Vaccination of poultry in Vietnam against H5N1 highly pathogenic avian influenza

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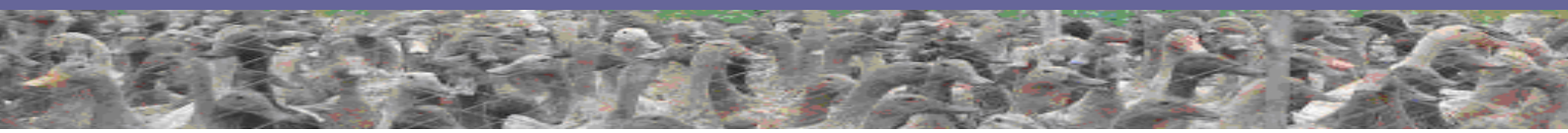
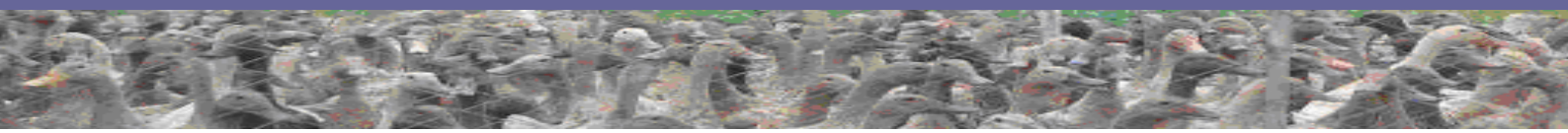
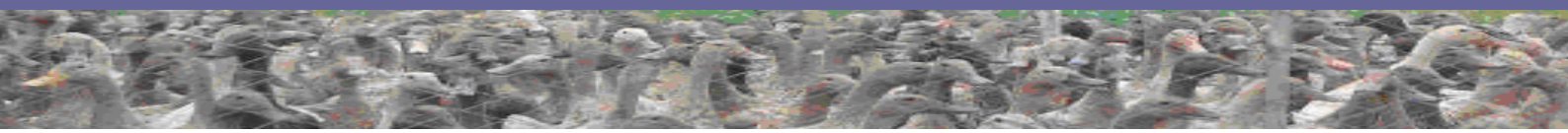


TABLE of CONTENTS





1. Introduction

This case study explores the many issues that were considered when vaccines were introduced and used in Vietnam against highly pathogenic avian influenza (HPAI) caused by viruses of the H5N1 subtype.

The case study has been prepared because the experiences from Vietnam will likely prove useful for other countries contemplating vaccination of poultry against this disease.

In 2005, Vietnam faced a public health crisis. The number of human cases of influenza A (H5N1) was increasing, such that Vietnam became the country with the most reported human cases. At the same time global fears of a human influenza pandemic were growing as H5N1 viruses extended their spread into Russia. Existing control measures had not prevented an increase in human cases and a decision had to be made whether vaccination of poultry had a role to play in the control and prevention of this disease if it was added to the measures already in place.

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Given the nature of the crisis, this decision had to be made quickly which meant that many aspects of the program were based on incomplete or fragmented information. This study point out the limits that existed at the time and provides guidance for others on the types of information required when considering introduction of vaccination.

By the time H5N1 HPAI viruses first emerged as a significant problem in poultry in South-East Asia in 2004, vaccination was already regarded as one of the measures that should be considered for use, but only a few countries had adopted it. Vaccination does not provide all of the answers for disease control and prevention and reliance on vaccination alone will not result in eradication of the virus.

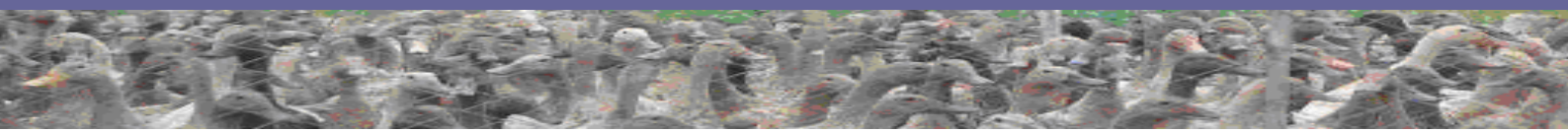
Vietnam faced a public health crisis

Above: Duck vaccination in Tien Giang
Right: Vaccination of fighting cocks in Tien Giang

There has been considerable debate about the merits of vaccination against H5N1 HPAI both in Vietnam and elsewhere, with some arguing that because vaccination failed to eliminate disease in Vietnam it has not been successful.

Some of these arguments arise from a misunderstanding of the overall objectives of the programs and the limitations of other control and preventive measures when used in developing countries with large poultry populations dispersed in millions of small flocks and sold through complex market chains. Nevertheless, a number of lessons have been learned from the vaccination campaigns in Vietnam and these lessons are valuable for other countries contemplating addition of vaccination to the measures used to control H5N1 HPAI.

Many people have compared the response to H5N1 HPAI in Thailand and Vietnam. Both are regarded as countries that have had success in containing the disease but it is often pointed out that Thailand banned the use of vaccines whereas Vietnam has embraced them. Some have argued that Thailand has been more successful than Vietnam because the disease appears to have been contained there with no new reports of human cases for several years, whereas avian and human cases have been reported every year in Vietnam, even after vaccination was introduced.



However, comparing Thailand to Vietnam is not a comparison of like-with-like because of the marked differences between the two countries especially in the nature of the poultry sector. The differences are presented in the table below.

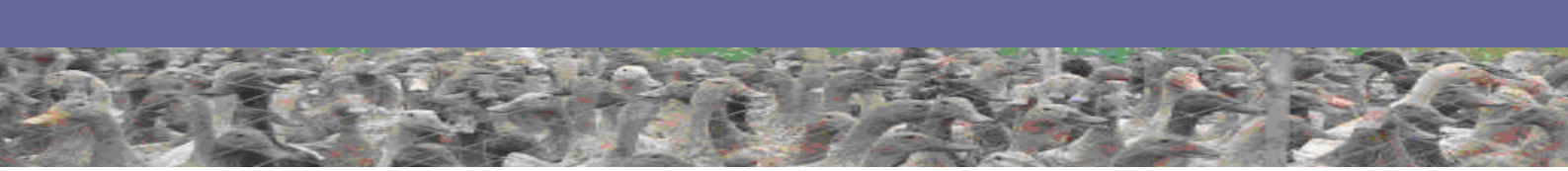
Table 1: A comparison of poultry industries in Thailand and Vietnam

Thailand	Vietnam	Significance
High proportion of poultry in large farms. Only 20% of national poultry population in small household flocks	>50% of poultry in small scale or village level flocks with some 8 million households rearing poultry	Fewer, larger farms in Thailand reduces the complexity of market chains and reduces the difficulty in conducting effective farm surveillance
Poultry production dominated by large commercial companies	Most poultry owned by individual farmers	Greater private sector investment to protect poultry from disease in Thailand including greater investment in farm biosecurity
Export oriented poultry industry	Local sales only	Greater financial incentives to control disease in Thailand to regain export markets
Approx. 20 million ducks	Approx. 60 million ducks, most reared under extensive conditions	Lower risk of perpetuation of viruses due to smaller duck population in Thailand
Gross domestic product per head > $US7000	Gross domestic product per head approx. $US700	More resources for veterinary services in Thailand
Few large live poultry markets	Live poultry sold through large markets in parts of the country	Lower risk of perpetuation of viruses in live bird market system in Thailand

Other Asian countries including Japan, the Republic of Korea and Malaysia have also eliminated H5N1 viruses (in some cases multiple times) without using vaccination. But again the structure of the poultry sector in these countries differs markedly from that in Vietnam and direct comparisons are not valid.

The ultimate goal of the Vietnamese program against H5N1 HPAI remains the sustained country-wide elimination of the virus. When vaccination was first introduced (2005) it was already recognized that this could not be achieved in the short to medium term due to the extent of infection, the difficulties encountered in conducting sufficient surveillance, and the presence of poultry management and marketing practices that facilitate the persistence and spread of H5N1 HPAI viruses. Even today, some production and marketing methods that facilitate disease spread persist because they are important for the livelihoods of many people.

Vaccination will remain an important part of the control and preventive program for this disease in the foreseeable future in Vietnam but the scope of the program will be adjusted over time as the risk of infection diminishes. Changes to the vaccination program will occur as other control and preventive measures are implemented, and as



surveillance data improve, providing more information on the factors that facilitate virus persistence and spread.

This paper explores a range of issues relating to vaccination, including some of the lessons that have been learned so far from the introduction of vaccination in 2005. Perhaps the main lesson is that the situation in each individual country must be considered before embarking on any broad-scale vaccination campaign to ensure that the investment is sound and the proposed program can be implemented. It should also provide a financial return on the investment and/or provide some sort of insurance both to individual farmers and to global public health.

The poultry sector in Vietnam

Vietnam's poultry sector consists of a small number of large intensive/industrial poultry farms, some 400,000 small and medium scale farms (50 to 5000 head of poultry) and at least 8 million households where small numbers of poultry (<50 head) are raised. The latest poultry census (2006) provides the following figures:

Table 2: Poultry Numbers in Vietnam

Farm/household size	Chicken	Duck	Muscovy	Total*
<50 birds	7,359,219 (94.7%)	1,452,573 (91%)	889,038 (96.45%)	9,700,830 (94.25%)
50-499	404,673 (5.2%)	123,898 (7.8%)	31,780 (3.45%)	560,351 (5.5%)
500-5,000	7,185 (0.1%)	19,423 (1.2%)	669 0.1%	27,277 0.25%
>5000	720 (0.01%)	118 (0.01%)	2 (<0.01%)	840 (0.01%)
7,771,797	7,771,797	1,596,012	921,489	10,289,298

***Total farm/households is an overestimate (probably by approximately 10 to 15%) because those households with mixed populations of chickens and other poultry species are counted more than once in this table.**

Source: GSO 2006 Rural Agricultural and Fishery Census as reproduced in FAO/USAID/Joint Government United Nations Program to Fight Highly Pathogenic Avian Influenza, Atlas of Poultry Production in Pilot Provinces, 2009

The greatest concentrations of poultry are in the Mekong River Delta in the south and the Red River Delta in the north. (See Appendix)

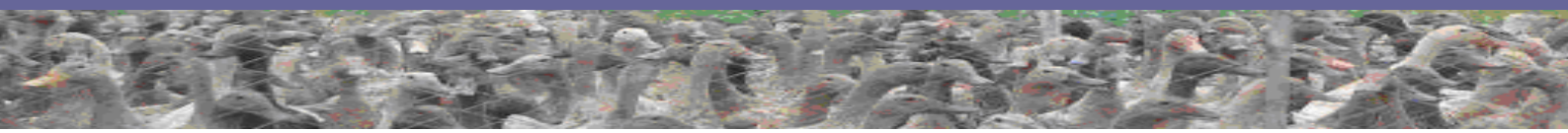
The distribution of poultry in millions of small flocks presents many challenges for disease control programs and veterinary services. Owners of most of these flocks and even of some commercial flocks rarely seek veterinary advice if their poultry are sick, and small flock owners do not need to seek approval before selling poultry. It is known that, on occasions, producers sell sick poultry as a coping mechanism in the face of a disease outbreak.

Another factor that makes disease control difficult is the complexity of production and marketing chains. Studies conducted in Vietnam have demonstrated that there are many different actors in production and marketing chains from the time poultry are hatched to the point where poultry or poultry products are sold for consumption. Thousands of traders move poultry and poultry products, often across provincial borders, with the motorcycle and boat remaining the most important modes of transport. Methods for the effective regulation of traders and others in the production and marketing chain are still being developed.

...motorcycle and boat remain the most important modes of transport

Many poultry in Vietnam are reared under conditions with few biosecurity measures in place. Practices such as free grazing of ducks or rearing of ducks on water channels or ponds are widespread but leave domestic birds exposed to potentially infected wild birds. Also, if domestic ducks are infected with H5N1 HPAI viruses they can contaminate the environment or the water in which they swim, potentially exposing other domestic and wild birds to these viruses. Practices such as all-in all-out management are only practised by some larger commercial farms. Few commercial farms in Vietnam have biosecurity measures equivalent to best practice, although standards have improved over the past few years.

