023-February 2024. *Emerg Infect Dis* 30:1410-1415.
24. Hurt AC, Lee RT, Leang SK, Cui L, Deng YM, Phuah SP, Caldwell N, Freeman K, Komadina N, Smith D, Speers D, Kelso A, Lin RT, Maurer-Stroh S, Barr IG. 2011. Increased detection in Australia and Singapore of a novel influenza A(H1N1)2009 variant with reduced oseltamivir and zanamivir sensitivity due to a S247N neuraminidase mutation. *Euro Surveill* 16.
25. Saubi N, Andres C, Prats-Mendez I, Gonzalez-Sanchez A, Davtyan A, Vasquez-Mercado R, Rando A, Nadal P, Esperalba J, Arnedo M, Vicente M, Balada E, Mendioroz J, Martin MC, Garcia-Camunas K, Vaz R, Najarro A, Bernalte S, Larrosa N, Anton A, network SIDs. 2025. Expansion of influenza A(H1N1)pdm09 NA:S247N viruses with reduced susceptibility to oseltamivir, Catalonia, Spain, and in Europe, July to October 2025. *Euro Surveill* 30.
26. Baz M, Abed Y, Papenburg J, Bouhy X, Hamelin ME, Boivin G. 2009. Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. *N Engl J Med* 361:2296-7.
27. Okomo-Adhiambo M, Nguyen HT, Sleeman K, Sheu TG, Deyde VM, Garten RJ, Xu X, Shaw MW, Klimov AI, Gubareva LV. 2010. Host cell selection of influenza neuraminidase variants: implications for drug resistance monitoring in A(H1N1) viruses. *Antiviral Res* 85:381-8.
28. Nguyen HT, Sheu TG, Mishin VP, Klimov AI, Gubareva LV. 2010. Assessment of pandemic and seasonal influenza A (H1N1) virus susceptibility to neuraminidase inhibitors in three enzyme activity inhibition assays. *Antimicrob Agents Chemother* 54:3671-7.
29. Nguyen HT, Trujillo AA, Sheu TG, Levine M, Mishin VP, Shaw M, Ades EW, Klimov AI, Fry AM, Gubareva LV. 2012. Analysis of influenza viruses from patients clinically suspected of infection with an oseltamivir resistant virus during the 2009 pandemic in the United States. *Antiviral Res* 93:381-6.
30. Ikematsu H, Kawai N, Kashiwagi S. 2012. In vitro neuraminidase inhibitory activities of four neuraminidase inhibitors against influenza viruses isolated in the 2010-2011 season in Japan. *J Infect Chemother* 18:529-33.
31. Leang SK, Kwok S, Sullivan SG, Maurer-Stroh S, Kelso A, Barr IG, Hurt AC. 2014. Peramivir and laninamivir susceptibility of circulating influenza A and B viruses. *Influenza Other Respir Viruses* 8:135-9.
32. Takashita E, Fujisaki S, Kishida N, Xu H, Imai M, Tashiro M, Odagiri T, Influenza Virus Surveillance Group of J. 2013. Characterization of neuraminidase inhibitor-resistant influenza A(H1N1)pdm09 viruses isolated in four seasons during pandemic and post-pandemic periods in Japan. *Influenza Other Respir Viruses* 7:1390-9.
33. Okomo-Adhiambo M, Sleeman K, Lysen C, Nguyen HT, Xu X, Li Y, Klimov AI, Gubareva LV. 2013. Neuraminidase inhibitor susceptibility surveillance of influenza viruses circulating worldwide during the 2011 Southern Hemisphere season. *Influenza Other Respir Viruses* 7:645-58.
34. Daplat C, Kondo H, Daplat IC, Baranovich T, Suzuki Y, Shobugawa Y, Saito K, Saito R, Suzuki H. 2013. Neuraminidase inhibitor susceptibility profile of pandemic and seasonal influenza viruses during the 2009-2010 and 2010-2011 influenza seasons in Japan. *Antiviral Res* 99:261-9.

35. Okomo-Adhiambo M, Nguyen HT, Abd Elal A, Sleeman K, Fry AM, Gubareva LV. 2014. Drug susceptibility surveillance of influenza viruses circulating in the United States in 2011-2012: application of the WHO antiviral working group criteria. *Influenza Other Respir Viruses* 8:258-65.
