JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Letter to the Editor

Global concerns on the recent resurgence of influenza A variant viral infection in humans

Subrat Kumar[1], Ritesh Pattnaik[1], Basavaraj Mathapati[2], Rik Ghosh[1], Sugato Tripathy[3]

[1] *School of Biotechnology, KIIT Deemed to be University, Patia, Bhubaneswar, Odisha, India*
[2] *ICMR National Institute of Virology, Dibrugarh Unit, Dibrugarh, Assam, India*
[3] *School of Management, KIIT Deemed to be University, Patia, Bhubaneswar, Odisha, India*

Key words: influenza; pandemic; resurgence; variant.

J Infect Dev Ctries 2025; 19(5):797-799. doi:10.3855/jidc.20750

(Received 20 August 2024 – Accepted 09 January 2025)

Dear Editor,

Influenza is a respiratory illness caused by viruses belonging to the Orthomyxoviridae family. The genome of influenza viruses consists of a segmented single stranded negative sense RNA which encodes 11 proteins [1]. The Orthomyxoviridae family comprises of four influenza virus genera (A, B, C, and D) based on the differences in glycoprotein/nucleoprotein (NP) and matrix (M). Influenza type A viruses infect multiple hosts including humans, avians, swine, equines, and others; while influenza B and C viruses infect only humans [2]. Influenza A viruses (bird flu, swine flu) are further classified into 18 HA and 11 NA subtypes based on differences in the surface glycoproteins, mainly hemagglutinin (HA) and neuraminidase (NA) [3]. Since influenza A is a respiratory virus, it can spread among humans by direct contact with infected individuals, by contact with contaminated items, or by inhalation of aerosols laden with the virus. Studies suggest that aquatic birds like ducks, geese, and swans can act as natural reservoirs of influenza A viruses. Since the influenza A virus can infect different avian and mammalian hosts, it possesses tremendous zoonotic and pandemic potential.

Influenza epidemiology

Swine flu or influenza A (H1N2) viruses have been reported to be circulating in countries across the globe [4]. If a swine influenza virus strain (H3N2 or H1N2) circulating in swine is detected in humans, it is referred as a "variant" virus (with a "v" placed after the subtype of the virus, e.g., H3N2v or H1N2v). This terminology has proven significantly beneficial and is being implemented to distinguish these virus strains from the human seasonal influenza virus strain (H3N2). Based on several reports and studies, the World Health Organization (WHO) has adopted a similar terminology for categorizing non-seasonal influenza viruses that share subtypes with human seasonal influenza viruses. This is especially pertinent to strains of H1N1 and H1N2 subtypes found in swine, which are occasionally detected in humans [5]. For instance, a non-seasonal influenza A (H1N1) virus identified in a human would be labeled as A (H1N1)v, while a non-seasonal influenza A (H1N2) virus found in humans would be designated as A (H1N2)v [5]. Till date, influenza A (H3N2)v, A (H1N1)v, and A (H1N2)v strains have only caused sporadic human infections resulting in mild clinical illnesses; and there is no clear evidence of human to human transmission. Table 1 summarizes the influenza variant viruses that have caused infections in humans globally, from 2013 to 2023.

In August 2023, WHO announced a case of human infection with the variant subtype of influenza virus A (H1N2) in the United States, which was promptly notified by the United States International Health Regulations (IHR) [6]. Subsequently, WHO reported a human case of swine-origin influenza A (H1N1) variant virus in the Netherlands [7], followed by another human case of swine-origin influenza A (H1N2) variant virus infection in Great Britain and Northern Ireland [8]. Later reports indicated human infections with swine-origin influenza A (H1N1) variant virus in Brazil [9] and Spain [10]. In each instance, human infections arose from exposure to swine influenza viruses via contact with infected swine or contaminated surroundings. The patients developed respiratory illness following exposure and exhibited symptoms such as

fever, cough, sore throat, muscle pain, headache, shortness of breath, diarrhea, nausea, dizziness, and lethargy. The virus was subsequently confirmed by reverse transcription polymerase chain reaction (RT-PCR) testing.