Scavenging poultry roam freely in villages and rural areas, which means that if H5N1 HPAI viruses do get into a village, transmission can occur readily. Fighting cocks, while not as important as in some other Asian countries, are also kept in households in a number of areas and are often moved between different households and locations.



Animal health services to support the livestock industries extend to the commune level but there is still significant room for improvement in the quality of these services in most areas, as a recent assessment by the World Organisation for Animal Health (OIE) confirmed[1].

2. Why use vaccination against HPAI and why use vaccination in Vietnam?

In 2004, when Vietnam first reported H5N1 HPAI and implemented control measures for this disease, veterinary authorities adopted the same measures used in most other countries (i.e. measures based on stamping out of infected and at risk flocks). Few countries at the time used vaccination against H5N1 HPAI. China was the exception, with official vaccination campaigns commencing in 2002 in Hong Kong SAR. In Mainland China, however, vaccination was not officially sanctioned for use against this disease until 2004 but was still available and used widely prior to this time. It was apparent from Hong Kong SAR that vaccination could play an important role in the control of HPAI under some circumstances (see below).

The possibility of using vaccination in Vietnam was considered by authorities in 2004 but was not pursued seriously as an option until it became clear in 2005 that the 'traditional' control methods based on stamping out were not preventing an increase in human cases of avian influenza.

The following sub-sections consider the two main issues that influenced the decision to include vaccination as one of the control measures for this disease.

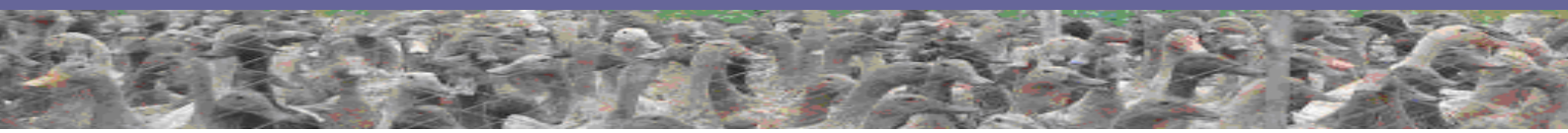
Vaccines against avian influenza viruses work if used correctly

Under laboratory conditions, chickens given properly formulated avian influenza vaccines containing an oil-based adjuvant and sufficient antigen have increased resistance to infection, providing the vaccine antigen is reasonable match for the challenge strain of virus. Levels of viral excretion in vaccinated chickens subsequently challenged with field virus are much lower than those from unvaccinated challenged controls.

…some countries have used vaccines to help contain and eliminate HPAI viruses

In fact, in experimental trials, the vast majority of fully vaccinated chickens with a well-developed immune response do not shed detectable quantities of virus even if

[1] The report of the assessment undertaken as part of the OIE's PVS scheme is not available in the public domain.



challenged with virulent virus. Some with lower level protection will excrete virus for a few days but in quantities much lower than that excreted by fully susceptible poultry. The quantity of virus excreted is often insufficient to transmit to non-immune poultry placed in contact with vaccinated infected birds. In a well vaccinated flock, even if a virus enters the flock there is a high probability that the infection will self extinguish. Systemic infection (in which virus is found throughout the body) occurs in unvaccinated infected chickens but does not occur in immune birds. This is important from a food handling perspective because those who handle and butcher infected carcasses appear to be one of the key risk groups for infection.

Experimental studies in which vaccines are tested have also been conducted in ducks. The results were similar to those in chickens when appropriate vaccines were used, although the magnitude of the antibody response in vaccinated ducks was generally lower than that in chickens. A larger (double) second dose of vaccine was required to generate a strong immunity and ducks required booster doses more frequently than chickens.

Even though most countries base their control programs for HPAI on stamping out, some countries have used vaccines to help contain and eliminate HPAI viruses. Mexico used vaccines as part of a successful campaign against HPAI caused by viruses of the H5N2 subtype (although they did not succeed in eliminating co-circulating low pathogenicity (LP) H5N2 viruses).

Hong Kong SAR provides one of the best examples of the benefits of the use of vaccines against HPAI. Vaccines against H5N1 HPAI were first used officially in government sanctioned programs in Hong Kong SAR on a trial basis in 2002 and for all local poultry in 2003.

By mid-2002, government officials in Hong Kong SAR recognized that they could not rely on biosecurity and quarantine measures alone at existing farms and markets to prevent further cases of infection in poultry. This recognition was based on evidence that:

- H5N1 HPAI viruses were still circulating in the broader region
- There was a high level of movement of live poultry (upwards of 100,000 live poultry per day and more during festivals) into and within Hong Kong SAR
- Despite improvements to farm biosecurity and marketing practices outbreaks of disease had recurred in Hong Kong.

As a result, vaccination was added to the preventive measures already in place.

From midyear 2001 until late 2003, which includes the period when vaccination was gradually implemented, H5N1 viruses were detected in Hong Kong's live poultry markets. However, once vaccination of all poultry destined for Hong Kong live poultry markets was implemented in late 2003 (covering farms in Hong Kong and the

Chinese mainland) H5N1 viruses have only been detected twice in poultry–once in markets in June 2008 and once on a farm in poorly vaccinated breeders in December 2008.

During the 4.5 years from late 2003 to mid 2008 farms and markets appear to have been free from infection, as shown by the regular intensive surveillance program. This period coincided with an increase in viral activity in wild/free-flying birds in Hong Kong SAR and in reported cases of disease in poultry in the neighbouring Guangdong province of China–indicating that the risk of introduction of viruses to local farms and markets had been reduced by the measures implemented, including mandatory vaccination.

...vaccination has been used successfully to control and eliminate LPAI viruses ...

The results of vaccination in Hong Kong SAR showed that it was possible to generate high-level flock immunity in properly vaccinated flocks under field conditions and that vaccination can assist in eliminating infection when combined with other control and preventive measures such as improvements to live poultry market management and hygiene, improved farm biosecurity and strict controls on supply of poultry to markets. Without vaccination, these other measures had not prevented the disease from occurring. Similar results have also been demonstrated in Italy (vaccination against low pathogenicity (LP) H5 and H7 viruses) where vaccination has been used successfully to control and eliminate LPAI viruses on a number of occasions.

Experimental studies in specific pathogen-free birds[2] has shown that immunity after vaccination usually lasts for at least 20 weeks in chickens after a single dose and experimental studies with Chinese vaccines (including the ones selected for use in Vietnam) demonstrated immunity after two doses extending for almost one year.

[2] Birds bred and kept in a manner that ensures they are free from certain diseases

Under field conditions the level of immunity in a flock is modified by a number of factors, including the presence of maternal antibodies, co-existing immunosuppressive diseases, and the introduction of new unvaccinated birds to the flock (especially if vaccine is given at certain times of the year rather than when poultry reach the recommended age for vaccination). Despite these constraints, however, it is still possible to generate high level immunity in most vaccinated flocks, at least for several months post-vaccination.

Other control and preventive measures had not prevented human cases of influenza associated with influenza A (H5N1) viruses in Vietnam

A strain of H5N1 HPAI virus (Clade 1 virus) probably entered Vietnam sometime in 2003. It was widespread by early 2004, affecting poultry throughout the country and it was reported to the World Organisation for Animal Health (OIE) in January 2004.

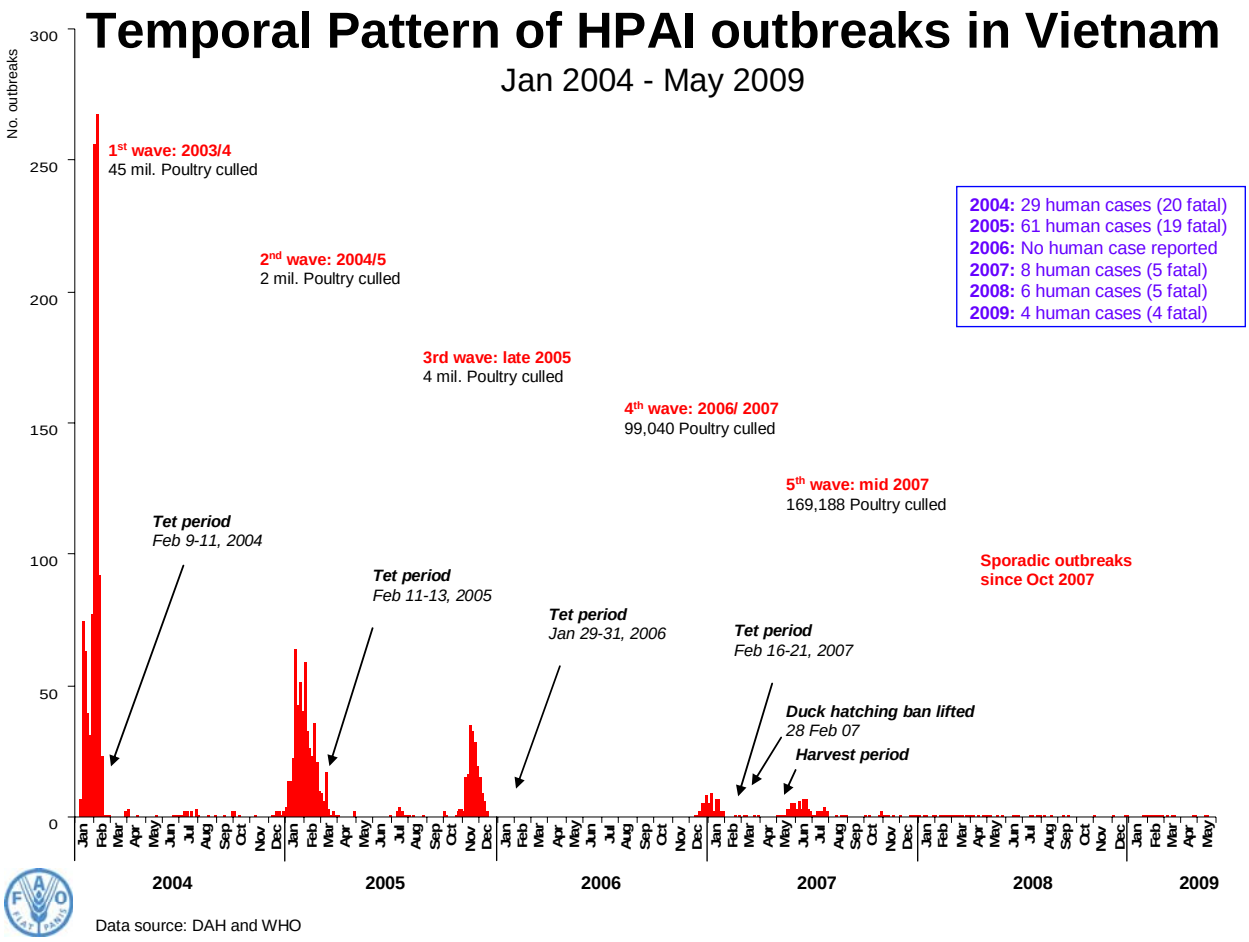
Government control programs were initiated in early 2004 and resulted in the loss of some 45 million head of poultry either directly from the disease or, in the majority of cases, from destruction of poultry in a wide zone around known infected flocks. This action was followed by a reduction in the number of new poultry cases. However, in late 2004 and the first half of 2005, the number of avian and, especially, human cases rose again to the point where Vietnam was the country with the largest number of human cases and fatalities. By then there were 93 confirmed human cases, with 61 of these confirmed cases occurring in 2005. This still remains the highest one year tally for any country.

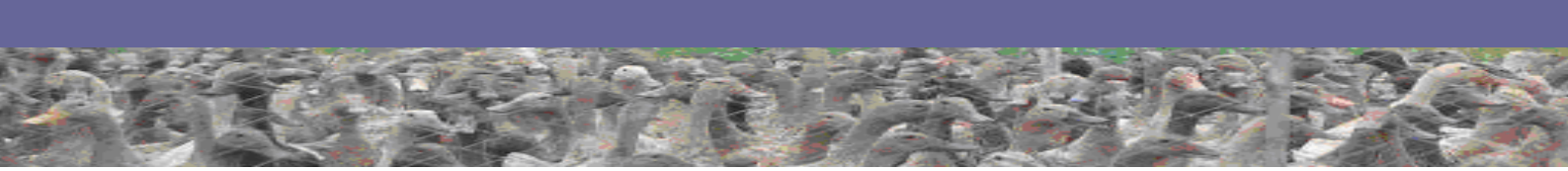
The vast majority of cases were in rural communities...

