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Review Article

A concise review on influenza

Pratibha L. Ayanar, Simran M. Jamadar, Shweta R. Bharati, Aishwarya R. Ghanwat, Kumudini R. Pawar*

Abhinav Education Society`s College of Pharmacy (B. Pharm), Narhe, Pune, Maharashtra, India

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***Correspondence:**
Dr. Kumudini R. Pawar,
E-mail: Kumudiniphd30@gmail.com

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ABSTRACT

Influenza, commonly known as the flu, is a contagious respiratory illness caused by influenza viruses. It can lead to mild to severe illness and can result in hospitalization and death. The flu virus is characterized by its ability to mutate, leading to seasonal epidemics and occasional pandemics. Understanding the types, risk factors, history, symptoms, causes, treatment, and mechanisms of action is crucial for effective prevention and management. It is classified into four types: A, B, C, and D, with types A and B being responsible for the seasonal flu epidemics. The flu is highly contagious and spreads through respiratory droplets when an infected person coughs, sneezes, or talks. The history of influenza dates back centuries, with notable pandemics occurring in 1918 (Spanish flu), 1957 (Asian flu), 1968 (Hong Kong flu), and the H1N1 pandemic in 2009. The 1918 pandemic was particularly devastating, infecting about one-third of the world's population and resulting in millions of deaths. For treatment of flu, vaccination is most effective method. This review focused on the symptoms, causes, treatment and mechanism of action of antiviral drug.

Keywords: Influenza, Flu, COVID-19, Pandemic, Swine flu, SARS-Cov

INTRODUCTION

Influenza is usually known as flu, and it is contagious disease. It belongs to the *Orthomyxoviridae* family, are responsible for this condition. The primary respiratory pathogen in influenza virus is to blame for a large portion of human morbidity and mortality. Compared to adults, the disease is more severe in youngsters, the elderly and those with underlying medical condition. It also triggers pandemics, endemics and seasonal outbreak. The recent cross-species transmission of avian influenza to human has increased the potential of pandemics. Seasonal and pandemic influenza have a big effect on economy and public health. The most frequent viruses that causes influenza like disease (ILI) are influenza A and B viruses.[1] The type of virus implicated determines the intensity and length of the illness. For the purpose of managing outbreak diagnosing diseases, initiating antiviral therapy in patients who are at high risk of complications. The careful management of antibiotic use and the implementation of virus surveillance have facilitated the timely and accurate identification of swine-origin influenza A and highly virulent influenza A in avian populations. This has underscored the significance of influenza viruses and their various subtypes. Identification of these viruses can be achieved through virus culture, RT-PCR, or rapid testing methods such as immunochromatographic tests. The gold standard techniques for diagnosing influenza viruses are RT-PCR and virus culture. Immunoassay referred to as rapid influenza diagnostic test (RIDTS) are to able to identify influenza A and B viral nucleoprotein antigen in respiratory specimen.[2] A pandemic is a wide spread epidemic of a communicable disease that rises the risk of morbidity considerably and death a broad variety of geographic regions because there is no immunity to the causal agent, the pandemic typically impacts large portion of population making it extremely severe. viruses are the primary cause of pandemics that affect society globally. Compare to other viruses in its family, the current critical acute respiratory syndrome, corona virus outbreak has

spread more severely and resulted in serious crises around the world. The 1918 parish flu epidemic is through to have more people killed than any other pandemic since 1900 worldwide outbreaks of such a disease.[3]

HISTORY

In the last century there have been four main worldwide pandemics.

