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REVIEW ARTICLE

Avian influenza revisited: concerns and constraints

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Abstract Avian influenza (AVI) is being known for its pandemic potential and devastating effects on poultry and birds. The AVI outbreaks in domesticated birds are of concern because the Low pathogenic avian influenza virus (LPAI) tends to evolve into a High pathogenic avian influenza virus (HPAI) resulting in the rapid spread and significant outbreak in poultries. The containment should be rapid and stringent precautions should be taken in handling the infected poultry cases or infected materials. In general, AVI viruses do not replicate efficiently in humans, indicating that transmitting these viruses to humans directly is a very rare preference. However, the HPAI ability to the cross-species barrier and infect humans has been known for H5N1 and H7N9. Recently, the world's first human case of transmission of the H5N8 strain from the avian species to humans has been documented. In this recent scenario, it is worth discussing the strain variations, disease severity, economic loss, and effective controlling strategies for controlling avian influenza.

Keyword Avian influenza · H5N1 · H7N9 · H5N8 · High pathogenic avian influenza virus (HPAI)

The avian influenza (AVI) is being known for its devastating effects in animal husbandry and human life. With a pandemic potential, it possesses a public health threat as humans have little or no immunity against the virus and the mortality among human is > 50%. Since the first occurrence of human case of AI was recognized in Hong Kong in 1997 following a poultry outbreak, it has spread to many countries in the world [51]. Recently increased concerns were felt as seven states in India got affected by avian influenza in the poultry. According to Ministry of Fisheries, Animal Husbandry and Dairying, Avian influenza outbreaks have spread over Kerala, Madhya Pradesh, Rajasthan, Haryana, Gujarat, Himachal Pradesh and Uttar Pradesh with the avian strain H5N8 whereas states like Himachal Pradesh and Haryana has H5N1 strain which is of more concern in human being. Human infections with H5N1 have been reported with high mortality, however till date there has been no documented case of human infection due to H5N8 except the first ever human case in Russia being notified to WHO in February 2021 [49]. This event marks the world's first human case of transmission of the H5N8 strain from the avian species due to cross species transfer. Even though the symptoms were milder to start with, in the lack of literature on its behavior the possibility of human adaptation and human to human transmission created a suspense and panicky situation. In face of recent devastation due to pandemic SARS-CoV-2, which thought to have jumped from bat species to adopt a fast human to human transmission and the mortality, thereof. It is worthwhile of discussing about the AVI on the strain variations, the disease severity, economic loss and the effective controlling strategies of controlling avian influenza.

Background

Influenza viruses are single-stranded, negative-sense ribonucleic acid (RNA) viruses belonging to the family

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Orthomyxoviridae, classified into types A, B and C based on antigenic differences in matrix protein (M1) and nucleoprotein (NP) (Fig. 1). Thus, 16 HA subtypes along with 9 NA subtypes have been in circulation with an additional of 2 HA and NA subtypes in bats [43]. The AVI strains belong to influenza type A [21]. The aquatic birds, belonging to the orders *Anseriformes* and *Charadriiformes* are ecological niche of AVI. These wild birds not only act as a natural reservoir but also are responsible for transmission of genes for all Influenza virus A strains except, H17N11 and H18N12 influenza A viruses, whose predominant transmission is via bats [43]. Chatziprodromidou et al. also described proximity to water as a significant risk factor for virus transmission [6, 10]. Ducks, geese and wild water fowl, suffer mild illness whereas poultry birds suffer more and are responsible for the large outbreaks and epidemics in poultry [21]. The faecal transmission remains to be the major route in avian species where the virus gets excreted in high titre though faecal matter. The AVI cases spread worldwide, via migrating birds and poultry trade activities [7].

Host range restriction and transmission to humans

The ability for the virus to cross species barrier is multifactorial (Fig. 2). The presence of intermediate host (viz. pigs) where it acts as a genetic mixing vessel among humans and birds, along with host susceptibility, exposure level to infected avian species, viral mutations, environmental conditions conducive for virus transmission are essential for transmission [8, 42]. Pigs and birds have been implicated in the origin of various pandemics. The reassortment between 1918 H1N1 and AVI virus resulted in the pandemic of Asian influenza (H2N2) in the year 1957 and the pandemic of Hong Kong influenza (H3N2) in the year 1968. In 1977, a Russian influenza pandemic H1N1 virus emerged with genetic similarity to 1950s H1N1 viruses. In 2009, an H1N1 virus emerged to the proportion of pandemic following quadruple ressortment between Eurasian swine, classic swine and North American avian virus [25].