Since then, there have been many reports of dissemination of influenza variant viruses from animals to humans and vice versa, resulting in sporadic outbreaks. Therefore, these viruses require continuous monitoring in order to establish their potential impact on public health [11]. Further, these novel influenza virus subtypes may acquire the ability of person-to-person transmission and undergo antigenic changes in the HA gene, threatening another influenza pandemic.

Control and diagnosis

Current measures to control the spread of this virus to humans include identification of circulating subtypes via constant surveillance, and annual vaccination before the onset of the flu season in every region. However, this is still hampered by many challenges. Swine influenza A viruses infecting pigs are antigenically distinct from human influenza A viruses; thus vaccines against human viruses will not provide protection against swine viruses. Currently there are no vaccines for influenza A (H1N2)v infections in humans and therefore human infections with these variant strains cannot be ignored [12]. The need of the hour is to develop an optimized vaccine composition that will elicit broad protection against antigenically diverse influenza strains.

Influenza A virus infections are diagnosed by detecting the presence of viruses (viral antigen or viral RNA) in upper respiratory tract specimens collected from nostrils, throat, or nasopharynx. Viral antigens can be detected by rapid antigen tests and by immunofluorescence tests, while nucleic acid testing assays such as RT-PCR can detect viral RNA [13]. Other laboratory techniques that are available for detection, identification, and characterization of the influenza A virus include virus isolation using cell culture or fertilized chicken eggs. Apart from these, serological assays such as hemagglutination inhibition, microneutralization, complement fixation, enzyme linked immunosorbent assay, and Western blotting are

Table 1. Global incidences of variant influenza virus infections in humans.

S. No	Year of detection	Type of variant strain (subtype)	Total number of cases	Total number of positive cases	Percentage of positive cases (%)
		H1(pdm09)	95,346		
1	2013	H1	13	33,795	20.19
		H3	71,949		
		H1 (pdm09)	78,853		
2	2014	H1	13	36,422	18.93
		H3	113,536		
		H1(pdm09)	37,791		
3	2015	H1	42	29,751	17
		H3	137,850		
		H1(pdm09)	143,493		
4	2016	H1	42	44,890	19.74
		H3	83,782		
		H1(pdm09)	49,158		
5	2017	H1	1	52,871	22.69
		H3	183,845		
		H1(pdm09)	130,881		
6	2018	H1	3	43,767	20.8
		H3	79,435		
		H1(pdm09)	197,968		
7	2019	H1	1	66,318	19.04
		H3	150,281		
		H1(pdm09)	66,517		
8	2020	H1	32	20,569	21
		H3	30,816		
		H1(pdm09)	3,264		
9	2021	H1	0	1,093	2.9
		H3	33,480		
		H1(pdm09)	50,555		
10	2022	H1	8	22,098	9.44
		H3	183,319		
		H1(pdm09)	238,372		
11	2023	H1	2	40,224	8.91
		H3	212,943		

The table lists the H1, H1pdm, and H3 variant cases reported globally; along with the total percentage of positive cases. The data was collected from the World Health Organization Flunet program [15].

typically used for detecting antibodies against the influenza virus [13].

The influenza A virus has a segmented genome, and can undergo genetic reassortment and antigenic shift to evolve into new subtypes with pandemic potential. Mutation in the HA antigen can become a challenge for detection, yielding false negative results. New generation assays are required to overcome this challenge. Constant genomic surveillance is the need of the hour to track the evolution of influenza viruses. With an increase in the population of humans, swine, and birds; and deforestation and transboundary activities; opportunities for exchanging the virus subtypes between species has also increased. Therefore, human infections with these novel influenza subtypes cannot be ignored.