36. Kwon JJ, Choi WS, Jeong JH, Kim EH, Lee OJ, Yoon SW, Hwang J, Webby RJ, Govorkova EA, Choi YK, Baek YH, Song MS. 2018. An I436N substitution confers resistance of influenza A(H1N1)pdm09 viruses to multiple neuraminidase inhibitors without affecting viral fitness. *J Gen Virol* 99:292-302.
37. Ghedin E, Laplante J, DePasse J, Wentworth DE, Santos RP, Lepow ML, Porter J, Stellrecht K, Lin X, Operario D, Griesemer S, Fitch A, Halpin RA, Stockwell TB, Spiro DJ, Holmes EC, St George K. 2011. Deep sequencing reveals mixed infection with 2009 pandemic influenza A (H1N1) virus strains and the emergence of oseltamivir resistance. *J Infect Dis* 203:168-74.
38. Leung RC, Ip JD, Chen LL, Chan WM, To KK. 2024. Global emergence of neuraminidase inhibitor-resistant influenza A(H1N1)pdm09 viruses with I223V and S247N mutations: implications for antiviral resistance monitoring. *Lancet Microbe* 5:627-628.
39. Centers for Disease C, Prevention. 2009. Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis--North Carolina, 2009. *MMWR Morb Mortal Wkly Rep* 58:969-72.
40. Hurt AC, Chotpitayasunondh T, Cox NJ, Daniels R, Fry AM, Gubareva LV, Hayden FG, Hui DS, Hungnes O, Lackenby A, Lim W, Meijer A, Penn C, Tashiro M, Uyeki TM, Zambon M, Antivirals WHOCPIAVRt. 2012. Antiviral resistance during the 2009 influenza A H1N1 pandemic: public health, laboratory, and clinical perspectives. *Lancet Infect Dis* 12:240-8.
41. Abed Y, Baz M, Boivin G. 2006. Impact of neuraminidase mutations conferring influenza resistance to neuraminidase inhibitors in the N1 and N2 genetic backgrounds. *Antivir Ther* 11:971-6.
42. Choi W, Shin JY, Jeong HE, Jeong MJ, Kim SJ, Lee JY, Kang C. 2013. Generation and Characterization of Recombinant Influenza A(H1N1) Viruses Resistant to Neuraminidase Inhibitors. *Osong Public Health Res Perspect* 4:323-8.
43. Hurt AC, Holien JK, Parker M, Kelso A, Barr IG. 2009. Zanamivir-resistant influenza viruses with a novel neuraminidase mutation. *J Virol* 83:10366-73.
44. Monto AS, McKimm-Breschkin JL, Macken C, Hampson AW, Hay A, Klimov A, Tashiro M, Webster RG, Aymard M, Hayden FG, 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* 50:2395-402.
45. Hurt AC, Holien JK, Barr IG. 2009. In vitro generation of neuraminidase inhibitor resistance in A(H5N1) influenza viruses. *Antimicrob Agents Chemother* 53:4433-40.
46. Sheu TG, Deyde VM, Okomo-Adhiambo M, Garten RJ, Xu X, Bright RA, Butler EN, Wallis TR, Klimov AI, Gubareva LV. 2008. Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008. *Antimicrob Agents Chemother* 52:3284-92.
47. Mishin VP, Hayden FG, Gubareva LV. 2005. Susceptibilities of antiviral-resistant influenza viruses to novel neuraminidase inhibitors. *Antimicrob Agents Chemother* 49:4515-20.
48. Boltz DA, Douangngeun B, Phommachanh P, Sinthasak S, Mondry R, Obert C, Seiler P, Keating R, Suzuki Y, Hiramatsu H, Govorkova EA, Webster RG. 2010. Emergence of H5N1 avian influenza viruses with reduced sensitivity to neuraminidase inhibitors and novel reassortants in Lao People's Democratic Republic. *J Gen Virol* 91:949-59.
49. Hurt AC, Selleck P, Komadina N, Shaw R, Brown L, Barr IG. 2007. Susceptibility of highly pathogenic A(H5N1) avian influenza viruses to the neuraminidase inhibitors and adamantanes. *Antiviral Res* 73:228-31.