In general, AVI viruses do not replicate efficiently in humans, implying that direct transmission of these viruses to humans is a very unusual occurrence. Majority of AVI does not affect humans, except subtypes Influenza A (H1N1), A(H5N1) and A(H7N9) which are known to cause established human infections [4]. Hemagglutinin (HA) binds to the sialic acid receptors at the cell-surface and which helps in attachment and entry of the virus in the host cell. Neuraminidase (NA) assists in spread of infection. The specificity of HA and uniqueness of binding to a species might in part explain the species barrier between avian and human influenza viruses. The host-restriction among various species is due to the specificity of sialic acid- galactose linkages on cell surface sialyloligosaccharides. The human tracheal epithelium predominates with α 2,6 linkage (NeuAc α 2,6Gal) while avian influenza predominantly attaches to the NeuAc α 2,3Gal linkages which are abundant in intestinal epithelial cells of birds and pigs [18, 48]. Importantly, pigs possess both α 2,6 and α 2,3 Gal receptors in their tracheal epithelium thereby facilitating frequent co-infection with avian and human strains giving rise to newer progeny as a result of reassortment and recombination. Thus, pigs

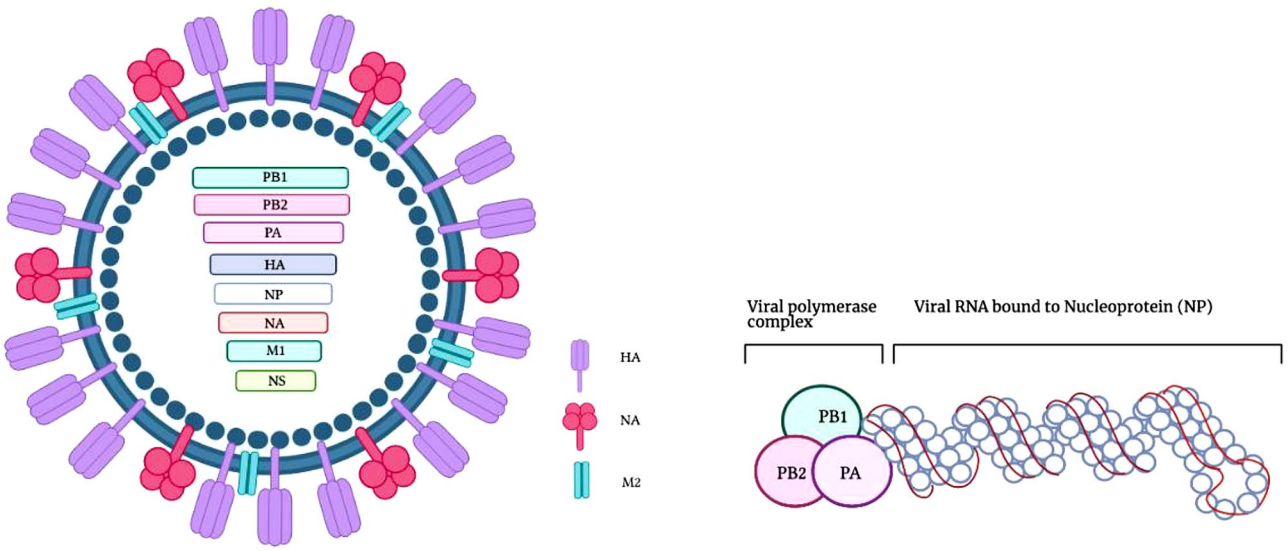

Fig. 1 Schematic structure of influenza virion: Hemagglutinin (HA) and neuraminidase (NA) are surface proteins present at an approximate 3:1 ratio along with M2 ion channels. M1 is the matrix protein that forms the inner capsid. RNA polymerase (formed by PB1, PB2 and PA) are bound to nucleoprotein (NP)

