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Avian influenza: A pandemic threat

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Abstract

Avian influenza is a highly contagious viral disease of poultry caused by enveloped Influenza A RNA viruses of Orthomyxoviridae family. The highly pathogenic H5N1 virus which was first isolated from a domestic goose in China in 1996 was responsible for the first mortality in the human. Viruses that cause severe disease in birds and result in high mortality rate are called highly pathogenic avian influenza (HPAI), whereas viruses that cause outbreaks in poultry but are not generally associated with severe disease are called low pathogenic avian influenza virus (LPAI). Till date, naturally occurring HPAI have been associated with H5 and H7 subtypes. Genetic reassortment between human and avian viruses is suggestive as the mechanism by which “new” human pandemic strains arise. The disease begins by inhalation or ingestion of LPAI or HPAI viruses in the nasal cavity, which is the major site of initial replication. Good husbandry measures, healthy diet and broad spectrum antibiotics to control secondary bacterial infections may reduce the mortality rate.

Keywords: Avian influenza, HPAI, LPAI

1. Introduction

Avian influenza commonly known as bird flu or fowl plague, is a highly contagious viral disease of poultry caused by Influenza A viruses of Orthomyxoviridae family. It is one of the most important diseases of poultry that negatively impacts poultry health, international trade, poultry products and ornithosis. Influenza is derived from the Latin word *Influentia*, means “influence”. Influenza viruses are classified into three types such as A, B and C. Influenza A virus has a wide host range including birds and mammals while type B and C are host specific. Type B virus affects only the human whereas type C affects human beings and pigs [1]. AI was first recorded in Italy in 1878. As poultry is an important source of food and livelihood, there are many direct losses through culling and mortality of bird, environmental pollution, losses due to trade restrictions, collateral losses to tourism, etc. Avian Influenza viruses with the vast silent reservoir in aquatic birds are impossible to eradicate. Zoonotic influenza infection in humans can continue to occur. To minimize the public health risk, quality surveillance in both animal and human populations, thorough investigation of every human infection and risk-based pandemic planning is essential.

2. Etiology

Avian influenza virus is an enveloped RNA virus. The viral genome is composed of eight segments of single-stranded RNA of a negative-sense. The virus particle (also called the virion) is 80–120 nanometres in diameter and usually roughly spherical, although some rare filamentous forms can occur [2]. The two large proteins found on the outside of viral particles are haemagglutinin (HA) and neuraminidase (NA). Haemagglutinin is a protein that mediates binding of the virion to target cell surface receptors (sialyl-oligosaccharides) and entry of the viral genome into the target cell, while neuraminidase is involved in the release of progeny virions from infected cells. The general structure of AI is given in Figure 1.

These proteins are usually the targets for antiviral drugs. Furthermore, they are also the antigen proteins to which a host's antibodies can bind and trigger an immune response. There are a total of known 18 HA and 11 NA serologically distinct influenza virus subtypes and any combination of HA and NA is possible. All known subtypes of influenza A viruses can infect birds, except subtypes H17N10 and H18N11, which have only been found in the bat [3]. There are strict rules for naming influenza isolates. The standard system of nomenclature proposes that the name should include [4].

1. Antigenic type (A, B or C)
2. Host of origin (e.g. duck, turkey)
3. Geographical location where first isolated (e.g. Albert, China)
4. Sequential number of isolation (e.g.1, 2, 3 etc.)
5. Year of isolation (e.g. 76,2013 etc.) and
6. HA and NA subtype