Conclusions

WHO advises that travelers to countries experiencing animal influenza outbreaks should refrain from visiting farms, handling animals in live animal markets, entering slaughter houses, and touching surfaces that could be contaminated with animal secretions or excreta. Travelers should frequently wash their hands with soap and water and adhere to proper food safety and hygiene practices. The influenza virus evolves constantly, and WHO emphasizes that continuous and systematic global surveillance and sharing of virus material will help to understand the extent of influenza viruses circulating in various animal species. The IHR requires that all human infections caused by new subtypes of influenza viruses must be notified to WHO [14]. It is critical that influenza viruses isolated from animals and humans are fully characterized in appropriate reference laboratories and their pandemic potential is assessed, which will help in developing an effective vaccine candidate.

Corresponding author

Subrat Kumar, PhD.
Campus-11, Patia, Bhubaneswar, Odisha 751024, India
Tel: +91 674 2725732
Fax: +91 674 2725466
Email: Subrat_kumar@yahoo.com

Conflict of interests

No conflict of interests is declared.

References

1. Bouvier NM, Palese P (2008) The biology of influenza viruses. Vaccine 26 Suppl 4: D49–53. doi: 10.1016/j.vaccine.2008.07.039.
2. Abdelwhab EM, Mettenleiter TC (2023) Zoonotic animal influenza virus and potential mixing vessel hosts. Viruses 15: 980. doi: 10.3390/v15040980.
3. Kosik I, Yewdell JW (2019) Influenza hemagglutinin and neuraminidase: yin-yang proteins coevolving to thwart immunity. Viruses 11: 346. doi: 10.3390/v11040346.
4. Komadina N, McVernon J, Hall R, Leder K (2014) A historical perspective of influenza A(H1N2) virus. Emerg Infect Dis 20: 6–12. doi: 10.3201/eid2001.121848.
5. FAO, OIE, WHO (2014) Standardization of terminology for the influenza virus variants infecting humans: update. Available: https://cdn.who.int/media/docs/default-source/influenza/global-influenza-surveillance-and-response-system/nomenclature/standardization_of_terminology_influenza_virus_variants_update.pdf. Accessed: 10 October 2024.
6. World Health Organization (2023). Disease outbreak news; influenza A(H1N2) in the United States of America. Available: https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON482. Accessed: 10 October 2024.
7. World Health Organization (2023). Disease outbreak news; influenza A(H1N1) variant virus — The Netherlands. Available: https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON486. Accessed: 10 October 2024.
8. World Health Organization (2023) Disease outbreak news; influenza A(H1N2) variant virus infection — United Kingdom of Great Britain and Northern Ireland. Available: https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON496. Accessed: 10 October 2024.
9. World Health Organization (2024) Disease outbreak news; influenza A(H1N1) variant virus — Brazil. Available: https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON502. Accessed: 10 October 2024.
10. World Health Organization (2024). Disease outbreak news; influenza A(H1N1) variant virus — Spain. Available: http://www.who.int/emergencies/disease-outbreak-news-/item/2024-DON503. Accessed: 10 October 2024.
11. Low ZY, Wong KH, Wen Yip AJ, Choo WS (2023) The convergent evolution of influenza A virus: implications, therapeutic strategies and what we need to know. Curr Res Microb Sci 5: 100202. doi: 10.1016/j.crmicr.2023.100202.
12. Nelson MI, Gramer MR, Vincent AL, Holmes EC (2012) Global transmission of influenza viruses from humans to swine. J Gen Virol 93: 2195–2203. doi: 10.1099/vir.0.044974-0.
13. Burrell CJ, Howard CR, Murphy FA (2016) Laboratory diagnosis of virus diseases. Fenner and White's Medical Virology 2016: 135–154. doi: 10.1016/B978-0-12-375156-0.00010-2.
14. World Health Organization (2008) International Health Regulations (2005). Second edition. Available: http://www.who.int/ihr/9789241596664. Accessed: 2 April 2025.
15. World Health Organization (nd) FluNet. Global influenza program. Available: https://www.who.int/tools/flunet. Accessed: 11 October 2024.