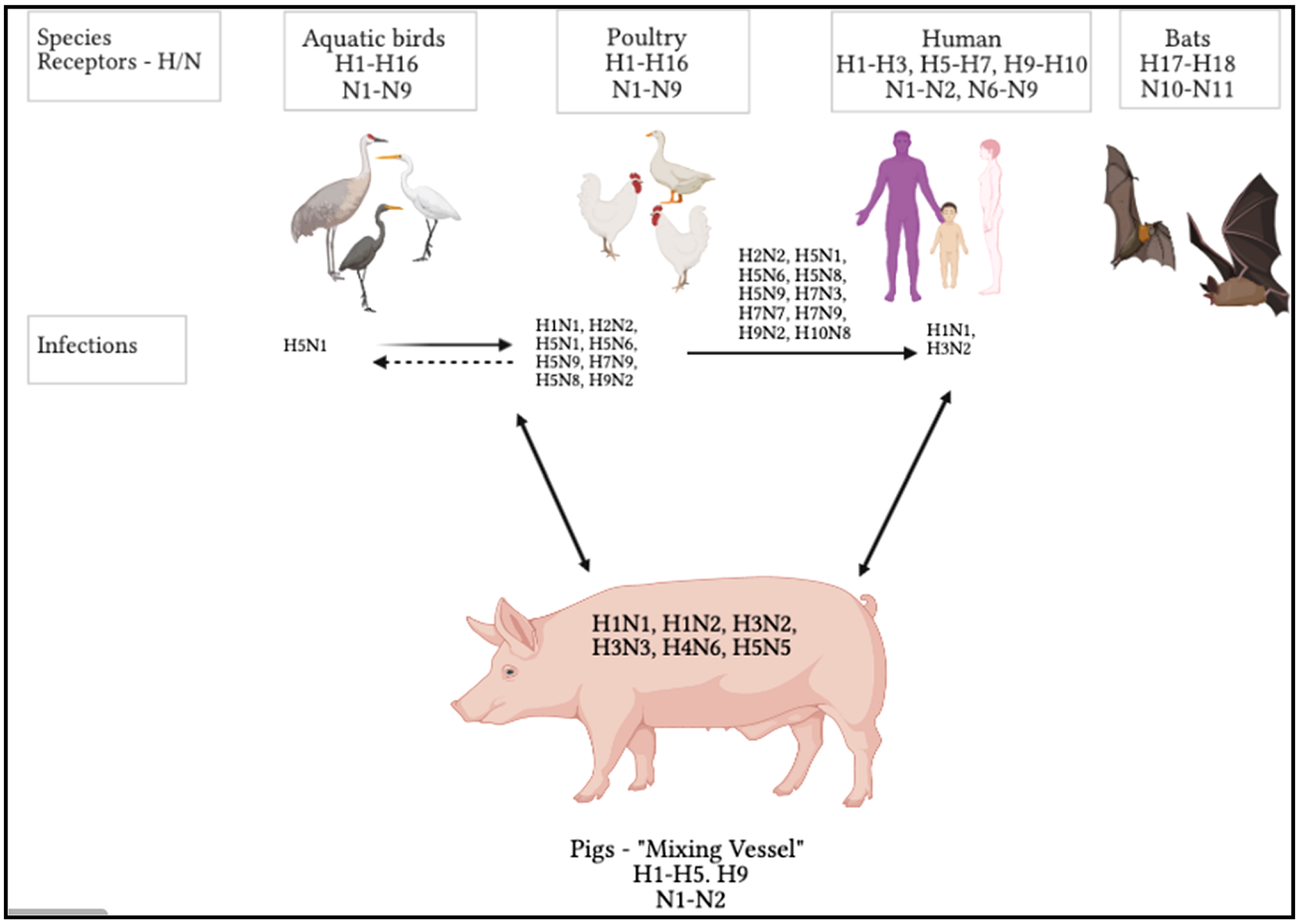

Fig. 2 Host Range Restriction and transmission to humans

possibly serve as mixing vessel for the generation of newer influenza strains in nature [22, 32]. A high density of human population in close proximity to intensive breeding of swine and ducks together and the presence of circulating influenza strains round the year favours generation and transmission of genetically distinct strains.

Emergence of highly pathogenic avian influenza (HPAI)

The term "highly pathogenic avian influenza" (HPAI) refers to strains that induce a "intravenous pathogenicity index" (IVPI) greater than 1.2 or a mortality rate higher than 75% in a given poultry population over a 10-day period. The HPAI AVI virulent strains belong to H5 or H7 lineages causing mortality up to 90–100% of the chickens within 48 h whereas the low pathogenic avian influenza (LPAI /avirulent) strains cause mild illness or no disease (like ruffled feathers and decrease in egg production) (Fig. 3) [13]. However, viruses of H5 or H7 subtypes can also be of low pathogenicity. According to the World Organization for Animal Health, AVI is defined as "an infection of poultry caused by any influenza A virus with high pathogenicity (HPAI) and by H5 and H7 subtypes with low pathogenicity (H5/H7 LPAI)" [42]. Moreover, all H5 and H7 have raised potential to mutate to HPAI, making it mandatory to notify out-breaks to OIE [25].

The predominant route of transmission is recognised in wild bird hosts, particularly in the orders Charadriiformes and Anseriforms [24]. The frequent spread of several AI viruses and their genetic segments across wild bird host species promotes the maintenance of avian influenza genetic diversity. The rate of contact increases during migration and at stopover sites with significant host biodiversity, allowing for the selection of LPAI that can sustain transmission cycles through diverse hosts. This allows the virus to survive in the host, allowing the virus to remain compatible with long-distance migration. The secondary pathway for AI transmission is through poultry farms and the connected food-chain network [12].