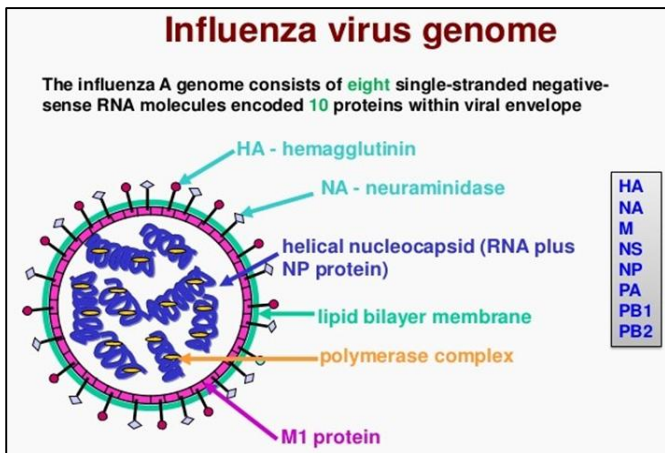


Fig 1: Genome of Influenza A virus

3. Geographical Distribution of Avian Influenza

The global occurrence of outbreak is presented in table 1. Avian influenza was first recorded in Italy in 1878. The disease, originally known as Fowl Plague, continuously caused massive outbreaks in poultry, including two outbreaks in the United States in the year 1924 and 1929. In 1955, it was discovered that the virus causing Fowl Plague was an influenza virus [5].

Table 1: Documented Epidemics of Highly Pathogenic Avian Influenza (HPAI) in Poultry

Year	Location	Strain	Losses (USD)
1924-1929	USA	Fowl Plague	Unknown
1983-84	USA	H5N2	17 million
1985	Australia	H7N7	238,518
1994-95	Mexico	H5N2	Unknown
1994-95,2004	Pakistan	H7N3	8.72 million
1996-2007	Guangdong and Hong Kong	H5N1	220 million
1997	New South Wales	H7N4	161,261
1997	Italy	H5N2	6,965
1999-2000	Italy	H7N1	13 million
2002	Chile	H7N3	617,800 +
2003	Netherlands	H7N7	30 million
2004	Canada	H7N3	16 million

“Asian influenza” (H2N2) in 1957 - Outbreak of Influenza occurred in East Asia and that subsequently spread to countries worldwide. It originated from mutation in wild ducks combining with a pre-existing human strain, estimated 2 million deaths was occurred. The Asian flu strain later evolved via antigenic shift into H3N2, which caused a milder pandemic from 1968 to 1969 [6]. “Hong Kong influenza” (H3N2) in 1968 was pandemic and considered as one of the deadliest disease events in human history with 1 million deaths. While, the pandemic human influenza viruses of 1957 (H2N2) and 1968 (H3N2) clearly arose through reassortment between human and avian viruses [7]. The highly pathogenic H5N1 virus was first isolated from a domestic goose in

Guangdong, China in 1996 [8]. This form of highly pathogenic avian influenza led to a poultry epidemic in Hong Kong and resulted in the first documented cases of human death, infected eighteen people and killed six [9]. Appearance of another strain in 2014, (H5N8) Highly pathogenic Avian Influenza viruses has been detected in South Korea in poultry birds. Although it is considered as one of the less pathogenic subtypes for humans. The re-emergence of strain again occurred in the year 2016 in Austria, Croatia, Denmark, Germany, Hungary, India, Israel, Netherlands, Poland, Russian Federation and Switzerland [10].

4. Outbreaks in India

The first outbreak of Avian Influenza occurred in domestic poultry on February 18, 2005 in Navapur village in Maharashtra. Over 1.5 lakh birds were killed and a loss of Rs.20 crores was estimated. The strain reported was H5N1. The outbreaks of bird flu in India are presented in Table 2.

Table 2: Outbreak of Avian Influenza in India

S. No	Year of outbreak (H5N1)	Affected State
1	Feb 2005	Maharashtra
2	March - April 2006	Madhya Pradesh
3	July 2007	Manipur
4	January - December 2008	West Bengal, Tripura, Assam
5	October 2009	Sikkim
6	January 2010	West Bengal
7	February - September 2011	Agartala, Assam, West Bengal
8	January- February 2012	Odisha, Meghalaya, Tripura
9	March 2013	Bihar
10	Nov - Dec 2014	Kerala, Chandigarh
11	January 2015	Kerala
12	Oct - Nov 2016 (H5N8)	Delhi, Kerala

