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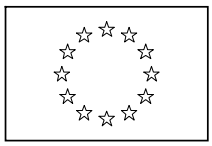


EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Health Opinions
Unit C3 - Management of scientific committees II

The Definition of Avian Influenza

The use of Vaccination against Avian Influenza

Scientific Committee on Animal Health and Animal Welfare

Adopted 27 June 2000

Contents

1. Request for opinion

The Scientific Committee on Animal Health and Animal Welfare is asked to consider if the current definition of Avian Influenza contained in Directive 92/40/EEC is now the most appropriate and whether it should be modified in the light of advances in scientific knowledge.

The Committee is also asked to report on the possible risks and benefits in the use of vaccination against avian influenza in order to eradicate the disease. The report should also consider criteria for the use of vaccine, if applicable and consider the implications of vaccine use for movement of live birds and poultry products.

Part 1 Definition of Avian Influenza

2. Introduction

A disease capable of causing extremely high (up to 100%) mortality in poultry was first distinguished from bacterial diseases, such as fowl cholera, by Perroncito in 1878. This disease is now termed highly pathogenic avian influenza (HPAI), but was known as "fowl plague" until 1981.

The ability of workers in different countries to identify and diagnose HPAI during the early part of the 20th century was very variable. Nevertheless from the literature it would appear that HPAI was endemic in Italy for at least 50 years up to the last outbreaks of HPAI recorded in the mid 1930s. The virus was reported in Germany in 1890 and probably remained endemic into the 1930s. Writing in 1930, Todd & Rice (1930) considered HPAI to have occurred in Austria, Switzerland, France, Belgium, The Netherlands, England, Egypt, China, Japan, USA, Argentina and Brazil.

In England outbreaks occurred in 1922 and 1929, but there did not appear to be much spread. This may well have been due to the common practice at that time of farmers faced with serious disease problems slaughtering the flock and restocking.

HPAI occurred in the USA in 1924-1925 and spread to nine eastern states. Spread appeared to be primarily as a result of the movement of birds and was especially associated with live bird markets. There were further outbreaks in 1929 and it was not clear whether the virus had remained since 1925 or there had been a new introduction.

Very few reports describing HPAI outbreaks appeared in the literature from the mid-1930s to 1959, but authors often stated that outbreaks were not uncommon in Africa, Asia and Eastern Europe.

Since 1959 there have been 18 reported outbreaks of HPAI in poultry (Table 1) 8 have been due to H5 viruses and 10 to H7 viruses. Seven were from current EU Member States. In about half of the 18 outbreaks there has been little or no spread from the farm where the virus was first identified. Significant spread to numerous sites resulting in huge economic losses was recorded in Pennsylvania in 1983, Mexico in 1994, Pakistan in 1994, Hong Kong in 1997 and Italy in 1999/2000.

Table 1: HPAI isolates from poultry* since 1959

1. A/chicken/Scotland/59 (H5N1)
2. A/turkey/England/63 (H7N3)
3. A/turkey/Ontario/7732/66 (H5N9)
4. A/chicken/Victoria/76 (H7N7)
5. A/chicken/Germany/79 (H7N7)
6. A/turkey/England/199/79 (H7N7)
7. A/chicken/Pennsylvania/1370/83 (H5N2)
8. A/turkey/Ireland/1378/83 (H5N8)
9. A/chicken/Victoria/85 (H7N7)
10. A/turkey/England/50-92/91 (H5N1)
11. A/chicken/Victoria/1/92 (H7N3)
12. A/chicken/Queensland/667-6/94 (H7N3)
13. A/chicken/Mexico/8623-607/94 (H5N2)
14. A/chicken/Pakistan/447/94 (H7N3)
15. A/chicken/NSW/97 (H7N4)
16. A/chicken/Hong Kong/97 (H5N1)
17. A/chicken/Italy/330/97 (H5N2)
18. A/turkey/Italy/99 (H7N1)

*Where outbreaks were widespread and affecting more than one species, the isolate from the first outbreak identified is listed.

3. Aetiology of Avian Influenza

HPAI was one of the earliest diseases to be shown to be of viral aetiology when several groups demonstrated the causative agent was "ultra-filterable" around the turn of the 20th Century. However, it was not until 1955 that the close relationship of this and other viruses isolated from birds, but causing much milder disease, with mammalian influenza A viruses (first isolated in the 1930s) was demonstrated (Schäfer, 1955). Influenza viruses have segmented, negative sense, single strand RNA genomes and are placed in the family *Orthomyxoviridae*. There are three types of influenza virus, A, B and C. Only influenza A viruses have been reported to cause natural infections of birds. Type A influenza viruses are further divided into subtypes based on the antigenic relationships in the surface glycoproteins haemagglutinin (HA) and neuraminidase (NA). At present 15 HA subtypes have been recognised (H1-H15) and nine NA subtypes (N1-N9). Each virus has one HA and one NA antigen, apparently in any combination. All influenza A subtypes in the majority of possible combinations have been isolated from avian species. To date only viruses of H5 and H7 subtype have been shown to cause HPAI in susceptible species, but not all H5 and H7 viruses are virulent.

For all influenza A viruses the haemagglutinin glycoprotein is produced as a precursor, HA0, which requires post translational cleavage by host proteases before it is functional and virus particles are infectious (Rott, 1992). The HA0 precursor proteins of avian influenza viruses of low virulence for poultry have a single arginine at the cleavage site and another basic amino acid at position -3 or -4. These viruses are limited to cleavage by host proteases such as trypsin-like enzymes and thus restricted to replication at sites in the host where such enzymes are found, i.e. the respiratory and intestinal tracts. HPAI viruses possess multiple basic amino acids (arginine and lysine) at their HA0 cleavage sites either as a result of apparent insertion or apparent substitution (Vey et al, 1992, Wood et al, 1993, Senne et al, 1996) and appear to be cleavable by a ubiquitous protease(s), probably one or more proprotein-processing subtilisin-related endoproteases of which furin is the leading candidate (Stieneke-Grober et al., 1992). These viruses are able to replicate throughout the bird, damaging vital organs and tissues which results in disease and death (Rott, 1992). All the HPAI viruses listed in Table 1 and all those prior to 1959 possess multiple basic amino acids at their HA0 cleavage sites.

4. Epidemiology of Avian Influenza

4.1 Natural Reservoirs

Influenza viruses have been shown to infect a great variety of birds (for reviews see Lvov 1978; Hinshaw et al., 1981a; Alexander 2000), including free-living birds, captive caged birds, domestic ducks, chickens, turkeys and other domestic poultry. Viruses have been isolated from species of free-living bird covering all the major families of birds. However, the frequency of isolation and variations in subtypes seen in ducks and geese has overshadowed those from other species. It seems likely that the viruses are perpetuated in free-living birds, particularly migratory waterfowl (Hinshaw et al., 1980).

