

# **Avian Influenza—Global Threats and Future Research Needs**

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### **Abstract:**

*Highly pathogenic avian influenza (HPAI) is one of a number of transboundary animal diseases (TADs) that have caught international attention. TADs in many cases affect human as well as animal health, have significant economic impacts and are a rising international threat due to growing animal populations in the developing world and due to rapidly growing trade in animals and animal products worldwide. The apparent incidence of HPAI also has grown in recent years due to four main factors: 1) better detection, 2) genetic and behavioral changes in the Asian H5N1 virus, 3) increases in the amount and intensity of poultry production, and 4) climatic factors. More research is needed to address this threat particularly in areas relating to diagnosis of HPAI infections, infection processes in key species, understanding why and how outbreaks occur and improving disease control methods and strategies. Greater investments in veterinary public health efforts at the local, national and international level are also needed.*

Highly pathogenic avian influenza (HPAI), or what the popular press calls "bird flu," is the latest in a recent string of transboundary animal diseases (TADs) that have made international headlines. TADs have been a major priority of my organization, the United Nations Food and Agriculture Organization (FAO), since shortly after its inception nearly 60 years ago when we were asked to combat the outbreak of foot and mouth disease in Europe in the early 1950s. We continue our efforts today to coordinate international endeavors in a range of globally significant animal diseases in addition to foot and mouth disease such as rinderpest, trypanosomiasis, avian influenza, classical and African swine fevers, Newcastle disease and other emerging and re-emerging pathogens.

TADs have caught the attention of the international community for a number of reasons. First and foremost, many TADs are zoonoses—they affect human health as well as animals. BSE (Mad Cow Disease), Rift Valley Fever, West Nile Virus, SARS are all animal diseases in the news recently that affect humans. HPAI is only the latest in a series of these diseases to grab media attention. Human

mortality of HPAI in SE Asia has been on the order of 60-70%. As of early this year, forty-two people have died of this strain of bird flu. The distinct threat of HPAI becoming easily transmissible to and among humans has medical professionals very alarmed about a major influenza pandemic.

Second, TADs can also have dramatic economic impacts. The direct and indirect costs of the Foot and Mouth Disease (FMD) outbreak in the United Kingdom in 2001 were estimated to be over \$9 billion. Classical Swine Fever in the Netherlands in 1997-98 had economic impacts of \$2.5 billion. Impact estimates for the avian influenza epidemic are dramatic even for a large continent like Asia. More than 140 million birds have died or were culled in an attempt to control HPAI in Asia. Combined losses to gross domestic product (GDP) have been estimated at \$10-15 billion. A recent FAO study estimates that in Vietnam alone the disease has directly affected nearly 115,000 people living near or in poverty.

Third, the risk of animal disease outbreaks likely will only grow in the future as higher incomes in developing countries continue to stimulate more demand for meat and animal products. As a result animal densities are increasing, livestock industries are growing larger, production is more intensive, and international trade is increasing. The number of animals raised for meat, milk and eggs is growing very rapidly. During the 1990s, poultry production in East Asia rose nearly 12% per year—a doubling every five to six years.

Consistent with this growing threat, on a global basis, data would indicate that HPAI has been found more frequently and in more places in recent years as well. Widespread highly pathogenic outbreaks of this disease were rare prior to the late 1990s. In light of this evidence of more frequent and widespread outbreaks of HPAI, what can science tell us about why has this occurred?

First, better detection can explain some of the apparent increase in HPAI. Prior to the devastating outbreak of HPAI in Pennsylvania in 1983, most surveillance of avian influenza viruses in poultry was passive, based on detection of disease outbreaks. Active surveillance and better laboratory testing since then have probably been responsible for the increased detection of low pathogenic avian influenza (LPAI) viruses (which normally produce sub-clinical infections) and additional HPAI outbreaks as well. The 2004 case in Texas most certainly was detected through better surveillance since

the virus in this case, while genotypically highly pathogenic, was not causing significant disease in poultry.