50. Pascua PNQ, Chesnokov AP, Nguyen HT, Champion C, Gao R, De La Cruz JA, Jang Y, Hatta Y, Guo Z, Uyeki TM, Di H, Stevens J, Davis CT, Gubareva LV. 2026. Antiviral susceptibility of clade 2.3.4.4b highly pathogenic avian influenza A(H5N1) viruses from humans in the United States, October 2024 to February 2025. *Emerg Microbes Infect* 15:2601372.
51. Kode SS, Pawar SD, Tare DS, Keng SS, Hurt AC, Mullick J. 2019. A novel I117T substitution in neuraminidase of highly pathogenic avian influenza H5N1 virus conferring reduced susceptibility to oseltamivir and zanamivir. *Vet Microbiol* 235:21-24.
52. Nguyen HT, Chesnokov A, De La Cruz J, Pascua PNQ, Mishin VP, Jang Y, Jones J, Di H, Ivashchenko AA, Killian ML, Torchetti MK, Lantz K, Wentworth DE, Davis CT, Ivachtchenko AV, Gubareva LV. 2023. Antiviral susceptibility of clade 2.3.4.4b highly pathogenic avian influenza A(H5N1) viruses isolated from birds and mammals in the United States, 2022. *Antiviral Res* 217:105679.
53. Ilyushina NA, Seiler JP, Reh JE, Webster RG, Govorkova EA. 2010. Effect of neuraminidase inhibitor-resistant mutations on pathogenicity of clade 2.2 A/Turkey/15/06 (H5N1) influenza virus in ferrets. *PLoS Pathog* 6:e1000933.
54. Le MT, Wertheim HF, Nguyen HD, Taylor W, Hoang PV, Vuong CD, Nguyen HL, Nguyen HH, Nguyen TQ, Nguyen TV, Van TD, Ngoc BT, Bui TN, Nguyen BG, Nguyen LT, Luong ST, Phan PH, Pham HV, Nguyen T, Fox A, Nguyen CV, Do HQ, Crusat M, Farrar J, Nguyen HT, de Jong MD, Horby P. 2008. Influenza A H5N1 clade 2.3.4 virus with a different antiviral susceptibility profile replaced clade 1 virus in humans in northern Vietnam. *PLoS One* 3:e3339.
55. Hurt AC, Lowther S, Middleton D, Barr IG. 2010. Assessing the development of oseltamivir and zanamivir resistance in A(H5N1) influenza viruses using a ferret model. *Antiviral Res* 87:361-6.
56. Naughtin M, Dyason JC, Mardy S, Sorn S, von Itzstein M, Buchy P. 2011. Neuraminidase inhibitor sensitivity and receptor-binding specificity of Cambodian clade 1 highly pathogenic H5N1 influenza virus. *Antimicrob Agents Chemother* 55:2004-10.
57. Andreev K, Jones JC, Seiler P, Kandeil A, Turner JCM, Barman S, Rubrum AM, Webby RJ, Govorkova EA. 2024. Antiviral Susceptibility of Highly Pathogenic Avian Influenza A(H5N1) Viruses Circulating Globally in 2022-2023. *J Infect Dis* 229:1830-1835.
58. Boltz DA, Douangngeun B, Phommachanh P, Sinthasak S, Mondry R, Obert C, Seiler P, Keating R, Suzuki Y, Hiramatsu H, Govorkova EA, Webster RG. 2010. Emergence of H5N1 avian influenza viruses with reduced sensitivity to neuraminidase inhibitors and novel reassortants in Lao People's Democratic Republic. *J Gen Virol* 91:949-59.

59. Le QM, Kiso M, Someya K, Sakai YT, Nguyen TH, Nguyen KH, Pham ND, Ngyen HH, Yamada S, Muramoto Y, Horimoto T, Takada A, Goto H, Suzuki T, Suzuki Y, Kawaoka Y. 2005. Avian flu: isolation of drug-resistant H5N1 virus. *Nature* 437:1108.
60. Nguyen HT, Nguyen T, Mishin VP, Sleeman K, Balish A, Jones J, Creanga A, Marjuki H, Uyeki TM, Nguyen DH, Nguyen DT, Do HT, Klimov AI, Davis CT, Gubareva LV. 2013. Antiviral susceptibility of highly pathogenic avian influenza A(H5N1) viruses isolated from poultry, Vietnam, 2009-2011. *Emerg Infect Dis* 19:1963-71.