Studies by Sharp et al., (1993), suggest that waterfowl do not act as a reservoir for all avian influenza viruses. It seems likely that part of the influenza gene pool is maintained in shorebirds and gulls, from which the predominant number of isolated influenza viruses are of a different subtype to those isolated from ducks (Kawaoka et al., 1988).

Evidence that initial outbreaks in domestic poultry occur as the result of spread from free-living birds is largely circumstantial, but nevertheless overwhelming (Easterday, 1975; Alexander, 1982b). As a consequence, considerable antigenic variation is seen in disease outbreaks in domestic poultry.

HPAI viruses have been isolated rarely from free-living birds and, apart from tern/S.Africa/61 (Becker, 1966), when they have been isolated it has usually been in the vicinity of outbreaks of HPAI in poultry or geographically and chronologically close to known outbreaks in poultry.

4.2 Spread

4.2.1 Transmission.

The mechanisms by which influenza viruses pass from one bird to another and bring about infection are poorly understood. Some attempts have been made to assess the transmissibility of influenza viruses experimentally (Narayan et al., 1969; Alexander et al., 1978, 1986; Westbury et al., 1979, 1981), usually in domestic poultry. The results suggest that bird to bird transmission, which is extremely complex, depends on strain of virus, the species of bird, and environmental factors.

In both natural and experimental infections virulent viruses have tended to show much poorer transmission from infected to susceptible chickens and turkeys than viruses of low pathogenicity. The ability of virus to spread easily must, to some extent, be related to the amount of virus released by the respiratory or intestinal route. The highly pathogenic viruses cause extremely rapid deaths in these birds and it is possible that relatively little virus is excreted during the course of such infections.

Hinshaw et al., (1980) considered that the perpetuation of influenza viruses in Canadian free-living waterfowl was related to the passage of virus from adult to

juvenile birds on lakes where the birds congregated before migration. Considerable quantities of the virus are excreted with the faeces, Webster et al. (1978) estimated up to $10^{8.7}$ mean egg infectious doses per g of faeces from infected ducks. This contaminates lake or pond water, to the extent that virus may be isolated from untreated lake water where large numbers of waterfowl are found (Hinshaw et al., 1979). Influenza virus may remain infective in lake water for up to 4 days at 22°C and over 30 days at 0°C (Webster et al., 1978). Stallknecht et al., (1990) estimated that from an initial concentration of 10^6 $TCID_{50}$/ml infectivity was retained for up to 207 days at 17°C and 102 days at 28°C. Contaminated lake or drinking water may therefore result in infection by the faecal/oral route, or possibly by the faecal/cloacal route as a result of 'cloacal drinking'. For all birds the ingestion of infective faeces appears to be the most important mode of transmission.

4.2.2 Primary introduction to domestic poultry.

On many duck farms the continual presence of influenza viruses is probably due to the repeated introduction of susceptible ducklings to fields where virus is already present, and influenza viruses may be considered enzootic in some commercial ducks, particularly fattening ducks. However, Shortridge (1982) and Sandhu and Hinshaw (1982) report considerable variation in the subtypes present in commercial flocks and it is assumed that fresh introductions by free-living birds also occur.

Despite the frequency with which influenza viruses are isolated in some countries (see above), in none is it considered that these viruses are enzootic in turkeys or chickens. It is significant that the majority of outbreaks in most countries have occurred in turkey flocks situated on the migratory routes of waterfowl. Even in Minnesota, USA, where influenza outbreaks in turkeys occur annually, the considerable variation in virus subtype, the differences in the number of outbreaks seen each year, and the seasonal relationship of outbreaks all suggest that the influenza epizootics are brought about as a result of new primary introductions each year.

4.2.2.1 From other domestic poultry.

Occasional outbreaks of influenza in one poultry species near flocks of other infected species have been reported, but there is little direct evidence of spread from one to the other. However, there have been several instances in which circumstantial evidence of such spread was strong. For example, viruses of the same subtype were isolated from birds on closely situated duck and chicken farms in Australia in 1976 (Westbury et al., 1979). Petek (1982) also reported a close association between hens and turkeys infected with virus of H5N2 subtype, and throughout the history of avian influenza in Italy infections have been seen simultaneously in turkeys, quail and other domestic birds. Similar findings have been reported from Minnesota, USA, where chickens, guinea fowl and pheasants became infected during influenza epizootics in turkeys (Halvorson et al., 1980; Pomeroy, 1982), and from Belgium where separate duck and chicken flocks were shown to be infected with the same subtype of influenza virus (Meulemans et al., 1979).

4.2.2.2 From free-living birds.

In the vast majority of influenza outbreaks occurring in domestic poultry, particularly turkeys, spread from free-living birds appears to be the most likely mechanism of primary infection, the evidence being weighty though mainly circumstantial.

The frequency with which free-living birds, particularly waterfowl, are infected and excrete influenza viruses has been discussed above. Waterfowl almost certainly disseminate influenza virus during their migration. Hinshaw et al., (1980) commented that the proportion of active excreters of influenza virus was far greater in ducks congregating on lakes in Alberta, Canada than in those actually on migration. Infection of domestic poultry by waterfowl, either directly or indirectly, is more likely to occur in geographical areas on migratory routes than in those that are not and more likely to occur at some stages on the routes than others. This is certainly true for infections in turkeys, which occur particularly in areas on migratory waterfowl flyways, e.g. Norfolk in England, and more frequently at some stages of the migratory route than others, e.g. Minnesota, USA compared to other states on the Mississippi flyway (Pomeroy, 1982). In addition, in areas such as Minnesota, a marked similarity between the subtypes prevalent in the waterfowl population and those infecting turkeys (Bahl et al., 1979; Halvorson et al., 1983, 1987).

The higher incidence of influenza virus infections in domestic ducks than in turkeys, and in turkeys than in chickens is compatible with introductions being made by free-living birds. Domestic ducks, particularly fattening birds, are in most countries raised in fields or on ponds and are open to contact with free-living birds. In some countries turkeys are at least partly raised on open range, as in Minnesota, USA. However in Canada, parts of which experienced outbreaks during the 1960s comparable with those seen in Minnesota, all turkeys have been placed in confinement proofed against free-living birds since the early 1970s. Lang (1982) concluded that this was the major reason for the decline in influenza infections in turkeys in Canada. Pomeroy (1987), reviewing influenza outbreaks in Minnesota, endorsed this view, contrasting the incidence of influenza infections in chickens and turkeys kept in confinement to that in turkeys reared on open range during May to November. In contrast, in most countries chickens are reared in substantial houses which resist free-living bird invasion and this may account for the low incidence of influenza in chickens discussed above.

