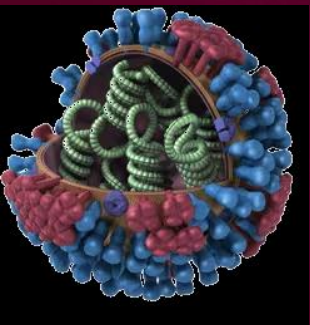


Influenza Drug Resistance

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What We Will Talk About

- Scope and perspectives
- Anti influenza therapies
- Mechanisms of resistance
- Contemporary status of influenza resistance



Scope of the Concern

- Influenza viruses are constantly changing
 - **Influenza A:** Primary surface proteins are hemagglutinin (HA), neuraminidase (NA). Currently circulating are subtype A(H1N1)pdm09 and A(H3N2)
 - **Influenza B:** not classified into subtypes. Currently circulating either B/Yamagata or B/Victoria
 - **Influenza C:** Less common. May cause mild infections. NOT a public health concern.
 - **Influenza D:** primarily affect cattle, not known to infect humans
- Flu A/B affect immune competent host, may be serious in IC conditions



Scope of the Concern

- **No drug is curative**
 - Usually reduce symptoms, hospitalization
 - Sporadic information on efficacy in special populations (critically ill, IC, chronic respiratory conditions)
 - Emergence of resistant or reduced susceptibility strains is of great clinical and public health concern
 - ➔ The need of constant surveillance for new variants



Influenza Surveillance

WHO's Global Influenza Surveillance and Response System (GISRS)
CDC National Respiratory and Enteric Virus Surveillance System (NREVSS)

- Surveillance for new strains done through
 - Passive surveillance
 - Active surveillance
 - Sentinel surveillance
- Surveillance for resistance 2022-23 season ([fda.gov](https://www.fda.gov))
 - NA inhibitors: Of 1,361 viruses tested, 4 showed resistance in genetic and/or phenotype analyses
 - Endonuclease inhibitor (baloxavir marboxil): Of 1,107 viruses tested, none showed resistance in genetic and/or phenotype analyses

<https://www.emro.who.int/health-topics/influenza/influenza-surveillance.html>

<https://www.fda.gov/media/165969/download>



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Status of Current Resistance

- Antiviral susceptibility patterns did not significantly change over the past few seasons
- During the past two seasons, only a very small number of viral strains were found to be resistant to oseltamivir
- 2022-23 was marked by Flu/RSV/COVID triple surges, esp late in 2022



Perspectives in Influenza Infections

- Per WHO
 - Infects 1 billion individuals/year
 - Mortality: 290-650 thousands/year

- Per the CDC, from October 1, 2022 through April 30, 2023
 - 27 – 54 million flu illnesses
 - 12 – 26 million flu medical visits
 - 300,000 – 650,000 flu hospitalizations
 - 20,000 – 60,000 flu deaths

- Lampejo T. Influenza and antiviral resistance: an overview. *Eur J Clin Microbiol Infect Dis.* 2020 Jul;39(7):1201-1208. doi: 10.1007/s10096-020-03840-9. Epub 2020 Feb 13. PMID: 32056049; PMCID: PMC7223162.
- <https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm>



Class	Drug	Name	Route of Administration	Comments
Neuraminidase inhibitors All active against Influenza A and B All US approved except Laninavir	Oseltamivir	generic, Tamiflu®	Oral tablet	Most commonly prescribed Susceptible to H275Y mutation
	Zanamivir	Relenza®	Inhalation via oral inhaler device	IV formation approved in Europe for severe influenza May have activity against Oseltamivir resistant strains
	Peramivir	Rapivab®	Intravenous ONE dose	Alternative to above NOT for hospitalized patients
	Laninavir		Inhaled, ONE dose: achieves a high concentration in the lungs, inhibits flu replication for at least 5 days	Sufficient antiviral effect to treat infection with H275Y-mutated oseltamivir-resistant virus
Cap-dependent endonuclease inhibitor	Baloxavir marboxil	Xofluza®	Oral Single dose	Newest- FDA approved Oct. 2018
M2 Inhibitors Adamantanes	amantadine rimantadine		Oral	They have not been recommended for use to treat flu in the US since 2016 because of widespread resistance (Activity against A only, NOT B)
RNA Polymerase Inhibitor	favipiravir		Oral	Approved only in Japan for novel influenza viruses during outbreaks. Teratogenic.