Stamping out and the other concurrent control measures had not prevented human cases from occurring. The vast majority of cases were in rural communities and many were associated with infected village poultry.

In order to tackle this problem, other measures were needed beyond the ones in place, both to contain infection in poultry and to reduce the risk of human exposure. Figure 1 below shows the number of poultry cases from 2004 to 2009.

Figure 1





Stamping out did not lead to the elimination of the virus for a number of reasons, including the difficulty in detecting all cases.

Issues with surveillance and disease reporting for H5N1 HPAI

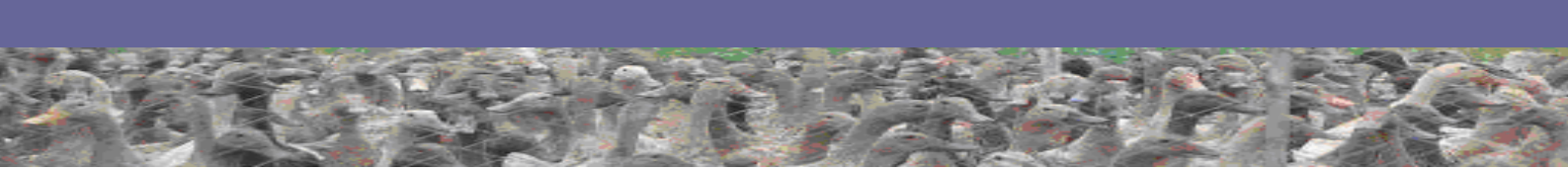
In countries such as Vietnam disease reporting and surveillance systems do not detect all cases of infection and disease. This occurs for a number of reasons:

i) not all farmers report disease when it occurs (in fact some farmers will sell their infected flock if they can)
ii) most poultry owners do not have close relationships with community animal health workers or veterinarians
iii) some infected poultry (especially ducks) do not display clinical signs of disease
iv) infected poultry in live poultry markets may go unrecognized particularly if birds are infected but still incubating disease when sold or slaughtered (which can happen in poorly managed live poultry markets if birds entering an infected market are kept for at least 18–24 hours before being slaughtered)
v) field and laboratory capacity are not sufficient to conduct the quantity of surveillance and disease tracing that is needed to detect all cases of disease and sub-clinical infection
vi) disease investigations and tracing are often relegated to secondary importance behind efforts to control known outbreaks
vii) even if outbreaks are investigated, complex market chains make tracing extremely difficult.

In many parts of Vietnam, poultry are sold through live poultry markets. The country normally has a standing population of approximately 60 million domestic ducks and some of the early H5N1 viruses isolated in Vietnam were capable of causing only mild disease or even sub-clinical infection in ducks. All of these factors allowed virus to persist and recur even after stamping out of reported cases was conducted.

3. Why vaccination alone could not be relied on to eliminate H5N1 viruses from Vietnam

At no stage during the development of the vaccination program in Vietnam was there any expectation that vaccination, as implemented, would lead to country-wide elimination of H5N1 viruses from Vietnam. Vaccination was used to reduce the level of infection in poultry which in turn would reduce the risk of human exposure and human disease caused by influenza A (H5N1) viruses.



A major factor considered in introducing the program was the concern that if H5N1 viruses were allowed to circulate unchecked and humans were infected, a human pandemic influenza strain might develop. Therefore vaccination was used to help reduce the likelihood of human infections.

A blanket vaccination campaign, as implemented in Vietnam, was not expected to provide sufficient immunity in enough poultry flocks in all 'at risk' parts of the country to guarantee that the virus would be eliminated. When implementing mass campaigns in the field, it is not possible to create high level immunity in all flocks, especially if other immunosuppressive diseases occur at or just before vaccination. Nevertheless, the vast majority of vaccinated flocks will develop good immunity and it is not necessary to achieve 100% vaccination coverage or even 70% to 80% coverage (the level normally considered necessary to prevent all onward transmission) to reduce the number of susceptible poultry and to have an effect on prevalence of infection. It has also been shown that human cases do not necessarily occur if low level virus circulation exists. Therefore, a reduction in the size of the susceptible poultry population can significantly reduce the risk of human infection. By reducing the number of susceptible poultry the environmental load[3] of H5N1 viruses was expected to fall.

Even if these viruses could be eliminated from Vietnam, the threat of virus reintroduction is ever present, as the detection of different strains of H5N1 HPAI virus has demonstrated. This threat is particularly high in the north of Vietnam, where illegal traffic in poultry has continued despite efforts to prevent it.

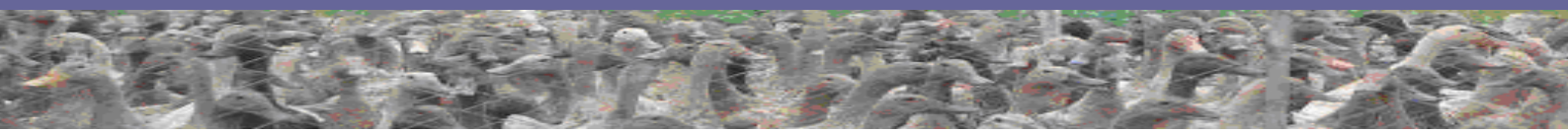
It has been suggested that if vaccination is not accompanied by other measures then infection will become endemic. In fact, infection was already endemic in Vietnam when vaccination was first used. As will be seen later, the goal is not to continue vaccination indefinitely. However, vaccination will still be required in the short to medium term because it is not possible to modify all the factors that contributed to this disease becoming endemic.

4. Which vaccine to use?

When choosing a vaccine a number of important decisions need to be made. These include:

- Which type of vaccine to use (e.g. killed antigen in oil adjuvant vaccine, live vector vaccine, DNA vaccine, live attenuated virus)
- Which antigen to use (e.g. how close a match between circulating virus and vaccine antigen is required? Is serological DIVA testing going to be used?)

[3] The amount of live virus present in the environment after excretion by poultry at any point in time



- Can the company supplying the vaccine guarantee that the product is made in accordance with international good manufacturing practices and the standards set in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals?
- Does the vaccine contain sufficient antigenic payload to produce consistently good immunity?
- Does the company supplying the vaccine also provide sound technical support and backup in the event of a problem?
- Are sufficient quantities of vaccine available for the size of the campaign?
- Is the vaccine suitable for all species of poultry?
- Is it affordable?
- Will a range of vaccines be used or will the number of vaccines be limited?

All of these issues had to be considered before commencing the vaccination campaign in Vietnam.

When vaccination was introduced to Vietnam, few vaccines were available on the global market to prevent H5N1 HPAI. This, in some ways, made the choice of products easier. No locally manufactured vaccines were available.

Most available vaccines contained a killed antigen combined with an oil adjuvant (the adjuvant helps to stimulate a broader and stronger immunity to viruses)[4]. Earlier work conducted in the USA demonstrated that such vaccines could provide broad cross protection against a range of H5 viruses, even when there was considerable molecular distance between the antigen and the field strain. However, it is better to use an antigen that is a close match to the field strain and this principle played a role in the choice of vaccine antigens.

The vaccine(s) chosen had to be suitable for the species being vaccinated (see next section), which included both ducks and chickens.

It was always the goal to minimize the number of different vaccines in use (and therefore the number of different antigens used). Some countries, notably Egypt and Indonesia, have used a range of different vaccines and vaccine antigens. Both countries have now experienced problems with emergence of antigenic variant viruses. Although it is not known whether the use of a large number of different vaccines played a part in this process, it may have contributed. This is even more likely to be the case if some of the vaccines delivered suboptimal immunity, thus allowing the generation of escape mutants (i.e. viruses that resist the antibodies generated by the vaccine).

[4] The use of an oil adjuvant is believed to be one of the main reasons why vaccines against avian influenza in poultry provide much broader cross protection than human influenza vaccines, which only offer limited cross protection to other viruses of the same subtype.

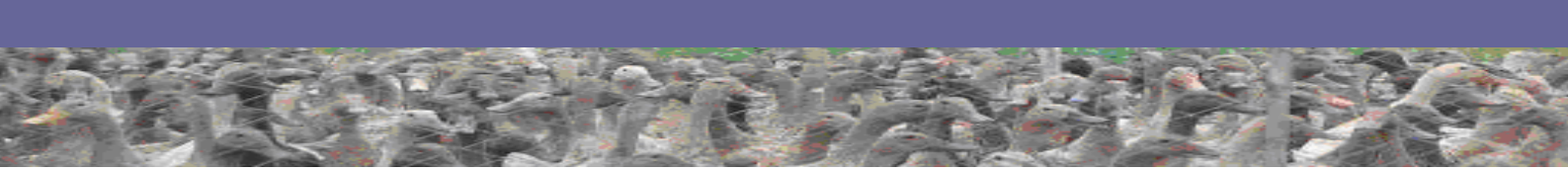
The track record of vaccines used elsewhere was also considered. Hong Kong had already recorded success using a commercial product based on a Mexican H5N2 antigen in controlling similar H5N1 HPAI viruses. China was using two vaccines in their vaccination program–one based on A/Turkey/ England/N28/73 (an H5N2 antigen) and one based on an antigen produced by reverse genetics. The latter contains a modified H5 glycoprotein (multiple basic amino acids at the cleavage site removed) and the N1 glycoprotein from Influenza A/Goose/Guangdong/ 96 – the first Asian lineage H5N1 HPAI virus isolated and a much closer relative to the circulating virus than the Turkey/England antigen. This antigen is referred to in China as Re-1.

The unit cost of the vaccines also influenced the decision. The objective was to obtain the greatest possible vaccination coverage for the least cost (assuming equivalence in the immunity generated). The vaccines from China were significantly cheaper than those from other places and experimental data generated prior to the campaign suggested that the immune response in experimentally infected poultry vaccinated with the Chinese vaccines was equivalent to or better than that obtained from other vaccines tested. Sufficient quantities of Chinese vaccine were also available to meet the needs of the campaign.

Vaccines…had to be suitable for…both ducks and chickens.

Some larger commercial farmers preferred to use vaccine from a European vaccine manufacturer that provided technical support to farms using their product. The Chinese manufacturers also provided good technical support to Vietnamese authorities. Through the Chinese Ministry of Agriculture, a team of vaccine specialists from Harbin was sent to Vietnam to provide advice to Vietnamese animal health authorities when vaccination programs were being designed. FAO and the World Bank also provided an independent expert to advise on developing the vaccination campaign.

The only live vector vaccine available commercially at the time (i.e. a vaccine containing a live genetically modified virus that contains genetic code for expression of the H5 haemagglutinin (HA) (the main surface protein on the influenza virus) was



a fowl pox vector vaccine[5]. Under field conditions, this vaccine is recommended for delivery to day old chickens. Older birds may have immunity to the pox virus vector that can interfere with the immunity generated by the vector vaccine.

Although this vaccine was not used in the mass vaccination campaigns for small household flocks of poultry, it was introduced to hatcheries for broiler chicken vaccination in late 2005. At present, this vaccine is not being used until issues related to the extent of protection afforded by the vaccine in Vietnam are clarified.

Once the list of possible vaccine candidates was narrowed down, trials were conducted in Vietnam to assess the immunity produced under experimental conditions before selecting products to use and proceeding with their registration.

Restricting the number of vaccines used was considered important in the decision making process. Other countries have used multiple vaccines, which makes monitoring of vaccination extremely difficult and also potentially increases the probability of being supplied with sub-standard products.

Capacity to allow DIVA testing – differentiating infected from vaccinated animals

Vaccination of poultry with vaccines containing killed whole virus antigens results in the production of antibodies to both the HA and neuraminidase (NA) proteins in the vaccine antigen[6]. Once a bird is vaccinated it is not possible to tell if antibodies to these surface proteins are due solely to vaccination or whether subsequent infection has occurred in the flock, unless the vaccine used contains an antigen that differs in some way from the field strain.

Several methods are available to achieve this differentiation, but all have some practical difficulties in implementation that precluded their use in Vietnam other than in experimental trials.

One system, developed initially in Italy, relies on the use of vaccines containing antigens with a different N subtype to the field strain (e.g. H5N2 antigen but H5N1 field virus) and then using tests based on anti-NA antibodies to determine if birds seropositive to the H5 antigen have been exposed to the field virus (i.e. if so, they should have antibody to N1) or just to the vaccine strain (in which case they will have antibody to the N2 antigen in the vaccine and will test negative on a test for anti-N1 antibody).