4.2.2.3 From other animals.

Influenza viruses can infect a large variety of animals and the so-called 'species barriers' are much less clear cut in the ecology of influenza viruses than they were once thought to be (Alexander, 1982a). Mammals and other animals must, therefore, be regarded as a potential source of influenza viruses for birds.

In particular there is good evidence of the interaction of influenza viruses of H1N1 subtype between turkeys and pigs (Mohan et al.. 1981). Pomeroy (1982) records that in five of the states in the USA which have only rarely reported influenza in turkeys, only infections with H1 viruses, similar to those reported in pigs, have been seen; and the occurrence of infected turkeys and sick pigs on the same farm has been recorded often (Bankowski, 1983).

4.2.3 Secondary spread.

The greatest threat of spread of avian influenza viruses is by mechanical transfer of infective faeces, in which virus may be present at concentrations as high as 10^7 infectious particles/gram and may survive for longer than 44 days (Utterback, 1984). Birds or other animals which are not themselves susceptible to infection may become contaminated and spread the virus. Shared water or food may also become contaminated. However, for domestic poultry the main source of secondary spread appears to be man. In several specific accounts strong evidence has implicated the movements of caretakers, farm owners and staff, trucks and drivers moving birds or delivering food, and artificial inseminators in the spread of the virus both on to and through a farm (Wells 1963; Homme et al., 1970; Halvorson et al., 1980; Alexander & Spackman, 1981; Glass et al., 1981).

Spread by personnel and fomites was also strongly suspected in the widespread and devastating epizootic in chickens in Pennsylvania during 1983-1984. Although there was some evidence that windborne spread may have played a role amongst very closely situated farms and that flying insects could become contaminated with infected faeces, it was concluded by most observers that secondary spread was principally due to the movement of personnel and equipment between farms (Johnson, 1984; King, 1984; Utterback, 1984). King (1984) listed six types of fomite that may be moved from farm to farm and 11 types of personnel that may be in contact with two farms or more; Utterback (1984) produced even longer lists. It is clear that at all times such movement must be strictly controlled, and strict hygiene enforced.

4.3 Zoonotic risk

Influenza is a highly contagious, acute illness in humans for which there are recognisable accounts of epidemics dating back to ancient times. In the 20th century the sudden emergence of antigenically different strains in humans, termed *antigenic shift*, occurred on 4 occasions, 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 1977 (H1N1), resulting in pandemics. 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 considerable 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. Occasionally the degree of antigenic drift is sufficient that a very large proportion of the population is susceptible and severe epidemics occur with world-wide spread. 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 the pandemic between 20 to 40 million people died. In well developed countries such as the USA about 0.5% of the population died, but in some communities in Alaska and the Pacific islands mortalities were closer to half the population.

The RNA of influenza viruses is segmented into 8 distinct segments that code for 10 proteins. Because the viral RNA is segmented, genetic reassortment can occur in mixed infections with different strains of influenza A viruses. 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 progeny virions possess the correct gene constellation required for viability. Demonstration 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, with genes almost certainly from an influenza virus of avian origin, 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 (Fang et al., 1981; Kawaoka et al., 1989). However, although volunteer experiments had shown that transitory infections resulted when humans were infected with viruses of avian origin (Beare & Webster, 1991) no natural infections of humans with avian viruses had been reported. 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 genome segments. Both human and avian viruses are known to infect pigs readily. It was, therefore, suggested that pigs acted as "mixing vessels" in which reassortment between human and avian influenza viruses could take place with the emergence of viruses with the necessary genome segments(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 (Scholtissek, et al., 1985). 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 (Shortridge & Stuart-Harris, 1982).

In the last 4 years avian influenza virus infections of humans have been detected on four occasions, with three different subtypes.

In 1996 an 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 8 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 (Banks et al., 1998).

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, six of whom died (Shortridge et al., 2000). There was evidence of very limited human to human spread of this virus (Buxton Bridges et al., 2000), but clearly the efficiency of transmission must have been extremely low. There have been no new cases since December 1997. 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 highly pathogenic disease. Both human and avian isolates possess multiple basic amino acids at the HA0 cleavage site (Suarez et al., 1998).

In recent years outbreaks in poultry due to viruses of H9 subtype, usually H9N2, have been widespread. During the second half of the 1990s outbreaks, due to H9N2 subtype have been reported in Germany, Italy, Ireland, South Africa, USA, Korea, China, the Middle East, Iran and Pakistan (Banks et al., 2000). These have often been associated with widespread and serious disease problems in commercial chickens. In March 1999 two independent isolations of influenza virus subtype H9N2 were made from girls aged one and 4 who recovered from flu-like illnesses in Hong Kong (Peiris et al., 1999a; 1999b). Subsequently, 5 isolations of H9N2 virus from humans on mainland China in August 1998 were reported.

The obvious inference is that the very high mortality, 6/18, amongst the people infected with the H5N1 virus in Hong Kong was because the virus was capable of systemic infection due to the presence of multiple basic amino acids at the HA0 cleavage site. This would allow cleavage to be mediated by a furin-like protease(s) and the virus to spread systemically. However, evidence that this was the case is lacking. Generally, the 18 patients presented with severe respiratory symptoms. For those that died, several of whom were vulnerable due to complicating medical conditions present prior to infection, pneumonia appeared to be the main cause as it often is in deaths occurring as a result of infections with influenza viruses "normally" in the human population. Infections of other mammals with avian influenza viruses also give few clues to the significance of multiple basic amino acids at the HA0 cleavage site. An infection of harbour seals during 1978-80 off the NE coast of the United States of America with H7N7 avian influenza resulted in death of an estimated 20% of the population (Webster et al., 1981). While this mortality rate is comparable to that occurring in humans in Hong Kong, the HA0 cleavage site of the H7N7 virus did not have a motif containing multiple basic amino acids. Conversely, H7N7 viruses responsible for equine influenza type 1, for which A/equine/Prague/56 (H7N7) is the type strain, do have multiple basic amino acids at the HA0 cleavage site and yet in infections of horses with this strain, virus replication is invariably restricted to the respiratory tract (Gibson et al., 1992).

The isolation of the H7 virus from the woman with conjunctivitis was fortuitous, the first isolation of H5N1 in Hong Kong as a result of the death of the patient and all other isolates of avian viruses from humans resulted from enhanced awareness and surveillance exercises. In all these cases there was no evidence of human to human spread except with the H5N1 infections where there was evidence of very limited spread. This is in keeping with the finding that all these viruses possessed all eight genes of avian origin. It may well be that infection of humans with avian influenza viruses occurs much more frequently than originally assumed, but due to their limited effect go unrecognised. For the human population as a whole the main danger appears to be if people infected with an "avian" virus are infected simultaneously with a "human" influenza virus. In such circumstances reassortment could occur with the potential emergence of a virus fully capable of spread in the human population, but with an HA for which the human population was immunologically naive. Presumably this represents a very rare coincidence, but one which could result in a true influenza pandemic.