5. Host

Depending upon the host, influenza can be classified as avian influenza, swine influenza, or other types of animal influenza. Examples include avian influenza "bird flu" virus subtypes A (H5N1) and A (H9N2), or swine influenza "swine flu" virus subtypes A (H1N1) and A (H3N2). Avian influenza A virus infects chickens, turkeys, partridges, pheasants, quail, pigeons, and ostriches whereas free flying aquatic birds like ducks, geese, shore birds, gulls being the major reservoir of virus. Avian influenza viruses are distributed globally without any geographical boundaries and the infection with Avian Influenza viruses has been detected in all type of birds across all the seven continents. It is basically a disease of birds, but also found in humans, pigs, horses, mink, marine mammals, tigers, dogs, eagles, cats, ferrets, mice, hamsters and macaques [11]. All AI viruses, with the exception of some viruses of the H5N1 and H9N2 subtypes possess HAs with high affinity for sialic acids attached to galactose sugars in the α 2,3- linkage. In contrast, human influenza viruses have HAs which preferentially bind to sialic acid attached to sugars in the α 2,6- linkage. Thus, for the poultry influenza viruses to infect human a mutation is required which should result in preferential binding from the α 2,3 to the α 2,6- linkage [12]. Three prominent subtypes of avian influenza A viruses are known to infect both birds and people.

Influenza A H5: There are nine known subtypes of H5 viruses (H5N1, H5N2, H5N3, H5N4, H5N5, H5N6, H5N7, H5N8, and H5N9). Most H5 viruses identified worldwide in wild birds and poultry are low pathogenic viruses, but occasionally highly pathogenic viruses have been detected.

Influenza A H7: There are nine known subtypes of H7 viruses (H7N1, H7N2, H7N3, H7N4, H7N5, H7N6, H7N7, H7N8, and H7N9). Most H7 viruses identified worldwide in wild birds and poultry are LPAI viruses. H7 virus infection in humans is uncommon, but has been documented in persons who have direct contact with infected birds. In humans, LPAI (H7N2, H7N3, H7N7) virus infections have caused mild to moderate illness. HPAI (H7N3, H7N7) virus infections have caused mild to severe and fatal illness.

Influenza A H9: There are nine known subtypes of H9 viruses (H9N1, H9N2, H9N3, H9N4, H9N5, H9N6, H9N7, H9N8, and H9N9); all H9 viruses identified worldwide in wild birds and poultry are LPAI viruses. Rare sporadic H9N2 virus infections of humans have been reported to cause generally mild upper respiratory tract illness.

6. Pathogenicity

Avian influenza has been currently defined by OIE terrestrial animal health code as an infection in poultry by any influenza virus either highly pathogenic avian Influenza (HPAI) or low pathogenic avian influenza (LPAI) H5 H7 subtypes. For the determination of strain virulence for birds intravenous pathogenicity index (IVPI) is used. Viruses that cause severe disease in birds and result in high death rates are called highly pathogenic avian influenza (HPAI), whereas viruses that cause outbreaks in poultry but are not generally associated with severe disease are called low pathogenic avian influenza virus. Till date, naturally occurring highly pathogenic avian influenza have been associated with H5 and H7 subtypes. Though most viruses of the H5 and H7 subtype have been of low pathogenicity for poultry, there is always a risk of becoming highly pathogenic by mutation. The disease course of avian influenza in poultry ranges from asymptomatic to fatal cases. Avian flu viruses do not normally infect humans. However, sporadic human infections with avian flu viruses have occurred. Pandemic strains of human influenza often arise as a result of recombination between human and animal strains. Genetic reassortment between human and avian viruses is suggestive as the mechanism by which “new” human pandemic strains arise. The frequency of variation among influenza virus is high and occurs in two ways: drift and shift. Antigenic drift involves minor antigenic changes in the haemagglutinin and/or neuraminidase, whereas antigenic shift involves major antigenic changes in the HA and/or NA.

7. Transmission

Effectively all birds are considered to be at risk of infection. On rare occasions, it can infect other species, including pigs, humans and produce serious epidemic condition. Though human to human transmission is rare but it can place mostly after intimate and constant physical contact. The infection is virulent and 60% cases are fatal. As the number of human infections grows, the risk increases that a new virus subtypes could emerge, triggering an influenza pandemic. Human as well as swine must now be considered a potential mixing vessel for the generation of such a virus. This links between

widespread infection in poultry and increased risk of human infection. Influenza become pandemic when a new influenza virus appears in the human population causes serious illness and spreads easily from person to person and causes outbreaks. It can sweep across a country and around the world in a very short time.