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[5] For more information on vector vaccines see the section on recombinant vaccines in the OIE's chapter on avian influenza from the Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. Available at: http://www.oie.int/eng/normes/mmanual/2008/pdf/2.03.04_AI.pdf

[6] Antibody to the HA component is by far the more important for protection

Other systems using tests that detect antibodies against non-structural proteins in the influenza virus (which are not present in significant quantities in some vaccines) were not considered for use in Vietnam because the methods were still under development.

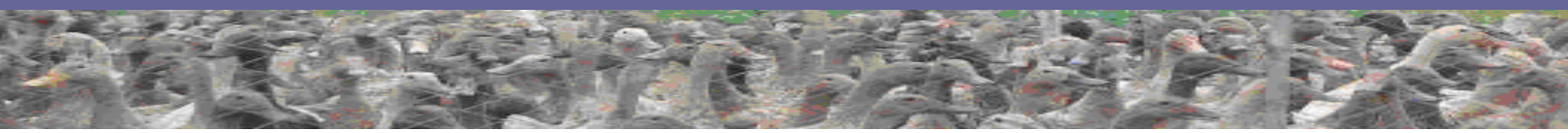
Vietnam did not initially implement a routine DIVA system for a number of reasons

The third 'DIVA' strategy relies on the use of unvaccinated sentinel poultry in vaccinated flocks but is complicated to use in the field especially when dealing with large numbers of small flocks (a few unvaccinated sentinels in a large flock probably have little effect on the overall flock immunity but depending on how many sentinels are used will have an effect on the level of flock immunity in smaller flocks). Sentinels have been used in experimental trials only and are not routinely used in Vietnam.

All international recommendations on avian influenza vaccination suggest that a DIVA strategy should be implemented. However, Vietnam did not initially implement a routine DIVA system for a number of reasons. These were:

i) International recommendations are more applicable to places working towards elimination of virus, which was not the initial objective of the vaccination campaign in Vietnam.

ii) Serological DIVA strategies depend on the absence of other circulating influenza viruses that might complicate interpretation of results. In other parts of Asia, H6N1 viruses (which could interfere with any NA based DIVA strategy) are known to be circulating as are H9N2 viruses (which would interfere with tests using non-structural proteins). The situation in Vietnam regarding circulation of other influenza viruses was poorly characterized.



iii) Assays for anti-NA antibody are not conducted routinely in most laboratories. Validated tests for anti-NA antibody in ducks were also unavailable at the time the campaign was implemented.

iv) At the time vaccination was introduced, laboratory capacity was not sufficient to cope with an influx of millions of blood samples (even for standard HI tests for post-vaccination surveillance most laboratories could only test a few hundred flocks each year)

v) Prior to the introduction of vaccination, no routine pre-market testing of unvaccinated flocks was done for HPAI. Therefore, it was already possible for recently infected flocks to be sold, especially if a flock owner noticed some mortality in his flock and sold it before disease was widespread within the flock. If a pre-market testing system for all poultry had been in place then there would have been a strong case for introducing a DIVA testing system to reduce the likelihood of infected vaccinated poultry being sent to market. Rather than implementing a DIVA system, a decision was made to improve the overall surveillance system once vaccination was implemented in order to detect circulating viruses, but pre-market testing of all flocks was not possible.

vi) The time between infection and seroconversion of birds in a vaccinated flock to allow anti-NA antibody to be detected in a small sample of birds is at least 3 weeks and possibly longer (allowing a minimum of one week for infection to spread in the flock and two weeks for enough infected birds to develop antibodies). This means that even if a negative serological DIVA test result is obtained, it provides no guarantee that infection has not occurred in the 3 week period before the samples were collected. For short lived broilers this represents almost half of their life span and therefore the capacity of such a system to detect infection for broilers was too low to justify the expense of introducing serological DIVA testing as a routine measure for all vaccinated broiler flocks.

Despite all of the above reasons, when the antigen for chicken vaccines was chosen, a decision was made to allow for the possibility of using serological DIVA testing as a tool to assist in investigations if required in the future. Accordingly, the first antigens chosen for vaccination of chickens (H5N2 antigens) were selected in preference to H5N1 antigens. No DIVA testing was done routinely because the laboratories were not in a position to offer the required test. The focus was on detection of virus and in conducting monitoring of the serological response to vaccination to ensure that the vaccines were providing some protection.

Given the lack of validated anti-NA tests for ducks and the desire to provide the best possible immunity, a Chinese vaccine containing an H5N1 antigen that provided a superior immune response than the Chinese H5N2 antigen was chosen for duck vaccination.

Subsequently, using two different vaccines–one for chickens and one for ducks–was found to be wasteful in mass campaigns, especially when so many households kept both species. After one year the H5N2 antigen in Chinese vaccines used for chickens was replaced in the government sponsored campaign. The H5N2 antigen is still used in commercial chickens, which means that DIVA testing could be used in these flocks at a later stage.

Sentinel poultry were not included routinely in all flocks because of the difficulties in managing these birds. Farmers were reluctant to leave unvaccinated poultry in their flock and marking and identification of sentinels proved to be difficult (although it has been used recently in a few experimental flocks).

Monitoring and surveillance of poultry was increased once vaccines were introduced. It was critical to determine whether viruses were still circulating and to characterize these to ensure that antigenic variants had not emerged. Market and farm monitoring for circulating H5N1 viruses was increased and viruses were detected. Unvaccinated Muscovy ducks (for which there was no suitable vaccine in 2005) present in a number of flocks were tested to determine whether virus was still circulating and some were found to be infected.

Vaccine packaging

In the early stage of the campaign vaccine was supplied only in large 1000 dose bottles. Given that many flocks are very small in Vietnam, vaccine has been rebottled under appropriate conditions locally by a commercial vaccine company in Vietnam into smaller vials to reduce wastage of vaccine in subsequent campaigns.

5. Where to vaccinate?

Initially, all provinces were required to undertake vaccination either across the entire province, just in lowland areas with greater concentrations of poultry (and humans) or along major trading routes such as the area around the main north-south national highway. By the second year, this program was modified to cover all of 33 high risk provinces, focusing especially on the provinces in the Mekong and Red River deltas but also in the low lying areas in central Vietnam. Parts of other provinces were also vaccinated.

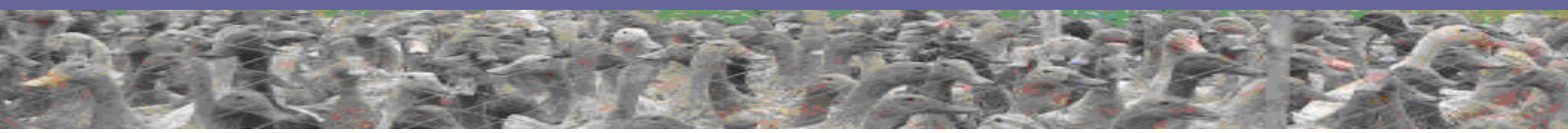
The extent of the vaccination campaign has been reviewed regularly, at least annually, although the evidence base for making scientifically sound modifications to the scope of the campaign is still limited. Therefore, a conservative approach has been taken to reducing the scope of the program.

In 2004 very few provinces escaped infection. In later waves of infection, the disease occurred less frequently, with many cases occurring in southern provinces in unvaccinated ducks. Some of the recent cases have occurred in mountainous areas where vaccination was not compulsory. These tend to be isolated events that do not lead to large outbreaks due to low poultry density in these areas.

6. Which types of poultry to vaccinate?

One of the biggest challenges faced was determining which poultry flocks to vaccinate. At the time the vaccination campaign was designed, most of the reported human cases were associated with village/household poultry rather than medium to large commercial flocks. If the vaccination campaign had only focused on the larger flocks and human disease continued to occur (in association with exposure to infected household poultry) it then would have appeared as if veterinary authorities were only protecting the commercial sector and not addressing the risk to humans.

This observation regarding human cases swayed the decision to include village/household level flocks in the initial campaign. This decision was not taken lightly because it meant a massive vaccination campaign had to be mounted and required mobilisation of a large number of people down to the commune level.



A campaign that only focused on commercial flocks with more than 50 poultry would have been much simpler to manage and would have covered far fewer farms. However it would have left a very large part of the poultry population unprotected including the poultry that have the closest association with people. Table 2 demonstrates the skewed distribution of poultry in Vietnam with more than 94% of chicken flocks and some 90% of duck flocks containing fewer than 50 birds.

The vaccination program was divided into two parts. Larger commercial flocks (above 2000 head) were required to purchase their own vaccine and were free to vaccinate whenever poultry reached the recommended age for vaccination. Smaller flocks below 2000 head were supplied with vaccine free of charge and most were vaccinated through large scale campaigns.

Issues relating to different types of poultry

A number of issues had to be considered in relation to the different types of poultry including decisions on which poultry to include.

i) Short-lived (white feathered) broilers

Short-lived broilers (life span of 45 days) were not included in the initial campaign largely because they represented a dead-end host if they were infected and sold direct to slaughter. In other words, the broilers' very short life span meant that any vaccine given to these birds only had a protective effect for a very short period.

There were also some initial concerns about the withholding period for the vaccine which meant that these birds were not likely to receive a second shot of vaccine. Most farmers were reluctant to vaccinate short-lived broilers anyway. Unfortunately not all of these birds were sold direct to slaughter and there was a risk that short-lived broilers sold through markets could enter the market system. In some parts of the country, especially in Ho Chi Minh City and within Hanoi, measures were taken to close live poultry markets, which diminished this risk.

Fowl pox vector H5 vaccine was seen as an ideal vaccine candidate for short-lived broilers and was introduced to hatcheries at an early stage. Use of this vaccine is currently suspended until such time as its efficacy under field conditions in Vietnam can be assessed.

Few households kept short lived broiler chickens–most were in medium to large scale commercial farms.

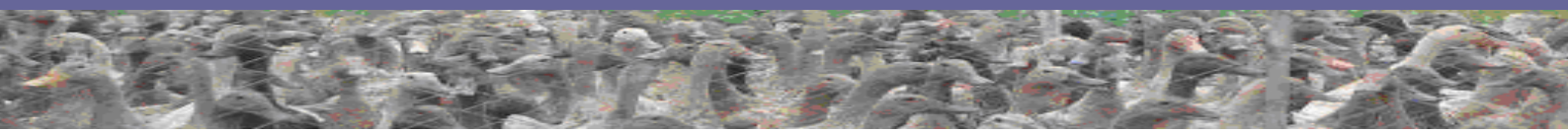
ii) Long-lived meat birds
Many of the Chinese-style and traditional breeds are kept for at least 90 days before reaching market weight. This provides ample opportunity for these birds to be vaccinated twice and they were included in the large scale campaign.

iii) Commercial chicken layers
Layers on large farms are usually given two doses of vaccine 3 to 4 weeks apart starting at 10 to 14 days of age. They are then revaccinated just prior to point of lay. This usually provides immunity for much of the subsequent period of lay. However antibody levels in some flocks of layers have been shown to fall below levels considered to be protective before they stop laying. Most owners of layers do not want to vaccinate their poultry while the birds are in lay because the stresses of vaccination can reduce egg production. The overall effect of this fall in immunity is that layers at or close to the end of lay may have minimal protection against HPAI if they are not boosted during the laying period. This low level of protection may be significant if these birds are sold through infected live poultry markets.

When large scale campaigns were implemented so that poultry were vaccinated at a set time rather than at the recommended age, a number of poultry owners experienced short term production losses and in subsequent rounds of vaccination were not prepared to have their poultry vaccinated.

iv) Meat ducks
At the time vaccination was introduced, a breeding ban on commercial ducks was in place so there were few ‘legal’ flocks of meat ducks. Nevertheless, some breeders and farmers chose to flout the law and thereby created a difficult situation where many illegal birds were not presented for vaccination and those that were could not be provided with free vaccine. This created some conflict for vaccination teams. The breeding ban was lifted in 2006 overcoming this particular problem.

Ducks in small household flocks were also vaccinated during the mass campaign.



As with short-lived broilers, one of the problems encountered with meat ducks was getting two shots of vaccine into the birds before they went to market. Many of these ducks were sold through live bird markets rather than slaughterhouses and therefore posed a significant risk if unvaccinated.