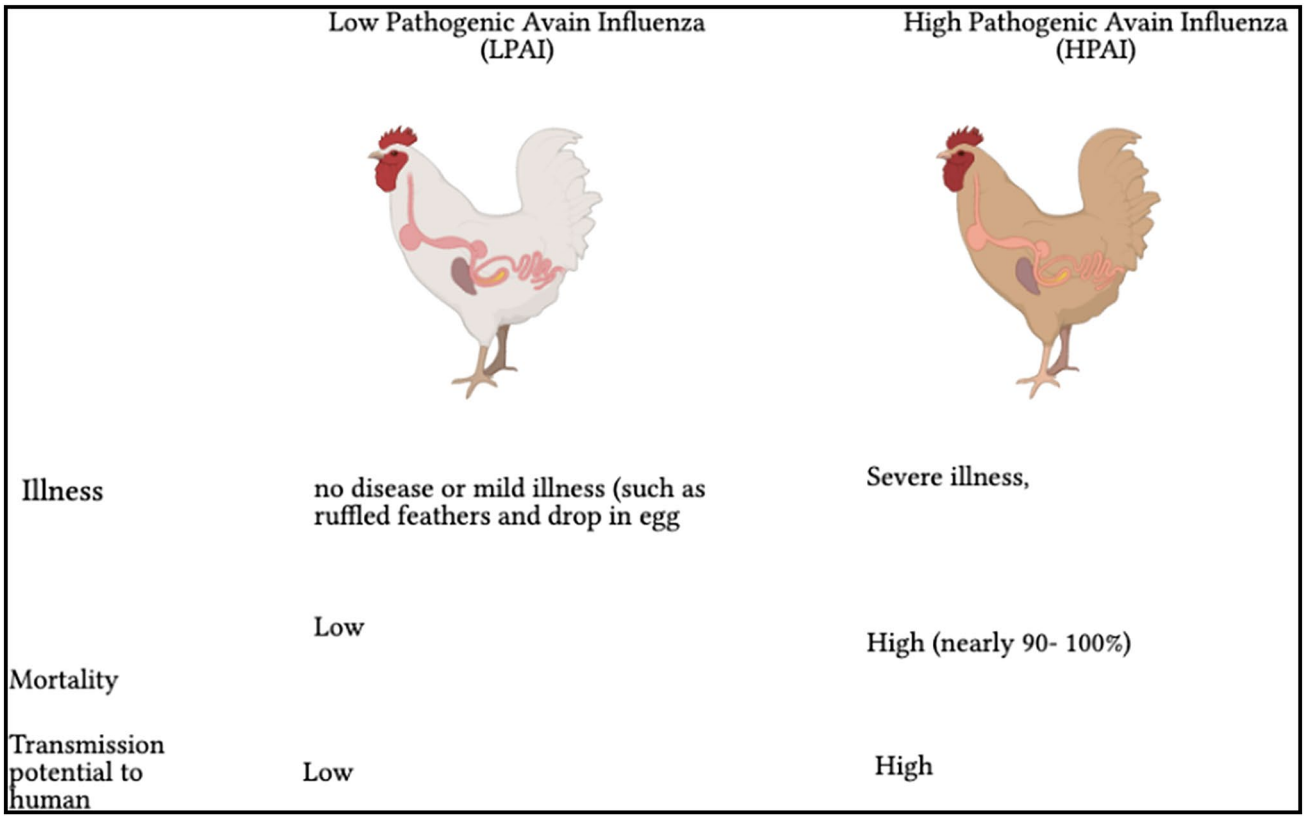

Fig. 3 Symptomatology in Low pathogenic Avian Influenza (LPAI) and High Pathogenic Avian Influenza (HPAI)

The evolution of LPAI to HPAI is determined by the evolutionary pressures that each system faces. Two primary pathways have been identified in the generation of novel HAPI (H5 and H7) strains throughout the years. The first is "conversion" to HPAI via basic amino acid uptake in LPAI. Antigenic drift is caused by the persistent accumulation of point mutations, deletions, and substitutions caused by a lack of proof reading in the RNA polymerase. Second, there is "ressortment," which is the interchange of genetic segments across viruses that are already in circulation, resulting in the creation of a novel HPAI [12, 16].

Currently, 103 of the 144 identified AVIs are circulating in migratory bird and farmed poultry populations. Of these, eight have been implicated in human transmission, with only H7N9 and H5N1 demonstrating high pathogenicity [42]. Many outbreaks occurred in between which were mainly contained by interventions such as mass culling and vaccination among the infected avian species. Most of the avian influenza viruses which have been isolated in the field are avirulent. The various avian influenza A viruses subtypes which is known to infect both birds and human beings are of the Influenza A H5 (H5N1, H5N9), Influenza A H7 (H7N1, H7N9) and Influenza A H9 (H9N1, H9N9). As of 1 April 2022, a total of 239, 1568, 75, 74 and one cases of human infections with AVI H5N1, H7N9, H5N6, H9N2, H7N4 virus have been reported respectively [37]. The most frequent zoonotic AVI is H5N1, which initially appeared in humans in Hong Kong in 1997 and subsequently resurfaced in Mainland China in 2003 [51]. The H5N1 virus started circulating in poultry in parts of Asia, some time before 1997. Initially it caused mild disease with ruffled feathers and decrease egg production and remained unnoticed. Later on the virus mutated to a highly pathogenic form in the year 1997 in Hong Kong after months of circulation in the chickens. 100% mortality was observed in the poultry birds. Towards the end of 2003, H5N1 suddenly became widely visible and effected large poultry belts [44]. The first H5N1 (HPAI) major outbreak in wild birds was recorded in April 2005 in Qinghai Lake, China [42]. Within three months, the same strain was detected in dead migrating birds in Russia, marking it the first country outside of Asia to report H5N1. H5N1 was then identified in the Middle East, Africa, Europe, and Asian countries [20]. Following infection among wild birds and poultry, cases of human infection began to be reported in similar geographical areas [17].