7.1 Birds

These viruses occur naturally among wild aquatic birds worldwide and can infect domestic poultry and other birds and animal species. Wild birds can be infected with AI viruses in their respiratory tract and intestine but usually not get sick. However AI viruses are very contagious among birds. Infected birds and reservoir can shed viruses in their saliva, nasal secretions and feces. Susceptible birds become infected when they have contact with the viruses as it is shed by infected or reservoir birds. They can also become infected by coming in contact with surfaces that are contaminated with virus from infected birds.

7.2 Human

Transmission of Avian influenza A from birds to humans is a rare event; but it may spread to humans, when they come into direct contact with infected chickens and their droppings. Inhalation of dust generated from infected poultry faeces. Eating of uncooked meat and eggs. If the virus mutates and combines with a human influenza virus, it could spread through person-to-person transmission in the same way the ordinary human flu virus spreads.

8. Pathogenesis

The disease begins by inhalation or ingestion of LPAI or HPAI viruses. In poultry, the nasal cavity is the major site of initial replication. Virions invade the submucosa of the respiratory or intestinal tract, and enter into minute blood vessels (capillaries). The virus replicates within endothelial cells of these vessels and spreads through the vascular or lymphatic systems to infect and grow in a variety of different cells in internal organs, brain and skin. Symptoms and death are due to multiple organ failure^[13].

9. Clinical Signs

9.1 Birds

Incubation period of avian influenza is from 3-14 days and is dependent on the dose or quantity of virus, the route of exposure, the species exposed. Some birds are found dead prior to observance of any clinical signs. There may be neurological signs and reduction in normal vocalizations. Respiratory signs are less prominent but can include rales, sneezing and coughing. In mature chickens, the combs and wattles are often swollen and may be cyanotic (Figure 2). Conjunctivitis, edema of the head and neck, coughing, sneezing and nasal discharge may also be seen. Egg production in hens stops; the last eggs laid often have no shells. Death is common but severely affected hens occasionally recover.



Fig 2: Clinical signs of AI in chicken

9.2 Humans

LP AI (H7N9); A virus infection in humans have ranged from conjunctivitis to influenza-like illness (e.g. fever, cough, sore throat, muscle aches) to lower respiratory disease (pneumonia) requiring hospitalization.

HPAI (H5N1): A virus infections in people have been associated with a wide range of illness from conjunctivitis only, to influenza-like illness, to severe respiratory illness (e.g. shortness of breath, difficulty breathing, pneumonia, acute respiratory distress, viral pneumonia, respiratory failure) with multi-organ disease, accompanied by nausea, abdominal pain, diarrhoea, vomiting and sometimes neurologic changes (altered mental status, seizures).

10. Diagnosis

The viruses that cause AI have the potential to spread from the laboratory if adequate levels of biosecurity and biosafety are not in place. Consequently, a risk assessment should be carried out to determine the level of biosecurity needed for laboratory diagnosis and chicken inoculation; Characterization of the HPAI virus should be conducted at biosafety level 3 and LP AI at biosafety level 2 (at least). Countries lacking access to such a specialized national or regional laboratory should send specimens to an OIE Reference Laboratory^[14].

National Reference Centers in India

1. National Institute of Virology, Pune.
2. National Institute of High Security Animal Diseases (NIHSAD), Bhopal.

Regional Reference Centers in India

1. The Centre for Animal Disease Research and Diagnosis (CADRAD), Bareilly.
2. Regional Disease Diagnostic Laboratory (RDDL), Jalandhar.
3. The Regional Reference Standards Laboratory (RRSL), Bangalore.
4. National Institute of Cholera and Enteric Diseases (NICED) Virus Unit Kolkata.
5. North Eastern Regional Disease Diagnostic Laboratory (NERDDL), Guwahati.

Specimen: Nasopharyngeal aspirates (NPA) and nasopharyngeal, throat, and nose swabs samples are to be used for the detection of avian influenza virus. Confirmatory diagnosis of the disease done by the isolation or detection of the causal virus by embryonated chicken egg inoculation, Haemagglutination test, Haemagglutination Inhibition test, ELISA. The CDC recommends real time RT-PCR as the

method of choice for diagnosing Avian Influenza virus. This method allows a specific diagnosis of strains.

11. Treatment

11.1 In Birds

There is no specific treatment. Good husbandry measures, healthy diet and broad spectrum antibiotics to control secondary bacterial infections may help reduce the mortality rate. When H5 or H7 avian influenza outbreaks occur in poultry, depopulation (or culling, also called “stamping out”) of infected flocks is usually carried out.