61. Earhart KC, Elsayed NM, Saad MD, Gubareva LV, Nayel A, Deyde VM, Abdelsattar A, Abdelghani AS, Boynton BR, Mansour MM, Essmat HM, Klimov A, Shuck-Lee D, Monteville MR, Tjaden JA. 2009. Oseltamivir resistance mutation N294S in human influenza A(H5N1) virus in Egypt. *J Infect Public Health* 2:74-80.
62. Creanga A, Hang NLK, Cuong VD, Nguyen HT, Phuong HVM, Thanh LT, Thach NC, Hien PT, Tung N, Jang Y, Balish A, Dang NH, Duong MT, Huong NT, Hoa DN, Tho ND, Klimov A, Kapella BK, Gubareva L, Kile JC, Hien NT, Mai LQ, Davis CT. 2017. Highly Pathogenic Avian Influenza A(H5N1) Viruses at the Animal-Human Interface in Vietnam, 2003-2010. *J Infect Dis* 216:S529-S538.
63. Zurcher T, Yates PJ, Daly J, Sahasrabudhe A, Walters M, Dash L, Tisdale M, McKimm-Breschkin JL. 2006. Mutations conferring zanamivir resistance in human influenza virus N2 neuraminidases compromise virus fitness and are not stably maintained in vitro. *J Antimicrob Chemother* 58:723-32.
64. Okomo-Adhiambo M, Demmler-Harrison GJ, Deyde VM, Sheu TG, Xu X, Klimov AI, Gubareva LV. 2010. Detection of E119V and E119I mutations in influenza A (H3N2) viruses isolated from an immunocompromised patient: challenges in diagnosis of oseltamivir resistance. *Antimicrob Agents Chemother* 54:1834-41.
65. Tamura D, Sugaya N, Ozawa M, Takano R, Ichikawa M, Yamazaki M, Kawakami C, Shimizu H, Uehara R, Kiso M, Kawakami E, Mitamura K, Kawaoka Y. 2011. Frequency of drug-resistant viruses and virus shedding in pediatric influenza patients treated with neuraminidase inhibitors. *Clin Infect Dis* 52:432-7.
66. Ison MG, Gubareva LV, Atmar RL, Treanor J, Hayden FG. 2006. Recovery of drug-resistant influenza virus from immunocompromised patients: a case series. *J Infect Dis* 193:760-4.
67. Simon P, Holder BP, Bouhy X, Abed Y, Beauchemin CA, Boivin G. 2011. The I222V neuraminidase mutation has a compensatory role in replication of an oseltamivir-resistant influenza virus A/H3N2 E119V mutant. *J Clin Microbiol* 49:715-7.
68. Tamura D, Nguyen HT, Sleeman K, Levine M, Mishin VP, Yang H, Guo Z, Okomo-Adhiambo M, Xu X, Stevens J, Gubareva LV. 2013. Cell culture-selected substitutions in influenza A(H3N2) neuraminidase affect drug susceptibility assessment. *Antimicrob Agents Chemother* 57:6141-6.
69. Eshaghi A, Shalhoub S, Rosenfeld P, Li A, Higgins RR, Stogios PJ, Savchenko A, Bastien N, Li Y, Rotstein C, Gubbay JB. 2014. Multiple influenza A (H3N2) mutations conferring resistance to neuraminidase inhibitors in a bone marrow transplant recipient. *Antimicrob Agents Chemother* 58:7188-97.
70. Hurt AC, Leang SK, Tiedemann K, Butler J, Mechinaud F, Kelso A, Downie P, Barr IG. 2013. Progressive emergence of an oseltamivir-resistant A(H3N2) virus over two courses of oseltamivir treatment in an immunocompromised paediatric patient. *Influenza Other Respir Viruses* 7:904-8.
71. Dapat C, Suzuki Y, Saito R, Kyaw Y, Myint YY, Lin N, Oo HN, Oo KY, Win N, Naito M, Hasegawa G, Dapat IC, Zaraket H, Baranovich T, Nishikawa M, Saito T, Suzuki H. 2010. Rare influenza A (H3N2) variants with reduced sensitivity to antiviral drugs. *Emerg Infect Dis* 16:493-6.