In contrast to 1997 H5N1, which was endemic only in Asia, the re-emergence strain of 2003 H5N1 has established its endemicity among birds in the various parts in the world and sporadic cases of human infection [38]. The vast geographical endemicity was maintained due to domestic

poultry trading among countries and migration of wild birds to long distance up to 2600 km [41]. The human infection usually occur in people working in close proximity with the infected poultry [20, 38, 41].

The first human case of H7N9 was reported in February 2013 in Shanghai, China. Soon, it was detected among wild birds and poultry in April 2013 in Mainland China [7]. Both H7N9 and H5N1 emerged through genetic ressortment, but the spread of H7N9 was faster and they differ significantly in human epidemiology. The H5N1 is distributed worldwide, while H7N9 is geographically restricted to Hong-Kong, China. In its first year of emergence H7N9 had high incidence of human cases with 10 times more cases in comparison to H5N1 [9]. This was opposite to the finding that close-contact with H7N9 cases was more sporadic, while contact-level for H5N1 was higher. Cowling et al., observed that the contact for H5N1 was to sick and dead poultry while exposure for H7N9 cases was visiting live poultry markets [11]. The H7N9 usually affect older population (~ 62 years), while young adult are affected by H5N1 affects younger adults (18–26 years) [11]. Also, the H5N1 has higher mortality (60%) while H7N9 has comparatively low fatality (22%) [39, 45].

Within first two weeks of December,2020 more than one lakh egg laying hen died in the poultry farms in Russia. This exceptionally high mortality rate prompted an immediate investigation, and samples were obtained from the birds and evaluated by the Russian regional veterinary laboratory. As a result, on December 11, 2020, the World Organization for Animal Health (OIE) Reference laboratory and the Federal Centre for Animal Health declared an H5N8 epidemic in Vladimir, Russian Federation (FGBI-ARRIAH). Thereafter containment operations were initiated immediately. On 18 February 2021, the Russian Federation alerted WHO and notified seven human cases of H5N8. For the first time, transmission of H5N8 from birds to human was reported [49]. This needs utmost attention as old virus in the new host is seldom known for its infectivity and potential outbreak ability. This might be an impending pandemic, if surveillance is not done.

The spread of H5N1 and H7N9

Infection of avian populations and poultry with specific subtypes of influenza A virus poses universal public health issues due to the risk of infection transmission to humans. The AI outbreaks are of concern among domesticated birds because of the capacity for LPAI H5 and H7 viruses have the ability to evolve into HPAI viruses which have a potential for rapid spread leading to significant outbreak among poultries. As these infected birds excrete large number of viruses in their feces, there is a possibility of transmission of AI to humans through contaminated materials (water, equipment, cages) etc. thereby contributing in the dissemination of the virus in the community [35].

The AVI transmission follows seasonal migratory routes of waterfowls and in wild birds like bar-headed geese (*Anser indicus*) and ruddy shelduck (*Tadorna ferruginea*). The yearly migration is also responsible for maintenance and spread of AVI to wider geographical areas. These birds gather in large number in common water bodies where it provides a conducive condition for viral transmission [2]. Numerous studies have been performed to investigate the association between the AVI outbreak and migratory birds. Liang et al. conducted a spatial–temporal and phylogenetic study to explain the global spread of H5N1 outbreaks and observed that the virus circulation coincided spatially with key migration routes (East Asia flyway, East Africa–West Asia flyway, Black Sea–Mediterranean Sea flyway and Central Asia flyway). Furthermore, the timing of outbreaks corresponded with the seasonality of bird migrations [29]. While Kilpatrick et al., based on phylogenetic relationships, observed that migration of wild birds was responsible for H5N1 introduction in European countries whereas in Asian countries it was introduced majorly by poultry trading activities [26].

There is a dearth of knowledge regarding the mechanism of spread of H7N9 compared to H5N1. Ling et al. conducted an epidemiological and gene sequence analysis and proposed that H7N9 spread could occur in three ways: migratory birds, farmers and wholesale distribution via logistics, and fragmented transportation [30].