1918 (Spanish influenza)

The 1918 influenza pandemic, which was brought on by an H1N1 strain was the worst known pandemic. At least 25-50 million people died as a result of it globally. According to more recent research, these numbers may be under estimate due to under reporting in developing nations and abnormally high mortality rates there in the US alone, there were at least 675,000 fatalities. The 1918 pandemic was particularly remarkable for its unusually high mortality rates among young adults aged 20 to 40.[4]

1957 (Asian influenza)

The first Asian flu to be studied and a vaccine to be developed was the 1957 strain (H2N2), which originated in East Asia. There was apparently a "second wave" of infection in this epidemic, which started with infections in children's and young people and then spread to the elderly. In the US, some 69,800 persons lost their lives.[5]

1968 (Hong Kong influenza)

The Hong Kong influenza pandemic (H3N2) began in Hong Kong and gradually made its way to the US, where it mostly affected people over the 65.in 1970 and 1972 the virus reappeared 33800 people died during the outbreak. Pre-existing immunity to the Asian flu virus, along with enhanced medical care and surveillance, could have potentially mitigated the severity of the 1968 outbreak.[4]

2009 (Swine influenza)

The more recent 2009 flu pandemic, also referred to as the swine flu despite not infecting pigs, originated in Mexican in 2009 and was caused by a combination human, swine and avian flu viruses. 3600 of the almost 14000 facilities worldwide were in North America, in addition to the trivalent seasonal flu vaccines, a mass vaccination campaign was launched, and by November 2009, over 65 million doses of the vaccine have been administered. The swine flu strain is still present in seasonal influenza, although the world health organisation declared the outbreak over in June 2010.[6]

Table 1: History of influenza.[7]

Year	1918	1957	1968	2009
Type	Spanish influenza	Spanish influenza	Hong Kong influenza	Swine (Pandemic) influenza
Virus	H1N1	H2N2	H3N2	Avian
MOA	Bird to human transmission of H1N1 virus	H2N2+H1N1 (Avian+human virus)	H3+H2N2 (Avain+human virus)	H3+H3N2 (Avian+human virus)

COVID -19

COVID-19 had initial reports from Wuhan, China, in 2019 indicated the emergence of a novel human virus. COVID-19 swept across the globe and became 5th pandemic. This has been officially documented since influenza pandemic of 1918. Nearly 2 years following the initial identification of COVID in September 2021, there have been>200 million confirmed cases and over 4.6 million deaths attributed to virus. Comprehensive history of COVID, detailing events from initial case to current global vaccination campaign designed to curb spread of disease.[8,9]

Table 2: History of COVID-19.[10,11]

Date	History
September 2019	A posterior identification of imported cases in Italy.
November 2019	A posterior identification of imported cases in France.
31 December, 2019	First report of pnemonia of unknown causes in Wuhan (China).
9 January, 2020	WHO indicate the emergency of an infection due to new type of virus.
10 January, 2020	SARS-COV-2 sequence published.
13 January, 2020	Official first case outside China (Thailand).
21 January, 2020	First case in USA.
30 January, 2020	WHO declares the outbreak as an international concern.
11 February, 2020	Severe actute respiratory syndrome Corona Virus-2 as the new Virus.
19 February, 2020	3D structure of spike molecule.
27 February, 2020	Angiotensin converting enzyme 2 suggested to be receptor of severe acute resiratory syndrome Corona virus-2.
11 March, 2020	World health organization declares COVID-19 as a global health crisis.

Table 3: Types of flu and its description.