Improved surveillance has probably aided in the detection of the current H5N1 HPAI virus in Asia as well. Limited surveys in the past few years have shown the presence of "silent" or sub-clinical concentrations of infection in many of these countries which likely would have been missed by the passive systems in place prior to 2003. Two different H5N1 viruses in geese were found in a one-off study of live bird markets in Hanoi as early as 2001, which strongly suggests that other farms and markets in Vietnam likely contained geese silently excreting HPAI virus well before the 2003 publicly-recognized outbreak.

It is also quite likely that outbreaks of HPAI in Asia also were often misdiagnosed as Exotic Newcastle Disease, fowl cholera, or gumboro disease, endemic poultry diseases in the region, which show similar clinical signs. Unless specific tests to identify H5N1 viruses are performed on sick or dead birds, the probability of a misdiagnosis is quite high. Experience has also shown quite large differences in the course of the disease and even in bird mortality depending on how the poultry was raised, e.g. on litter in high density vs. village "free range" methods. These differences could only add to the potential for misdiagnosis.

The fact that human cases of HPAI occurred in Hong Kong SAR in 1997 and that there were human cases associated with the SE Asian outbreak since 2003 likely also aided in the enhanced detection of HPAI in poultry. No doubt veterinary authorities searched harder for HPAI in poultry as the serious human health consequences became apparent and more widespread.

One of the major problems in under-detection of HPAI is that there is often little or no incentive for farmers to report the disease and few, if any, penalties for not reporting. In fact, in the early stages of the 2003-04 outbreak there were probably disincentives: a villager reporting the disease in his flock would see all of his poultry and those of his neighbors destroyed with no guarantee of compensation. This led to sick birds being sent to market ensuring the spread of the disease. Additional compensation is now being offered in a number of countries which should aid in disease reporting.

Second, and perhaps the most significant factor in explaining the rapid expansion of HPAI in Asia, is the ability of the H5N1 HPAI viruses

to be carried, at least for short periods of time, by domestic and wild waterfowl. Asia is by far the world's largest producer of domestic ducks and geese. Prior to 1999, highly pathogenic avian influenza viruses were detected rarely in domestic ducks. Changes in the virus, as shown by genetic analysis, apparently led to its ability after this time to expand its host range to both domestic and wild waterfowl. One study showed that by 2004 waterfowl excreted the virus up to 17 days, a factor likely to have increased significantly the viral load in the regional environment.

Significant genetic and behavioral changes have occurred in the Asian H5N1 HPAI virus since it was first identified in 1996 in geese in Guangdong province of China. The most striking feature is the extent of the diversity in the virus that has developed over a relatively short period of time. This diversity is striking, but it is not inconsistent with earlier scientific studies showing high mutation frequency in most RNA viruses.

In some recent cases in Asia, H5N1 viruses associated with epidemics in the same geographic area were genetically very similar, suggesting a common origin. This occurred in Thailand and Vietnam where a unique "Z" genotype was found. Japan and South Korea also appear linked by a "V" genotype that differed from the type found in SE Asia. However, viruses isolated in China displayed quite wide genetic variation although all are linked back to the 1996 goose lineage. In the end, this genetic analysis demonstrates the large pool of AI viruses that have become endemic in Asia which only magnifies the likely difficulty in eradicating the disease.

Third, increases in the overall poultry population in Asia have been dramatic in recent years. Between 1990 and 2004 poultry production in the developing countries of Asia increased nearly threefold. In many of these countries smallholder producers have increased the size of their flocks to meet market demand but often have not made the necessary investments in biosecurity levels needed to protect these larger flocks. This has also fostered the emergence of HPAI in the region.

Greater production usually goes hand-in-hand with more intensive production practices, i.e. more birds per farms. On the positive side, the largest intensively-raised poultry farms usually have some degree of biosecurity which has tended to prevent HPAI incursions, even in Asia. However, the diverse mix of production systems found in close proximity in SE Asia, from village free range

systems to large commercial operations, probably increases risks for the biggest facilities especially where biosecurity measures are less than ideal.

Fourth, global climate change, perhaps through shifts in migratory bird movements and other shifts in the determinants of the disease epidemiology, has been suggested as an explanation for the growth in global AI cases. However, little evidence supports this to date. On the other hand, local climatic factors in Asia in early 2004, where severe drought reduced the flow of the Mekong River, could have aided the spread of HPAI as more wild birds were attracted to ponds near farms which were one of the few remaining sources of food and water.

