Avian Influenza H5N1 at the human-animal interface:
Update on selected projects

Among its many activities, the WHO Global Influenza Programme (GIP) provides technical and financial support to field-level projects designed to answer specific questions of interest to the department. One topic of interest to the GIP human-animal interface (HAI) group is how to decrease public health risks from highly pathogenic avian influenza (HPAI) H5N1 virus. On 23 April 2010, a small meeting was held at WHO Headquarters, Geneva, to bring together researchers collaborating with GIP in this area and WHO technical staff for an update of ongoing work.

Presentations

Sirenda Vong, Head of the Epidemiology Unit, Institut Pasteur of Cambodia (IPC; Phnom Penh, Cambodia) presented a comprehensive summary of HPAI H5N1 and the role of poultry in households in Cambodia, and gave an update on national work at the HAI.

Cambodia is the second poorest country in South East Asia. Of its 14.4 million people, 80% live in rural areas, and approximately 90% of households keep poultry (Ly et al 2007; Van Kerkhove et al 2008). To date, 10 confirmed human infections with H5N1 virus and 26 poultry outbreaks have been reported in the country. Human cases tended to occur after big movements of poultry (e.g. Chinese New Year), and were associated with poultry outbreaks. However, many of the human cases were reported prior to identification of the disease in the poultry flocks.

To improve surveillance in poultry, IPC has developed a practical field case definition for investigation of outbreaks of H5N1 infection in poultry flocks based on flock-level mortality in ducks and chickens of different ages (report in publication). This field definition has so far been useful for targeting surveillance and sampling, with preliminary results suggesting a large percentage of positive villages tested (152/211, 72%).

As part of its comprehensive H5N1 Programme, IPC is also conducting seroprevalence studies in humans. Recent studies in Cambodia have shown very low seropositivity rates among residents after poultry outbreaks, including rates of 0% (0/351; Vong et al 2008), 1% (7/674; Vong et al 2009), and 2% (18/700; Cavailler et al 2010), suggesting previous infection. Other work suggests that H5N1 titers in asymptomatic Cambodian patients decrease within 1 year, in contrast to titers of symptomatic patients in Viet Nam which reportedly persist (Buchy et al 2010). Risk factors for seropositivity included bathing and swimming in ponds, suggesting a potential role of the environment in human exposure. Environmental sampling following poultry outbreaks has
identified the H5N1 virus in water plants, mud, and feathers, strengthening the hypothesis that the environment could be contributing to human exposure in areas of H5N1 virus circulation.

In 2009, IPC began a 2-year randomized controlled intervention trial, partially funded by WHO GIP, to evaluate the effectiveness of sanitary measures that are less drastic (and thus more acceptable and sustainable) than those previously proposed. The overall purpose of the study is to increase productivity of livestock, but an intended side benefit is to decrease risk of zoonotic diseases, including influenza, at the HAI. Nine study group villages (where interventions will be implemented) and 9 control villages in Takeo Province have been selected. The project includes outbreak investigation as well as (1) training on biosecurity and husbandry, (2) collecting comprehensive demographic and socioeconomic data and (3) collecting blood and fecal samples from cows, pigs, and ducks. After 2 years, the villages will be evaluated on livestock health and disease rates, socioeconomic status, and the perception and acceptance of new practices in the study group.

**Farid Hosny**, the STOP AI team leader in Cairo, Egypt, gave updates on H5N1 in Egypt and research on environmental contamination in Egyptian live bird markets (LBMs). In Egypt, the number of human cases of H5N1 infection has fluctuated each year with 39 cases (4 deaths; CFR=10%) reported in 2009 and 20 cases (7 deaths; CFR=30%) to date in 2010. The number of confirmed cases in children increased in recent years, possibly due to better health care seeking for children than adults. Most human cases have been reported to have been exposed to poultry in the household.

In Egypt, total animal protein consumption is very low and more than 50% comes from poultry. Poultry production is also a critical source of income for poor households in both rural and
urban areas, making the endemicity of H5N1 virus a food security issue, as well as a zoonotic and potentially pandemic threat. Egypt has a variety of poultry production systems, with biosecurity remaining a problem in many of them. The virus is entrenched in both the commercial and the household poultry production sectors, providing extensive opportunity for human exposure at the HAI.