5. The Disease

5.1 Low Pathogenic Avian Influenza

The severity of the disease produced by viruses inducing little or no disease in chickens infected experimentally and without multiple basic amino acids at the HA0 cleavage site (termed Low Pathogenic Avian Influenza (LPAI) viruses) is greatly influenced by: the strain of virus, the species and age of host; the immune status of the host against the virus and particularly the presence of other infectious agents such as: *Pasteurella spp*, Newcastle disease viruses (including vaccine strains), avian pneumovirus, infectious bronchitis virus, *E. coli* and *Mycoplasma spp*, immunodeficiency conditions and environmental factors (such as excess ammonia, dust, hot or cold temperatures).

At one extreme the disease seen may be inapparent or slight. For example, Alexander and Spackman (1981) reported that an LPAI infection in a turkey laying flock resulted in only transient mild respiratory signs and 2% white-shelled eggs. Other LPAI outbreaks occurring in turkeys at about the same time produced 20-40% egg production drops and respiratory disease with low but significant mortality.

At the other extreme infections with LPAI viruses may be associated with severe disease and with high mortality. In outbreaks in chickens in Alabama in 1975 with a LPAI virus of H4N8 subtype up to 69% mortality was recorded in infected flocks (Johnson et al., 1977). In 1995 major outbreaks caused by LPAI viruses of H7N3 subtype affected turkeys in Utah USA and was associated with significant mortality especially in young birds, with about 40% mortality in 0- to 4-week-old birds (Halvorson et al., 1998). In most cases mortality was associated with dual infections with *Escherichia coli* or *Pasteurella multocida*. During the LPAI H7N1 infections in Italy in 1999 turkeys were particularly affected. In turkeys reared for meat the severity of the clinical and post mortem disease varied considerably, clinical signs were dominated by respiratory distress with mortality ranging from 5% to 97% depending on the age of the affected birds. In young meat birds the signs were usually sufficiently severe to result in 40-97% mortality. In turkey breeders a milder form of the same clinical condition was observed that consisted of exhibited rales, coughing and swelling of the infraorbital sinuses and a febrile condition associated with loss of appetite. Egg production dropped by 30% to 80% during the acute phase, but partially recovered to subnormal levels within three weeks from the onset of the disease. Mortality rates ranged from 5 to 20% (Capua et al., 2000). Equally serious problems have been reported in recent years associated with widespread outbreaks of viruses of H9N2 subtype particularly in Pakistan and Iran.

5.2 Highly Pathogenic Avian Influenza

Often the first signs of HPAI in chickens or turkeys, especially birds not in cages, are the sudden onset of high mortality, which may approach 100% within a few days. Clinical signs that may be associated with high mortality are: cessation of egg laying,

respiratory signs, rales, excessive lacrimation, sinusitis, oedema of the head and face, subcutaneous haemorrhage with cyanosis of the skin, particularly of the head and wattles, and diarrhoea, occasionally neurological signs may be present. Usually, these signs are most marked in birds that take some time to die. Mortality in susceptible turkeys or chickens is often 100%.

5.3 Emergence of Highly Pathogenic Avian Influenza

As discussed above viruses of H5 or H7 subtype isolated from free-living birds are invariably of low pathogenicity for poultry. Apart from the die-off of large numbers of terns in South Africa in 1961 (Becker, 1966), from which A/tern/South Africa/61 (H5N3) was isolated, isolations from free-living birds have been associated with contact with infected poultry, usually as a result of surveillance of birds trapped or found dead on infected premises. In addition results of phylogenetic studies of H7 subtype viruses indicate that HPAI viruses do not constitute a separate phylogenetic lineage or lineages, but appear to arise from non-pathogenic strains (Rohm et al., 1995; Banks et al., 2000). This is supported by the *in vitro* selection of mutants virulent for chickens from an avirulent H7 virus (Li et al., 1990).

These findings are in keeping with the theories of the molecular basis for the mutation of avian influenza subtype H5 and H7 viruses from low to high virulence in poultry put forward by Garcia, et al., (1996) and Perdue et al., (1998). Essentially it is proposed that spontaneous duplication of purine triplets results in the insertion of basic amino acids at the HA0 cleavage site and that this occurs due to a transcription fault by the host polymerase complex. The assumption is that this transcription fault occurs more readily with chicken or turkey enzymes than those of free-living bird hosts. As pointed out by Perdue et al., (1998) this may not be the only mechanism by which HPAI viruses arise as some appear to result from nucleotide substitution rather than insertion while others (including the recent Italian H7N1 HPAI virus) have insertions without repeating nucleotides.

6. Current definitions

6.1 EU

European Union legislation on avian influenza is contained in Council Directive 92/40/EEC. The disease is defined as follows in Annex III of the directive;

"For the purpose of the diagnostic procedures for the confirmation and differential diagnosis of avian influenza the following definition shall apply.

'Avian influenza' means an infection of poultry caused by any influenza A virus which has an intravenous pathogenicity index[1] in six-week-old chickens greater than 1.2 or any infection with influenza A viruses of H5 or H7 subtype for which nucleotide sequencing has demonstrated the presence of multiple basic amino acids at the cleavage site of the haemagglutinin."

6.2 OFFICE INTERNATIONAL DES EPIZOOTIES (OIE)

Broadly similar rules to the above are used by The Office International des Epizooties (OIE). The following definition is taken from the Manual of Standards for Diagnostic Tests and Vaccines (OIE, 1996)

"*a) Any influenza virus that is lethal for six, seven or eight of eight 4- to 8-week-old susceptible chickens within 10 days following intravenous inoculation with 0.2 ml of a 1/10 dilution of a bacteria-free, infective allantoic fluid.*

b) The following additional test is required if the isolate kills from one to five chickens but is not of the H5 or H7 subtype: growth of the virus in cell culture with cytopathogenic effect or plaque formation in the absence of trypsin. If no growth is observed, the isolate is considered not to be a HPAI isolate.

c) For all H5 and H7 viruses of low pathogenicity and for other viruses, if growth is observed in cell culture without trypsin, the amino acid sequence of the connecting peptide of the haemagglutinin must be determined. If the sequence is similar to that observed for other HPAI isolates, the isolate being tested will be considered to be highly pathogenic."