72. Yen HL, Hoffmann E, Taylor G, Scholtissek C, Monto AS, Webster RG, Govorkova EA. 2006. Importance of neuraminidase active-site residues to the neuraminidase inhibitor resistance of influenza viruses. *J Virol* 80:8787-95.
73. Mishin VP, Sleeman K, Levine M, Carney PJ, Stevens J, Gubareva LV. 2014. The effect of the MDCK cell selected neuraminidase D151G mutation on the drug susceptibility assessment of influenza A(H3N2) viruses. *Antiviral Res* 101:93-6.
74. Richard M, Ferraris O, Erny A, Barthelemy M, Traversier A, Sabatier M, Hay A, Lin YP, Russell RJ, Lina B. 2011. Combinatorial effect of two framework mutations (E119V and I222L) in the neuraminidase active site of H3N2 influenza virus on resistance to oseltamivir. *Antimicrob Agents Chemother* 55:2942-52.
75. Abed Y, Baz M, Boivin G. 2009. A novel neuraminidase deletion mutation conferring resistance to oseltamivir in clinical influenza A/H3N2 virus. *J Infect Dis* 199:180-3.
76. Tamura D, Okomo-Adhiambo M, Mishin VP, Guo Z, Xu X, Villanueva J, Fry AM, Stevens J, Gubareva LV. 2015. Application of a seven-target pyrosequencing assay to improve the detection of neuraminidase inhibitor-resistant Influenza A(H3N2) viruses. *Antimicrob Agents Chemother* 59:2374-9.
77. Carr J, Ives J, Kelly L, Lambkin R, Oxford J, Mendel D, Tai L, Roberts N. 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.
78. Yen HL, Herlocher LM, Hoffmann E, Matrosovich MN, Monto AS, Webster RG, Govorkova EA. 2005. Neuraminidase inhibitor-resistant influenza viruses may differ substantially in fitness and transmissibility. *Antimicrob Agents Chemother* 49:4075-84.
79. Kiso M, Mitamura K, Sakai-Tagawa Y, Shiraishi K, Kawakami C, Kimura K, Hayden FG, Sugaya N, Kawaoka Y. 2004. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 364:759-65.
80. McCauley JW DR, et al. 2017. Report prepared for the WHO annual consultation on the composition of influenza vaccine for the Southern Hemisphere 2018. Accessed 10th September 2024.
81. Hussain S, Daniels RS, Wharton SA, Howell S, Halai C, Kunzelmann S, Whittaker L, McCauley JW. 2021. Reduced sialidase activity of influenza A(H3N2) neuraminidase associated with positively charged amino acid substitutions. *J Gen Virol* 102.

82. Baz M, Abed Y, McDonald J, Boivin G. 2006. Characterization of multidrug-resistant influenza A/H3N2 viruses shed during 1 year by an immunocompromised child. *Clin Infect Dis* 43:1555-61.
83. Sleeman K, Mishin VP, Guo Z, Garten RJ, Balish A, Fry AM, Villanueva J, Stevens J, Gubareva LV. 2014. Antiviral susceptibility of variant influenza A(H3N2)v viruses isolated in the United States from 2011 to 2013. *Antimicrob Agents Chemother* 58:2045-51.
84. Gubareva LV, Sleeman K, Guo Z, Yang H, Hodges E, Davis CT, Baranovich T, Stevens J. 2017. Drug Susceptibility Evaluation of an Influenza A(H7N9) Virus by Analyzing Recombinant Neuraminidase Proteins. *J Infect Dis* 216:S566-S574.
85. Marjuki H, Mishin VP, Chesnokov AP, Jones J, De La Cruz JA, Sleeman K, Tamura D, Nguyen HT, Wu HS, Chang FY, Liu MT, Fry AM, Cox NJ, Villanueva JM, Davis CT, Gubareva LV. 2015. Characterization of drug-resistant influenza A(H7N9) variants isolated from an oseltamivir-treated patient in Taiwan. *J Infect Dis* 211:249-57.
86. Tang J, Gao R, Liu L, Zhang S, Liu J, Li X, Fang Q, Feng Z, Xu C, Huang W, Wang D. 2021. Substitution of I222L-E119V in neuraminidase from highly pathogenic avian influenza H7N9 virus exhibited synergistic resistance effect to oseltamivir in mice. *Sci Rep* 11:16293.
