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Letter to the Editor

# The re-emergence of H3N2 influenza: An update on the risk and containment

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*Dear Editor*

The menace of emerging and re-emerging infectious diseases has not been over yet. The potentially re-emerging infectious diseases from COVID-19 to mpox and others have caused significant global health crises over the past few years, the most recent being the H3N2 influenza viral infections. At least two people have succumbed to the H3N2 subtype of seasonal influenza in India, as confirmed by the Health Ministry confirmed as of March 10, 2023. So far, countrywide surveillance has found at least 451 confirmed cases of H3N2 this year.

Influenza viruses are of four types (namely A, B, C, and D) from which only influenza type A is capable of causing the pandemic. The influenza A virus has been known to cause seasonal flu disease in humans. There are subtypes based on two viral surface proteins: hemagglutinin (H) and neuraminidase (N). More than 130 influenza A subtype combinations have been identified in nature so far, but the virus reassortment, a process by which influenza viruses swap genetic information, makes many more subtypes possible, as per the U.S. CDC statement.

The H3N2 subtype appears to cause more hospitalizations than any other influenza subtype, as noted by the MoHFW in India. About half of all the inpatient sevre acure respiratory viruses (SARI) and outpatient illnesses displaying influenza-like symptoms seen in surveillance data collected between December 15, 2022, and March 10, 2023, were found to have H3N2 infections.

Infection by the H3N2 subtype of influenza A virus is manifested clinically with classic flu symptoms, including fever, cough, body ache, breathlessness, wheezing, and pneumonia. Seasonal influenza can also cause a severe cough lasting around two or more weeks, although most patients recover within a week without medical intervention. In severe infections, it can even lead to hospitalizations and need for an external oxygen supply. According to the WHO, pregnant women, children under five years of age, the elderly, individuals with chronic medical conditions like chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver, or hematologic diseases, and individuals with immunosuppressive conditions e.g. HIV/AIDS or receiving chemotherapy or steroids, or with malignancy, are at a greater risk of developing a severe form of flu, including that from the H3N2 subtype (WHO, https://www.who.int/news room/fact-sheets/detail/influenza-(seasonal). (see Fig. 1).

The progeny influenza virus differs from the parent virus due to the possibilities of gene assortment, antigenic shift, and drifts. In addition, it may have antigenic properties sufficiently different from the circulating strain to escape pre-existing acquired or induced immunity. It might rapidly overgrow and replace the current strain triggering a pandemic threat [1]. Aquatic birds are the natural reservoirs, while pigs serve as mixing vessels where different influenza strains may reassert, and cross the species barrier. Influenza virus has shown both zoonosis and zooanthroponosis, and present H3N2 infections in humans might be the result of zooanthroponosis from swine to humans.

WHO has recommended the use of oseltamivir (Tamiflu®) for H3N2 infection. The drug is availabe free of cost in India through the public health systems. Some drugs identified serendipitously may also be repurposed for influenza treatment in the current scenarios. The examples are Nitazoxanide, an anti-parasitic drug that selectively blocks the maturation of the viral glycoprotein HA; acetylsalicylic acid (ASA), an anti-inflammatory medicine that inhibits the release of infectious viral particles; and Naproxen, an inhibitor of inducible cyclooxygenase type 2. These drugs have been shown to display antiviral properties against a large panel of circulating influenza strains. In addition, the effect of doxycycline has been evaluated as a matrix metalloprotease inhibitor, which prevents influenza-associated pulmonary injury [2].

The surge of influenza cases has prompted the identification of potential sources of viral infection. A 2021–2022 vaccine-resistant influenza A (H3N2) 3C.2a1b.2a.2 subclade has been identified in wastewater in the elementary schools in Las Vegas, Nevada, USA, pointing towards the requirement of extensive public health surveillance at the community level and not to overlook the environmental factors in the era of pandemics [3]. According to experts, washing hands with soap and water is the best way to prevent infection from the H3N2 subtype. The government has also advised citizens to wear masks and practice social distancing to avoid infection.

Covering mouth and nose while sneezing and coughing, avoiding

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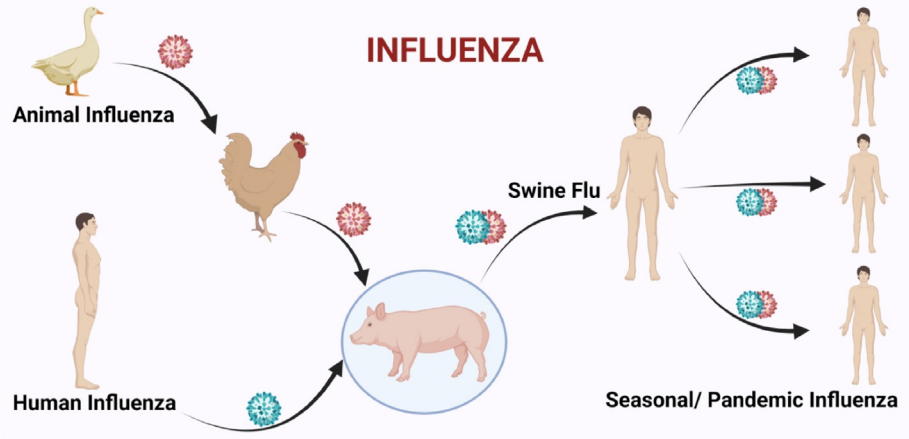



**Fig. 1.** An illustration showing the origin of different influenza from the pigs considered as a mixing vessel.

touching eyes and nose, and drinking fluids are other measures that can prevent H3N2 infection, as per the press release from the Health Ministry. The ministry has also advised against taking antibiotics or other medications without the doctor's consultation.

Vaccines have been, since antiquity, the effective mode of protection from diseases; however, in viruses like influenza, where the strain keeps changing its antigens due to adaptive pressure, the demand for an effective vaccine against the current circulating strain keeps changing. Still, there is some evidence to prove that the non-matching live attenuated influenza vaccine (LAIV) also showed significant protection based on the data obtained from 47 influenza seasons and 94,821 participants [4]. The nucleoside-modified mRNA-LNP may also be a promising alternative for egg-based influenza vaccines since these are not subjected to adaptive pressures [5]. Furthermore, a microneedle-based vaccine has also been developed using the dip-coating process. The vaccine administration causes the development of a cross-protective immunity in animal models against the H3N2 antigenic variants. However, the clinical trials have elucidated an insufficient number with a total of 25 clinical trials entered in the database, out of which eight clinical trials have been completed with results 13 clinical studies have been completed without any outcome, while 04 clinical trials are still under investigation. That shows how much clinical translation is still pending for the prophylaxis of the H3N2 virus infection.

As the threat of emerging and re-emerging infectious diseases looms globally including the recent H3N2 influenza, the impetus of the worldwide administrative, medical and research fraternity should be directed towards the trail of instant identification, effective vaccination and containment.

## Author contributions

**Priyanka:** Conceptualization; Data curation; Writing – original draft; Writing – review & editing. **Rekha Khandia:** Writing – original draft; Writing – review & editing. **Hitesh Chopra:** Writing – original draft; Writing – review & editing. **Om Prakash Choudhary:** Supervision, Writing – original draft; Writing – review & editing. **D. Katterine Bonilla-Aldana:** Writing – original draft; Writing – review & editing. **Alfonso J. Rodriguez-Morales:** Supervision; Writing – original draft; Writing – review & editing.

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Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

## Ethics statement

This manuscript does not contain any studies with animals performed by the author.

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## Declaration of competing interest

All authors report no conflicts of interest relevant to this article.

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