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Survey of Highly Pathogenic Avian Influenza Virus (H5N1) and Its Reoccurring Threat: A Brief Review on Different Quails Worldwide

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ABSTRACT

This Review aims to understand the present status of influenza viruses and its epidemiology. The first case in India has been reported in the Dasarahalli village near Bangalore after six months of India's declaration that it is free from H5N1 and H5N8 from world organization for animal health. The recent controversy regarding outbreaks and cross-species barrier resulted in highly contagious infection with fatal outcomes, triggered menace all over India with remarkable economic consequences. Thus, we had reviewed epidemiology, virology, surveillance, transmission, detection, treatment and associated control measures to depict the current perspective of Influenza epidemic. We also studied different Quails and its comprehensive portal susceptible to influenza and in-depth genetic characterization of virus due to new viral mutant causing host-virus complications, virus mutation, and vaccination with its prompt administration as it is the urgency of the era. Addressing aspects of the epidemiology of the H5N1 and drug resistance genomic signatures infecting poultry and Humans helps to frontier our ability to minimize data gaps and maximize the better results of the available H5N1 studies.

Keywords: H5N1, Avian influenza viruses, Quail, Transmission, Detection

INTRODUCTION

The first avian influenza infection was recorded in Nandurbar and Jalgaon districts in Maharashtra, India during February 2006. The villagers were isolated from infected places and blood samples from 150 people showing symptoms of infection were sent to the National Institute of Virology, Pune, India (Mascarenhas, 2018). An episode of the exceedingly pathogenic avian influenza strain H5N8, which spread through Asia, Europe and the Middle East over the most recent years, has been accounted in India, as per the World Organization for Animal Health (OIE, Office International des Epizooties). Recently, India has reported in excess of 900 birds after it revealed an instance of approximately 942 birds at Humnabad, Bidar district of Karnataka, said by Karnataka health and family welfare department and its associated officials in India (Aiyappa, 2016). There has been no further outbreak reported in the country thereafter. But soon after it had reported outbreaks of highly pathogenic Avian Influenza Viruses (AVI) at various epicenters in Delhi, Gwalior (MP), Rajpura (Punjab), Hissar (Haryana), Bellary (Karnataka), Allappuzha and Kottayam (Kerala), Ahmedabad (Gujarat), Daman (Daman), Khordha and Angul (Odisha) during October, 2016 to February, 2017. India declared itself free from avian influenza (H5N8 and H5N1) from 6th June, 2017 and notified the same to OIE (Mohan, 2017). Once again, an outbreak of the highly contagious H5N8 bird flu virus that popped up in poultry birds in Dasarahalli village near Bangalore, after six months, India declared itself free of this virus by OIE (Mudur, 2018). Recently detected H5N8 is a mutant of earlier H5N1 and H7N7 viruses said by Department of Neurovirology, at the National Institute of Mental Health and Neurosciences (NIMHANS). The episode is a reoccurrence of the H5N8 avian influenza strain. The infection was detected after nine birds died out of 951 susceptible birds. The remaining 942 birds were killed as

reported by OIE. Therefore, a wellspring of the episode stays uncertain at this stage, for recent worldwide look up, Saudi Arabia's capital city, Riyadh, has effectively detailed four instances of the avian strain H5N8. Iraq was compelled to win now 43000 chickens, following episodes of the same avian flu strain. Also, the Russian military was brought in to Kostroma Oblast to manage the result of biggest H5N8 avian influenza flare-up in the district, which culled six lakh chickens (Vorotinkov, 2018).

Figure 1. Highly pathogenic avian influenza viruses outbreaks as reported in start of 2018 in domestic bird's subtypes of different regions like Asia: H5N1, H5N2, H5N3, H5N6, H5N8, H7N9; Africa: H5N1, H5N2, H5N8; Europe: H5N1, H5N2, H5N5, H5N6, H5N8, H5N9, H7N7; America: H5N1, H5N2, H5N8, H7N3, H7N8, H7N9; Oceania: H7N2 (world organization for animal health, 2018)

Epidemiology and Genotypic characteristics of the influenza virus

Eastern region of India has experienced continual outbreaks of H5N1 HPAI virus since February 2006 particularly in the states of Maharashtra, Gujarat and Madhya Pradesh. Subsequently, the outbreaks of the HPAI were reported from the states Manipur, Assam, Sikkim and West Bengal (Murugkar et al., 2008). Since then repeated outbreaks of the HPAI have been reported in the states West Bengal, Assam and Tripura (Nagarajan et al., 2009; Nagarajan et al., 2012)

