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REVIEW

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Human Health Implications of Avian Influenza Viruses and Paramyxoviruses

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Abstract Among avian influenza viruses and avian paramyxoviruses are the aetiological agents of two of the most devastating diseases of the animal kingdom: (i) the highly pathogenic form of avian influenza, caused by some viruses of the H5 and H7 subtypes, and (ii) Newcastle disease, caused by virulent strains of APMV type 1. Mortality rates due to these agents can exceed 50% in naïve bird populations, and, for some strains of AI, nearly 100%. These viruses may also be responsible for clinical conditions in humans. The virus responsible for Newcastle disease has been known to cause conjunctivitis in humans since the 1940s. The conjunctivitis is self-limiting and does not have any permanent consequences. Until 1997, reports of human infection with avian influenza viruses were sporadic and frequently associated with conjunctivitis. Recently, however, avian influenza virus infections have been associated with fatalities in human beings. These casualties have highlighted the potential risk that this type of infection poses to public health. In particular, the pathogenetic mechanisms of highly pathogenic avian influenza viruses in birds and the possibility of reassortment between avian and human viruses in the human host represent serious threats to human health. For this reason, any suspected case should be investigated thoroughly.

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Influenza A Infections

Natural infections with influenza A viruses have been reported in a variety of animal species including humans, pigs, horses, sea mammals, mustelids and birds (for reviews see [1, 2, 3]). Occasionally, devastating pandemics occur in humans. Although viruses of relatively few haemagglutinin (HA) and neuraminidase subtype combinations have been isolated from mammalian species, all subtypes, in most combinations, have been isolated from birds [4].

In the 20th century the sudden emergence of antigenically different strains transmissible in humans, termed antigenic shift, occurred on four occasions, 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 1977 (H1N1), and each shift resulted in a pandemic. Pandemic viruses evolve through genetic reassortment, whereby strains exhibiting novel antigenic combinations are generated and, provided there is a suitable internal gene constellation, these may spread easily in a naïve population. This occurred in 1957 and 1968, when the new viruses completely replaced the previous virus in the human population, but in 1977 this did not happen and H3N2 and H1N1 viruses both circulate currently.

Frequent epidemics have occurred between the pandemics as a result of accumulated point mutations in the prevalent virus leading to gradual antigenic change, termed antigenic drift, which in turn results in infections in a proportion of the population that has become immunologically susceptible. The intra-pandemic influenza epidemics may have a substantial impact on a given population as a result of significant mortality, especially amongst the elderly and other vulnerable groups, and the severe economic cost associated with debilitating illness in a large portion of the population. However, the true influenza pandemics are unmistakable and may have catastrophic consequences.

By far the worst influenza pandemic was the one beginning in 1918. It has been estimated that during this pandemic between 20 and 50 million people died [5]. Since 1918 one of the main aims in the study of human influenza has been to understand how antigenic shift occurs and to predict when and how it will occur next. Since the greatest variety of influenza viruses has been found in birds, it is reasonable to assume that the next human pandemic virus will contain some or all genes of avian origin. The possible mechanisms by which this may occur, the implications of the molecular basis for pathogenicity and an overview of human infections with avian influenza (AI) viruses are reported below.

Avian Influenza

All AI viruses belong to the *Influenzavirus A* genus of the *Orthomyxoviridae* family and are negative-strand, segmented RNA viruses. Influenza A viruses, can be divided into subtypes on the basis of the possession of 1 of 15 antigenically distinct haemagglutinin antigens (H1–H15) and 1 of 9 neuraminidase antigens (N1–N9). Virtually all haemagglutinin and neuraminidase combinations have been isolated from birds. The genetic pool for all AI viruses is primarily in aquatic birds, which are responsible for the perpetuation of these viruses in nature [4]. Infection can spread from the wild to the domestic bird population, and it is in the latter that the most serious consequences can be seen.

Influenza A viruses infecting poultry can be divided into two distinct groups on the basis of their ability to cause disease. The very virulent viruses cause highly pathogenic AI (HPAI), which may result in mortality within a flock as high as 100%. These viruses have been restricted to subtypes H5 and H7, although not all viruses of these subtypes cause HPAI. All other viruses cause a much milder disease, known as low pathogenicity avian influenza (LPAI), consisting primarily of mild respiratory disease, depression and egg production problems in laying birds.