Types of flu	Description
Influenza A	Influenza A is a variant of the influenza virus that predominantly affects avian and mammalian species, including humans. Infections can differ significantly, with manifestations ranging from asymptomatic instances to critical respiratory conditions, and in certain situations, resulting in death.[12]
Influenza B	Influenza B is a species of the influenza virus that primarily infects humans and, to a lesser extent, seals. Influenza B is capable of triggering seasonal flu epidemics that may result in serious respiratory conditions, such as bronchitis and pneumonia.[13]
Influenza C	Influenza C viruses primarily infect humans and pigs. Infections caused by the influenza C virus is typically mild.[14]
Influenza D	Influenza D primarily impacts cattle and has also been identified in other species, including swine, sheep, and goats. At present, there is no indication that influenza D represents a risk to human health.[15]
Swin flu	Swine flu is attributed to a specific strain of the influenza A virus known as H1N1. The mortality rate associated with H1N1 has consistently remained low, comparable to that of the standard influenza virus.[16]
SARS-COV	SARS is brought on by this virus in Chinese region of Guangdong. The disease initially stroke human in 2002. Over 8000 cases of SARS were reported during epidemic that spanned 26 nations. There haven't been any SARS cases in human reported since 2004.[17]
MERS	MERS is brought on by this coronavirus, 2012 saw earliest occurrence in Saudi Arabia. About ¾ out of every 10 individuals with verified MERS pass away from illness. According to WHO report from 2019, MERS- CoV has the potential to be transmitted through interactions with animals, particularly camels. Close contact with sick individuals can also result in spread of disease from person to person.
SARS-COV	The SARS-CoV-2 virus is responsible for the disease known as COVID-19. The initial cases were detected in the city of Wuhan, China in the year 2019. Older and people with medical conditions are at risk of critical COVID 19.

Table 4: Causes and symptoms of all types of flu.

Types of flu	Causes	Symptoms
Influenza A, B, C and D[18]	Influenza is caused by flu virus, by breath tiny airborne droplets from cough and sneezes of someone who has flu, touch something with virus on it.	Cold with rhinitis, sneezing, pharyngitis, pyrexia muscle ache, others (Migraine, dry subacute cough, fatigue, eye irritation, vomiting and diarrhoea.)
Seasonal flu[19]	Influenza is caused by flu virus, by breath tiny airborne droplets from cough and sneezes of someone who has flu, touch something with virus on it.	Fatigue, sore throat, fever, aching muscle, others (headache, dry persistent cough, tiredness and weakness, eye pain, vomiting and diarrhoea.)
Swine flu (H1N1)[20]	Influenza is caused by flu virus, by breath tiny airborne droplets from cough and sneezes of someone who has flu, touch something with virus on it.	In children-(trouble breathing, dull skin, angina pectoris, thirsty, myalgia, seizures) in adults-(cough, sore throat, body and muscle pain, head ache, fatigue, fever, chills)
COVID-19[21]	The transmission of the coronavirus occurs through the air via minuscule droplets of fluid exchanged between individuals who are in close proximity to one another, Corona disease reach human through contact with animals. (livestock, including camel and others as bat and cat).	Cough, difficulty in breathing, ageusia and hyposmia, fatigue, digestive symptoms (vomiting, diarrhea), pain (headache), pyrexia, congestion, runny nose or sore throat

TREATMENT OF FLU

Treatment strategies for COVID-19 and influenza exhibit certain similarities, especially in realm of supportive care; however, they also possess notable differences that arise from distinct characteristics of each virus.[22]

Treatment of influenza

According to centres for disease control and prevention (CDC) has not recommended the use of Amantadine and Rimantadine for the influenza viruses that are currently in circulation. Recommendations may be subject to change

should there be a future resurgence of specific virus strains exhibiting susceptibility patterns that support such usage. The CDC recommends using four FDA-approved influenza antiviral medications as follows,

Oseltamivir: An oral antiviral medication that is effective against both influenza A and B viruses. The treatment is most advantageous when initiated within 48 hours of the onset of symptoms.

Zanamivir: An inhaled antiviral is appropriate for specific patients, and it is advisable to commence treatment within 48 hours of the onset of symptoms.

Peramivir: An intravenous antiviral treatment designed for patients who are unable to utilize oral or inhaled medications.

Baloxavir marboxil (Xofluza): An oral antiviral medication given as a single dose for the treatment of uncomplicated influenza; it is most effective when administered within 48 hours of the onset of symptoms.[23]

Treatment of COVID-19

The FDA has granted approval for Paxlovid (nirmatrelvir and ritonavir tablets, co-packaged for oral administration) to be used in the treatment of COVID-19 in certain adult patients who are infected and are receiving care outside of a hospital setting. An intravenous (IV or drip) COVID-19 therapy is called Veklury. Veklury (Remdesivir)has been Authorized by the Food and Drug Administration for use in specific COVID-19 adult and child.