Aquatic wild birds are the natural reservoir of influenza viruses (Slemons, et al., 1974, Hinshaw, et al., 1980, Webster, et al., 1992, Alexander, 2000). AIV predominantly replicate in the gastrointestinal and respiratory tracts of the Quails and are excreted from the oral cavity, nostrils, conjunctiva, and cloaca of infected birds (Swayne, et al., 2008). AIV belongs to the family *Orthomyxoviridae* and the genus influenza virus A (Palese, 2007). These have negative sense, single stranded and segmented RNA genome with eight segments of gene encoding for at least ten Proteins Namely Polymerase Basic 1 (PB1), PB2, Matrix 1 (M), M2, Polymerase Acid (PA), Haemagglutinin (HA), Nucleoprotein (NP), Neuraminidase (NA), Non-Structural (NS1and NS2). These NA and HA have a role in virus infectivity and type of surface glycoproteins. The HA protein attaches to the host cell with the help of virus and also a significant target of the humoral immune responses (Chen et al., 2018). NA removes sialic acid from glycoproteins and thus helps to increase and spread of progeny virions. Low Pathogenic Avian Influenza Viruses (LPAIVs) contain an HA cleavage site and can be cleaved by proteases which resides in intestinal and respiratory tracts (Alexander, 2007). Highly Pathogenic Avian Influenza Virus (HPAIVs) causes systematic infection and high mortality in chickens and other terrestrial poultry like ducks,waterfoels in correspondence to their subtype of HPAIVs. Two subtypes namely H5 and H7 of LPAIVs can naturally switch to a highly pathogenic phenotype by the process of spontaneous acquisition of a multibasic cleavage site during circulation in poultry (Kawaoka et al., 1985; Webster et al., 1989; Horimoto et al., 1995). Avian and Human viruses preferentially bind to sialic acid linked to galactose via an α2-3 linkage (SAα2, 3Gal) and galactose via an α2-6 linkage (SAα2, 6Gal), respectively (Kumlin et al., 2008). The Receptor Binding Site (RBS) is located at the distal membrane end of each HA monomer and essential amino acids for host determinant are in the residues 222 and 224 in the HA of H5 (equivalent to residues 226 and 228 in the HA of H2 and H3 (Kawaoka et al., 1985; Webster et al., 1989; Connor et al., 1994; Horimoto et al., 1995). Avian influenza viruses H5N1 (Yuen et al., 1998), H9N2 (Cheng, et al., 2011), H7N7 (Banks, et al., 1998), H7N3 (Tweed et al., 2004) and H10N7 (Arzey et al., 2012) had jumped species barriers and caused Human infection. Among these, H5N1 exhibits the property of most virulence, having mortality rate of approx. Sixty percent causing havoc situation worldwide. Influenza viruses do not cause infection in Humans, but influenza A (H7N9) and A (H5N1) virus strains tend to cause severe infections among people. This H5N1 has been linked with direct or indirect means by infected/dead poultry. It has seemed to cause infection in approximately all age group of individuals. Likewise in pandemic influenza, adolescents and young adults are disproportionately affected (Miotto et al., 2010; Fiebig et al., 2011; Zhang et al., 2011). Consumption of raw duck blood is suspected for some cases of Human H5N1 virus infection (Gambotto et al., 2008) and this mode of transmission is compatible with studies in mammals that intragastric inoculation of the

H5N1 virus can lead to systemic dissemination via the lymphatic's and venous route (Shinya et al., 2011). The H5N1 virus could be detected in preserved poultry in freezing condition and contaminated eggs, although transmission into the Humans through these food items routes has not been yet recorded (Harder et al., 2009). All pandemic or seasonal epidemic Human influenza viruses have a preferential binding for a2, 6 SA, which is predominant in the upper respiratory tract in Human and might be served as a precursor for efficient Human-to-Human transmission (Imai et al., 2012). Secondly, in addition to the host cell surface receptor requirement, the avian- and Human-adapted influenza viruses also have different importin-α isoform requirements (Gabriel et al., 2011). Finally, mutations that are responsible for Human adaptation seem to be unstable in H5N1 viruses (Miotto et al., 2010). To date, just the H5 and H7 subtypes have been ended up being HPAI infections, not all H5 and H7 infections are HPAI infections (Senne et al., 1996; Alexander 2007; Abdelwhab et al., 2011). In any case, LPAI H5 or H7 infections may move toward becoming HPAI infections because of changes that happen after the disease of poultry (Alexander, 2007).