[1] The intravenous pathogenicity index (IVPI) is the mean score per bird per daily observation over 10 days of 10 six-week-old chickens inoculated intravenously with the virus under test when birds are scored:- Score 0 = normal, Score 1 = sick, Score 2 = very sick or paralysed, Score 3 = dead. An IVPI = 0 means that no signs were seen in the 10 day observation period. An IVPI = 3 means that all birds died within 24 hours.

6.3 Comment

Both the EU and OIE definitions were originally formulated over ten years ago at a time when the understanding of the molecular biology of the pathogenicity of AI was in its infancy. Essentially the definitions were aimed at including viruses that were overtly virulent in *in vivo* tests and those that had the potential to become virulent. At that time the only virus known to have mutated to virulence was the one responsible for the 1983/84 Pennsylvania panzootic. In this epizootic viruses isolated at the beginning of AI infections of poultry in Pennsylvania were of low virulence for chickens although possessing multiple basic amino acids at the cleavage site (Kawaoka et al., 1984, 1987). However, these early viruses possessed a carbohydrate chain close to the cleavage site in the three dimensional structure of the HA molecule that was absent in the later HPAI isolates. The inference is that the presence of this carbohydrate chain prevented access of host proteases (but not trypsin-like enzymes) to the cleavage site and when lost the potential virulence of the virus was realised. This mechanism has not been seen in other viruses. However, these definitions have set a precedent for including potentially pathogenic as well as overtly virulent viruses in definitions of HPAI.

7. Reasons for reviewing definition

The accumulating evidence that HPAI viruses arise from LPAI H5 or H7 viruses infecting chickens and turkeys suggests that when viruses of these subtypes spread from free-living birds there is a potential that they may become virulent. However, when and if this will occur remains unpredictable. Presumably in outbreaks of HPAI such as that occurring in England in 1991 (Alexander et al., 1993), in which only a single house of turkeys was affected the mutation may happen very quickly after introduction. In Australia in 1976 there was evidence of limited spread before mutation took place (Westbury, 1998, Perdue et al., 1998). Whereas in Pennsylvania in 1983 (Webster & Kawaoka, 1988), Mexico in 1993/94 (Campos-Lopez et al., 1996, Villarreal & Flores, 1998) and Italy 1999/2000 (Capua et al., 2000) there had been extensive outbreaks of LPAI for a considerable period of time before the emergence of HPAI. It can only be assumed that mutation to virulence is a random event. In that case the longer the presence and greater the spread in poultry the more likely it is that HPAI virus will emerge. It would therefore seem reasonable to limit the spread and presence of LPAI viruses of H5 and H7 subtype in poultry to limit the probability of a mutational event occurring. This in turn would require redefining Statutory AI.

8. Conclusions

It would appear unwise to ignore the current theories that HPAI viruses emerge from LPAI viruses of H5 and H7 subtypes by mutation. The outbreaks in Pennsylvania, Mexico and Italy are demonstrations of the consequences of failing to control the spread of LPAI viruses of H5 and H7 subtypes.

There appears to be three options in bringing about more rigorous control of infections with H5 and H7 AI viruses.

1. **Retain the current definition and control measures in Directive 92/40/EEC with a recommendation that Member States impose restrictions to limit the spread of LPAI.**

2. **Define AI for the purposes of Directive 92/40/EEC as an infection of poultry with any AI virus of H5 or H7 subtype.**

3. **Define statutory AI as any infection with AI virus of H5 or H7 subtype, but modify the control measures imposed for different categories of virus and/or different types of host.**

Option 1 essentially maintains the status quo. Since adoption of the control measures laid down in Directive 92/40/EEC HPAI has occurred on three occasions in the EU. The 1991/92 H5N1 outbreak in England appeared to be self-limiting and there was no spread beyond the single infected flock (Alexander et al., 1993). The 1997/98 H5N2 outbreaks in NE Italy were limited to 8 farms and the control measures were effective (Capua et al., 1999). The 1999/2000 H7N1 epizootic in North East Italy has proven far more devastating and over a period from the middle of December 1999 to the first week in April 413 outbreaks were recorded. The widespread dissemination of LPAI H7N1 virus in Italian poultry prior to the emergence of the HPAI virus may well be the significant factor that contributed to the difficulty in controlling this most recent epizootic.

The H5 and H7 subtype LPAI viruses isolated from poultry since 1992 are listed in Table 2.

Table 2: Isolations of LPAI viruses of H5 and H7 subtypes from poultry in EU Member States since 1992.

Year	Type of poultry	Country	Influenza subtype
1992	Geese	Italy	H5N2
1994	Ratites	Netherlands	H5N9
1996	Ostriches	Netherlands*	H5N2
1996	Ostriches	Denmark*	H5N2
1998	turkeys (28 outbreaks) chickens (one outbreak)	Ireland	H7N7
1998	turkeys (2 outbreaks) chickens (one outbreak)	Northern Ireland	H7N7
1999	poultry (195 outbreaks)	Italy	H7N1
1999	Chickens	Belgium	H5N2

*Imported birds kept in quarantine.

The outbreaks of most significant threat to the poultry industry were those occurring on the island of Ireland in the Republic of Ireland (29 outbreaks) and Northern Ireland (3 outbreaks). In both countries the potential to mutate to HPAI viruses and the potential public health risks were considered serious threats by regulatory authorities and industry. The spread of virus was successfully eliminated by a programme of biosecurity measures, voluntary slaughter, early marketing, cleansing and disinfection and extensive surveillance (Graham et al., 1999; Campbell & De Geus, 1999). In effect additional control measures were imposed locally.

Option 2 would involve slaughter of all poultry (i.e. including ducks and geese) infected with either H5 or H7 subtype AI virus regardless of the virulence of the virus in *in vivo* tests or the number of basic amino acids at the HA0 cleavage site. This option is clear and simple and would result in quicker diagnosis and implementation than the current definition as it requires neither *in vivo* testing or sequencing of the amino acids at the HA cleavage site. However, it would also involve slaughtering birds such ducks and geese infected with LPAI H5 and H7 viruses even though there is no evidence that mutation to virulence may occur in these hosts. There is also a natural resistance amongst poultry farmers to slaughter birds that may be showing few if any clinical signs. This could lead to failure to investigate mild respiratory disease or even to covering up infections with LPAI.

Option 3 is an intermediate position. In this option all infections of poultry with H5 and H7 AI viruses would be notifiable within the EU and measures to control their spread would be a statutory requirement. However, the measures enforced for HPAI would differ from those for LPAI. For HPAI the control measures in Directive 92/40/EEC, including compulsory slaughter of infected birds would be mandatory. For outbreaks of LPAI the most important and urgent safeguard is the need to prevent further spread. Voluntary slaughter or early marketing should be considered. Although, it is important birds are not moved while they are still excreting virus. Infected birds

that are not immediately slaughtered must be subjected to stringent biosecurity measures. For LPAI epizootiological tracing and surveillance are crucial, especially since birds may be infected without showing any remarkable clinical signs. It is therefore important that tracing and surveillance zone measures, similar to those defined in Directive 92/40/EEC are put into place for LPAI outbreaks. It will be necessary to apply these measures to all species of poultry, including ducks and geese, since the intention would be to prevent spread to other species and ultimately the emergence of HPAI viruses.