Many meat ducks, especially in the Mekong Delta, are only reared under confined conditions for the first few weeks of life before being moved to harvested paddy fields to feed on spent grain and snails. Once these ducks leave the household/farm, it is more difficult to get them vaccinated. Efforts are continuing, through applied field and laboratory research, to establish a vaccination protocol that allows two shots of vaccine to be delivered to these ducks before 21 days of age without interference from maternal antibody.

v) Layer ducks

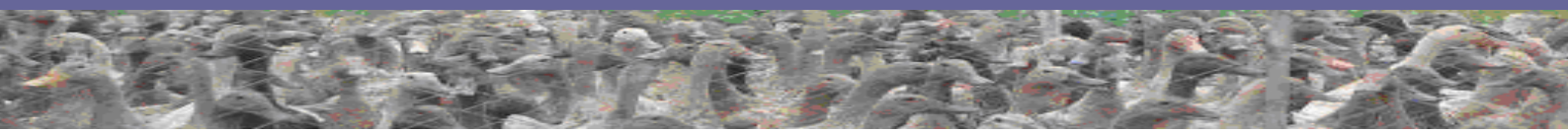
These birds were included in the campaign. As with meat ducks, many of these birds leave the household/farm to graze on paddy fields at an early age. This practice makes it hard to ensure that all layer ducks received two doses of vaccine and a booster dose every six months.

vi) Other poultry

The other main species of poultry kept on farms are Muscovy ducks, but as no suitable vaccine for these birds had been identified when the first campaign was launched they were not included in the initial vaccination campaign. They represented a form of sentinel for infection as many households keep small numbers of these birds. Later, a commercial vaccine was used, but the immune response generated was not deemed to be satisfactory. Chinese vaccine will be used in the next mass campaign in late 2009.

Vaccination of quail, pigeon and geese was not conducted. In the case of pigeons, no evidence for a major role in the spread of H5N1 HPAI was evident and for quail no suitable vaccine was available given the small size of the birds. There are few commercial geese in Vietnam.

The end result of this selective vaccination was that a considerable number of susceptible poultry were not vaccinated. This meant that other measures such as enhanced biosecurity measures were required to protect unvaccinated poultry such as short-lived broiler chickens.



7. When to vaccinate

The best immune response to inactivated vaccines is obtained if the vaccine is given at the ages recommended by vaccine manufacturers. Usually, two shots of vaccine are required to generate a long lasting immunity and for layers a third shot just prior to lay is also required. Some farmers in other countries have noted a drop-off in immunity during the laying period and have revaccinated their birds.

Large commercial chicken layer flocks generally followed guidelines from the vaccine manufacturer and vaccinated their poultry as they reached the appropriate age. However, the logistics of arranging for all poultry in smaller household flocks to be vaccinated when they reached the appropriate age were such that a decision was made for the blanket campaign to occur during a concentrated vaccination period prior to the main festival season in winter (i.e. vaccination during the autumn).

By vaccinating a large proportion of the population twice during this period it was expected that the quantity of circulating virus would diminish dramatically in the months after vaccination. Even though flock immunity in individual flocks would wane over time, it was expected that the reduced circulation of virus created by having a high percentage of immune poultry would delay the build up of infection otherwise expected during winter. It was not possible to model this effect precisely before the vaccination campaign because such a system had never been used before with HPAI and limited data were available upon which to build the model. Based on experiences from Hong Kong, not all older birds were expected to mount a strong immune response.

…reduced circulation of virus…
…would delay the build up of infection otherwise expected during winter…

By delivering vaccination in October and November to a high percentage of eligible poultry, peak population immunity would be achieved in December and would be expected to fall over the next few months. Subsequent post-vaccination serology has shown that this was, in fact the case. Within four months of vaccination, fewer than 50% of birds in vaccinated flocks had protective levels of immunity.

In reality, the first campaign extended over a longer period than initially planned and some poultry were not vaccinated until the winter.

A second campaign is conducted in the spring (first implemented in 2006) with the goal being to boost the immunity of longer-lived poultry and to prime any new long-lived poultry that entered in the system since the last campaign.

The need for the second mass campaign has been queried given that this is not generally regarded as a high-risk period for infection.

At present, significant numbers of short lived ducks are missing out on vaccination because they are hatched to coincide with the rice harvests, the timing of which varies both within and between different parts of Vietnam. The hatching of these birds does not coincide with vaccination periods in all parts of the country. Studies are currently underway to examine ways of modifying vaccination in order to reduce the cost to government without increasing the risk of disease outbreaks.

8. How to conduct the vaccination campaign?

One of the main issues that had to be resolved was how to deliver the vaccine to the millions of small household flocks and free-ranging duck flocks. The national Department of Animal Health (DAH) took the lead role in driving the campaign but each province then had to arrange its own campaign based on guidance provided centrally.

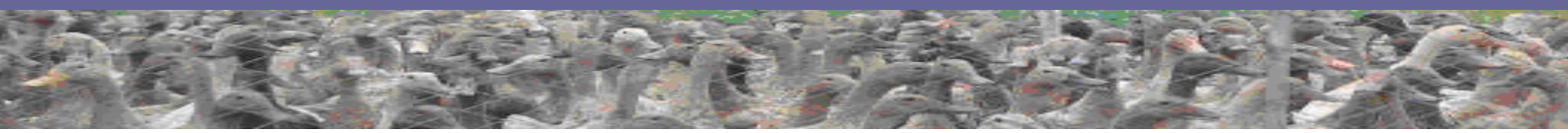
In Vietnam, the sub-departments of animal health (SDAH) at provincial level are employed by provincial authorities and not by the central government, although there are strong links between the Department of Animal Health and provincial sub-department through national decrees, decisions and laws.

Each provincial SDAH has a number of district veterinary centres (one for each district) that have refrigerators for vaccine and drug storage and are manned by veterinarians. Within communes, the next level down the administrative ladder, veterinary paraprofessionals referred to as community animal health workers (CAHWs) provide basic veterinary services and are engaged in the campaign as vaccinators. At the time of the first campaign, most CAHWs were not employed directly by government, although some were paid an allowance to provide support and information to district centres.

...farmers handle their own birds at the vaccination point...

Bringing poultry to a vaccination point – Dong Thap, August 2005

Rates of pay for vaccinators had to be



established that were deemed fair but which also enabled the campaign to be implemented within the available financial resources. Those who vaccinated large flocks at a single location were able to vaccinate many more birds than those who had to travel door-to-door to household flocks, so a daily rate was used as well as a per bird rate in some instances.

In some communes, vaccination for very small flocks was organized at specific vaccination points. Poultry for vaccination were brought to these points by their owners rather than requiring vaccinators to visit each household. The risk of cross infection at these points was minimized by having individual farmers handle their own birds at the vaccination point and presenting them to vaccinators; by minimizing the time birds were held at the vaccination points; and by avoiding contact with other poultry.

Each commune had an avian influenza committee that...assisted in keeping records of vaccine use

Each commune had an avian influenza committee that played a key role in ensuring all commune members were aware of the vaccination program, organizing campaigns and assisting in keeping records of vaccine use.

Vaccination teams generally travelled by motor cycle, and sometimes by boat, and were provided with a cool box, an automated vaccine gun, replacement needles and vaccine as well as gloves and disinfectant. Much of this was provided by the central government with support from donors.

Vaccine was stored at provincial level and distributed to district offices, where it was stored in refrigerators, for onward distribution in cool boxes to vaccinators.

9. Some other issues considered in setting up the government sponsored vaccination campaign

All of the following issues had to be considered when establishing and running the vaccination campaign in Vietnam. They would also have to be dealt with by other countries or places implementing vaccination.

Vaccine registration

All vaccines for livestock in Vietnam must be registered before they can be used. This meant that the vaccines had to undergo a series of safety and efficacy tests to meet local registration requirements. The vaccines used against H5N1 viruses in Vietnam had all been registered for use elsewhere; so much of the background

information on efficacy was already available. Nevertheless, prior to the first mass campaign, a series of trials were conducted to ensure that the vaccines used were appropriate before they were registered for use. Facilities had to be available in which to conduct these tests.

Getting support for the program – the importance of communication

A vaccination campaign of this magnitude is a major undertaking and must be backed at all levels of government and by poultry owners if it is to be successful.

In 2005, support was obtained from the highest levels of government, from the Prime Minister and Minister for Agriculture down to the commune level, to ensure that the first round was completed successfully.

The political system in Vietnam reaches down to the commune level and was used to communicate the importance of vaccination. Each province, district and commune had an avian influenza control committee and these committees were responsible for ensuring that messages regarding the importance of vaccination were transmitted and understood by the public. Members of these committees played a key role during vaccination by ensuring that all households were aware of the procedures for vaccination, and by keeping records and advising households when vaccination teams were in the area or vaccine points had been set up.

Support for the vaccination program was not universal. Some veterinarians felt that the campaign was an expensive waste of resources that would never be implemented effectively. Others were opposed to vaccination for a disease that in their view should continue to be handled using ‘traditional’ methods based around culling. Some wanted to see a campaign in which DIVA testing was performed on all vaccinated flocks and were not convinced that vaccination aimed at reducing levels of infection was justifiable.

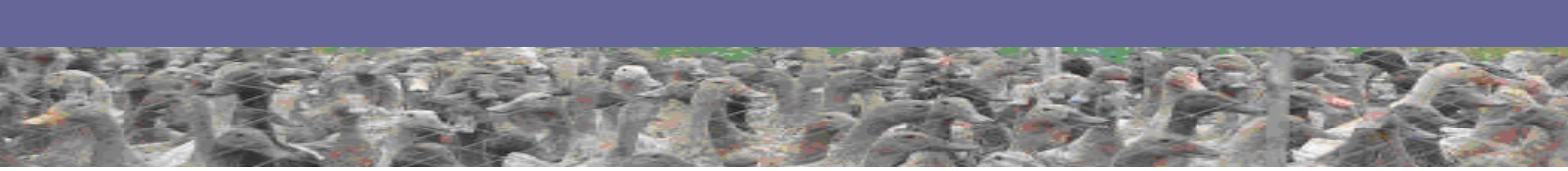
Support for the vaccination program was not universal

Some farmers saw little benefit in vaccination, especially those with poultry in lay. This resistance increased after the first vaccination round because vaccination (or handling of birds associated with vaccination) resulted in temporary reductions in egg output in some flocks. Farmers experiencing or hearing of such losses were more reluctant to have their birds vaccinated in subsequent rounds.

Duck farmers posed a particular problem. Despite the role that ducks are thought to play in the transmission of H5N1 viruses, few duck farmers had experienced outbreaks of disease associated with these viruses and therefore did not see it as a disease they needed to prevent through vaccination (in contrast with other diseases such as duck virus enteritis for which vaccination is used in many parts of Vietnam). Given that the main beneficiary from duck vaccination is the general public (who, potentially, would be exposed to lower quantities of circulating virus as a result of duck vaccination) there is a compelling case for duck vaccination to remain subsidized or free to ensure uptake.

Movement controls were also used to ensure ducks were vaccinated. If ducks crossed provincial boundaries they had to have a record of vaccination or were then expected to be vaccinated on arrival in the new province. Large consignments of ducks in some parts of the country could not move to market without a valid vaccine certificate from local authorities.

From the time that a blanket vaccination program was first contemplated in Vietnam it was considered inevitable that the enthusiasm for such a large scale vaccination campaign would diminish with each round, unless there were strong financial incentives for those involved and buy-in from poultry owners on the importance of vaccination.



As predicted, maintaining the sort of coverage obtained in the early stages of the campaign has proved to be difficult. To overcome this resistance, messages from the highest level of government have continued to urge all households to ensure their poultry are vaccinated in accordance with national directives. These announcements are reinforced and reiterated after disease outbreaks (or human cases of influenza A (H5N1)) occur and have been targeted, in particular, at duck farmers.

Determining costs and benefits of vaccination …. who pays?

It is not possible to conduct a sensible cost-benefit analysis of vaccination against H5N1 in Vietnam given that the principle reason for controlling the disease is to prevent human infection and the possible emergence of a severe human pandemic influenza strain. It is, however, possible to assess the relative cost of various control measures and to determine the overall cost of the vaccination program. Some studies have already been conducted on these costs and provide a baseline against which the costs of other control measures can be assessed.