The diversity in the virulence of HPAI and LPAI strains has a molecular basis that has been determined. It has been demonstrated that the HA0 precursor of the main functional HA glycoprotein requires cleavage, to proteins HA1 and HA2, by host proteases before virus particles are infectious. HA0 proteins of AI viruses of low virulence for poultry are limited to cleavage by host proteases such as trypsin and trypsin-like enzymes; thus, they are restricted to replication at sites in the host where such enzymes are found, i.e. the respiratory and intestinal tracts. In contrast, virulent viruses appear to be cleavable by a ubiquitous protease(s), which remains to be fully identified, but appears to be a proprotein-processing subtilisin-related endoprotease(s) of which furin is the leading candidate [6]; this enables these viruses to replicate throughout the animal, damaging vital organs and tissues, which brings about disease and death in the infected bird [7].

Comparisons of the amino-acid sequences at the HA0 cleavage site of AI viruses of high and low pathogenicity revealed that while viruses of low virulence have only two basic amino acids, at positions −1 and −4 from the cleavage site for H5 and at positions −1 and −3 for H7 subtype, all HPAI viruses possessed multiple basic amino acids (arginine and lysine) adjacent to the cleavage site, either as a result of apparent insertion or apparent substitution. The presence of the additional basic amino acids results in a motif recognised and cleavable by the putative ubiquitous protease(s) [8, 9, 10].

Current evidence [11, 12, 13, 14, 15] strongly supports the hypothesis that HPAI viruses are not normally present in wild bird populations and only arise as a result of mutation after H5 or H7 LPAI viruses have been introduced to poultry from wild birds [16, 17].

Human/Avian Influenza Link

The RNA of influenza viruses is segmented into eight distinct genes and, as a result, genetic reassortment can occur following coinfection of a single cell with different strains of influenza A virus [18, 19]. This means that when two viruses infect the same cell, progeny viruses may inherit sets of RNA segments made up of combinations of segments identical to those of either of the parent viruses. This gives a theoretical possible number of 2^8 (=256) different combinations that can form a complete set of RNA segments from a dual infection, although, in practice, only a few combinations possess the correct gene constellation required for viability [20, 21].

It was shown that the H3N2 1968 pandemic virus differed from the 1957–1968 H2N2 virus in the substitution of two genes, PB1 and the important surface glycoprotein HA gene [22, 23, 24]. These "new" genes almost certainly came from an influenza virus of avian origin, which led to the suggestion that antigenic shift occurred as a result of reassortment of genes in dual infections with viruses of human and avian origin [23, 25]. As a result, systematic surveillance studies investigating the presence of influenza viruses in avian species were undertaken. These revealed enormous pools of influenza A viruses in wild birds, especially in migratory waterfowl.

This large number of influenza viruses in the bird population challenged the reassortment theory, since transfer and reassortment would seem likely to occur much more frequently than subtype changes have appeared in the human population. Volunteer experiments had shown that transitory infections resulted when humans were infected with some viruses of avian origin [26]. But very few natural infections of humans with avian influenza viruses had been reported, and it was clear that there was some barrier to the establishment of avian influenza viruses in the human population that was related to one or more of the gene segments. In contrast, both human and avian viruses are known to infect pigs readily. This led to the theory that pigs acted as "mixing vessels",

where reassortment between human and avian influenza viruses could take place.

Pigs have been shown to have specific cell receptors for "mammalian" and "avian" viruses, and through genetic reassortment "novel" genes could be made available. This could result in the emergence of viruses with the necessary gene(s) from the virus of human origin to allow replication and spread in the human population, but with a different haemagglutinin surface glycoprotein, so that the human population could be regarded as immunologically naïve. This theory was also thought to account for the apparent emergence of pandemics in the 20th century in the Far East, where agricultural practices mean high concentrations of people, pigs and waterfowl live closely together [27].

Zoonotic Aspects

Although it has been known for some time that the human pandemic viruses of 1957 and 1968 appeared to arise by reassortment between viruses present in the human population and AI viruses [22, 23, 24], until recently, direct infection of humans with AI viruses had not been considered an important zoonosis. Up to 1996 there were three instances on record of the isolation of an AI virus from humans. The first instance was of a HPAI virus of H7N7 subtype obtained from a patient with hepatitis in 1959 [28]. The second case related to a laboratory worker in Australia who developed conjunctivitis after accidental exposure directly in the eye with a HPAI virus of H7N7 subtype [29]. The third case was again related to conjunctivitis with an avian virus of H7N7 subtype, but this was a LPAI virus that spread to an animal handler from an infected seal [30]. In the last case, four other people handling the infected seals also developed conjunctivitis, but the cause of these infections was not confirmed by virus isolation.

Due to the sporadic nature of these incidents, human infections with AI viruses were considered rare events of little consequence. This view was largely supported by volunteer experiments, which had shown that only transitory infections resulted when humans were infected with some viruses of avian origin [26]. However, since 1996, a series of events has dramatically raised the profile of human infections with AI viruses.