H5N1 Outbreaks status

The epidemiology of avian influenza is complex. The virus continually evolves, the behavior of each new subtype (and strains within subtypes), the risks they present can vary in different countries. The epidemiology of AIV for the past thirteen years was characterized by two main global panzootics (Gao et al., 2018). The first panzootic wave started in 2004 peaked up in 2006, and progressively increase the virus activity which somewhat slows down in 2012. The Asian lineage shoes a remarkable continuation in its spread from countries in Asia and Africa in poultry and wild birds. The virus has become enzootic in Asia and Africa and continues to cause outbreaks in poultry and sporadic Human infections. Since 1997, an exceptionally pathogenic avian influenza virus of the H5N1 subtype had caused abundant episodes in poultry in Southeast Asia (Li et al., 2004; Chen et al., 2006; Smith et al., 2006) and have the range to more than 60 nations turned out to be more pathogenic in mammalian species (Chen et al., 2004; Maines et al., 2005). These flare-ups caused approximately fifty percentage of transmission from HPAI H5N1 to people. An occasionally refreshed timetable of H5N1 flare-ups can be found at as of February 2018, eight hundred sixty Human infections have been reported to WHO from sixteen countries and territories. All cases of H5N1 infection occurs due to its close contact with infected live/dead birds in H5N1 contaminated environment. The objective of this review is to provide a historical background of HPAI epidemiology from 2015 till present to provide context to the current situation and consider what might happen next (Table 1).

Disease transmission and its global distribution

The Northern Hemisphere winter season is mainly associated with an increased risk for AIV. New and reoccurring outbreaks of HPAI H5N8 and H5N6 in Asia, Europe, and the Middle East as observed in the 2017-2018 perspective. The zoonotic AIV that had been detected in China (H7N9 and H5N6) and some parts of Africa and Asia (H5N1), proved to cause the most significant public health risks. During the period January 2013 – January 2018, twelve different influenza A subtypes were reported by OIE 2018 (Adlhoch et al., 2018). Europe reported the highest virus diversity (seven subtypes), followed by Asia and the Americas (six subtypes each), Africa (three subtypes), and Oceania (one subtype) by OIE 2018 (Adlhoch et al., 2018). Subtypes H5N1, H5N2 and H5N8 were the most geographically widespread and commonly reported (Figure1).

Highly pathogenic avian influenza A (H5N1) virus had caused approximately 1,000 Human infections since the first case was reported in 1997 (overall case-fatality rate 54%) (Abubakar et al., 2016). The highest cumulative number of confirmed Human cases was reported in Egypt (Abdelwhab et al., 2016). This virus has been detected in poultry and wild birds in more than fifty countries worldwide and the virus is now epizootic in Bangladesh, India, China, Egypt, Indonesia and Vietnam.

Current Situation: Human H5N1 infection globally

According to reports received by the OIE, various influenza A (H5) subtypes continue to be detected and examined in birds of Africa, Europe and Asia. However, these Influenza A (H5N6) viruses are different from the A (H5N6) influenza viruses that have infected Humans in China (OIE, 2018). In the past five years, total of 1567 Human cases of H7N9 reported globally. Since March, 2014, there were 19 Human cases of avian influenza A (H5N6) reported globally and all occurred in Mainland, China (Hui et al., 2017). From 2011 to 2016, 10 to 145 confirmed Human cases of avian influenza A (H5N1) were reported to WHO annually. In 2017, there were three cases in Egypt and one case in Indonesia, WHO 2018 (Benitez, 2018). The latest case was reported on

September 27, 2017 by AIV report 2018 where avian influenza A (H7N4) virus was reported with one laboratory-confirmed Human case infection as reported to WHO. During January 26 to March 2, 2018, new Human infections with avian influenza A (H7N4), (H7N9) and (H9N2) viruses were reported (WHO, 2018). Thus, overall perspective to be depicted in Figure 2 for cumulative number of confirmed Human cases for avian influenza A (H5N1).