- Świerczyńska M, Mirowska-Guzel DM, Pindelska E. Antiviral Drugs in Influenza. Int J Environ Res Public Health. 2022 Mar 4;19(5):3018. doi: 10.3390/ijerph19053018. PMID: 35270708; PMCID: PMC8910682.
- Palomba E, Castelli V, Renisi G, Bandera A, Lombardi A, Gori A. Antiviral Treatments for Influenza. Semin Respir Crit Care Med. 2021 Dec;42(6):859-872. doi: 10.1055/s-0041-1733830. Epub 2021 Dec 16. PMID: 34918326.



Anti-Influenza Drugs Available in Lebanon

ATC	Name	B/G	Ingredients	Dosage	Form	Price
J05AH02	FLUMIVIR	G	Oseltamivir - 75mg	75mg	Capsule	1,045,464 L.L
J05AH02	TAMIFLU	B	Oseltamivir (phosphate) - 75mg	75mg	Capsule	2,377,475 L.L
J05AH02	TAMIFLU	B	Oseltamivir (phosphate) - 75mg	75mg	Capsule	2,377,475 L.L
J05AH02	VIRIFLU	G	Oseltamivir - 75mg	75mg	Capsule	1,035,991 L.L

In reality only Oseltamivir is available

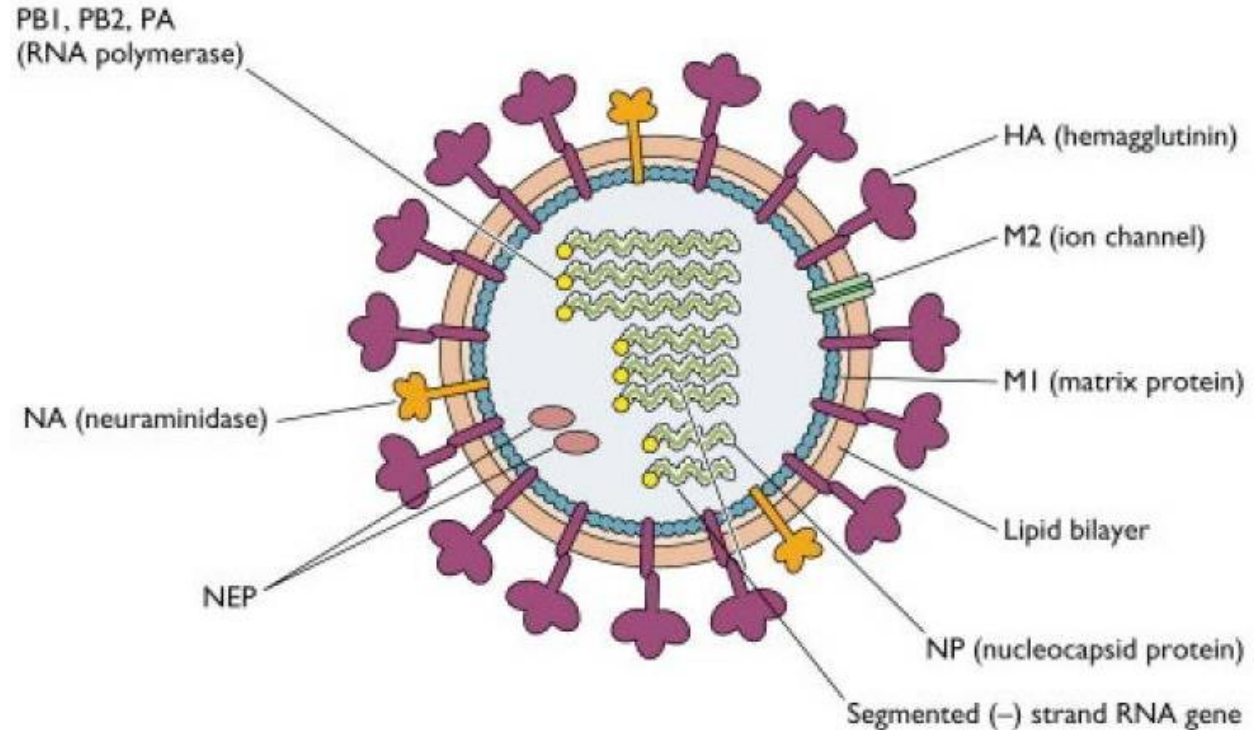
Relenza is out of stock. Not available for the past 10 years.