11.2 Human

Patients with suspected or proven for Avian Influenza virus should be hospitalized in isolation. Supportive care with oxygen and ventilators may be essential. The pathogenesis of influenza illness suggests that inhibiting viral replication as early as possible after infection will reduce the duration and intensity of symptoms. Treatments may either directly target the influenza virus itself; or instead they may just offer relief to symptoms of the disease, while the body's own immune system works to recover from infection. The two main classes of antiviral drugs used against influenza are (i) Neuraminidase Inhibitors (ii) Inhibitors of the viral M2 Protein.

11.3 Neuraminidase Inhibitors

Neuraminidase enzyme promotes release of virus from infected cells and facilitates viral movement within the respiratory tract. In the presence of neuraminidase inhibitors, virions stay attached to the membrane of infected cells and are also entrapped in respiratory secretions.

11.4 Inhibitors of the Viral M2 Protein

It appears to mainly prevent the release of infectious viral nucleic acid into the host cell by interfering with the function of the transmembrane domain of the viral M2 protein. It is also known to prevent virus assembly during virus replication. These medications must be taken within 48 hours after symptoms begin. They are effective only if taken at the earliest signs of symptoms. These drugs [Amantadine (Symmetrel) and Rimantadine (Flumadine)] can reduce the severity of symptoms and can also be taken to decrease the risk of infection. H5N1 virus that causes Human Avian Flu is resistant to these antiviral medicines^[16]. Early intervention can reduce the total illness duration by up to one half compared with later treatment, resulting in faster recovery and resumption of normal activities.

The U.S. Centers for Disease Control and Prevention currently recommends (Neuraminidase Inhibitors) Oseltamivir, Peramivir, or Zanamivir for treatment and/or prevention of infection with avian influenza viruses.

Table 3: Therapeutic and Prophylactic Anti-viral Medications for Bird flu

	Oseltamivir (Tamiflu)		Zanamivir (Relenza)	
	Treatment	Prophylaxis	Treatment	Prophylaxis
Adults	75 mg capsule twice per day for 5 days	75 mg capsule once per day	Two 5 mg inhalations (10 mg total) twice per day	Two 5 mg inhalations (10 mg total) once per day
Children	15 kg or less: 60 mg per day divided into 2 doses	30 mg once per day	Two 5 mg inhalations (10 mg total) twice per day (age, 7 years or older)	Two 5 mg inhalations (10 mg total) once per day (age, 5 years or older)
	15–23 kg: 90 mg per day divided into 2 doses	45 mg once per day		
	24–40 kg: 120 mg per day divided into 2 doses	60 mg once per day		
	>40 kg: 150 mg per day divided into 2 doses	75 mg once per day		

Over The Counter Medications (OTC): They do not directly affect the disease, but they do provide relief from influenza symptoms, as illustrated in the table 4 below.

Table 4: Over the Counter Medications (OTC)

Symptom(s)	OTC Medicine
Fever, aches, pains, sinus pressure, sore throat	Analgesics / Antipyretics
Nasal congestion, sinus pressure	Decongestants
Sinus pressure, runny nose, watery eyes, cough	Antihistamines
Cough	Cough suppressant
Sore throat	Local anesthetics
Complications like pneumonia	Antibiotics

11.5 Nutritional Supplements and Herbal Medicines

Malnutrition can reduce the ability of the body to resist infections and is a common cause of immunodeficiency in the developing world. Micronutrient deficiencies were found to be common in the elderly, especially for Vitamin C, Vitamin D, Vitamin B₆, Vitamin B₁₂, Folic Acid and Zinc, and these are thought to weaken the immune system or cause anemia and thus place people at greater risk of respiratory infections such as influenza. Seasonal variation in sunlight exposure, which is required for Vitamin D synthesis within the body, has been proposed as one of the factors accounting for the seasonality of influenza. Evidence suggesting that N-acetylcysteine, elderberry, or a combination of *Eleutherococcus senticosus* and *Andrographis paniculata* may help to shorten the course of influenza infection [16].

12. Prevention and Control

12.1 Sanitary Prophylaxis - The basic approach in the control of avian influenza is preventing the first introduction of the virus and controlling the spread if it is introduced.