Reconnaissance in different quails

Quail (*Coturnix* spp.) had attracted and kept in attention because the internal genes of the H5N1 HPAI viruses detected in Hong Kong during 1997 showed quite a similarity to those found in an H9N2 virus in Quail (Guan et al., 1999). This finding may be suggested as a possible threat for this type of species in the evolution of the Hong Kong/97 genotype HPAI virus. Quail was also among the first avian species here it as reported that higher quantities of influenza virus could be excreted through the respiratory tracts as compared to faeces, as compared to earlier reports with AIV in aquatic avian species. H5N1 outbreak has been reported in many countries, mainly in Indonesia and Vietnam (Peiris et al., 2007). Practically, Quails are more prone to infection with H5N1 HPAI viruses (Perkins et al., 2001). Thus, they are no longer allowed to sell Quail in live and backyard poultry markets in Hong Kong, they can be the potential reservoir of other influenza viruses that could be linked with H5N1 viruses and its subtypes. From previous literature, quail also played a significant role in the supportive growth of swine influenza viruses (Makarova et al., 2003). Quails refer to 130 species of small, short-tailed game birds of the family Phasianidae (order Galliformes), resembling partridges but generally more modest and less robust. Common quail species include Bobwhite (*Colinus virginanus*), Chinese Painted (Button) Quail (*Coturnix, Excalifactoria chinensis*), Coturnix (*Japanese* or *Pharaoh*) Quail, Gambel's Quail (*Callipepla gambelli*), Mearns Quail (*Cytonyx montezuma*), Mountain Quail (*Oreortyx pictus*), Scaled Quail (*Callipepla squamata*), and California Valley Quail (*C. californica*) (Kennedy, et al., 1980). Old world migratory Quails (genus *Coturnix*) are classified by morphology and territorial range into their subspecies, range varies from one another as listed in IUCN Red list 2017. The European quail (E quail), also called common or wild quail, is a partial migrant whose breeding range extends from the Atlantic to Lake Baikal and from the Arctic Circle to the tropics (Del Hoyo et al., 1992). The Japanese quail (J quail) (*Coturnix c. japonica*), also called domestic quail, found in the wild in Asia (Barilani et al., 2005) best known for its domestic form in Europe, Asia, North America, and India where it is generally ranged in outdoor game farms for restocking and hunting purposes (Slota et al., 2011) as well as for meat and egg production (Mills et al., 1997).

Quails are susceptible to infection having several subtypes including both mammalian and AIVs (Figure 3). It served as one of the intermediate hosts, pushing up the generation of newly reassortment AIVs having remarkable potential to cause infection among Human (Thontiravong et al., 2012). The quail is a land-based bird commonly raised by Humans worldwide. Previous study showed that Quails can naturally be infected with various influenza subtypes as in avian, Human, swine origins such as H3, H4, H5, H6, H7, H9 and H10 subtypes, altogether with Human H1N1 and sine H3N2 influenza viruses (Liu et al., 2003; Nfon et al., 2011). Only viruses of the influenza virus A genus have been isolated from birds and termed AIVs, but viruses with all sixteen HA (H1-H16) and all nine NA (N1-N9). Quails are more susceptible than chickens to cause infection, and generation of recombinant H9 viruses by reverse genetics showed that changes in the HA gene are quite sufficient to initiate efficient replication mode and transmission in quail (Perez et al., 2003). Several finding suggested that quail supports an environment where in the adaptation of influenza viruses from ducks generated novel variants , which helps to cross the species barrier (Perez et al., 2003). Since the first reported case of avian influenza in J quail in Italy (1966–1968), influenza viruses of several subtypes have been isolated from quail in North America, Europe, and Asia through periodic surveillance and sporadic outbreaks (Guo et al., 2000, Suarez et al., 2000; Yee et al., 2011). J Quails may provide an optimal environment for the adaptation of wild bird AIVs, generating novel variants that can cross the species barrier to domestic poultry and Human beings. Infected birds showed neither clinical signs nor mortality. Virus isolation and real-time RT-PCR confirmed the presence of the H9N2 virus in cloacal swab samples collected at 35 days of age and the absence of other AIV subtypes, including H5 and H7. AIV was recovered from the internal contents of eggs, including a mixture of albumen and allantoic fluid, and from the oviduct of naturally infected J quail flocks in the southern part of Thailand.

Table 1. Latest report of highly pathogenic avian influenza virus's outbreaks in various global regions pandemic to poultry, migratory birds' species and Human's cases since 2015 to 2018 from worldwide