87. Hai R, Schmolke M, Leyva-Grado VH, Thangavel RR, Margine I, Jaffe EL, Krammer F, Solorzano A, Garcia-Sastre A, Palese P, Bouvier NM. 2013. Influenza A(H7N9) virus gains neuraminidase inhibitor resistance without loss of in vivo virulence or transmissibility. *Nat Commun* 4:2854.
88. Sleeman K, Guo Z, Barnes J, Shaw M, Stevens J, Gubareva LV. 2013. R292K substitution and drug susceptibility of influenza A(H7N9) viruses. *Emerg Infect Dis* 19:1521-4.
89. Brown SK, Tseng YY, Aziz A, Baz M, Barr IG. 2022. Characterization of influenza B viruses with reduced susceptibility to influenza neuraminidase inhibitors. *Antiviral Res* 200:105280.
90. Fujisaki S, Takashita E, Yokoyama M, Taniwaki T, Xu H, Kishida N, Sato H, Tashiro M, Imai M, Odagiri T. 2012. A single E105K mutation far from the active site of influenza B virus neuraminidase contributes to reduced susceptibility to multiple neuraminidase-inhibitor drugs. *Biochem Biophys Res Commun* 429:51-6.
91. Farrukee R, Leang SK, Butler J, Lee RT, Maurer-Stroh S, Tilmanis D, Sullivan S, Mosse J, Barr IG, Hurt AC. 2015. Influenza viruses with B/Yamagata- and B/Victoria-like neuraminidases are differentially affected by mutations that alter antiviral susceptibility. *J Antimicrob Chemother* 70:2004-12.
92. Jackson D, Barclay W, Zurcher T. 2005. Characterization of recombinant influenza B viruses with key neuraminidase inhibitor resistance mutations. *J Antimicrob Chemother* 55:162-9.
93. Sheu TG, Deyde VM, Garten RJ, Klimov AI, Gubareva LV. 2010. Detection of antiviral resistance and genetic lineage markers in influenza B virus neuraminidase using pyrosequencing. *Antiviral Res* 85:354-60.
94. Burnham AJ, Baranovich T, Marathe BM, Armstrong J, Webster RG, Govorkova EA. 2014. Fitness costs for Influenza B viruses carrying neuraminidase inhibitor-resistant substitutions: underscoring the importance of E119A and H274Y. *Antimicrob Agents Chemother* 58:2718-30.
95. Barnett JM, Cadman A, Burrell FM, Madar SH, Lewis AP, Tisdale M, Bethell R. 1999. In vitro selection and characterisation of influenza B/Beijing/1/87 isolates with altered susceptibility to zanamivir. *Virology* 265:286-95.
96. Baranovich T, Vongphrachanh P, Ketmayoon P, Sisouk T, Chomlasack K, Khanthamaly V, Nguyen HT, Mishin VP, Marjuki H, Barnes JR, Garten RJ, Stevens J, Wentworth DE, Gubareva LV. 2017. Antiviral Drug-Resistant Influenza B Viruses Carrying H134N Substitution in Neuraminidase, Laos, February 2016. *Emerg Infect Dis* 23:686-690.
97. Fage C, Abed Y, Checkmahomed L, Venable MC, Boivin G. 2018. In Vitro Properties and Virulence of Contemporary Recombinant Influenza B Viruses Harboring Mutations of Cross-Resistance to Neuraminidase Inhibitors. *Viruses* 11.
98. Fujisaki S, Imai M, Takashita E, Taniwaki T, Xu H, Kishida N, Yokoyama M, Sato H, Tashiro M, Odagiri T. 2013. Mutations at the monomer-monomer interface away from the active site of influenza B virus neuraminidase reduces susceptibility to neuraminidase inhibitor drugs. *J Infect Chemother* 19:891-5.
99. Gubareva LV, Webster RG, Hayden FG. 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* 45:3403-8.
100. Gubareva LV, Matrosovich MN, Brenner MK, Bethell RC, Webster RG. 1998. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis* 178:1257-62.
101. Sleeman K, Sheu TG, Moore Z, Kilpatrick S, Garg S, Fry AM, Gubareva LV. 2011. Influenza B viruses with mutation in the neuraminidase active site, North Carolina, USA, 2010-11. *Emerg Infect Dis* 17:2043-6.
