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Mini Review Article

H3N2 Virus Outbreak: A latest global threat

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Abstract
The current H3N2 virus outbreak has sent shockwaves worldwide, with health officials rushing to stop its spread. This form of influenza has been wreaking havoc around the globe, culminating in an alarming number of hospitalizations and fatalities. The H3N2 virus is extremely transmissible and can cause severe symptoms, making it a major global danger. This outbreak has demonstrated the need to be always aware and prepared in such scenarios. Health officials have been working diligently to keep the virus contained and spread to a minimum. The H3N2 virus is a major threat that must be addressed immediately by health experts, lawmakers, and the general population. Aside from the health hazards posed by the H3N2 virus, there are additionally substantial economic repercussions. The spread has led to lost productivity, higher healthcare expenses, and pressure on global healthcare systems. The international community must collaborate to discover answers to the H3N2 virus outbreak's challenges. Overall, the H3N2 disease outbreak is a significant global concern that must be addressed immediately. Health professionals must make aggressive efforts to stop the virus's spread, while legislators must work to guarantee that adequate resources are available to deal with the outbreak. The general people must also take precautions against the virus, such as maintaining good hygiene and being vaccinated. Failing to respond to the H3N2 virus infection might have disastrous health and economic effects.
***Keywords**:* H3N2 virus, influenza, outbreak, global threat

Introduction

Influenza is a pulmonary illness that impacts between 5-15% of the world's population each year and is responsible for a significant global mortality rate (Allen and Ross, 2018). There are four types of influenza viruses within the *Orthomyxoviridae* family, which are influenza A-D (Uyeki et al., 2022). Influenza A viruses can infect humans, birds, pigs, horses, and other animals, thus zoonotic, whereas influenza B and C viruses can only infect humans (Vemula et al., 2016). Influenza D viruses typically affect cattle, with secondary infections in other animals. Although it is unknown if influenza D viruses may infect and transmit illnesses to humans, the discovery of influenza D virus antibodies in cattle has been reported (Liu et al., 2020). Influenza A viruses are classified based on the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) (Poucke et al., 2015). There are now 18 known HA subtypes (H1-18) and 11 known NA subtypes (N1-11), however only a few of these, namely H1N1, H3N2, and H3N3, are currently circulating in

humans (Ushirogawa et al., 2016; Shim et al., 2017; Vadala et al., 2020).

According to the World Health Organization's (WHO), most recent report, cases of influenza A(H3N2) viruses are found worldwide, impacting more than 30% of the global population. The WHO expects these pathogens to cause 250,000 - 500,000 deaths per year (Allen and Ross, 2018).

Fever, sore throat, coughing (mainly dry cough), runny nose, headache, and muscle aches are all frequent symptoms of influenza infection. More serious occurrences might also result in the development of illnesses like bronchitis or pneumonia. Influenza A and B viruses are thought to be spread across short distances (1-2 meters) from person to person via large (≥5 μm) droplets and small-particle (<5 μm) droplet nuclei (aerosols) expelled by infected patients through coughing (Leung, 2021). The symptoms and transmission of the H3N2 virus are similar to the coronavirus which, creates an environment of fear among the patients because of their past traumatic experiences with the coronavirus pandemic.

The H3N2 is a zoonotic virus that already caused a global pandemic in 1968, causing the deaths of millions worldwide and after more than fifty years, it again has reemerged and can be another global threat for the world. This review focuses on the history, epidemiology of H3N2, etiology, pathogenesis, clinical manifestation, diagnosis, prevention, and treatment of the H3N2 virus.

Methods of review

Data Sources

From January 2023 to March 2023, a literature search was conducted on PubMed, Medline, Google Scholar, Embase, and the WHO website using the subsequent vital terms: H3N2 virus, pandemic, virus, history, zoonotic illness, disease epidemiology, assessment, signs and symptoms, prevention, and treatment of H3N2 virus. A total of 42 papers were evaluated, with 23 of them being included in this review.

Data Selection and Data Extraction

This review collected all English literature with important information such as history, disease epidemiology, diagnosis, clinical symptoms, prevention, and therapy of H3N2 virus disease that are citable.

Data synthesis

The present level of knowledge on the human H3N2 virus will be examined in this article, with a focus on the disease's history, epidemiology, pathogenesis and, clinical symptoms, assessment, management, and prevention.

History of H3N2 virus

The 1968 pandemic was triggered by an influenza A (H3N2) virus that carried the N2 neuraminidase from the 1957 H2N2 virus and two genes from an avian influenza A virus. It was discovered in the USA for the first time in September 1968 (Jester et al., 2020; Grais et al., 2003). The projected number of deaths globally was one million, with around 100,000 in the United States. The majority of extra deaths occurred in those aged 65 and above. The H3N2 virus is still circulating as a seasonal flu virus worldwide. Seasonal H3N2 viruses, which are linked to severe sickness in the elderly, exhibit antigenic drift regularly (Centers for Disease Control and Prevention, 2019).