Global distribution	Regional distribution	Year	Culled birds/chickens (poultry to poultry transmission) (in numbers)	Avain influenza viruses subtypes	Human cases (poultry to Human transmission)
India perspective (Orissa, Telangana, Tamil Nadu regions, Maharashtra border districts, Delhi , Madhya Pradesh, Uttar Pradesh mainly Lucknow, on high alert since 2016 for H5N8/H5N1)	Bangalore	2018	942 cases	H5N8 / H5N1	No cases
	Maharashtra	2018	900 cases	H5N1/H7N9	150 cases show medical complications
	Ahmedabad	2017	1,50 cases	H5N1	No cases
	Telangana	2015	2 lakhs	H5 strains	No cases
	Manipur	2015	1,000	H5 strains	No cases
	Tripura	2016	8,500	H5 strains	No cases
Worldwide perspective (most of the countries Europe, Africa regions, Asia, Americas etc. for H5 and H7 serotypes)	China	2018	26 million	H7N9/H7N4	79 people died
	Netherlands	2018	230 cases	H5N6	1 people died
	Northwest provinces Madibeng and Macquarie Hills	2018	3 cases	H5 strain	No cases
	Japan	2017	310,000	H5N6	No cases
	South Korea	2017	12,300	H5 strains	No cases
	Japan's Gifu	2017	80,000	H5 strains	No cases
	Philippines	2017	470,000	H7N9	34 cases susceptible
	Bangladesh	2017	2,268	H5 strains	No cases
	Paris	2017	10,000	H5 strains	No cases
	South Africa	2017	260,000	H5N8	No cases
	Ireland	2016	550 cases	H5N8	No cases
	South Arabia	2018	38,000	H5N8	No cases
	North Holland	2018	230	H5N6	No cases
	Mexico	2018	539	H7N3	No cases

Transmission among different Quails and their comparative study: its viral shedding and bodily symptoms

Quails exhibited a high susceptibility to both HPAIV, as demonstrated by severe clinical signs and high mortality rates with its phenotypic characterization and its detailed information as depicted in (Table 2). Quails carry receptors of sialic acid with the potential and ability of binding of avian and Human influenza viruses hence, serving as an intermediate host for the zoonotic transmission of influenza viruses (Wan et al., 2006).The overall combination of gallinaceous species J. quail (Jeong et al., 2009; Saito et al., 2009). European quail (*Coturnix c. coturnix*) (E. quail) can be considered efficient shedders of HPAIV. With the earliest onset, the most rapid progression of the disease, and shortest in H5N1/HP-infected quail, it is apparent that this virus is more virulent for this species than the H7N1/HP. Quails have been proposed to be an intermediate host of influenza A virus. The pathogenicity, virus shedding, and transmission characteristics of pH1N1, swine H1N1, and avian H3N2 (dkH3N2) influenza viruses in Quails were examined in various studies E. quail may share with J. quail its potential as an intermediate host and reservoir of AIV. With the earliest onset, most rapid progression of the disease, and shortest MDT in H5N1/HP-infected quail, it is apparent that this virus is more virulent for this species than the H7N1/HP (Spickler et al., 2008). High level of pathogenicity were observed for both HPAIV corresponding with natural and experimental H5N1 HPAIV infections in chickens and other gallinaceous species, most importantly observed in J quail (Perkins et al., 2001; Jeong et al., 2009; Bertran et al., 2011). Previous studies reported minimal clinical signs or even sudden deaths without apparent symptoms in J quail (Perkins et al., 2001; Jeong, et al., 2009; Saito et al., 2009). Clinically neurological dysfunction was an evident sign in most of the HPAIV-infected quail of the present study. Certain gross findings indicative were not as extensive and obvious as for chickens (e.g., the presence of edematous, hemorrhagic, and necrotic cutaneous lesions), but affected tissues were known target organs for influenza A viruses in other gallinaceous species, including J quail (Perkins et al., 2001; Antarasena et al., 2006; Jeong et al., 2009; Saito et al., 2009; Bertran et al., 2011). Effective viral transmission from inoculated Quail

to naive contact birds was confirmed for the past studied viruses, even though their origin, avian hosts were as diverse as chicken, mallard, and great crested grebe. This finding suggests that adaptation may not be needed to allow AIV to replicate and transmit in E quail, confirming the substantial role that this species may play in AI epidemiology. As in previous work with H5N1 HPAIV in J Quail (Jeong et al., 2009), both HPAIV used in for study confirmed to be able to transmit among E quail. The HPAI H5N1 strains tested so far are all pathogenic in chickens (Hikono et al., 2013; Lee et al., 2013) and J Quails (Makarova et al., 2003; Isoda, et al., 2006; Jeong et al., 2009; Yamada et al., 2010). Chinese painted Quails are superior to that of chickens and J Quails due to their ease of handling, general care, hardiness, excellent reproductive performance, and less expensive maintenance (Tsudzuki, 1994). Chinese painted Quails is extensively used for vaccine studies with HPAI H5N1 viruses which requires enhanced biosafety level 3 conditions and provides an effective opportunity for the inclusion of the birds in appropriate numbers and groups for the experiments to achieve better scientifically remarkable and acceptable outcomes. Viral transmission among these birds like LPAIV probably occurs through the oral-oral route (Jeong et al., 2009; Saito et al., 2009; Sun et al., 2011; Bertran et al., 2013). Some HPAIV-infected gallinaceous birds, like E. quail may shed virus at high concentrations before the appearance of clinical signs and/or death. Therefore, spreading disease into the wild by releasing apparently healthy farm reared birds for hunting purposes could represent a substantial threat, which highlights the need for effective surveillance programs among these species. Projects undergoing discussed in table 3.