Intravenous (IV) therapy for the treatment of COVID-19 is approved for use in both hospitalized patients and those not requiring hospitalization. The food and drug administration has also granted authorization for the use of olumiant (baricitinib) and actemra (tocilizumab) in specific hospitalized patients diagnosed with COVID-19. [24]

Remdesivir

Approved for patients in the hospital who need additional oxygen support, individuals who have mild to moderate symptoms associated with COVID-19. Remdesivir injection should be administered at the earlier, ideally within 7 days from the onset of initial symptoms.

The medication is to be administered through intravenous infusion once daily up to 3 days.[25]

Molnupiravir

An oral antiviral treatment is available for non-hospitalized patients exhibiting mild to moderate symptoms, demonstrating efficacy when given at an early stage.[25]

MECHANISM OF ACTION OF ANTIVIRAL DRUGS

Acyclovir, penciclovir, ganciclovir, and lamivudine are antiviral medications classified as nucleoside analogs, which impede viral replication by acting on viral polymerases. Their main mode of action consists of competitively inhibiting the synthesis of viral DNA and causing premature termination of the elongating viral DNA strand.[26]

Common steps in the mechanism of action

Selective phosphorylation (Activation)-acyclovir, penciclovir, and ganciclovir necessitate the involvement of viral kinases for the initial phosphorylation process, specifically the thymidine kinase (TK) from herpes simplex virus (HSV) and varicella-zoster virus (VZV).

Competitive inhibition of viral DNA polymerase: The active triphosphate forms of these medications compete with natural nucleotides for incorporation into the elongating viral DNA chain.

Chain termination and inhibition of viral replication: The absence of a 3'-hydroxyl group in these nucleoside analogs leads to the premature cessation of the viral DNA chain. This interruption hinders further viral replication, thereby decreasing the viral load within the infected host.[27]

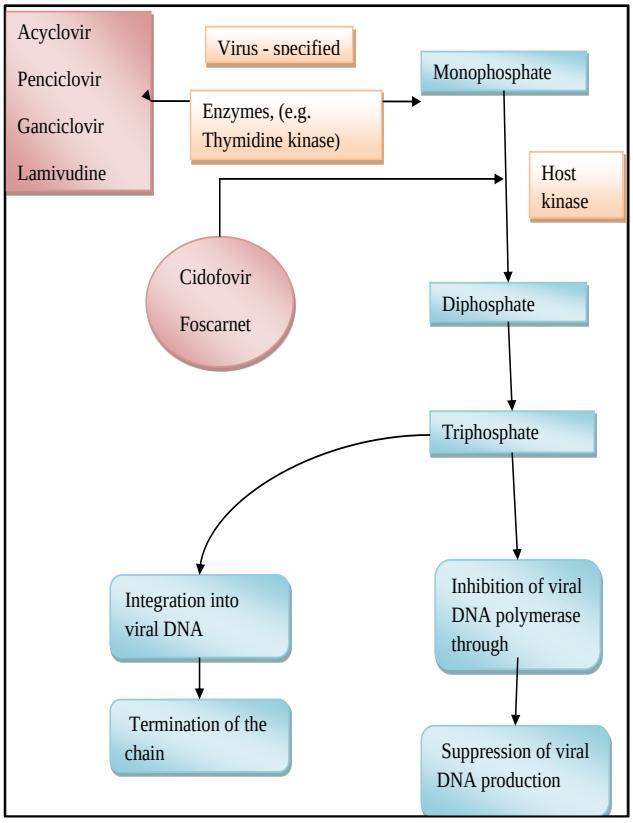

Figure 1: The general mechanism of action of antiviral medications.[28]

Amantidine and rimantidine

Amantadine and Rimantadine are antiviral medications that function by inhibiting the M2 protein of the influenza A virus. The M2 protein serves as a proton-selective ion channel, which is essential during the initial phases of viral replication, particularly in the uncoating stage. By blocking the M2 ion channel, these drugs effectively hinder the virus's ability to replicate within host cells. [29]