Epidemiology of H3N2 virus outbreak

The illness ranges from minor to severe, and some may result in death. Hospitalization and death are most common among high-risk groups. Such annual epidemics are predicted to cause 3 to 5 million episodes of severe disease and 290 000 to 650 000 pulmonary deaths worldwide (Macias et al., 2021). All age groups can be affected; however, some are more vulnerable than others. When infected, pregnant women, children under the age of 59 months, the elderly, people with persistent health problems (such as severe cardiac, respiratory, renal, metabolic, neurodevelopmental, liver, or hematologic diseases), and people with immunosuppressive situations (like HIV/AIDS, taking chemotherapy or steroids, or cancer) are at a higher risk of severe illness or complications (Fell et al., 2017).

Healthcare personnel are at high risk of influenza virus infection because of their increased exposure to patients and the risk of subsequent transmission, particularly to susceptible individuals (World Health Organization, 2023).

Pathogenesis of the H3N2 virus

Infection with the human influenza virus occurs mainly within the respiratory epithelium. Different cell types, including numerous immune cells, can become infected with the virus and begin producing viral proteins. However, the efficacy of viral replication varies between cell types, in humans, the respiratory epithelium layer is the only place where the hemagglutinin (HA) protein is successfully cleaved, resulting in infectious virus particles. Transmission of the virus occurs when a susceptible person comes in contact with or interacts with respiratory particles or spores of an infected person (Dou et al., 2018). The fundamental mechanism of influenza pathogenesis resulted from direct viral infection of the respiratory epithelium, mixed with the impact of lung inflammation generated by immune responses recruited to deal with the spreading virus. Acute inflammation can extend systemically and cause multiple organ failures; however, these consequences are usually secondary to lung damage and severe respiratory distress (Kalil and Thomas, 2019).

Antigenic drift and antigenic shift can cause genomic alterations in the H3N2 virus. Antigenic drift is a progressive change in the virus's surface glycoproteins, whereas antigenic shift is an abrupt change caused by genetic material reassortment between distinct influenza viruses. These genetic changes can result in the development of new variations, that can elude immunity and potentially cause sickness (Krammer et al., 2018).

Clinical manifestations of the H3N2 virus

The H3N2 virus's clinical presentation is comparable to other types of influenza viruses. Sudden onset of fever, cough (usually drug cough), sore throat, runny or stuffy nose, body aches, headache, chills, and weariness flu symptoms. The virus can cause pneumonia, acute respiratory distress syndrome, and death in extreme cases. The H3N2 virus is hazardous and can cause severe sickness, particularly in the older adults and those with pre-existing medical problems. Complications from the virus include bacterial pneumonia, ear infections, sinus infections, and exacerbation of chronic medical issues (Leung, 2021).

Diagnosis of H3N2 virus

Due to similar symptoms from infections with various co-circulating respiratory viruses, particularly SARS-CoV-2, clinical diagnosis of influenza virus is frequently erroneous. Influenza testing can improve therapeutic decisions, but results, particularly negative ones, must be assessed in terms of predictive values that consider the incidence of influenza flu strains in the tested community, test sensitivity, and specificity. Upper-respiratory-tract samples from outpatients should ideally be collected within four days of disease start, but viral RNA may be detected for prolonged periods, especially in small children and immunocompromised persons. Although nasopharyngeal samples yield the most influenza viruses, a mid-turbinate nasal swab or a combination of nasal and throat swabs are acceptable samples depending on the test. If upper-respiratory samples are negative, lower-respiratory tract samples should be evaluated in patients with respiratory failure (Uyeki et al., 2019). Various diagnostic tests can be performed, including rapid antigen test, rapid molecular assay, immunofluorescence assay, virus culture, and molecular assay (Centers for Disease Control and Prevention, 2020).

Rapid antigen test

Antibodies identify influenza viral antigens using a lateral flow immunoassay or a fast immunofluorescent assay, usually with digital analyzer equipment. It usually takes 10-15 min to give results with low-to-moderate sensitivity (40-80%) and high specificity. It can detect and differentiate between influenza A and B viral infections; the sensitivity of tests that use an

analyzer device is higher; they are available for point-of-care use; and multiplex assays can identify and distinguish between SARSCoV-2 and influenza A and B virus infections.

Rapid molecular assay

Nucleic acid amplification is used to detect influenza virus RNA; a small-footprint device with an embedded analyzer device is required. It usually takes 15-40 min to provide results with high sensitivity (>95%) and high specificity (<99%). Multiplex tests can identify and distinguish between influenza A and B viral infections; specific assays are accessible for point-of-care usage; multiplex tests can detect and differentiate between SARS-CoV-2 and influenza A and B virus infections; and some assays can detect the respiratory syncytial virus (RSV).