Symptomatology

AVI viruses cause a wide range of symptoms in birds, including asymptomatic to mild upper respiratory infections, decreased egg production, and rapidly progressive systemic lethal illness. Reduced egg production, excessive lacrimation, respiratory signs, rales, sinusitis, ruffled feathers, cyanosis of unfeathered skin, haemorrhage on the shanks, edoema of the head and face, diarrhoea, and nervous system involvement, depression, and loss of appetite are typical signs and symptoms seen in poultry. The symptoms are determined by the strain of the infecting virus, as well as the species and age of the bird. Occasionally, birds die without displaying any signs of sickness [14, 15, 33].

In humans, the period of transmissibility in humans is usually one day before to 4–5 days after onset of symptoms. The incubation period ranges between 2 and 4 days. Patients present with rapid onset of symptoms like fever, chills, myalgia, breathlessness, headache, vomiting, diarrhea and abdominal pain. Serious complications like respiratory

failure, multiorgan failure, Reye's syndrome, pneumothorax and pulmonary hemorrhages can occur [35].

Laboratory diagnosis

Clinical specimen from human and avian sources should never be tested in the same room. They should be tested at different centers or different rooms in a centre in order to avoid genetic recombination or reassortment of human and animal strains. Therefore, the diagnostic centers testing for AI in humans are being done in National Institute of Virology (NIV), Pune and National Centre for Disease Control (NCDC), Delhi. Whereas National Institute of High Security Animal Diseases (NIHSAD), Bhopal, is an apex center for testing of animal's strains.

Pooled tracheal, lung samples and intestine samples from minimum 5 diseased birds should be collected and post mortem examination should be done following BSL-4 precautions and guidelines. Also, cloacal and tracheal swabs should be collected from > 10 up to 30 healthy birds. At least one gram of faecal material and acute sera from 10 birds should be collected. All samples should be transported in dry-ice to (High Security Animal Diseases Laboratory) HSADL Bhopal. All the laboratory diagnosis should be performed under strict precautions in a BSL-3 laboratory facility. The viral RNA can be detected by RT-PCR or Real Time RT-PCR. In humans, the nasopharyngeal or oropharyngeal swab from the upper respiratory tract (nose or throat) collected during first few days of illness and for severely ill patients, lower respiratory tract specimens are ideal samples.

Conventional cell-culture or shell-vial cell culture can be performed. The sample is inoculated directly in embryonated eggs or Mardin-Darby canine kidney (MDCK) cell lines. Most AVI readily grow and amplify within embryonated eggs and also allows further characterization of the virus. However, HPAI H5N1 are quite virulent and kill the egg rapidly, preventing virus amplification. The disadvantage of virus culture is that it require 1–2 weeks for the result. Positive cultures are then observed for virus-induced cytopathic effects (CPE). Since, CPE in influenza is not distinct, confirmation can be done by various methods like immunofluorescence, hemagglutination—inhibition (HI) or RT-PCR.

In serological diagnosis, antigen and antibody detection can be done. Detection of viral antigen can be performed by enzyme immunoassay (EIA) and immunofluorescence assays. Also, rapid antigen detection cards are available. These test target conserved viral antigen (NP and M), hence are not able to differentiate between avian and human origin subtypes. These rapid antigen test have poor sensitivity and have limited utility in AVI diagnosis [36].

Agar Gel immunodiffusion test can be done for antibody detection. Various assays like enzyme immunoassay (EIA), hemagglutination inhibition test (HI) and virus neutralization tests (VN) test can be performed. Currently, microneutralization (MN) assay is the recommended test for antibody quantification in AVIs. The antibody require weeks to develop and are not advisable for prompt diagnosis. Also, constraints like cross-reactivity with previous influenza infection limits the utilization. Antibody detection is usually carried out for epidemiological purpose [36].

The rapid detection of AVI is important for containment strategies. Hence, molecular methods can provide an efficient option for the preliminary detection. Polymerase Chain Reaction (PCR)is performed on clinical samples by targeting conserved gene (e.g. matrix gene) or to the subtype specific genes haemagglutinin or neuraminidase. The turn-around time of conventional RT-PCR (6–8 h) is longer than Real time RT-PCR (3–4 h) assays. The Real time RT-PCR provide increased specificity, sensitivity and quantification of target gene. Other rapid molecular techniques like the Loop-Mediated Isothermal Amplification (LAMP) are under pipeline [3]. The result of LAMP reactions can be interpreted by direct visual inspection and limit of detection is equivalent to that of RT-PCR [1, 23]. The Next-generation sequencing (NGS) analyses using targeted and whole-genome sequencing is an upcoming technique with an ability to provide complete description of the genetic, chronological, and geographical aspects of the outbreak [28]. NGS enables study of high-resolution molecular epidemiology and highlights the importance of poultry as a source of novel genetic variations originated from multiple reassortment events [27, 50].