Table 2. Quails infected with highly pathogenic avian influenza viruses and its elaborative information

Quails more susceptible to highly pathogenic avian influenza viruses	**International Union for Conservation of Nature Red List by Birdlife international year 2016**	**Affected Place (year)**
Japanese quail *(Coturnix. coturnix japonica)* Temminck & Schlegel, 1849	Near threatened list	Hong Kong (1997)
European quail *(Coturnix. coturnix coturnix)* Linnaeus, 1758	Least concern list	Italy (1999), Spain (2009)
Bobwhite quail *(Colinus viriginainus)* Linnaeus, 1758	Near threatened list	Hong Kong (1997)
Chinese painted quail (Cotunix chinensis/Synoicus chinensis) Linnaeus, 1766	Least concern list	London (2006)

The references: Bertran K et al., 2013; Sarkadi et al., 2013; Perkins and Swayne, 2001

Table 3. Quail conservation programs undergoing worldwide

Name of the program for *Q*uail species	**The aim of the project**	**Country**	**Year**	**Land area under usage (acre)**	***Quail variety***	***Q*uail survey**
Unique restoration project by Denise Attaway, Forestry and Life Sciences; Public Service and Agriculture, 2018	Habitat restoration	New Jersey	2018	40,000	Northern Bob white *Quail*	320 Bob white (target 500 birds)
			Till 2015	16,000		117
Quail forever (commonly known as One stop shop)	Quail conservation	Texas	2018	17 million	United states naïve *Quail species*	13,000 habitat projects across the nation

The reference: Ammoland Inc. 2018

Virology and virulence factors

Gross observation and comparative study of the phylogenetic relationship of different types of AIV strains. The morphology of influenza A (H5N1) is essentially that of an orthomyxo virus as it's far a subtype of the kind A influenza virus. The typical virion is enveloped, round (100 nm), with a nucleocapsid of helical symmetry surrounding a minus sense, unmarried stranded eight segmented RNA. The envelope is internally covered by way of a matrix protein (M) and externally with glycoprotein peplomers-rod formed HA which might be homotrimers of sophistication I membrane glycoproteins and mushroom-shaped NA molecules which might be tetramers of a class II membrane protein. The H5N1 viruses acquired enhancedbird-to-Human transmissibility by (1) altering amino acids in HA that enable

bindingaffinity to Human-type receptors, (2) loss of the glycosylation site and 130 loops in the HA protein and (3) mutation of E627K in the PB2 protein to enhance viral replication in mammalian hosts (Kim, 2018). The genetic analysis of the virus HA suggested that the virus prefer to bind α (2–3)–linked sialic acids present in avian species. Adult Humans have a preponderance of α (2- 6)–linked sialic acids located in their upper respiratory tract, and H5N1 virus disease. Thus, the virus gains access to the alveolar epithelium where α (2-3)–linked sialic acids are present. It has been reported that young children differ in this respect and have a preponderance of α (2-3)–linked sialic acids in their upper respiratory tract (Short, et al., 2015).Vaccination in Human is still in the testing phase. Human studies have shown that antibodies against HA and NA could be able to elicit by vero cell and insect cell-derived vaccines (Ehrlich et al., 2008; Khurana et al., 2011). Phylogenetically informative amino acid positions (PIPs) were identified in influenza A NA of subtypes N1 and N2. NA evolves in a lineage-specific way as the virus adapts to a new host or changes to evade the host's immune system. Thus, deep study of viral genetic constituents may come out as a positive outcome for the present day perspective, if occurs due to the environment or genetic mutation as described in Figure 4 and 5. The surface proteins of influenza viruses, NA, plays anessentialrole in virulence, host specificity, and the Human immune response (Thomason, et al., 2012). Recent observations suggest that the potential role of quail (*Coturnix coturnix*) as intermediate hosts in the interspecies transmission of influenza viruses has been underestimated (Liu et al., 2003) and reported the isolation of a Human influenza A virus from the trachea of the quail.