The demonstration that AI viruses may represent a threat, with potentially serious consequences, to humans further complicates the issue for LPAI of all subtypes if birds are not slaughtered and disposed of. Birds should not be prepared for human consumption while they are viraemic, but at present there is little information in the literature concerning the occurrence, onset and length of viraemia in LPAI infections.

Part 2 Vaccination

9. Historical use of vaccines

In some countries, vaccines designed to contain or prevent HPAI are specifically banned or discouraged by government agencies because they may interfere with stamping out control policies. However, most HPAI control regulations reserve the right to use vaccines in emergencies.

There is little doubt, both in experiments and in the field, that if birds are sufficiently well immunised against the HA subtype corresponding to that of the challenge virus they will be protected from the worst effects of HPAI and the clinical disease and mortalities associated with LPAI. There is therefore economic pressure to invest in vaccination to insure against a potential short term but significant economic loss whenever there is a perceived threat from AI. However, conversely the high cost of vaccination, since it is necessary to use inactivated vaccines, means there is economic pressure to stop once the threat has lessened.

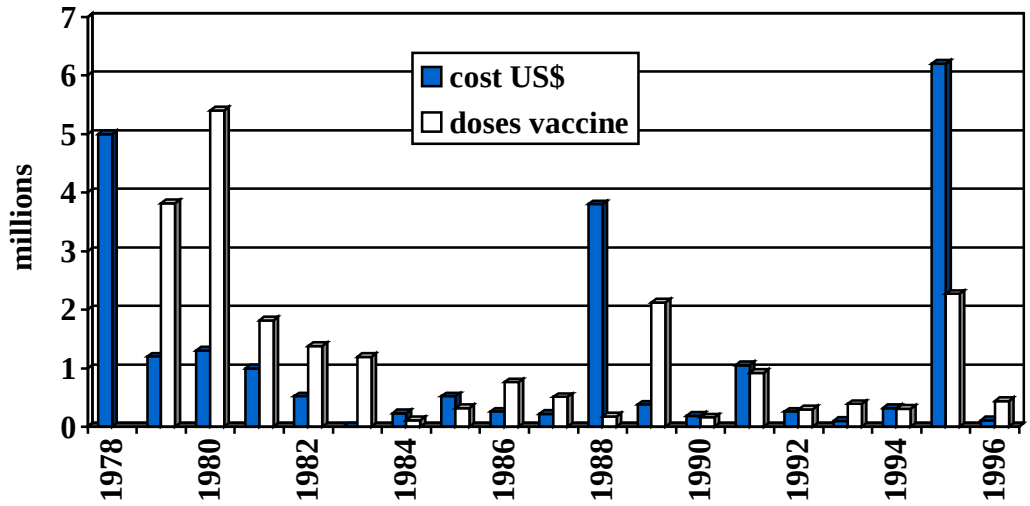
The existence of a large number of virus subtypes together with the known variation of different strains within a subtype pose serious problems when selecting strains to produce influenza vaccines. In addition, some isolates do not grow to a sufficiently high titre to produce adequately potent vaccines without costly prior concentration. The vaccines produced have either been autogenous, i.e. prepared from isolates specifically involved in an epizootic, or have been prepared from viruses possessing the same haemagglutinin subtype that yield high concentrations of antigen. In the USA, some standardisation of the latter has been carried out in that the National Veterinary Services Laboratories have propagated and hold influenza viruses of each subtype for use as seed virus in the preparation of inactivated vaccines (Bankowski, 1985). The vaccines used extensively in the USA (Halvorson, 1998) and in Italy (D'Aprile, 1986) against viruses of low pathogenicity, and against HPAI in Mexico (Garcia et al., 1998) and Pakistan (Naeem, 1998) have been prepared from infective allantoic fluid inactivated by betapropiolactone or formalin and emulsified with mineral oil.

Recently vaccines have been developed employing new technologies such as baculovirus derived H5 and H7 haemagglutinins (Crawford et al., 1999) and fowl poxvirus recombinants expressing H7 haemagglutinin (Boyle et al., 2000).

In the USA since the 1970s there has been widespread use of inactivated vaccines produced under special licence on a commercial basis (Halvorson, 1998; McCapes & Bankowski, 1987; Price, 1982). These vaccines have been used primarily in turkeys against viruses that are not highly pathogenic but which may cause serious problems, especially in exacerbating circumstances. Significant quantities of vaccine have been used in Minnesota to protect turkeys against LPAI (Halvorson, 1998) This involves prediction and/or early detection of the subtype likely to cause problems each year for incorporation into the vaccine. Vaccine uptake has varied considerably and generally reflected the number of outbreaks of LPAI or the cost of LPAI to the industry (Fig 1). The 178 outbreaks of LPAI caused primarily by virus of H9N2 subtype occurring in

turkeys in Minnesota 1995 resulted in the highest loss recorded of over US$ 6,000,000 (Halvorson et al., 1998).

Figure 1. Estimated losses to the turkey producers in Minnesota due to LPAI and number of vaccine doses used each year (From Halvorson, 1998 and Halvorson et al., 1998)



Up to July 1995, the use of vaccines of H5 or H7 subtype had been banned in the USA but from that time they have been allowed if used within a control programme under federal, state and industry control (Myers & Morgan, 1998). Inactivated vaccine was prepared from the LPAI virus of H7N3 responsible for a series of outbreaks in turkeys in Utah in 1995 and used, with other measures, to bring the outbreaks under control (Halvorson et al., 1998).

Outside the USA vaccination against AI has not been used widely or consistently. Zanella et al., (1981) described the production and testing of inactivated vaccines intended to combat the respiratory problems seen in turkeys in NE Italy and associated with LPAI influenza infections. Papparella et al., (1995,1996) reported that while vaccination against AI was only allowed officially in Italy in certain specific circumstances (i.e. as a ring vaccine), inactivated vaccines against H6N2 and H9N2, strains considered enzootic in Italian turkeys, were in common use in breeder birds. Werner (1999) reported use in turkeys of an inactivated vaccine to protect against H9N2 virus.

An inactivated H5N2 vaccine was used in Mexico as a result of the widespread HPAI outbreaks caused by H5N2 virus that began in December 1994 (Villareal & Flores 1998). Between the beginning of 1995 and May 1997 847 million doses of vaccine were licensed for use. Inactivated H7N3 vaccine was also used extensively in Pakistan following the widespread HPAI outbreaks in 1995 (Naeem, 1998).