Containment and disposal of poultry

With the emergence of pandemic influenza strains the infection of avian populations with certain subtypes of avian influenza A virus possess a global threat as it leads to the occurrence of sporadic human infections The AVI outbreaks in domesticated birds are of concern because of the capacity for LPAI,H5 and H7 viruses have a tendency to evolve into HPAI viruses resulting in rapid spread and significant outbreak in poultries [35]. The containment should be rapid and stringent precautions should be taken in handling the infected poultry cases or infected materials (Fig. 4). All poultry and egg markets/shops within a 10-km radius of the infected location should be closed immediately, and an infected area sign-board should be installed within a 3-km radius. The surveillance perimeter (buffer zone) should have a radius of 3–10 kms. A disease-free zone should be defined as a radius of more than ten kilometres [34]. If no vaccination method is implemented, trading may restart only four weeks after all birds within three kilometres have been culled. Furthermore, no new cases should appear within 3–10 kms of the observation zone. Decapitation and neck

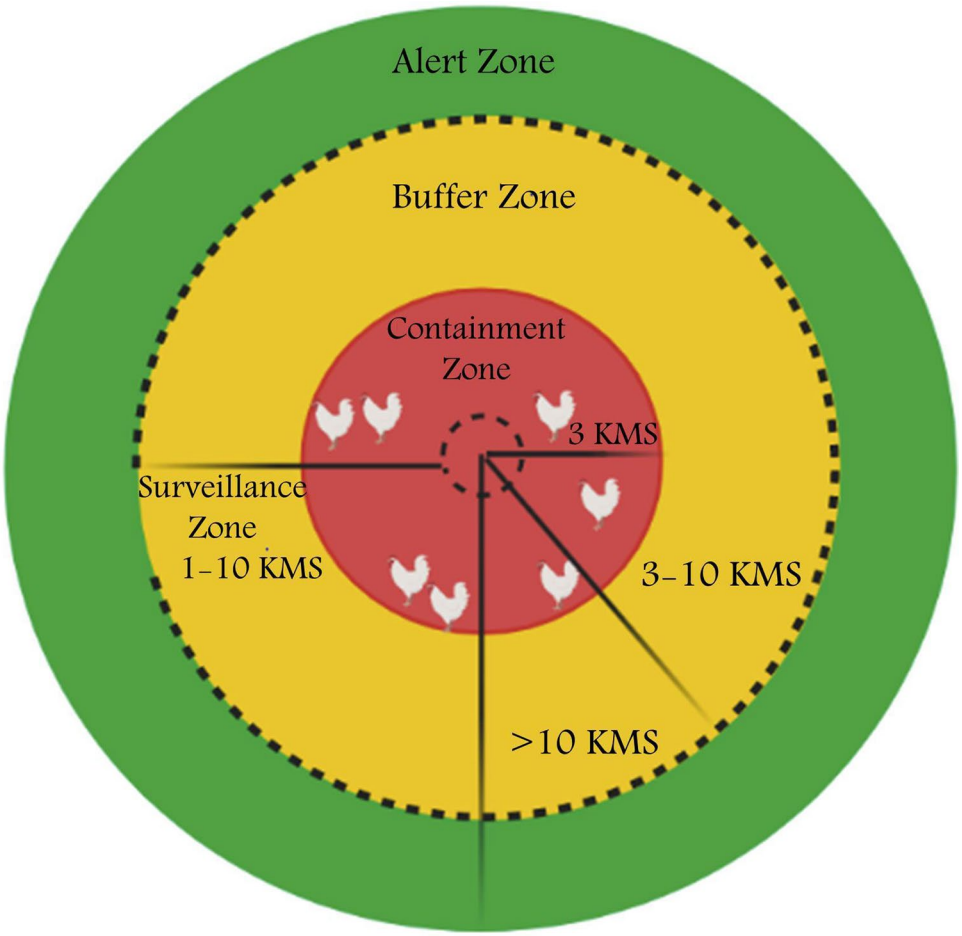

Fig. 4 Schematic representation of zones in an area infected with Avian Influenza

dislocation can be employed to depopulate diseased flocks. Infected waste should be disposed of in appropriate receptacles. (Fig. 5) To completely burn 100 kg of dead birds, 5 quintals of wood are required. The burial trench must be 8 m long, 2 m wide, and 1 m deep. This enables disposal of about 300 birds. The pit should be sprinkled with a layer of lime to reduce the likelihood of any live virus. The carcasses must be covered with a 400 mm layer of soil followed by a layer of lime and finally cover with 0.2 m of soil. The top lime layer ensures proper decomposition of the carcass [31].

Control and surveillance of avian influenza

The containment area should be blocked for further movement and all entrances should be disinfected meticulously. Closing of the shops and markets should be considered if spread to more farms is suspected. Transport of poultry products from the farms should be banned. Proper maintenance of the records for poultry bird in each farm should be done. Proper surveillance with early case detection and isolation should be done. Poultry workers, cullers and people exposed to the farm should be quarantined for 10 days. Also, Tablet Temiflu (75 mg twice daily) should be given as prophylaxis for 10 days for symptomatic people and their contacts. Samples should be tested for AVI by RT-PCR following all recommended BSL-3 facility [5].