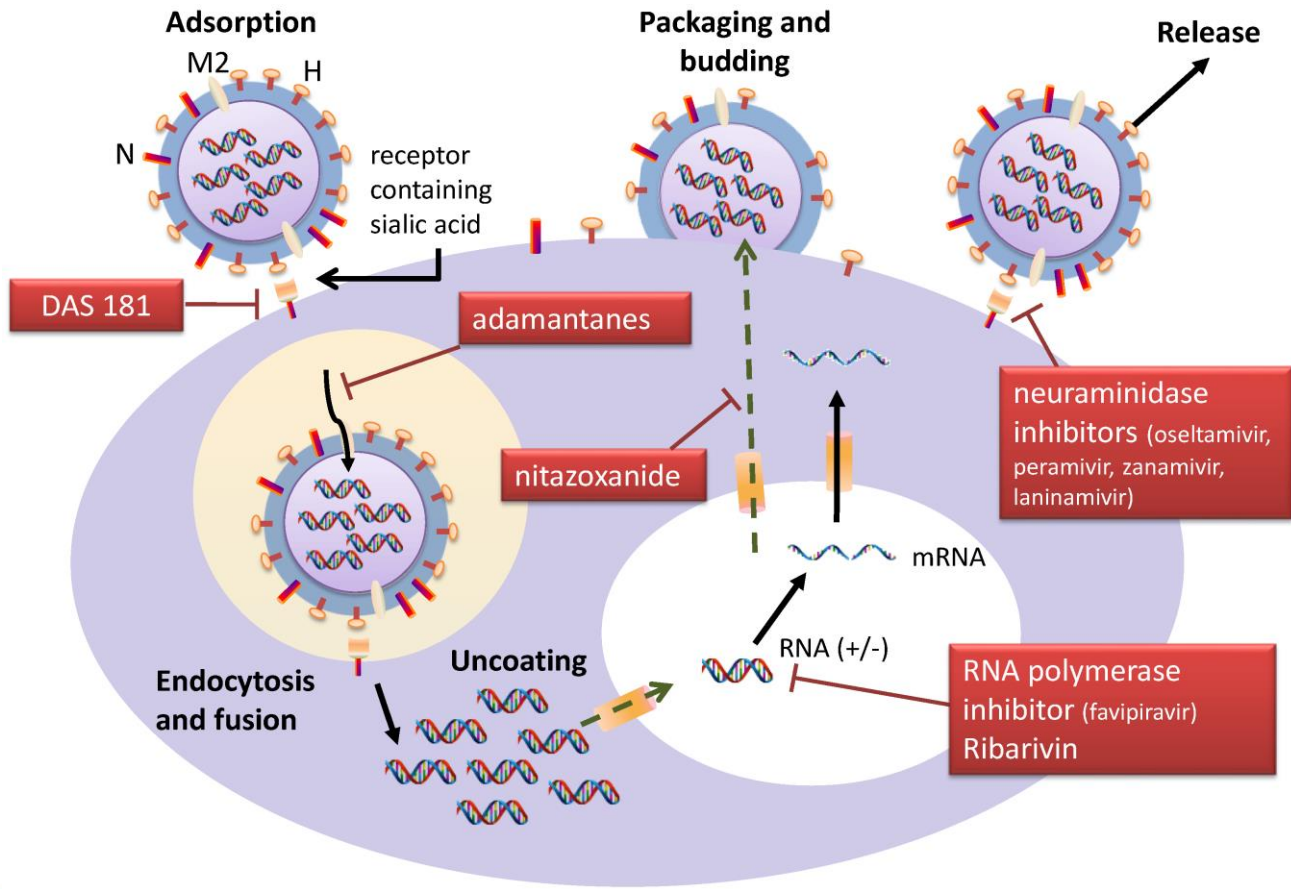
ATC	Name	B/G	Ingredients	Dosage	Form	Price
J05AH01	RELENZA	B	Zanamivir - 5mg, Lactose monohydrate - 20mg	5mg	Inhalation powder	2,139,113 L.L