10. Risks and benefits associated with vaccination

10.1 Vaccination against Low Pathogenic Avian Influenza

Adoption of any of the three options for the definition of HPAI stated above results in two categories of LPAI viruses: 1. Viruses of H5 and H7 subtype (since these will either be included in the definition or will also offer protection against HPAI), 2. Viruses of other subtypes. The use of vaccination aimed at protecting birds against these different groups of viruses will need to be considered separately.

10.1.1 Influenza viruses of subtypes other than H5 and H7

The arguments for and against the use of vaccination against LPAI either prophylactically or in the face of outbreaks have been covered on numerous occasions (Beard, 1982, 1987, 1992, Halvorson, 1987, 1998, McCapes & Bankowski, 1987, Donahoe, 1998, Easterday et al., 1997). It is most noticeable that where use of vaccine is advocated it is stressed that its use should only be regarded as complementing strict biosecurity, quarantine and other measures aimed at preventing spread of the virus. This is an extremely important point as reliance on vaccination in a situation where delay is inevitable while virus is identified, characterised and the vaccine produced is doomed to failure. Although many biosecurity measures may often be regarded as costly, laborious and time consuming by those involved, in fact they represent a good investment into the future profitability of poultry production. Such measures should not only reduce the risk of introduction of AI, but will also reduce the spread of other endemic diseases that may affect the birds and reduce their yield.

Currently, LPAI infections other than those caused by viruses of H5 and H7 subtype are not covered by EU legislation, vaccination against such infections is not prohibited and does not need Commission compliance.

10.1.2 LPAI viruses of H5 and H7 subtypes

Vaccination against infection with LPAI viruses of H5 and H7 subtypes represents a special case due to two important considerations. Firstly H5 and H7 LPAI viruses have been known to mutate to HPAI viruses. Secondly vaccination against LPAI H5 and H7 vaccines is in effect vaccinating against HPAI.

The crucial question relevant to the first point is what effect vaccination has on the excretion of virus from immunised birds challenged with field virus? Most studies aimed at assessing the efficacy of putative vaccines have addressed this problem to an extent. Halvorson et al., (1987a) reported vaccination experiments in breeder turkeys with an inactivated H4N8 vaccine and challenge with an H4N2 subtype strain. Isolation of challenge virus from the trachea was reduced from 100% of the non-vaccinated birds to 50% of the birds given a single dose of vaccine and 10% of birds

given two doses. Isolation of virus from the faeces was 40%, 20% and 10% respectively. Virus titres in the faeces were reduced by about 2.8 $\log_{10}$. Kouwenhoven & Burger (1986) prepared an inactivated vaccine from the virulent A/tern/S. Africa/61 H5 virus and challenged 3 weeks after vaccination. They tested for virus in the faeces of birds 3 days after challenge and reported the same number of birds excreting virus at the same levels in vaccinated and non-vaccinated groups. Donahoe (1998) concluded in a study using an H5N2 vaccine and challenge with the homologous virus that while the number of birds excreting virus after challenge was reduced by vaccination by about two thirds, some vaccinated birds were still excreting virus 28 days after challenge. Swayne et al., (1999) examined the efficacy of different H5 virus strains in inactivated vaccines when challenged with a virulent H5 isolate from Mexico 3 weeks after vaccination. They concluded that chickens were protected from clinical signs and death but the vaccines did not generally prevent infection by the challenge virus. They found that vaccination reduced the number of birds shedding virus and the titres of virus in oropharyngeal and cloacal swabs, but in most cases virus was still detected, particularly in the trachea.

One of the problems with experimental assessment of vaccine protection, especially in terms of virus shedding is that the assessment is usually done close to the optimum immune response. Donahoe (1998) suggested that even where adequate protection is achieved in chickens it may last no more than five weeks and probably for a shorter period in turkeys. He further considered it unrealistic to expect whole virus inactivated vaccines to protect entire populations of birds against infection by invasive field strains. He further concluded that while reduction in virus shed may be brought about by the use of vaccines this alone would be of little value in a large epidemic unless rigorous quarantine and biosecurity measures could be sustained.

The second point, that LPAI H5 and H7 vaccination is essentially vaccinating against HPAI means that all the problems discussed in the next section apply.

10.2 Use of Vaccination against Highly Pathogenic Avian Influenza

HPAI is a rare disease. It has appeared only 18 times in poultry in the last 41 years (Table 1). As a consequence no one has suggested that the use of pre-emptive prophylactic vaccination on a large scale, similar to vaccine policies adopted for Newcastle disease in many countries, is necessary or desirable. The general consensus amongst those advocating that vaccination has a useful role in the control of HPAI is that it should only be practised as “ring vaccination” to establish a buffer zone around an outbreak or more extensively once it is clear that the disease is spreading rapidly.

The general arguments of those that consider vaccination against HPAI is unwise, except in extreme circumstances, are similar to those outlined for H5 and H7 LPAI viruses. It is argued that since immunised birds are still able to become infected and excrete virus the virus may continue to spread. In addition since immunised birds may show no clinical signs, infection may go undiagnosed for long periods and even exacerbate the spread of the virus. The vaccination protagonists counter this argument with the view that immunised birds excrete far less virus and this will reduce the spread of the disease.

There are two crucial considerations in assessing the role of vaccination against HPAI:
i) does the current stamping out policy in the EU involving slaughter, biosecurity and quarantine work?
ii) if vaccination is to be used will it be as an alternative to stamping out or in conjunction with a stamping out policy?

Vaccination has been used in the control of HPAI on two occasions since 1959 in Pakistan (Naeem, 1998) and Mexico (Villareal & Flores, 1998). On both occasions to combat disease which was spreading rapidly, and on both occasions instead of a stamping out policy, but with increased biosecurity measures. There are detailed records of 14 (excluding Germany 1979 and China 1997) of the other HPAI epizootics occurring since 1959 and each of these was controlled by a stamping out policy that included strict biosecurity and surveillance measures. Only in Pennsylvania and Italy was significant spread seen.

It is worth noting that three of the five extensive epizootics, in Pennsylvania, Mexico and Italy, occurred following widespread epizootics of LPAI for some months prior to the mutation of the virus to HPAI. This implies that disease security measures practised prior to the emergence of HPAI were inadequate. In these outbreaks the earlier presence of LPAI meant that birds were immunised against the HPAI and this led to complications in diagnosis, probably resulting in further spread of the HPAI virus.

The evidence suggests that stamping out policies will be successful if applied early and correctly.