In Egypt, as in the rest of the world, LBM provide an opportunity for H5N1 virus amplification and dissemination. In contrast to reports from some other countries (e.g. China), exposure of most human cases of H5N1 infection in Egypt likely occurred outside of markets. Published rates of H5N1 virus detection in poultry and/or environmental samples collected from LBM has ranged from <1% in Nigeria (n=13,597; Joannis et al 2008), 1.3% in Thailand (n=930; Amonsin et al 2008) 2.9% in Vietnam (n=207; Nguyen et al 2005), 4.2% in Myanmar (n=738; Kyaw et al 2009), and 12.4% in Egypt (n=573; Abdelwhab et al. 2010, in press). To decrease virus spread, Egypt has enacted measures to restrict selling of live poultry in LBM, but these measures are difficult to implement, especially considering the consumer preference for freshly-killed poultry and the low national slaughterhouse capacity.

A survey was conducted in 2009, with WHO GIP funding, in which approximately 8000 environmental samples were collected from markets, poultry shops and vendors throughout Egypt. Preliminary results suggest that approximately 9% of the samples tested positive for

Environmental Contamination at Live Bird Markets in Egypt (Photos: Farid Hosny)
H5N1. All influenza viruses characterized were H5N1, and were most closely related antigenically and genetically to strains circulating in the backyard sector, which are the predominant strains circulating in the country.

**Maria Van Kerkhove**, of the MRC Centre for Outbreak Analysis and Modelling, Imperial College (London, UK) presented a systematic review of the literature on H5N1 virus exposure at the HAI. The purpose of the review, which was done in technical collaboration with WHO GIP, the Food and Agriculture Organization (FAO), and US Centers for Disease Control (CDC), was to update previous publications by critically reviewing available information on H5N1 infection in humans in order to better understand pathways of exposure at the HAI.

The review of studies reporting research conducted in 8 countries (Thailand, Vietnam, Indonesia, Cambodia, Nigeria, China, Azerbaijan, and Germany) and one territory (Hong Kong SAR China) provided evidence that most human H5N1 cases are attributed to exposure to sick poultry or contaminated environments, most commonly through contact with infected blood or other bodily fluids via food preparation practices; touching and caring for infected poultry; consuming uncooked poultry products; swimming or bathing in potentially virus laden ponds; and at LBMs. According to WHO press releases and several publications, a proportion of the 292 WHO confirmed human infections (as of 21 April 2010) have no reported exposure to sick or unexpectedly dead poultry. Given the presence of the H5N1 virus in LBMs and elsewhere in the environment, people could potentially be exposed without ever touching poultry.

Results from seroprevalence studies were also included in the review, and suggest that asymptomatic or subclinical infection with H5N1 virus is rare.

Differences across age, gender and country were presented for discussion. The demographic differences in human cases of H5N1 infection among countries are likely because contact patterns with poultry - in addition to animal husbandry practices, biosecurity systems and surveillance systems - differ between countries. For example, based on reported poultry contact patterns (including slaughtering of poultry and working with fighting cocks), males in rural Cambodia have a higher exposure risk potential to H5N1 than females across all age groups. However, variability in H5N1 incidence may not be due to exposure alone; there may be differences in intrinsic immunologic susceptibility to infection, pre-existing immunity against human influenza viruses, clinical presentation of disease, and/or presentation to health care facilities.

The existing data gaps which limit our understanding of the epidemiology of H5N1 in humans were also presented for discussion. These included the likelihood that not all human cases and poultry outbreaks are being detected or reported, limitations to interpreting human serologic testing, our limited understanding of genetic and/or immunological impacts to susceptibility, lack of clarity on potential routes of transmission of H5N1 from poultry to humans and the lack of data on prevalence of risky practices at the HAI. It was greed that collaboration between human health and animal health sectors for surveillance, case investigation, information sharing and risk assessment is essential to understand and reduce the risk of virus transmission at the interface between domestic poultry and humans.
Overall discussion

The demographic and epidemiological differences in human H5N1 cases among countries, including age and gender differences, was discussed. It was agreed that there are some similarities among countries (such as that gender differences in who cares for and slaughters poultry in Egypt and Cambodia, and likely other countries, and the existence of risk from environmental contamination) that can be assessed generally, at the global level. However, substantial differences do exist among countries. Such differences demonstrate that the potential risk of transmission of H5N1 to humans at the HAI must be evaluated at the national level and these risks managed on a country-by-country basis.

There was much discussion on specific variables for human exposure at the HAI. The ongoing question of why so few people actually get infected when so many thousands have had apparently the same exposure to the virus was again raised. It is possible that adequate data on specific exposures in the face of background exposures could not ever be collected that would allow WHO to make practical recommendations to decrease risk of H5N1 infection in humans. It was agreed that countries should be encouraged to collect and analyse their national data and make the findings publicly available.

Selected references


Compiled by WHO GIP staff from information presented at the meeting by Drs Vong, Hosny, and Van Kerkhove.

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