Immunofluorescence assay

Antibodies detect influenza virus antigens via immunofluorescence staining, which involves collecting cells from the upper respiratory tract and a fluorescent microscope. It can identify and differentiate influenza A and B virus infection and must be performed in a registered laboratory or public health laboratory, which requires qualified laboratory employees and skilled staff. The sensitivity is affected by sample preparation and less frequently used. It generally takes around 1-4 h with moderate specificity and high sensitivity.

Virus culture

The process of virus culture requires 1-10 days to provide results with high specificity and sensitivity. It isolates the viable influenza virus using tissue cell culture. It demands a sophisticated laboratory area ideal for virus multiplication; shell-vial cell culture can produce results in 1-3 days, and standard tissue cell culture can produce results in 3-10 days.

Molecular assay

Nucleic acid amplification is used to identify influenza virus RNA; specific procedures need complicated equipment, preanalytical nucleic-acid extraction, and downstream analysis done in high-end laboratories. It can identify and discriminate influenza A and B viral infection; must be performed in a recognized clinical lab or public health care laboratory; competent laboratory workers are required; Multiplex assays can detect and differentiate SARS-CoV-2 and influenza A and B virus infections, and some can also identify influenza A virus subtypes and other respiratory viral and bacterial pathogens. It generally requires 45-80 min to give results with high sensitivity (>95%) and high specificity (<99%).

Latest data on the recent outbreak of the H3N2 virus

According to the most recent statistics available on the IDSP-IHIP (integrated health Information Platform), the states reported a total of 3038 confirmed cases of different subtypes of influenza, including H3N2, through March 9th, 2023. There were 1245 cases in January, 1307 in February, and 486 in March (till March 9th) (Press Information Bureau, 2023). India confirms 451 cases and seven deaths from the H3N2 influenza virus between January 2 and March 5, according to data released by the Ministry of Health (Business Today, 2023).

Steps were taken by the WHO to counter the threat

The WHO, in partnering with national and international partners, monitors influenza virus activity worldwide through the Global Influenza Surveillance & Response System (GISRS), suggests influenza vaccine combinations a couple of times annually for the Northern and Southern hemisphere influenza seasons, help guide nations in tropical and subtropical areas in vaccine formulation selection (Northern hemisphere vs. Southern hemisphere), supports decisions on vaccination campaign timing, and assists Member States in developing prevention and control strategies (World Health Organization, 2023).

The WHO strives to improve national, regional, and global influenza response capabilities, such as diagnostics, antiviral resistance monitoring, illness surveillance, and outbreak response, as well as to enhance vaccine coverage among high-risk populations and prepare for a coming influenza pandemic (Nair et al., 2011).

The WHO also collaborates with vaccine manufacturers to produce and distribute seasonal flu vaccines that target circulating strains of the virus. The group also advises on the prevention and control of infections through techniques such as hygiene practices, respiratory etiquette, and mask use.

How to protect yourself from the latest global threat

Vaccination is the most efficient method of illness prevention. Vaccines that are both safe and effective have been used for more than sixty years. Vaccine immunity fades with time, thus annual vaccination is suggested to safeguard against influenza. Inactivated influenza vaccines that have been injected are the most regularly utilized worldwide.

For healthy individuals, the influenza vaccine provides protection, even though the circulating viruses may not look exactly like the vaccine viruses. However, influenza vaccination might not be as successful in avoiding sickness among the elderly, but it does reduce disease severity and the occurrence of complications and fatality. Immunization is especially crucial for persons who live with or care for individuals who are at serious risk of complications from influenza.

The WHO recommends annual vaccinations for children between 6 months and 5 years, the senior population (over 65 years), pregnant women, individuals with chronic illness, and healthcare workers (Centers for Disease Control and Prevention, 2012). Various prevention techniques for this global threat are mentioned in Figure 1.