Science and technology are playing an increasingly important role in our understanding and control efforts of HPAI. FAO's efforts have focused on improving and strengthening four main areas, all of which have a strong scientific basis: 1) country level surveillance systems and data management; 2) epidemiology and data gathering; 3) government diagnostic laboratories and staff; and 4) contingency planning for new outbreaks.

Much has been achieved in the past 15 months in reducing the impact of HPAI in Asia. However, infections remain and the disease is endemic in the region. If control measures and surveillance are relaxed, disease resurgence and further spread to uninfected areas are likely.

For countries where the H5N1 virus has become widespread and entrenched, local veterinary services will have to focus on preventing the spread of the virus rather than eradication in the short to medium term. Improving biosecurity on all types of farms, stamping out known infections, targeted and carefully monitored vaccinations and basic public health measures will all play an important role.

In the longer term, major restructuring of the smallholder/village poultry production systems will need to be made to improve biosecurity. Live bird markets will also need to be much more carefully controlled, in particular to minimize contact among waterfowl and other bird species. Both of these types of changes have very significant social and economic implications for the countries involved.

There are also significant gaps in our knowledge of HPAI which should draw the immediate attention on the global scientific

community. First, there are significant needs in improving the diagnosis of HPAI infections. Among these are serological tests for use in ducks and other waterfowl, and, given the usual progression of these viruses, in pigs as well. Rapid agent detection tests for both field and laboratory use would also assist greatly in early detection of outbreaks.

Second, there is much more to be learned in understanding the infection process in key species. Research is needed on the dynamics of transmission, virus excretion, immune response and determinants of the infection outcome by species, type, age, virus and concurrent diseases. Molecular research on virus evolution, rapid genotyping methods, determinants of host range and the genetic correlates of transmissibility and pathogenicity are also critical.

Third, we need a better understanding of why and how outbreaks of HPAI occur. Fertile areas for research include the role of wild birds, virus survival in the environment, resistance of native breeds and the role of bird and product movement in disease spread.

Fourth, there are a number of areas in improving disease control that deserve urgent research attention. For instance, there is not an internationally validated study available to show that HPAI vaccine is effective in domestic waterfowl. Research on alternative, non-injection based vaccine delivery systems and discriminating vaccinated animals through marker vaccines and gene deletion vaccines will also be very helpful. Research on alternative surveillance strategies, modeling infection dynamics and even transgenic poultry resistant to infection could all add to our ability to control this disease.

The key to meeting the threat of avian influenza and other transboundary animal diseases is early detection and early response. To accomplish this we need to invest in veterinary public health services along with traditional human public health in developing countries. Without a strong veterinary service, even the best national public health strategies are jeopardized. We need better training and laboratories. Preparedness plans for human diseases are weak in many developing countries—yet they are even weaker for animal diseases.

These issues tend to fall in the realm of national governments. Yet to address the growing threat of transboundary animal diseases we need to strengthen both decentralized government structures as well as improve international coordination; diseases do not respect either

local or national boundaries. We need government support at the lowest administrative level to assure early detection and ready disease reporting. But this must be coupled with adequate coordination at national and regional levels to assure that sufficient response is given to avoid spread of disease through livestock movement controls, closing of live markets, sharing of diagnostic services, etc.

Finally, international coordination is also critical. In 1994, FAO established the EMPRES program for the emergency prevention of transboundary animal and plant pests and diseases to improve FAO's early warning and early reaction to disease threats. This effort has greatly increased our ability to respond to emerging animal disease risks.

The Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) both work on various aspects of transboundary animal diseases as per their complementary mandates. This work is closely coordinated with the World Health Organization when zoonotic diseases are concerned. Coordination among these three international agencies has strengthened significantly in recent years and has been quite evident in dealing with HPAI. But donor support for these efforts tends to rise and fall from crisis to crisis. As animal numbers rise to meet the growing global demand for meat, milk and eggs, growing and more constant support for the international coordination functions performed by these agencies will also be essential.