- Avoidance of contact between poultry and wild birds or their fomites (including surface waters) particularly with the waterfowls.
- Avoidance of the introduction of birds of unknown disease status into flock.
- Birds should not be returned to the farm from live bird markets or other slaughter channels.
- Control of human traffic: strict hygiene and biosecurity measures to prevent fomite transmission.
- One age/species group per farm ('all in-all out') breeding is recommended.

12.2 In Outbreaks

- Flock to be depopulated ("stamping out"). The FAO manual on HPAI control recommends a zoning strategy which begins with the identification of an infected area where sick or dead birds have tested positive. Poultry in this zone are culled while the area 1 to 5 km from the outer boundary of the infected area is considered the restricted area placed under strict surveillance. 2 to 10 km

from the restricted area is the control area that serves as a buffer zone in case of spread.

- Disposal of carcasses and all animal products by burying, composting or rendering.
- The manure and feed should be removed down to a bare concrete floor. If the floor is earthen, one inch or more of soil should be removed. The manure can be buried at least five feet deep. It may also be composted for 90 days or longer, depending on the environmental conditions. The compost should be tightly covered with black polyethylene sheets to prevent entry of birds, insects and rodents. Feathers can be burned or composted; alternatively, they may be removed and the area wet down with disinfectant.
- Thorough cleaning first, then disinfection. High-pressure spray equipment should be used to clean all equipment and building surfaces (beware of aerosols, personal protection equipment required). Once all surfaces are clean and free of all organic material, the entire premises should be sprayed with an approved residual disinfectant.
- Allow at least 21 days before restocking.
- Cats and dogs should not be fed poultry or other birds that may be infected especially with H5N1 avian influenza viruses. During outbreaks, they should be kept indoors.
- People should avoid wild birds and observe them only from a distance; avoid contact with domestic birds (poultry) that appear ill or have died; and avoid contact with surfaces that appear to be contaminated with faeces from wild or domestic birds. People in contact with known infected or possibly infected birds should take precautions to protect against infection. Consumption of properly cooked egg and chicken at temp 165⁰ F. Use of PPE (personal protective equipment) like N-99 respirator and indirectly vented safety goggles. For the prevention of human to human transmission, avoid travelling in places where outbreak occurred.

12.3 Vaccination

Based on the immune status of the populations and on antigenic and genetic information about circulating viruses (obtained through surveillance studies), the vaccine strains are recommended each year by the WHO. Since this decision has to be made more than 6 months prior to the influenza season, the selected vaccine strains occasionally differ antigenically from the viruses circulating during the subsequent influenza season. Limited antigenic match between the selected vaccine strains and the actually circulating strains may result in low efficacy. Vaccination may place selection pressure on avian influenza viruses, and might eventually result in the evolution of vaccine-resistant isolates. Killed vaccines are available in limited areas, but have limited efficacy. Most approved vaccines for H5, H7 and H9 viruses are based on inactivated whole virus preparations, although some live recombinant vaccines based on New castle disease and fowl pox virus are

in use. Official vaccination programmes against H5N1 viruses are being carried out in Hong Kong, Indonesia, China, Vietnam, Russia, India, Pakistan, Egypt but failed to eradicate H5N1 viruses in some of these countries. Possible reasons include limited coverage of vaccination campaigns, failure to induce sterilising immunity that may result in undetected virus spread and evolution and limited cross reactivity with viruses of different clades.

13. Conclusion

Avian influenza viruses remain a major health issue for poultry around the world. The greatest concern typically has been for HPAI because of its severe and detrimental effects on the international poultry trade and mortality. H5N1 avian influenza in humans is still a rare disease, but is severe one that must be closely watched and studied, particularly because of the potential of this virus to evolve in ways that could start a pandemic. Avian influenza (H5N1) pandemic is an event of low probability but one of high human health impact. It is certain that H5N1 panzootic already impacts human health via its economic and consequent nutritional impacts on rural societies and by occasional zoonotic transmission, leading to severe human disease. Even after tremendous development in the molecular biology, the mysteries surrounding the complex viral genetic reassortments giving rise to new pathogenic viral mutants remain to be unraveled. Nonetheless, virologists and biotechnologists will unveil the mechanism and develop strategies for mitigating the detrimental effects of AI.

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