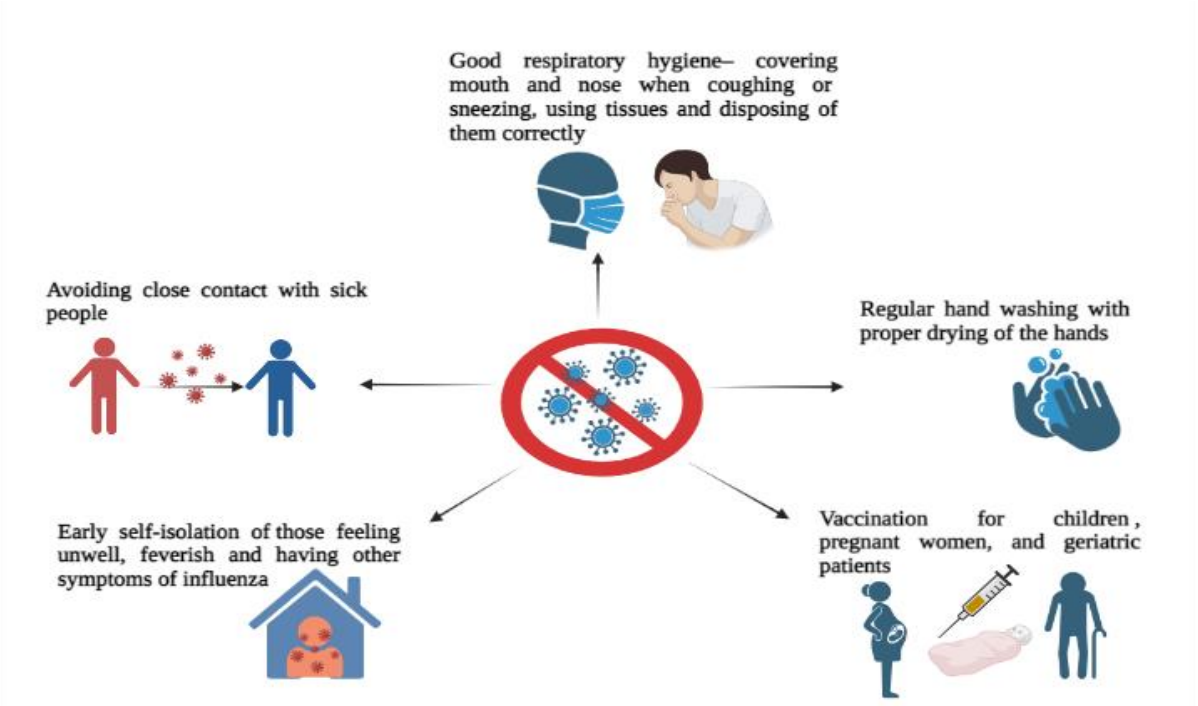

Fig. 1. Prevention techniques from the H3N2 virus.

Treatment for the H3N2 virus

Treatment with a neuraminidase inhibitor (NAI) is successful reduces the possibility of severe complications and death if initiated within two days of symptom onset, and in some cases even beyond that time (Muthuri et al., 2014; Alchikh et al., 2023). Oral oseltamivir might not be adequately absorbed in patients in the critical care unit with multi-organ dysfunction and poor stomach motility.

There are few intravenous (IV) antiviral treatment alternatives for children with severe and worsening influenza infection who already have failed five

days of oral oseltamivir treatment. IV peramivir has already been authorized in Japan, South Korea, as well as the United States (Birnkrant and Cox, 2009; Wester and Shetty, 2016). From 2010 to 2013, IV oseltamivir was accessible as a compassionate use program for adults and children older than one year (European Medicines Agency, 2011). From 2010 through 2019, the only IV option was IV zanamivir for compassionate use (European Medicines Agency, 2021). The EMA approved zanamivir (IV) in 2019 with a specific indication for severe influenza in adults and children over the age of six months. Within the pediatric population, there have been few investigations of peramivir, but even fewer studies of IV zanamivir.

In addition to antiviral treatment, other measures which can be included are proper rest, plenty of fluid intake, over-the-counter drugs for body aches and fever, oxygen therapy in severe cases, and hospitalization for individuals at higher risk for complications.

Limitations of the study

The limitation of the study is that mainly the recent articles on the subject discussed were assessed, and the older articles were given lesser priority which might have led to omission/bias.

Conclusion

The H3N2 virus outbreak has emerged as the most recent worldwide menace, prompting considerable anxiety and panic worldwide. This type of influenza has shown to be very hazardous and has inflicted substantial death in recent years. Because the H3N2 virus is highly infectious and propagates quickly, it isn't easy to contain. This has resulted in outbreaks throughout the globe, such as in the United States, Europe, and Asia. The H3N2 virus is a variant of the influenza A virus, which is recognized as causing severe disease and even death. When infected individual coughs or sneezes, respiratory droplets are released, and they can also be transferred by touching cotaminated surfaces. The H3N2 virus causes symptoms comparable to other flu strains, such as fever, cough, and body pains. The H3N2 strain, on the other hand, might be more severe and cause life-threatening consequences such as pneumonia. The global threat presented by the H3N2 virus pandemic has spurred healthcare officials to take preventative steps to halt the virus's spread. This includes greater surveillance, early identification, and rapid epidemic response. Vaccines have also been created to guard against the H3N2 strain, albeit their efficiency varies depending on the virus strain. Notwithstanding these measures, the H3N2 virus continues to pose a substantial threat, and sustained vigilance is required to prevent future outbreaks and preserve public health.

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Conflict of Interest Statement

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Ethical approval

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