There was no point having a lower cost control system if it was not effective in preventing human cases.

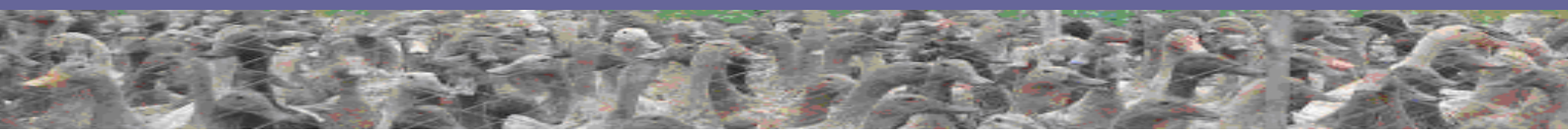
One fact on costs and benefits stands out. Vaccination was introduced because the other measures implemented had not prevented the increase in human cases in 2005. There was no point having a lower cost control system if it was not effective in preventing human cases.

Vaccination against H5N1 HPAI was viewed as being of benefit to the public both in Vietnam and globally and the government of Vietnam has accordingly provided most of the funds for the vaccination campaigns, with support from international donors.

The overall cost of vaccination has been estimated at approximately $US10 million per round. As vaccination is likely to continue for some time, it is important that this substantial cost to government is reduced over time to ensure that the vaccination campaign can be sustained in those places where it is needed.

One option is reduce the scope of the program. The other is to shift the cost to producers, but as noted in the previous section, producers will need to see that the disease represents a risk or that vaccination provides some economic benefit to them before they are likely to agree to pay its cost.

It was decided at an early stage in the campaign that owners of larger scale farms should pay for vaccine and vaccination because they stood to gain considerably from



the protection afforded to their birds. Vaccination was a form of insurance. It also provided a marketing advantage for their poultry products (i.e. allowed free access to urban markets and birds could be marketed as vaccinated poultry).

Owners of smaller flocks (flocks containing up to 2000 birds) were not required to pay for the vaccine, although in some provinces they were required to contribute to the cost of vaccinators.

If H5N1 HPAI had not been viewed as a potential threat to global public health then it is extremely unlikely that a mass vaccination campaign for household poultry would have been implemented.

Available data (although incomplete and subject to considerable reporting bias) suggest that the number of reported household cases as a proportion of total households rearing small numbers of poultry is much lower than the proportion of infected commercial flocks. This is probably due to the higher contact rates of commercial farms with traders and contaminated fomites such as poultry cages and (potentially) egg flats that can result in transmission of disease.[7]

The loss of household poultry from HPAI has a negative effect on household income and nutrition and may have a disproportionate effect on women and children (who often benefit the most from rearing household poultry). However, the vast majority of households have not been affected directly by this disease, except during the mass culls in early 2004. In addition, the inputs provided to household poultry are minimal and if disease occurs the invested capital lost is very low.

Some simple calculations show why it is not possible to justify a blanket vaccination campaign of household flocks on the basis of poultry losses for small households alone unless broad culling around infected premises is also used as a control measure.

If we assume that 90% of the government expenditure for the vaccination campaign is used on small flocks of poultry (i.e. $9 million per round) and the average value of a bird in these flocks is $US2 then each round of vaccination would need to prevent the loss of 4.5 million poultry just to cover this cost. In early 2004, 45 million poultry were lost, which is 10 times this number, but much of this loss was due to wide area culling, a practice that was abandoned later in 2004. The number of poultry lost from HPAI or culled in the second wave 2004-05 was 2 million and in late 2005 (before vaccination was fully implemented) was 4 million. However this latter figure did not reflect the number of poultry culled to control the disease. The market for poultry was very poor at that time and a large number of poultry were culled because they could

[7] See Otte et al. (2008) *Flock size and HPAI risk in Cambodia, Thailand and Vietnam*, available at http://www.hpai-research.net/docs/Research_briefs/FAO_2008_%20HPAI_rbr05.pdf

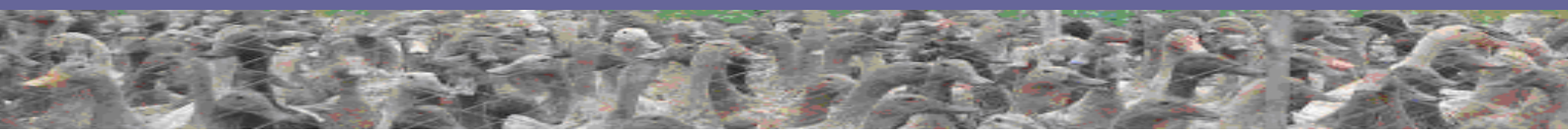
not be sold (see Figure 1 for numbers of poultry culled/lost in each ‘wave’ of disease).

The equation changes if it includes the cost of human lives lost and the reduced threat of pandemic emergence from a reduction in human exposure, but it is only possible to derive crude estimates for the costs of the latter. The recent human influenza pandemic caused by an H1N1 virus, although relatively mild, has demonstrated that novel influenza viruses can emerge as human pandemic strains and has also shown how these can spread globally once established in one part of the world. If an influenza A (H5N1) virus ever emerges as a human pandemic strain capable of sustained human-to-human transmission, and retains even some of its current virulence for humans, the effects would be devastating.

Recording of vaccination details – Tien Giang

The challenge for the future is to see if it is possible to reduce the extent of household flock vaccination without increasing the number of outbreaks in these flocks and, more importantly, without increasing the number of human cases. Some low risk districts (those with low poultry density) in provinces outside of the Red and Mekong river deltas have already adopted this approach by only vaccinating commercial flocks. Whether it is possible to use this approach in the more densely populated areas is not yet known.

A number of the factors that are believed to have resulted in persistence and spread of H5N1 HPAI are being addressed, including improvements in marketing practice and biosecurity measures in commercial farms. However, some practices such as free grazing of ducks and allowing household poultry to scavenge for feed are still practised and there are sound economic reasons why these practices persist. Live poultry marketing also still occurs and there are still thousands of poultry traders and transporters moving poultry from farms to markets and slaughterhouses, potentially spreading disease. As long as these practices continue, the risk of infection will persist. Therefore, it will be some time before the risk of infection is reduced sufficiently to stop vaccination of all household poultry. Additional research is still needed to provide more data to determine the level of risk faced by farmers and households to support decisions on this and similar questions.



Training of vaccinators

Although vaccination has been practiced by CAHWs, farmers and veterinarians for many years for other diseases, blanket vaccination campaigns of poultry had not been conducted before and presented somewhat different issues to routine vaccination. Therefore, those involved as vaccinators and support staff required training.

In a blanket campaign, the potential risk posed by vaccinators as spreaders of disease is high. Vaccinators also have to ensure that they keep vaccine at appropriate temperatures and vaccine guns are working properly. They must also deliver the vaccine in a manner that does not harm the bird, which can be an issue when delivering vaccine intramuscularly in very young birds. All of these issues were considered in training programs.

Training of vaccinators had to be done prior to commencement of the campaign. A video compact disc was prepared showing proper vaccination technique and was used as a training tool.

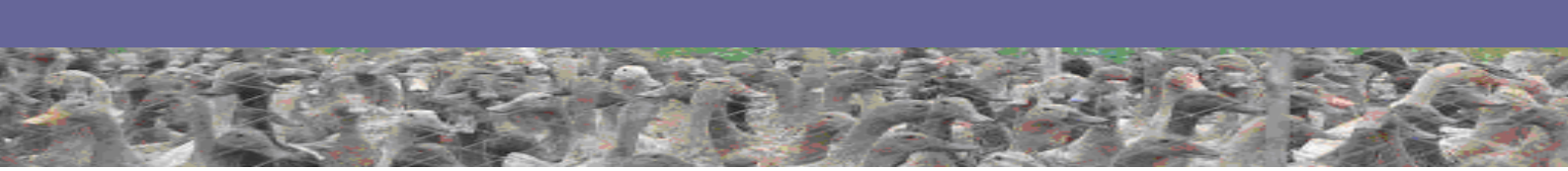
Training is continuing on ways to improve the quality of vaccination in the event of a disease outbreak through simulation exercises in selected provinces and subsequent assessment of the problems encountered in conducting emergency vaccination, including prevention of spread of disease by vaccination teams.

Cold chains

Avian influenza vaccines are heat labile[8] and must be stored at four degrees Celsius in order to avoid product degradation. Most district offices had refrigerators in which it was possible to store vaccines, although many of these contained other vaccines and medicines. Aid agencies also provided additional refrigerators. Some provincial centres had suitable places to store large quantities of vaccine but for others makeshift methods had to be used to keep vaccines cool until such time as suitable cold rooms were available. These were not always effective and poor temperature control may have played a role in the poorer performance noted in post-vaccination surveillance in some provinces.

Not all district and provincial offices had reliable power supplies or generators and this had to be addressed as a matter of urgency during the initial stages of the vaccination program.

[8] Destroyed or altered by heat



Supply of vaccines and other equipment needed for the campaign

Large quantities of vaccine were supplied by vaccine manufacturers in China. This was then delivered to provincial centres through a distribution network established by contract with existing veterinary pharmaceutical companies in Vietnam.

Legal basis for vaccination

The requirement for vaccination was stipulated in a number of formal decisions issued by the Minister of Agriculture. These decisions provided information on the geographic extent of the campaign and details on poultry eligible for vaccination.

Quality assurance

New batches of vaccine imported into Vietnam are subjected to quality control tests in accordance with OIE guidelines before being sent to the provinces

Testing the system

The capacity of provinces to implement vaccination was tested in two trial provinces in September 2005 (Nam Dinh in the north and Tien Giang in the south) to ascertain the types of problems that might be encountered. The information from these trials was used to improve the program in other provinces. The short period between the trials and the rolling out of the campaign to all provinces limited the scope for major changes.

Withholding periods (WHP) for poultry post-vaccination[9]

The vaccines currently in use contain a killed antigen and an oil-based adjuvant, neither of which are known to be toxic to humans. However, the label for the Chinese vaccine recommended a 28 day WHP. A WHP of this duration meant that many short-lived poultry would only receive one dose of vaccine because the second dose would be required within 28 days of going to market.

Some concerns were expressed that poultry sent to market soon after vaccination would have visible tissue residues of vaccine in their meat. In addition, if poultry are sent to market within 14 days of vaccination they would not have optimal immunity when sold. As vaccination of poultry is not only done to protect poultry on farm but also when they go to market it was decided that a 14 day WHP should be adopted to allow vaccinated poultry to develop an immune response. This 14 day WHP also reduced the likelihood of finding significant blemishes in carcasses from vaccination.

[9] The withholding period (WHP) is the minimum period of time which must elapse between last administration or application of a veterinary chemical product and the slaughter, collection, or use of the animal commodity for human consumption

10. Measuring the effects of vaccination – both positive and negative. The importance of post-vaccination monitoring and surveillance

Vaccination was introduced into Vietnam as an emergency measure and therefore it was not possible to implement it as a controlled trial in which some provinces were vaccinated and others were not, which might have allowed the positive effects of vaccination to be determined. Implementing vaccination in all provinces at the same time meant that it was not possible to determine the overall effectiveness of vaccination and the contribution it made to reductions in the incidence of HPAI that followed.

After the first mass vaccination campaign was fully implemented, no more human cases were reported for over 12 months

Ultimately, the main measures of overall success for the control program in Vietnam were reduction in the number of reported human cases and deaths, and the reduction in poultry deaths directly or indirectly (i.e. as a result of culling) from this disease.

After the first mass vaccination campaign was fully implemented, no more human cases were reported for over 12 months. It is still not known whether this was a coincidence, the result of other control measures implemented concurrently, or the result of vaccination.

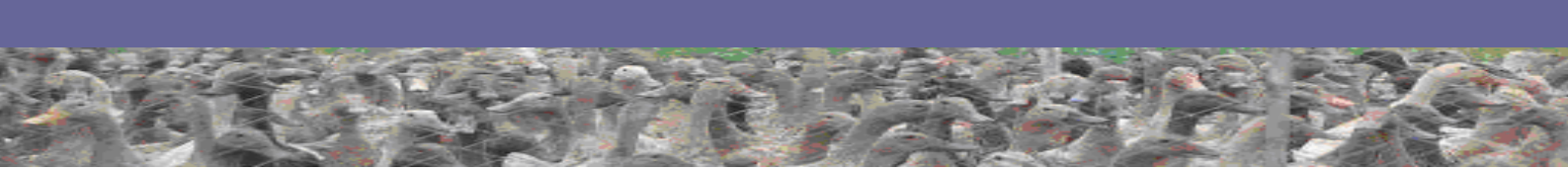
In the two years before vaccination (2004 and 2005), a marked increase in the number of human and poultry cases occurred in the period from late December coinciding roughly with the winter festivals (including Tet), a period of intense trade and movement of poultry. This did not occur in 2006 after the first round of vaccination was fully implemented.