102. Hurt AC, Iannello P, Jachno K, Komadina N, Hampson AW, Barr IG, McKimm-Breschkin JL. 2006. Neuraminidase inhibitor-resistant and -sensitive influenza B viruses isolated from an untreated human patient. *Antimicrob Agents Chemother* 50:1872-4.
103. Hatakeyama S, Sugaya N, Ito M, Yamazaki M, Ichikawa M, Kimura K, Kiso M, Shimizu H, Kawakami C, Koike K, Mitamura K, Kawaoka Y. 2007. Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. *JAMA* 297:1435-42.
104. Escuret V, Frobert E, Bouscambert-Duchamp M, Sabatier M, Grog I, Valette M, Lina B, Morfin F, Ferraris O. 2008. Detection of human influenza A (H1N1) and B strains with reduced sensitivity to neuraminidase inhibitors. *J Clin Virol* 41:25-8.
105. Escuret V, Collins PJ, Casalegno JS, Vachieri SG, Cattle N, Ferraris O, Sabatier M, Frobert E, Caro V, Skehel JJ, Gamblin S, Valla F, Valette M, Ottmann M, McCauley JW, Daniels RS, Lina B. 2014. A Novel I221L Substitution in Neuraminidase Confers High-Level Resistance to Oseltamivir in Influenza B Viruses. *J Infect Dis* 210:1260-1269.

106. Pascua PNQ, Marathe BM, Bisen S, Webby RJ, Govorkova EA. 2020. Influenza B viruses from different genetic backgrounds are variably impaired by neuraminidase inhibitor resistance-associated substitutions. *Antiviral Res* 173:104669.
107. Wang D, Sleeman K, Huang W, Nguyen HT, Levine M, Cheng Y, Li X, Tan M, Xing X, Xu X, Klimov AI, Gubareva LV, Shu Y. 2013. Neuraminidase inhibitor susceptibility testing of influenza type B viruses in China during 2010 and 2011 identifies viruses with reduced susceptibility to oseltamivir and zanamivir. *Antiviral Res* 97:240-4.
108. Leang SK, Deng YM, Shaw R, Caldwell N, Iannello P, Komadina N, Buchy P, Chittaganpitch M, Dwyer DE, Fagan P, Gourinat AC, Hammill F, Horwood PF, Huang QS, Ip PK, Jennings L, Kesson A, Kok T, Kool JL, Levy A, Lin C, Lindsay K, Osman O, Papadakis G, Rahnamal F, Rawlinson W, Redden C, Ridgway J, Sam IC, Svobodova S, Tandoc A, Wickramasinghe G, Williamson J, Wilson N, Yusof MA, Kelso A, Barr IG, Hurt AC. 2013. Influenza antiviral resistance in the Asia-Pacific region during 2011. *Antiviral Res* 97:206-10.
109. Patel MC, Nguyen HT, Mishin VP, Pascua PNQ, Champion C, Lopez-Esteve M, Merced-Morales A, Budd A, Kirby MK, Rambo-Martin B, Laplante J, Bateman A, St George K, Sullivan M, Steel J, Kondor RJ, Gubareva LV. 2025. Antiviral susceptibility monitoring: testing algorithm, methods, and findings for influenza season, 2023-2024. *Antiviral Res* 244:106299.
110. Carr S, Ilyushina NA, Franks J, Adderson EE, Caniza M, Govorkova EA, Webster RG. 2011. Oseltamivir-resistant influenza A and B viruses pre- and postantiviral therapy in children and young adults with cancer. *Pediatr Infect Dis J* 30:284-8.
111. [Rongyuan Gao](#), [Philippe Noriel Q Pascua](#), [Anton Chesnokov](#), [Ha T Nguyen](#), [Timothy M Uyeki](#), [Vasiliy P Mishin](#), [Natosha Zanders](#), [Dan Cui](#), [Yunho Jang](#), [Joyce Jones](#), [Juan De La Cruz](#), [Han Di](#), [Charles Todd Davis](#), [Larisa V Gubareva](#). Antiviral Susceptibility of Swine-Origin Influenza A Viruses Isolated from Humans, United States. *Emerg. Inf. Dis.* 2024 11:2303-2312.
112. Organization WH. 2012. Meetings of the WHO working group on surveillance of influenza antiviral susceptibility - Geneva, November 2011 and June 2012. *Wkly Epidemiol Rec* 87:369-74.