In the last 6 years, AI virus infections have been detected in humans on five occasions, with four different viruses, belonging to three subtypes, being isolated. In 1996 a LPAI H7N7 virus was isolated in England from the eye of a woman with conjunctivitis who kept ducks. This virus was shown to be genetically closest in all eight genes to viruses of avian origin and to have >98% nucleotide homology in the HA gene with a virus of H7N7 subtype isolated from turkeys in Ireland in 1995 [11, 31].

In May 1997 a virus of H5N1 subtype was isolated from a young child who died in Hong Kong and by December 1997 the same virus was confirmed by isolation to have infected 18 people, 6 of whom died [32]. There was some evidence of very limited human-to-human spread of this virus, but clearly the efficiency of transmission was extremely low [33]. The viruses isolated from the human cases appeared to be identical to viruses first isolated from chickens in Hong Kong in March 1997 following an outbreak of HPAI. Both human and avian isolates possess multiple basic amino acids at the HA0 cleavage site.

In 2003 a H5N1 virus was isolated from a father and his son in Hong Kong, who both presented with respiratory illness after returning from the Chinese mainland, and the father died. A daughter of this man had also become ill and died while visiting the Chinese mainland, but it is not known if she was infected with H5N1 virus. There were reportedly some genetic differences between the 1997 and the 2003 H5N1 viruses (WHO website: http://www.who.int/mediacentre/releases/2003/pr17/en/).

In March 1999 influenza virus subtype H9N2 was isolated independently from two girls, aged 1 and 4 years, who recovered from influenza-like illnesses in Hong Kong [34]. Subsequently it was reported that H9N2 virus had been isolated from humans on mainland China on five occasions in 1998 [35].

During the 2003 outbreak of HPAI H7N7 in The Netherlands 82 of the 260 people involved in some aspect of the outbreak (i.e., presenting with conjunctivitis and/or influenza-like illness) were confirmed to be infected with H7 virus [36]. There was also evidence of three cases of human-to-human transmission within families. Six of the 260 people tested proved positive for H3N2 influenza, but none of them was also positive for H7N7. Following these cases veterinary, technical and support staff involved in the outbreak were treated prophylactically with antiviral drugs and subjected to vaccination against human influenza (to reduce the chance of reassortment between human and avian viruses). During this outbreak one human fatality also occurred. The victim was a 57-year-old veterinarian who had not received prophylactic antiviral drugs and who had contact with infected birds during outbreak management. He was admitted to hospital with severe headache and fever, subsequent to which he developed a severe respiratory condition and kidney failure and died. H7 virus was recovered from a bronchoalveolar lavage sample collected 9 days after the onset of illness [36].

From the data presented above, it appears that some strains of AI are capable of infecting humans directly without passing through a "mixing vessel". This poses a series of challenges that must be faced from a diagnostic point of view. In addition, the possibility of these avian strains reassorting with human viruses in human beings must be considered.

Newcastle Disease

Newcastle disease (ND) is a viral infection of birds caused by an avian paramyxovirus serotype 1 (APMV-1), which, together with eight other APMV serotypes, has been placed in the genus *Avulavirus*, sub-family *Paramyxovirinae*, family *Paramyxoviridae*, order *Mononegavirales* in the current taxonomy [37, 38].

ND is a highly contagious and diffusive disease that can cause a very severe condition in susceptible birds, with mortality rates exceeding 50% of the flock in chickens. However, there is considerable variation in strain virulence, ranging from the very virulent viruses to those that cause little or no disease in chickens. The least virulent viruses are used in many countries as live vaccines.

The molecular basis for virulence in ND viral strains appears to be very similar to that for AI viruses. In the case of ND virus, the fusion (F) protein appears to be the most important determinant of virulence. The viral F protein brings about fusion between the virus membrane and the cell membrane so that the virus genome enters the cell and replication can begin. The F protein is therefore essential for replication, but during replication, ND virus particles are produced with a precursor glycoprotein, F0, that has to be cleaved to F1 and F2 polypeptides, which remain bound by disulfide bonds, for the virus particles to be infectious. This post-translation cleavage is mediated by host cell proteases.

The cleavability of the F0 molecule has been shown to be related directly to the virulence of viruses in vivo. A large number of studies has confirmed the presence of multiple basic amino acids at the F0 cleavage site in virulent viruses (e.g. [39]). Usually the sequence has been 113RQK/RR ↓ F117 in virulent viruses, but most have had a basic amino acid at position 112 as well. In contrast, viruses of low virulence usually have the sequence 113K/RQG/ER ↓ L117. Thus, there appears to be the requirement of a basic amino acid at residue 113, a pair of basic amino acids at 115 and 116, plus a phenylalanine at residue 117 if the virus is to be virulent for chickens. The presence of these basic amino acids at these positions means that cleavage can be effected by one or more protease(s) present in a wide range of host tissues and organs, but for viruses of low virulence, cleavage can occur only with proteases recognising a single arginine, i.e. trypsin-like enzymes. Viruses of low virulence for chickens are therefore restricted in the sites where they are able to replicate to areas with trypsin-like enzymes, such as the respiratory and intestinal tracts, whereas virulent viruses can replicate and cause damage in a range of tissues and organs resulting in a fatal systemic infection.