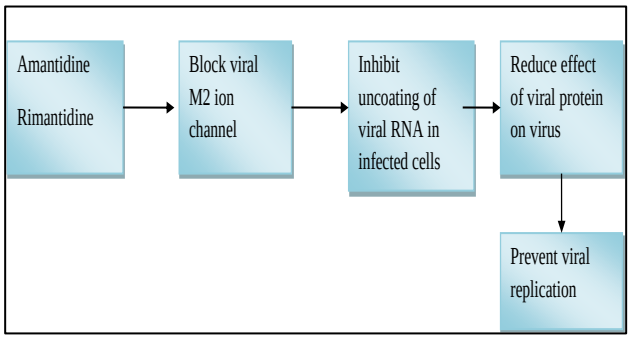

Figure 2: Mechanism action of amantadine and rimantidine.[30]

Remdesivir

This prodrug, which inhibits the viral RNA polymerases, is a nucleotide analogue that Processed by metabolic pathways intracellularly to an ATP analogue. It restrain RNA-dependent RNA polymerase, and studies on Middle East respiratory syndrome-CoV and severe acute respiratory syndrome-CoV infections have examined its properties and pharmacokinetics. Due to alterations in the function of the viral exonuclease and impaired proofreading mechanisms, this medication diminishes the replication and production of the viral genome. Given that it stops the virus from replicating, it can be advised to stop the severity of the condition in COVID-19 patients. Double blind randomised clinical trials with such patients are being conducted in phase III to confirm its promise as a treatment against corona virus.[31]

Remdesivir demonstrates effectiveness in both virologic and clinical aspects within a non-human primate model, as well as effectiveness against COV in individual airway, according to *in vitro* investigations.

Remdesivir possesses broad-spectrum antiviral activity against multiple members of the virus family, such as filoviruses like Ebola and cov like MERSCoC and SARSCoV. When used in non-therapeutic models, Remdesivir has demonstrated both therapeutic and preventive efficacy against these coronaviruses. Remdesivir demonstrated efficacy against SARS-CoV. This suggests that nonhuman primate models are likely to be the source of Remdesivir's working concentration. The first COVID-19 patient in US32 responded significantly to intravenous remdesivir treatment, and a trial has now been launched to quickly assess the safety and effectiveness of remdesivir in hospitalized COVID-19 patients.[32,33]

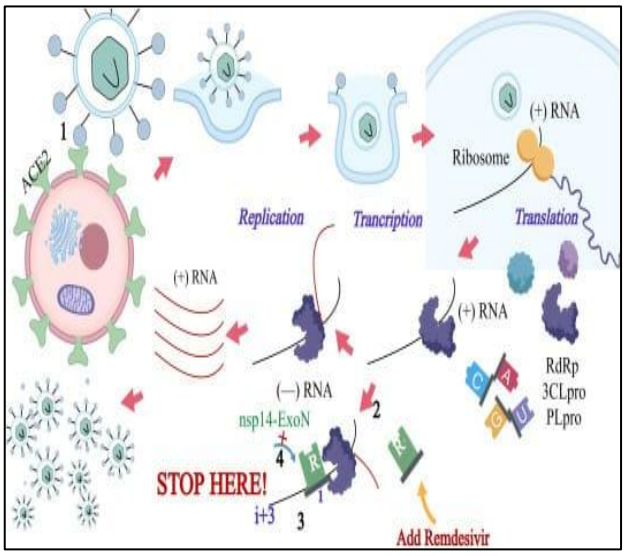

Figure 3: Mechanism of action of remdesivir.[32]

Oseltamivir

Oseltamivir phosphate serves as a prodrug for oseltamivir carboxylate, which is the active metabolite that effectively and specifically inhibits the neuraminidase enzymes, glycoproteins located on the surface of the influenza virus. The function of the viral neuraminidase enzyme is essential for the penetration of the infectious virus into healthy cells, the liberation of newly formed virus particles from infected cells, and the ensuing spread of the virus within the organism. The effectiveness of oseltamivir reducing viral infection and overall infectivity.