If vaccination is to be used to complement rather than replace a stamping out policy this raises other issues. Possibly the most important of these will be how to identify a vaccinated flock infected with HPAI virus. This could be done by routine surveillance of vaccinated flocks, either by virus isolation or by using a marker vaccine (none are available at present) or one with a different neuraminidase to the field virus so that cheaper serological monitoring can be done or by using unvaccinated sentinel birds. Limited vaccination of part of the poultry industry considered most at risk has also been suggested. For example, breeder birds that live longer or replacement stock. However, if a stamping out policy is to be retained such birds would still be slaughtered if they became infected with HPAI virus. Vaccination in these circumstances would therefore be accepting that biosecurity measures (Zander et al., 1997) and, for replacements, cleaning and disinfection were unlikely to be successful.

11. Movement of poultry and poultry products to and from a vaccination zone

If a vaccination is used for HPAI viruses or LPAI viruses of H5 or H7 subtype it should be applied in a designated area. For the purposes of movement of poultry or poultry products that area would then be treated as an AI infected surveillance zone until the last vaccinated birds are slaughtered, provided the absence of disease cases or detection of field virus.

11.1 Movements into the vaccination zone

Young birds
Movement of birds may take place provided that they are vaccinated in the zone after their arrival and that the virus no longer appears to be circulating in the area. Vaccination prior to movement will have the effect of extending the vaccination zone.

Birds for slaughter
Movement may take place to a slaughterhouse in the vaccination zone provided that the disease is no longer circulating in the area.

11.2 Movements out of the vaccination zone

Cooked products
Fully cooked meats are of little danger provided that normal precautions to avoid recontamination following cooking are taken.

Table eggs
Eggs for human consumption can be allowed to leave the vaccination area as currently allowed from a surveillance zone. However, the consumer packaging has to take place inside the area. Precautions should be taken at egg packing centre to ensure that packaging materials originating on vaccinated farms are not recycled to non vaccinated farms or to farms outside the vaccination zone.

Products derived from table eggs
Such products are usually derived from cracked and downgraded eggs and therefore represent a greater risk than whole table eggs. They should only be allowed to leave the area if treated in a way considered to adequately reduce the survival of any virus present.

Hatching eggs
Chicks hatched from vaccinated birds will be seropositive and should therefore not be placed on farms outside the vaccination area. Movement of hatching eggs from a surveillance area to a hatchery outside the area is permitted at present. Movement to a hatchery should only be allowed if there is no risk of mixing with other chicks destined to farms outside the vaccination area. A dedicated hatchery for the vaccination zone is the best option. If pathogenic virus is still in circulation in the vaccination area, all

chicks from a hatchery that receives any hatching eggs from vaccinated hens (regardless of the status of the breeders) should be confined to the vaccination area.

Young birds for restocking
See above. Vaccinated birds or chicks from vaccinated hens will be seropositive and should therefore not be allowed move outside the vaccination area.

Birds for slaughter and fresh meat
Movement of birds for slaughter may take place as currently allowed from a surveillance zone.

However because (as described in 10.1) vaccinated birds infected with virulent virus could show no clinical signs but yet shed the virus certain precautions are necessary. Movement to the slaughterhouse should be direct and under official control. Once there the birds should be slaughtered as soon as possible after arrival. The fresh meat should be marketed only in the vaccination zone and should not be permitted to be marketed outside.

12. Recommendations

12.1 On definition of AI for which control measures should be applied.

Recommendation I.
It is recommended that the definition contained in Annex III of Council Directive 92/40/EEC is rewritten:-
"For the purpose of the diagnostic procedures for the confirmation and differential diagnosis of avian influenza the following definition shall apply:
'Avian influenza' means an infection of birds caused by any influenza A virus which has an intravenous pathogenicity index in six-week-old chickens greater than 1.2 or any infection with influenza A viruses of H5 or H7 subtype."

However, in making this recommendation the Committee was concerned at the current lack of knowledge on the prevalence of LPAI viruses of H5 and H7 subtypes in poultry populations. It would seem a wise precaution that before the recommendation is implemented serological surveys of poultry populations in Member States should be undertaken to determine this prevalence and the likely economic impact that would be involved (see Recommendation V at 12.3.2).

12.2 On vaccination against AI

Recommendation II.
Whether or not Recommendation I in 12.1 is adopted, vaccination against influenza A viruses of H5 and H7 subtype should not normally be allowed. The possible use of emergency vaccination against viruses of these subtypes as outlined in Article 16 of Council Directive 92/40/EEC should be retained.

12.3 Other recommendations

12.3.1 Definition of poultry

There was some concern that current definitions of poultry in Directive 90/539/EEC, modified by Directive 92/65/EEC or recommended previously (SCAHAW, 1998) were slightly ambiguous and could be considered to include captive endangered species, the following definition is therefore recommended:

Recommendation III.

Poultry are all birds that are reared or kept in captivity for: the production of meat or eggs for consumption, the production of other commercial products, for restocking supplies of game or for breeding these four categories of birds.

12.3.2 Surveillance

Throughout the EU there is a marked lack of surveillance for avian influenza, particularly in free-living birds, and yet routine surveillance could give an early warning of the prevalence of viruses of H5 or H7 subtype in the locality of domestic birds. As stated at 12.1 there is also a need for a point prevalence assessment of the current situation of infection of poultry with viruses of H5 and H7 subtypes.

Recommendation IV

Member States should put in place routine surveillance systems for the detection of influenza viruses in free-living birds.

Recommendation V

Member States should undertake serological surveys of poultry populations, especially those types of poultry reared or kept under conditions where contact with wild birds is likely, to determine the prevalence of infections with influenza A viruses of H5 and H7 subtypes, so that the potential economic impact of implementing Recommendation I can be assessed.

12.3.3 Zoonosis

Recommendation VI

The possible zoonotic impact arising from the risk of reassortment between influenza viruses should be kept under review in the light of the occurrence of influenza in birds and other animals.

12.3.4 New vaccines

Although the Committee considers Recommendation II to be correct at the present time, it considers that there is a potential for a greater role of vaccination in the control of avian influenza, that could be realised by the development of novel marker vaccines.

Recommendation VII

In order to improve the efficacy of emergency vaccination as an aid to avian influenza control the Commission is urged to support the development of novel marker vaccines.

12.3.5 *In Vivo* tests

The Committee, recognising that there is at present no adequate *in vitro* alternative, agreed to the continued inclusion of an *in vivo* test for virus virulence in Recommendation I, but with some reluctance.

Recommendation VIII

The Commission is urged to encourage and support further research into the development of in vitro tests aimed at replacing the use of birds in virulence tests for avian influenza.

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14. Acknowledgements

This report of the Scientific Committee on Animal Health and Animal Welfare is substantially based on the work of a working group of the Committee, chaired by Dr D.J. Alexander. The members of the group are listed below.

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