The following table demonstrates the change in the number of human cases and deaths that have been recorded in Vietnam since 2003. Note that the number of reported cases fell dramatically in 2006 and have remained low ever since.

Table 3: Confirmed human cases of Influenza A (H5N1) in Vietnam 2003-2009 (deaths/cases)

2003	2004	2005	2006	2007	2008	2009 (June)	Total
3/3	20/29	19/61	0/0	5/8	5/6	4/4	56/111

It is noteworthy that none of the human cases in Vietnam for which the source of infection is known have been associated with vaccinated flocks. The vast majority have an association with sick, unvaccinated poultry. Several recent cases have involved people in remote locations where vaccination is not practiced.



Unfortunately, records of investigations of all cases are not available or are incomplete.

Since 2004, the surveillance and reporting systems for both poultry and humans have improved, so it is unlikely that reductions are due to change in diagnostic systems (improvements should have instead resulted in more cases being recognized).

In case-control studies of duck disease outbreaks in 2006, one of the key factors for cases occurring was not vaccinating.

The results presented above do not prove that vaccination is responsible for all of the apparent gains made in preventing disease – the best that can be said is that the combination of measures introduced since mid 2005 appear to have reduced the incidence of disease in both humans and poultry.

Post vaccination surveillance

The key reasons for conducting post vaccination surveillance in Vietnam are:

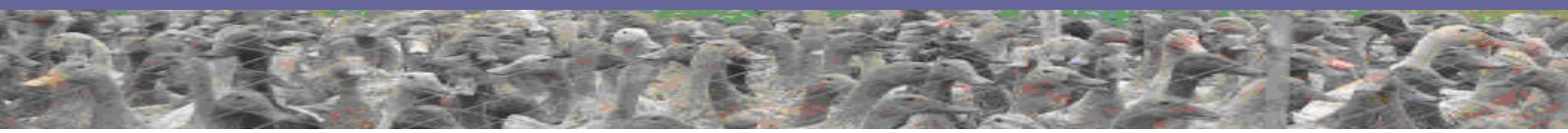
1. to establish the levels of protection provided by vaccination and, if this is unsatisfactory, to try to determine the cause and to take some remedial action including providing some warning to provinces that results are potentially sub-standard;

2. to determine whether viruses are still circulating and, if they are, to assess their antigenic makeup and their distribution.

Post-vaccination surveillance has focused on the antibody response in vaccinated flocks and on detecting virus in unvaccinated poultry, smuggled poultry and poultry in markets. It is supported by case investigations of suspect outbreaks.

Blood samples have been collected from selected flocks one month and four months after vaccination to monitor the levels of antibody to H5 virus. The manpower required to collect these samples and the laboratory capacity required to perform the tests accurately need to be taken into account when planning vaccination campaigns. International donors have provided considerable funding for enhancing laboratory activities in the wake of the emergence of H5N1.

Unvaccinated ducks and Muscovy ducks have been used as ‘sentinels’ for infection. Both seroconversion and positive virus isolation have been achieved from ducks and muscovy ducks even during periods when no cases of disease have been reported. This result demonstrated that virus had not been eliminated after vaccination was introduced, but–combined with data on human cases–suggested that control and preventive measures were reducing the quantity of circulating virus.



It is still not possible for all vaccinated flocks to be tested before they are sent to market or slaughter. Instead selected flocks are bled after vaccination based on a surveillance plan reviewed and prepared annually by the Department of Animal Health in association with international agencies.

The first round of vaccination appeared to achieve reasonable coverage approaching 66% of the reported census population in chickens and almost 80% in ducks (although the estimate for ducks is probably an overestimate due to unrealistically low census figures).

Coverage was lower in the second campaign for both chickens and ducks. Coverage in the third campaign remained around 50% for chickens but was estimated at over 70% for ducks (again the census figures for ducks used to calculate this percentage seemed low).

After the first round of vaccination, 67% of vaccinated birds sampled at one or two months post-vaccination had developed antibodies as measured in serological tests (Haemagglutination Inhibition (HI) test). This percentage was 60% after the second round.

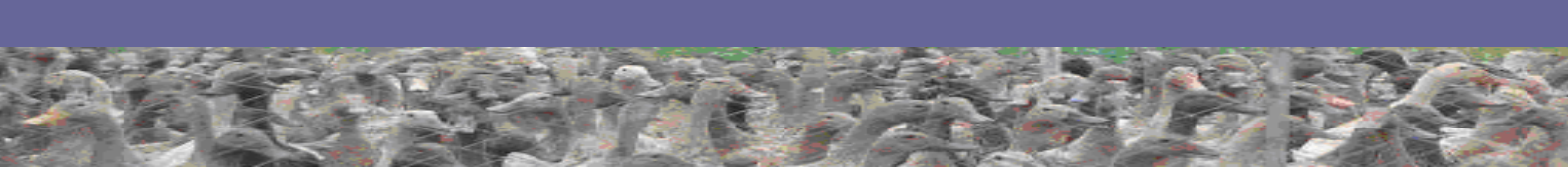
The percentage of tested flocks that achieved ≥70% with positive HI titres in sampled birds was around 55% following both rounds of vaccination.

As sero-monitoring was targeted only on flocks and birds that were known to have been vaccinated it is estimated that 44% of the 'known' chicken population was effectively immunised in the first round (i.e. 66% x 67%). This was achieved when over 90% of eligible birds were reported to have been vaccinated, a rate that was not improved in subsequent campaigns.

The first round of vaccination appeared to achieve reasonable coverage…

These figures demonstrate the immense difficulty in maintaining a high percentage of immune individuals within a very large population of poultry that has a high rate of turn-over when using a 'mass campaign' approach.

The Vietnamese HPAI vaccination campaigns did not achieve over 70% of poultry flocks protected, but when the vaccination campaign was initiated there was no likelihood of achieving this level of flock immunity that would lead to elimination of infection, given the many constraints of such a campaign and the rapid rate of turnover of the population. In fact, the achievement level was nearer 50% of flocks. The effect of vaccination of this number of poultry is to reduce the size of the



susceptible population even if a level of population immunity that will prevent transmission of infection is not reached.

Monitoring for antigenic variants

One of the biggest threats to vaccination campaigns is the emergence of strains of virus capable of resisting the antibodies generated by vaccines. Vaccines containing killed antigens and oil-based adjuvants provide broad cross protection against a wide range of strains but some antigenic variants have been detected following implementation of vaccination. The first case of this happening with avian influenza viruses was detected in Mexico, following vaccination against low pathogenicity H5N2 avian influenza viruses, and other cases have now been seen in China, Indonesia and Egypt.

Systems are now in place to ensure that isolates from Vietnam are sent to international reference laboratories for genetic and antigenic characterization. In addition, challenge trials have been conducted in Vietnam against a range of newly isolated viruses to determine whether existing vaccines can still protect against these virus.

One of the strains of virus (clade 7 virus) that has been found in Vietnam appears to be an antigenic variant but so far this particular virus has only been found in smuggled poultry and does not appear to have become established in local poultry.

Once an antigenic variant is detected in local poultry, preparations will be made to incorporate a new antigen to existing vaccines, as has been done previously in China to cope with an antigenic variant (Clade 7 virus) that emerged in 2006 in northern China.

11. Lessons learned so far

Many lessons have been learned so far from the vaccination campaign. These are important for other countries contemplating vaccine use and also form the basis for modifications to the program in Vietnam.

The importance of trial vaccination

In 2005, once a decision was made to vaccinate, two trial provinces were chosen (one in the north and one in the south) and vaccination was implemented there. The experiences from the two trial provinces provided vital information on many of the difficulties likely to be encountered once the program was scaled up. Difficulties identified included poor quality vaccine guns, the effects of bad weather on vaccination, limited cold storage facilities, and managing withholding periods.

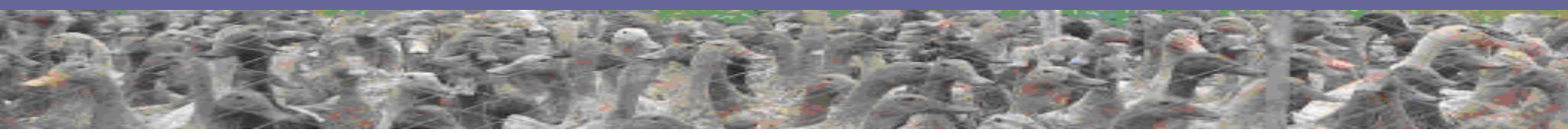
Meeting expectations

It was probably not recognized by, or made entirely clear to, all at the senior political level that vaccination would require more than one or two rounds to contain and eliminate infection. The expectation in some parts of government was that the expenditure would be a short term one. However, for those who understood the nature of the disease and the structure of the poultry sector, it was evident that vaccination would be required as a control measure for a considerable period of time, depending on the rate of change to the factors that allow the virus to persist and spread.

Vaccination was introduced, in part, to buy some time to allow an assessment of existing production and marketing practices and to make appropriate changes to these practices. For example, changes to some large live poultry markets are being implemented to reduce the risk of these markets remaining infected and providing a reservoir of virus that can be spread by traders who visit the market and then travel back to farms and households. However, such changes take time to implement. Further, issues such as the availability of suitable land and capital for new production zones or new markets must be considered. Obtaining approval for new farms and markets can also take time, especially when other factors such as environmental impact of new facilities must be taken into account.

Another dilemma is that, because the use of vaccines reduces the likelihood of disease occurring in flocks of poultry, it can reduce the incentive for making other necessary changes to production and marketing methods, such as enhancements to farm biosecurity.

All international recommendations on avian influenza state that surveillance and disease reporting systems must be strengthened.



The need for better vaccines

Current vaccines require the injection of two doses to every bird in a flock and, although effective in reducing the risk of infection and disease, administration is very labour intensive. Improved vaccines are required that generate a broad protective immunity, can be delivered at an early age (preferably by mass administration rather than individual injection) and stimulate long lasting broad immunity, preferably extending beyond the limited immune response (antibody mediated protection) provided by current vaccines. A number of new vaccines are under development, including a range of vector vaccines. As these products move from the laboratory to commercial production, they should be considered for adoption if they are shown to be effective under field conditions and also reduce the extent of handling of poultry.

The problems of surveillance and disease reporting

All international recommendations on avian influenza state that surveillance and disease reporting systems must be strengthened. This is being done in Vietnam but the cost of a comprehensive surveillance system for a poultry industry dispersed into millions of flocks with limited traceability should not be underestimated. There are still many impediments to disease reporting by farmers, not the least being that compensation alone does not cover the losses associated with culling of a flock and subsequent down time when poultry cannot be reared. Until there is considerable consolidation of the poultry sector into fewer well-managed flocks and enhanced veterinary services, surveillance systems will not be able to detect all cases of infection and disease. This is especially the case where poultry do not show clinical signs of disease.

Deaths and production loss in vaccinated poultry

Some instances occurred where vaccinators did cause some damage to birds as a result of vaccination in the neck that prevented young birds from feeding. Vaccination and the associated handling of poultry resulted in some flocks experiencing production loss (usually for about five days post vaccination) and creating some resistance to future rounds of vaccination.

In designing a mass program, then, some form of compensation is required for farmers who can demonstrate deaths or serious illness in poultry as a result of vaccination, otherwise farmers will be reluctant to continue participation in the program.

If production losses are likely to occur, it is better to time vaccination to coincide with periods of moult (when poultry are not laying) wherever possible.

Did the vaccination campaign in 2005 spread infection?