The assessment of surveillance data promotes disease control programme planning, implementation, and evaluation. With the emergence and spread of HPAI in South-East Asia, the Food and Agriculture Organization (FAO) developed and launched the Emergency Prevention System for Transboundary Animal and Plant Pests and Diseases (EMPRES) programme in 1994 [19]. The geographic information system (GIS) -based surveillance systems provides functions like interpolation, cluster detection, and identification of risk factors for outbreak of avian influenza [46, 47]. Fang et al. using the GIS analyzed the environmental parameters related to HPAI [40]. Further, the information gained helps towards the disease dispersion hypothesis [46]. More research involving spatiotemporal interface between the pandemics could point towards the mechanism of spread from localized to pandemic situation. Such statistics would be valuable in limiting the global spread of HPAI [47]. The GIS has the potential to indicate early warning systems which can assist in disease spread and control.

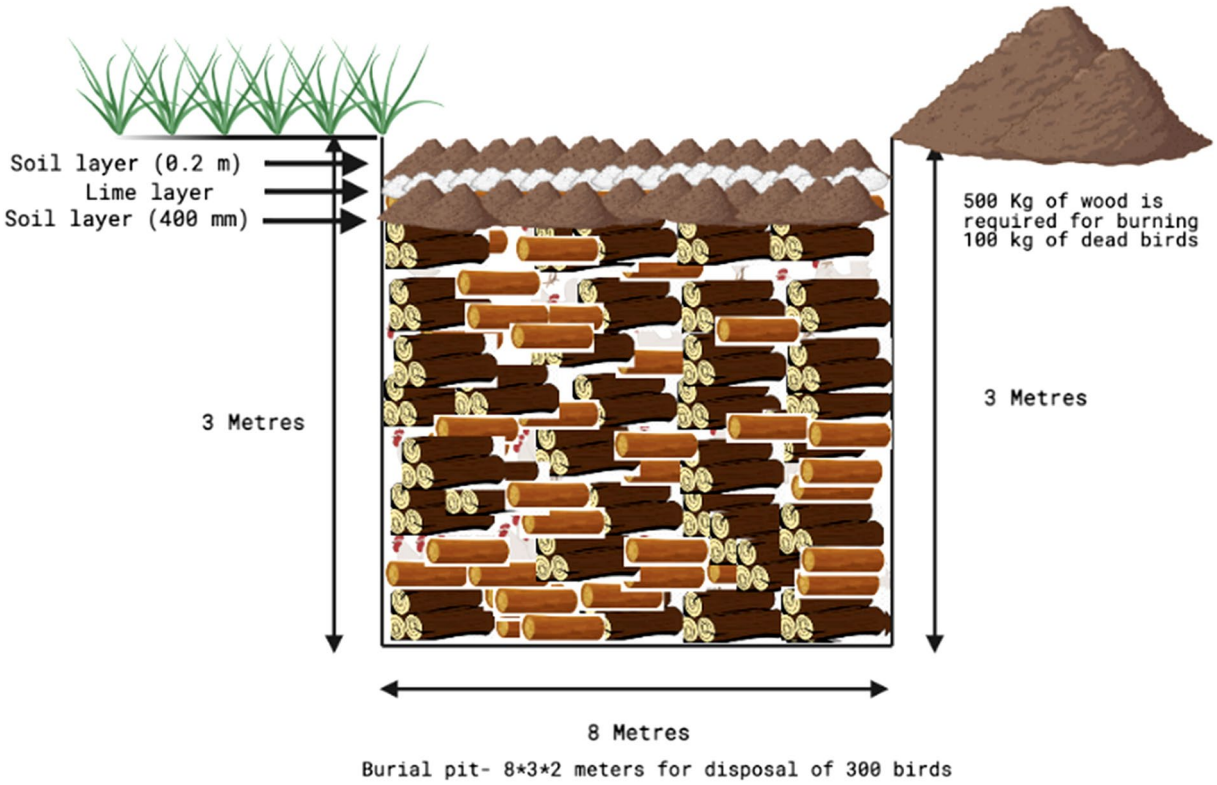

Fig. 5 Schematic representation for disposal of poultry infected with Avian influenza

Conclusion

The circulation of AVI in poultry possess a serious risk for sporadic human infection due to exposure to infected poultry and contaminated environments. The ability for a virus to cross species barrier with continued incidence of AVI and emergence of new strains, proper surveillance is important to prevent infections among poultry and human. Community awareness along with health care personnel's training should be performed regularly. Development of any signs of infection among poultry should be informed to the local authorities. Following outbreak, rapid diagnosis with immediate containment strategy should be made. Sampling under proper PPE and hand hygiene should to be maintained.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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