Structure of Influenza Viruses

Structure of influenza A virus showing the two major surface glycoproteins (HA) and (NA), the nucleocapsid and polymerase proteins (NP, PB1, PB2, and PA), the matrix proteins (M1 and M2), the non-structural proteins (nuclear export protein (NEP)), lipid bilayer and segmented negative-strand RNA genes





The H275Y Mutation

The Basic Premise of NA Inhibitor Resistance

- Changes in the influenza viral NA proteins can reduce oseltamivir's binding to them, causing diminished activity or resistance
- The H275Y mutation is known to confer oseltamivir resistance in H1N1 pdm09 flu viruses. This mutation causes
 - Highly reduced inhibition by oseltamivir in laboratory assays
 - Also reduces effectiveness of peramivir
- Other mutations in the NA proteins of circulating viruses have been shown to reduce oseltamivir's activity, but not making it completely resistant
- Detection of H275Y Oseltamivir Resistance Gene Mutation: molecular/NextGen sequencing



Practical Application of Flu Resistance

- Assessing for risk factors
 - IC patient, peds, hospitalized with severe infection
 - Prior use of lower doses e.g. after prophylaxis
 - Treatment-emergent resistant influenza variants may occur during NAI and baloxavir use
 - Exposure to known resistance or outbreaks
- When to think resistance?
 - Slow clinical response or relapse after treatment
 - Slow virologic response (slow VL decline on PCR, repeated positive cultures)
 - Viral rebound during treatment

- Li TC, Chan MC, Lee N. Clinical Implications of Antiviral Resistance in Influenza. *Viruses*. 2015 Sep 14;7(9):4929-44. doi: 10.3390/v7092850. PMID: 26389935; PMCID: PMC4584294.
- Chan KKP, Hui DSC. Antiviral therapies for influenza. *Curr Opin Infect Dis*. 2023 Apr 1;36(2):124-131. doi: 10.1097/QCO.0000000000000910. Epub 2023 Jan 30. PMID: 36752709



Testing and Treatment

- Serial testing
 - Samples, esp before/after treatment
 - Phenotypic/genotypic assays, detection of H275Y
- Treatment for resistant strains:
 - No established therapy for NA inhibitor resistant influenza infections
 - IV zanamivir (through a compassionate program) and/or Baloxavir should be considered for H275Y mutants. NOT Peramavir.
 - Investigational therapies, including combination regimens and novel agents (e.g., favipiravir) have shown promising results



Combination Therapy Studies

- Oseltamivir, amantadine, and ribavirin combination antiviral therapy versus oseltamivir monotherapy for the treatment of influenza: MC/DB/Randomized phase 2 trial in 2017 showed:
 - Significant decrease in viral shedding at day 3 relative to monotherapy
 - No commensurate improvement in clinical benefit
- Current evidence does not suggest routine use of combined antiviral agents in patients with influenza infection





Thank you



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