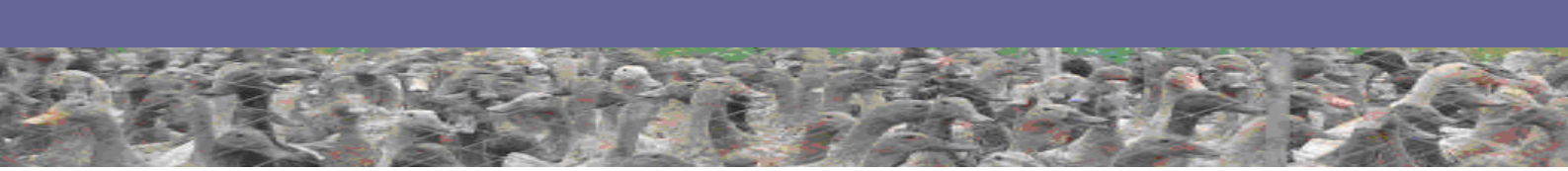
It has been suggested that some of the transmission of virus in late 2005 in northern Vietnam may have been associated with vaccinators[10]. The evidence for this remains circumstantial. Superficially, there is a clear temporal link between the two events, but when specific cases were investigated in one province in northern Vietnam in November 2005 it was found that most of the cases occurred in unvaccinated poultry and none occurred within a week of vaccinators visiting the premises. Regardless of whether vaccinators spread the virus or not, it was evident that transmission could occur through fomite transfer if vaccinators visited an infected flock and then moved to other flocks. Therefore, training programs emphasized the importance of taking necessary precautions.

This is also an important consideration if emergency vaccination is used around cases of infection. Some countries have already abandoned use of this method because of fears of spreading disease. Emergency vaccination is only effective if the initial case is reported and diagnosed early. Unfortunately, this is not usually the case and often it is not until several generations of infection have occurred that disease is reported. In fact, in Vietnam and other countries it is often the case that the first indication of infection in poultry in an area is the detection of a sick human infected with influenza A (H5N1). As transmission of this virus between humans occurs rarely and remains inefficient, any case that does occur must be derived from animals (or from an environment contaminated by infected animals). When these cases are investigated it is not unusual to find that poultry deaths have occurred in the area recently and that the infected person had contact with sick or dead poultry.

12. Refining the system - Where to from here with vaccination?

Vaccination was implemented in Vietnam to buy time so that other measures could be introduced to reduce the risk of avian influenza.

[10] See Pfeiffer et al (2007) Vet J 174 (2) 302-9 (see the following link for abstract)



Annual reviews and adjusting the program

Each year since vaccination was undertaken formal reviews of the program and of the scope of the program for the next year have been conducted and recommendations prepared for the Ministry of Agriculture.

The ultimate goal is to stop vaccinating once it is no longer required but it has proven difficult to make the changes required to reduce the need for vaccination.

Since the first round of vaccination, Vietnamese animal health authorities have been working to modify the program, based on new information as it becomes available, to make the program sustainable, more efficient, less costly and more acceptable to farmers and animal health staff.

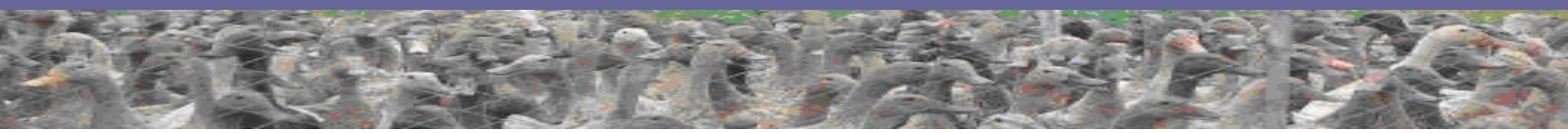
Clearly, however, any changes to the vaccination program must be made in a manner that prevents a resurgence in the number of avian and human cases of disease associated with these viruses.

As the introduction of vaccination immediately preceded a marked fall in the number of cases of disease in poultry and humans, it is not surprising that there is a reluctance to tamper with the program even though the precise relationship between vaccination and the fall in the number of cases is not known. Nevertheless, some adjustments to the program will have to be made over time if the government contribution to vaccination is to be reduced.

The exit strategy

International guidelines on vaccination against HPAI stipulate that all countries using vaccination must have an ‘exit strategy’. In other words, they must have a plan in place to eventually stop using vaccination. This recommendation is based on the premise that HPAI is eradicable and that at some point in the future it will be possible to remove vaccination from the mix of control and preventive measures and return to the use of other measures such as stamping out and movement controls, the cornerstones of HPAI control programs in the past.

The main reason for this exit strategy recommendation by international agencies is to prevent complacency that would allow vaccination against H5N1 to become a routine procedure as it is for many other important diseases such as Newcastle disease. However, complacency is not an issue in Vietnam. The vaccination campaign has been kept under constant review and additional changes made to the scope of the program as new information on the disease emerges, and this review process will continue. However, Vietnam will not be forced into stopping vaccination until it is clear that such a move is warranted and will not lead increase the number of human cases of influenza A (H5N1).



In the case of Vietnam, vaccination will also only cease once it is clear that the production and marketing methods that allow virus to persist and spread have been modified. Modifications would need to reduce the risk of infection to the point where it occurred only rarely and surveillance and disease reporting systems would need to be capable of ensuring that all cases of suspected HPAI were investigated and diagnosed early. Vietnam is still some distance away from achieving either of these objectives.

In addition, while infection remains present in neighbouring countries and new viruses are introduced on a regular basis to Vietnam, vaccination will be needed to help prevent the spread of these introduced viruses.

Getting the information to change the system

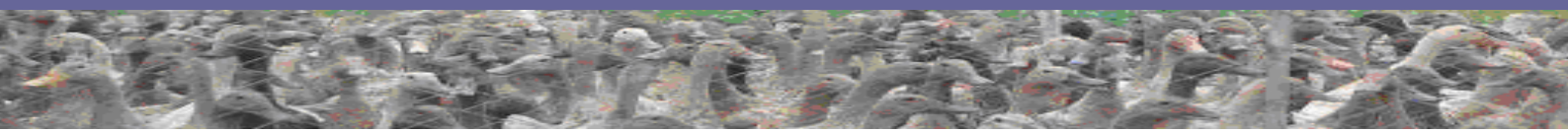
The information needed to move towards reduced reliance on vaccination is improving but the issues relating to disease reporting and surveillance highlighted earlier are difficult to overcome.

It is clear that more can be done to improve case investigations in Asia, namely greater emphasis needs to be placed on tracing and testing around infected flocks to ascertain the source of infection, but these changes will take time to implement.

Other ways to modify vaccination programs

Several research projects–including one funded by USAID that is gathering evidence for a transitional strategy for vaccination (the 'GETS' program)–are looking at ways to move away from the current vaccination strategy. A range of different methods are being considered.

One alternative method of vaccinating small flocks would be to increase vaccination for a range of severe disease so as to increase poultry survival. For a poultry flock of 10 birds, having even one additional chick survive per year would cover the cost of vaccination. However, earlier experiences in Vietnam with Newcastle disease vaccine suggest that uptake of vaccine is low even when a clear benefit can be demonstrated. This may stem from the fact that poultry are often reared in cash poor households and vaccines cost money. It costs nothing to raise a chicken if it is fed on scraps and allowed to scavenge for food. If these poultry die then there has been no loss of investment, apart from the time invested in looking after the bird. In the past, consumption of sick and dead poultry was widely practiced, so even if poultry became ill some of the value of birds lost to disease was salvaged.



Local vaccine production

Up to mid 2009, all vaccines used in Vietnam were imported. Recently it was decided that vaccines will be produced locally and modern equipment suitable for large scale vaccine production is available in Vietnam for this purpose. However, before using locally manufactured vaccine, it will be necessary to establish that the vaccine is providing protection against the range of different H5 viruses found in Vietnam and to ensure that manufacture of the vaccine is done in accordance with the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. Ideally, trials should be conducted comparing the efficacy of the new vaccine against existing products before a decision is made on whether to scale up production.

13. Selected references and resources available on line

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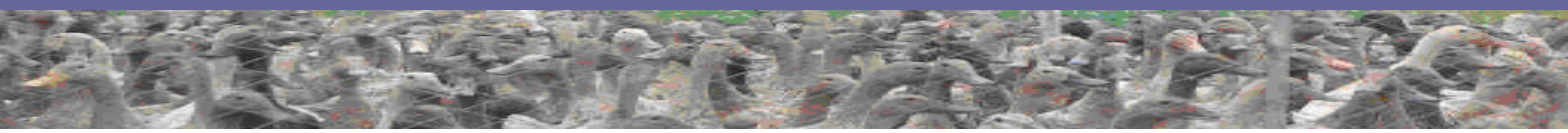

APPENDIX

Appendix 1

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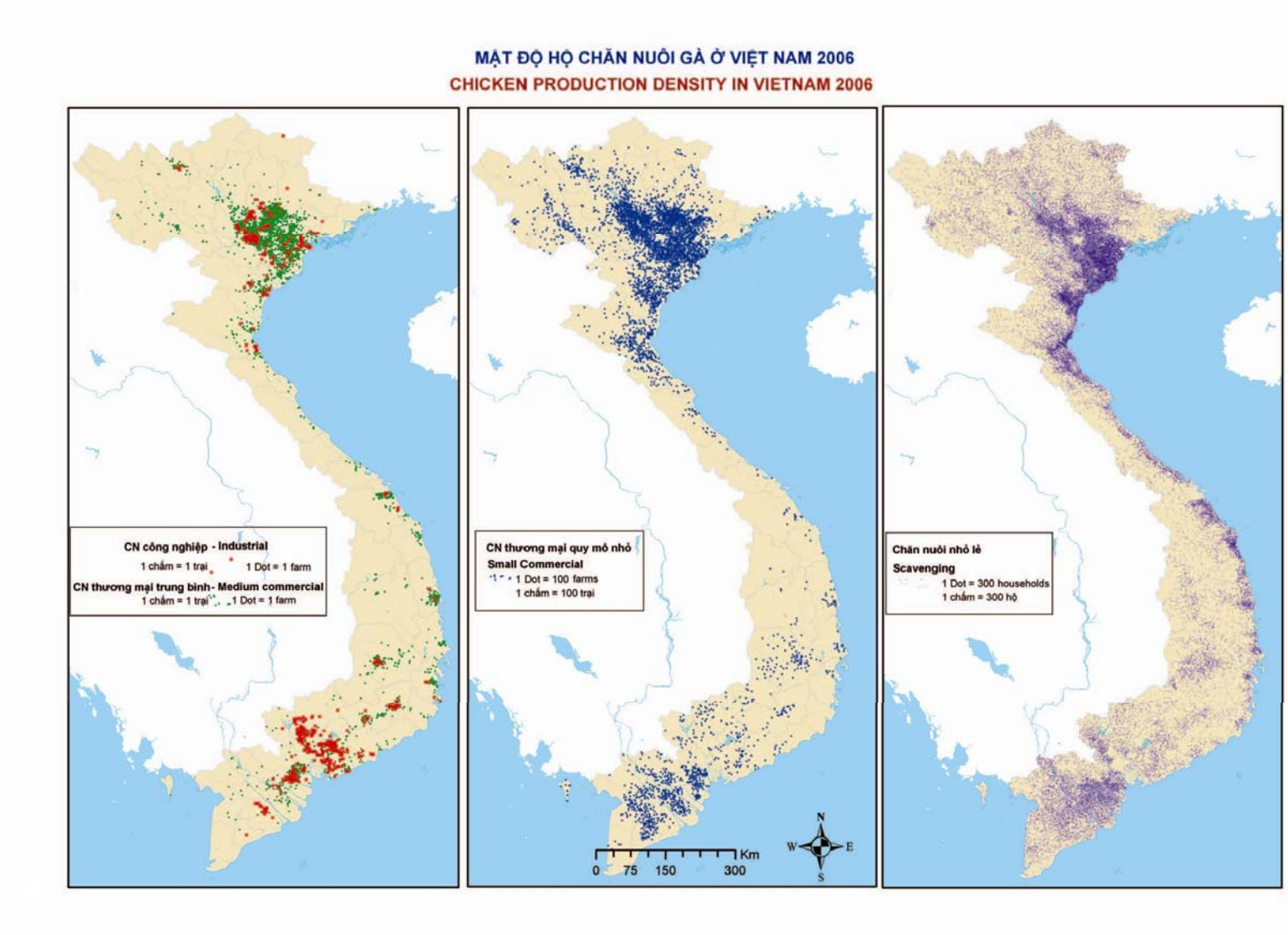

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