Oseltamivir is effective in combating the neuraminidase of both influenza A and influenza B viruses which includes the pandemic swine flu.[34-36]

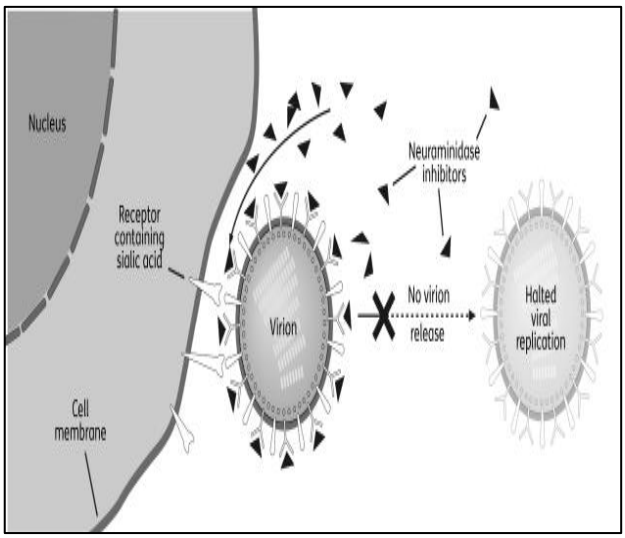

Figure 4: Mechanism of action of oseltamivir.[34]

Nitazoxanide

Nitazoxanide and its active ingredient, tizoxanide, potential against MERS CoV and SARS CoV-2. Along with coronaviruses, it also shown broad spectrum activity against rotavirus, parainfluenza, influenza, respiratory syncytial virus, and norovirus. The antiviral effect is attributed to the mechanism of action that targets the pathways of virus reproduction controlled by the host, rather than those of the virus itself. This drug increases the activity of innate antiviral systems by amplifying type 1 IFN and cytoplasmic RNA sensing. Nitazoxanide increases the specific host processes that interfere with the virus's invasion and its ability to evade the host cellular defences.[37, 38]

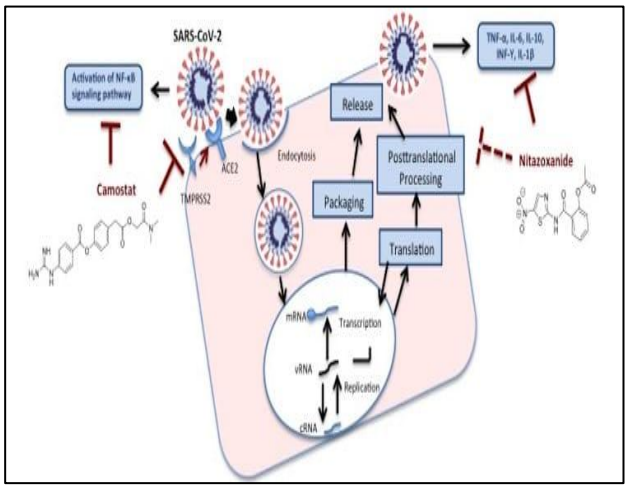

Figure 5: Mechanism of action of nitazoxanide.[37]

CONCLUSION

Influenza (flu) is a highly contagious viral infection that primarily affects the respiratory system. It can range from mild to severe, with symptoms such as fever, cough, body aches, and fatigue. The flu is caused by influenza viruses, which mutate frequently, leading to seasonal outbreaks. While most people recover with rest and supportive care, antiviral medications can be used to shorten the illness and reduce severity if administered early. Vaccination is the most effective preventive measure against the flu, helping to reduce the spread of the virus and the risk of severe complications. Public health efforts focusing on hygiene practices, vaccination, and timely treatment are essential in controlling the impact of the flu globally.

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