Modes and detection

Several epidemiologic researchers have evaluated the danger of transmission of HPAI from poultry to people. These studies have identified several substantial chance factors that may be related to infection along with near direct touch with a rooster and oblique transmission through environmental infection. Direct routes of bird-to-Human infection of H5N1 can also encompass touch with aerosolized virus, infected blood or physical fluids via meals, education practices (e.g., slaughtering, boiling, defeathering, reducing meat, cleansing meat, eliminating and/or cleansing inner organs of hen), consuming uncooked products, or through the care of birds (both commercially or regionally). H5N1 transmission is progressively increasing day by day although, recent studies have cautioned an association between exposure to the contaminated surroundings (e.g., water, cleaning rooster cages or their specific areas, the usage of poultry faeces for fertilizer (Indriani et al., 2010, Gutiérrez et al., 2012) and disease through either ingestion or conjunctival or intranasal vaccination of defiled water and soil. Poultry markets have additionally been appeared to be a potential wellspring of H5N1 flow in poultry and disease source to people (Mounts, et al., 1999, Wang, et al., 2006, Abdelwhab, et al., 2010, Indriani, et al., 2010, Negovetich, et al., 2011, Samaan, et al., 2011). Because birds are known to shed high concentrations of the virus into water sources, transmission from poultry to Humans through contaminated water is also possible.

H5N1 RNA can be detected in the spleen, and can be cultured in the cerebrospinal fluid of infected Humans (De Jong et al., 2005). Currently, antigen detection by rapid immune chromatographic assays or direct immunofluorescence and nucleic acid detection by RT-PCR provides a quick diagnosis, which guides immediate management. In contrast, viral culture and serology allow for retrospective diagnosis, which is essential for epidemiological studies. Respiratory tract specimens are the best samples for detecting the virus, although the virus can also be found in blood or rectal swabs (De Jong et al., 2006). RT-PCR, HA restraint with horse red platelets as a corroborative test and DNA sequencing can prove to be helpful for detection purposes. Such testing ends up imperative when the poor inspecting system, poor example quality, or different issues discount segregation of the infection or block the utilization of PCR-based tests. The sequences of the primer sets defined in advance for PCR-primarily based detection of deadly disease may be suitable for the detection of virus traces presently circulating in Human beings (Claas et al., 1992; Claas et al., 1993; Cherian et al., 1994; Atmar et al., 1996) but display considerable numbers of mismatches when they are compared with the sequences of animal influenza A viruses. Many approaches still to come on the right path as an introduction from the US Centers for Disease Control and Prevention demonstrating many awareness programs in demonstrative testing, including lab affirmation of H5N1 contaminations given serological tests.

Bodily symptomatic and diagnosis

In contrast to Human seasonal influenza viruses, H5N1 viruses are more likely to cause severe pneumonia. In addition to pulmonary disease, H5N1 virus infection also leads to extra pulmonary manifestations more often

than infections caused by pandemic influenza viruses (To et al., 2010). Elevated creatine kinase is also common, but true rhabdomyolysis has not been described. The higher virulence of the H5N1 virus, which leads to a high pulmonary and extrapulmonary viral load, together with its intrinsic pro-inflammatory property, often causes a cytokine peak in these patients. Other common laboratory abnormalities included leucopenia, lymphopenia, thrombocytopenia and impaired coagulation profiles (Yuen et al., 1998). Serial specimens of CSF, nasopharyngeal aspirate (NPA), rectal swab, stool, urine, plasma, and serum were tested by real-time quantitative RT-PCR (qPCR) targeting M gene for influenza A virus and the HA gene for the H5N1 virus. Some case reports of H5N1 infections reported for manifestations of central nervous system (CNS) disease (Mak et al., 2017). Previous studies have indicated that chemokine levels were higher in fatal rather than nonfatal patients with H5N1 disease (De Jong et al., 2006). This amino acid substitution has been shown to increase the replication and pathogenicity of avian H5N1, H9N2, and H7N9 viruses in mammals in a manner analogous to previously reported mammalian adaptation signatures E627K and D701N (Mok et al., 2014).