ND is a serious problem for poultry health throughout Africa, Asia and parts of Central and South America either as an enzootic disease or as a cause of regular, frequent epizootic outbreaks. In other areas, such as Europe, the situation appears to be that of sporadic epizootic diseases occurring despite vaccination programmes.

Over 250 species of birds have been reported to be susceptible to natural or experimental infections with ND virus [40], and it seems probable that many more are fully susceptible. ND virus strains have been shown to infect all the major and minor species of domestic poultry, although some species, such as ducks, tend to show few signs of disease even when infected with the strains of ND virus that are the most virulent for chickens.

ND virus is also a recognised human pathogen, and in the UK the virus is placed in hazard group 2 by the Advisory Committee on Dangerous Pathogens [41]. This means ND is considered to be: "A biological agent that can cause human disease and may be a hazard to employees; it is unlikely to spread to the community....".

The first report of human infection with ND virus, described a case of conjunctivitis that developed in a laboratory worker who had accidentally introduced infective allantoic fluid into the eye [42]. Many of the reported instances of ND virus infecting humans have been the result of direct inoculation into the eye, either by laboratory workers or those handling vaccines [43].

Chang [44] produced a detailed review of the publications on ND virus as a zoonosis in 1981, but since that time there have been few additional publications, which probably reflects the lack of serious, lasting effects resulting from such infections and the fact that they are commonplace. Reported infections have been non-life-threatening and usually not debilitating for more than a day or two. The most frequently reported and best substantiated clinical signs in human infections have been eye infections, usually consisting of unilateral or bilateral reddening, excessive lacrimation, oedema of the eyelids, conjunctivitis and sub-conjunctival haemorrhage [44]; infections are usually transient and the cornea is not affected.

Reports of other clinical symptoms in humans infected with ND virus have included more generalised infections resulting in chills, headaches and fever, with or without conjunctivitis [44], but such infections appear to be rare.

Human infections with ND virus have usually resulted from direct contact with the virus, with infected birds or with the carcasses of diseased birds. There have been no reports of human-to-human spread, although spread by contact is theoretically possible. The types of people known to have been infected with ND virus include laboratory workers, veterinarians in diagnostic laboratories, workers in chicken processing plants and vaccination crews. Pedersden et al. [45] reported significantly higher antibody titres to ND virus in people who had a known association with poultry. ND viruses virulent for poultry and those used as live vaccines appear to be equally able to cause conjunctivitis in humans.

There have been no reports of other APMV serotypes infecting humans. However, the potential may exist, and a virus of the APMV-2 serotype was isolated from cynomolgus monkeys [46].

Discussion

From the data presented it appears that AI infections pose a serious threat to human health, while infection with Newcastle disease does not. However, the two infections may in some instances be confused or treated as bacterial "conjunctivitis". If the patient has a history of rearing or being in contact with poultry, it would seem prudent to process conjunctival swabs for virus isolation.

One of the most alarming aspects of the recent AI infections is the significant increase in the number of cases compared to prior years. The five incidents reported in the last six years raise several important issues. The fact that AI viruses appear to be able to infect humans fairly regularly, especially via the conjunctival route, and cause signs of disease is likely to have public health repercussions pertaining to the handling of all AI outbreaks in poultry. It should be noted, however, that all AI viruses causing conjunctivitis in humans were of the H7N7 subtype, regardless of their virulence for chickens. Whether this represents a coincidence or not remains unclear.

The H5N1 HPAI infections in Hong Kong have been particularly alarming because of the high associated mortality rates. The particular concern for HPAI viruses is that mammals, including humans, also possess furin, the putative ubiquitous protease that cleaves HPAI virus HA0 cleavage sites with multiple basic amino-acid motifs leading to systemic infections in birds. Linked to this is possibly the most important consideration related to AI virus infections in humans, namely, that while infections to date have been extremely limited in their human-to-human spread, it is quite feasible that AI and human influenza viruses could infect the same individual. This could result in reassortment between the two viruses with the consequence that a virus emerges with the internal genes from the human virus, allowing easy transmission in humans, but with the HA from the avian virus, which, inevitably, would lead to a new pandemic.

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