Treatment and preventive strategy

Several antivirals in development have targeted important parts of the viral life cycle. Nucleozin, a NP inhibitor, has potent *in vitro* and *in vivo* activity against the H5N1 virus in a mouse model (Kao et al., 2010). The neuraminidase inhibitors oseltamivir or zanamivir are the mainstays of treatment for H5N1 infection (Table 4). Zanamivir is usually administrated by oral inward breath. Intravenous zanamivir, which was effectively utilized for Human during the 2009 H1N1 pandemic, is compelling against H5N1 infection disease in a macaque model (Stittelaar et al., 2008). Oseltamivir used as prophylaxis and orally controlled to people >1 yr. of age up to 10 days after a definitive exposure as reported (75 mg/d for grown-ups and 35 mg/d for youngsters). People are showing symptoms and manifestations of influenza, oropharyngeal swab examples were gathered and inspected at the national Influenza focus by using real-time RT-PCR (Farah et al., 2018). Determination of new immunization against infections (Farah, et al., 2018). Selection of new candidate vaccine viruses (CVVs) for zoonotic influenza causing pandemic was made during a recent WHO consultation. Various WHO authorities in collaboration with other centers for the overall epidemiology, its regulation and control situated all over the world (Figure 6). Currently, use of live attenuated influenza vaccines in poultry is not recommended by the OIE because of the ability danger of reassortment or transformations for producing AIV. Undoubtedly, the best immunization program to be brought upon, the segment infection should be observed for antigenic changes, and the antibody should be analyzed against new versions or at the very least the immunization should be re-assessed each 2– 3 years against currently circulating field viruses (Swayne et al., 2014). Nowadays, H9N2 detaches from quail have demonstrated antigenic buoy (Alderton 1992; Kandeil et al., 2017).

The antigenic relatedness of various sub-lineages needs further examination to select suitable vaccine strains. It can also be beneficial to reduce inter-governorate inter-regional movements associated with poultry trade through the promotion of regional trade to prevent the spread of AIV (Elmasry et al., 2017). The Food and Agricultural Organization of the United Nations has also recommended implementing a policy of not exchanging or carryover of animals (i.e., housing the same animals in the marketplace for multiple days), which improves live-market strategy to reduce AIV exchange.

Table 4. Collectively data set of influenza viruses for detection, diagnosis and treatment.

Subtypes combination detected	Antiviral drugs		Lab detection methods	Surveillance authority
Haemagglutinin (17 subtypes) and neuraminidase (10 subtypes) surface proteins.	Adamantanes, amantadine, rimantadine (currently not recommended for use due to widespread resistance)	Neuraminidase inhibitors, oseltamivir and zanamivir, developed in the 1990s, are effective against both influenza A and B viruses, and are widely available.	Genotypic assays and phenotypic assays	World Health Organisation Global Influenza Surveillance and Response System, World Health Organisation Collaborating Centres and some national influenza centres, World Health Organisation Expert Working Group on Surveillance of Influenza Antiviral Susceptibility

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CONCLUSION

In people, plenty latest studies have targeted at the factors that are responsible for the pathogenicity and transmissibility of the H5N1 virus. A few lines of confirmation recommend vital parts for the polymerase qualities. However, no single quality has yet been succeeded nor can the distinctive age profile of this disease be adequately explained at present. Notwithstanding, data about these infections and their related study of disease transmission in the locale is rare. Due to the lack of resources, early detection is one of the major problems in the developing countries. In affluent countries, detection is generally delayed due to the lack of awareness. Analysis of the viral genome with its virulence affecting pathway allows the scientific community to identify virulence determinants but proved to be little impact on a clinical level. Despite antiviral discovery and treatment procedures, many patients are still struggling to cope up with the viral disease and its associated symptoms. Since the introduction of neuraminidase inhibitors for more than 10 years back, no new antiviral that is active and capable of resisting outbreaks against the influenza virus have been yet approved. Many preventive strategies like proper vaccinations are effective in limiting H5N1 virus transmission in poultry but can prove more beneficially if limiting cross-species spread into poultry farms and the lack of cross-protection between different clades or subclades. Despite aggressive and triggered control measures in this particular area, sporadic Human H5N1 infections still occur, highlighting the need for high vigilance, especially when encountering patients who have poultry contact or have visited a poultry market. Despite worldwide surveillance, various schemes launched by the government regularly, periodically launching reported perspective timely into different avian linked sites and aggressive strategies to eliminate the H5N1 virus instead this virus continues to cause fatal outbreaks in both the avian and human population and causing havoc situation all over the world so on and so forth. The viruses can be evolved, generating many subclades with potentially enhanced virulence factors and remarkable transmissibility. Productive epidemiological observation frameworks are required additionally to permit the opportune distinguishing proof of new these infections presented in the Indian locale. It is essential to amplify local endeavours for the early discovery of AIVs in both nearby and transitory untamed life and to keep up biosafety and biocontainment boundaries to counteract disease in poultry.

DECLARATIONS

Author's contribution

Dr Vijay Laxmi Saxena has provided the conception and framework designing of the research article. Roshani Gupta and Khushboo Arya have involved in the data collection and analysis part. All the authors have contributed to drafting and critical revision of the article.

Competing interests

The authors have no conflicts to declare.

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