

Ten years of fighting bird flu

This year marks a decade since the first human outbreak of H5N1 avian influenza in Hong Kong. Since then, US \$1.9 billion has been pledged to fight avian influenza and a global effort is under way to prevent and be prepared for a pandemic.

In May 1997 a three-year-old boy died of respiratory failure in a Hong Kong hospital. The cause was given as viral pneumonia of unknown etiology, but three months later the infection was identified as H5N1 avian influenza. While the virus had been detected in geese the previous year in China's Guangdong province and chickens in Hong Kong in March and May 1997, this was the first evidence that H5N1 had jumped the species barrier to threaten humans. Avian flu went on to kill six people and sicken 18 in Hong Kong until a comprehensive cull of the city's poultry in December that year.

Despite the cull, H5N1 started surfacing around the globe. The virus has infected wild birds and domestic flocks in at least 55 countries in Asia, the Middle East, Africa and Europe. As of 13 November 2006, there had been 258 confirmed cases of human infection killing 153 people.

Ten years later, there is greater awareness and understanding of the threat of a future global influenza pandemic, for which H5N1 is seen as the most likely trigger. A huge interdisciplinary effort is under way to prevent a pandemic and, at the same time, to be prepared for the worst. Despite this, much remains unknown about H5N1.

Experts in fields ranging from virology and public health policy to epidemiology, clinical medicine, and the laboratory and veterinary sciences have learned from the milestones of the last decade that will help deal with the threat in the future.

The 1997 Hong Kong outbreak was caused by an avian-to-avian reassortment of the virus and, whilst swift and comprehensive culling effectively wiped out that strain, the parent strain continued to reassort and cause subsequent outbreaks in geese and ducks. By the end of 2002 the virus had become lethal to ducks. "By that time we were

getting quite concerned, because the virus was making very unusual changes in behaviour and was also affecting wild birds such as egrets," recalled Professor Malik Peiris, a microbiologist at the University of Hong Kong.

In early 2003, a mysterious outbreak of atypical pneumonia in Guangdong province was emerging, and by March of that year the outbreak of a new disease, severe acute respiratory syndrome (SARS), had become the focus for academic circles and the media, while having a huge economic impact on travel and other sectors throughout Asia. A cluster of H5N1 cases in a Hong Kong family who had travelled to China's Fujian province was another significant development, but concerns about avian flu were largely eclipsed by SARS.

With hindsight, the SARS outbreak was in itself an important milestone. Without heightened surveillance in January 2004 in Viet Nam, the avian flu outbreak there might have escaped detection. Similarly, SARS exposed weaknesses in China's disease surveillance and response systems.

"The ministry of health has taken on board the lessons of SARS," said Dr Julie Hall, WHO's coordinator of epidemic alert and response in China. "It was a pivotal moment in China's public health history, as during SARS there was a transparency issue and a huge information vacuum. A lot of that has since been resolved, also in terms of investment in infection control in hospitals."

Since early 2004, H5N1 human

outbreaks have been reported in 10 countries and the death toll has risen every year, with South-East Asia suffering the greatest losses of life. Viet Nam and Thailand fared worst in 2004, with 46 cases and 32 deaths between them. By 2005, control measures in Thailand were having an effect, but the disease was emerging in Indonesia, which reported 19 cases and 12 deaths. By 2006, Viet Nam appeared to have reduced the number of human infections to zero, while 55 cases and 44 deaths were reported in Indonesia by mid-November.

Progress has been made in Indonesia on the animal health side, although this will remain a five-to-ten-year challenge, said Dr David Nabarro, senior UN system coordinator for avian and human influenza. The task ahead is long-term and must be tackled on several fronts: safer animal rearing practices, faster public health response to new human diseases, and more investment in early warning systems to handle all kinds of outbreaks.

"There's been a transformation, a recognition that sickness is an economic and political issue," said Nabarro. "And that's where WHO, with its focus on international health regulations and outbreak surveillance and response, comes in."

Surveillance and response present a major challenge, given several factors. H5N1 infection has non-specific early symptoms and is easily confused with other diseases. The clinical spectrum is broad: not all patients develop fever and symptoms in the lower respiratory tract and diagnostic testing is expen-

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Dr Keiji Fukuda, WHO's Global Influenza Programme coordinator.



WHO/G. Hampton

Poultry workers in Indonesia in 2006.

sive and technically difficult. Even in countries with the most experience with H5N1, cases are still being misdiagnosed as dengue or typhoid fever.

In some countries, safer animal rearing practices are catching on. In early 2006 after four H5N1 deaths, the Turkish government launched a public awareness campaign to encourage people to change livestock handling practices. Since then, there has not been a single case of human infection, despite the fact that H5N1 outbreaks in poultry continued.

There are wide variations within regions in terms of pandemic preparedness plans, but a lot of practical steps are being taken at national and regional levels, said Dr Keiji Fukuda, WHO's coordinator for the Global Influenza Programme within WHO's department of Epidemic and Pandemic Response.

"The challenge is to close the gaps within regions, and once plans are in place, to back them up with concrete capabilities such as better laboratory facilities and more trained staff," Fukuda said. In 2004, about 30 countries had pandemic influenza preparedness plans. Now 178 countries have published or are drafting plans, while at least 50

countries have undertaken exercises or joined regional simulation exercises to test these plans.

"Investing in pandemic preparedness is essentially like investing in an insurance policy," said Dr Margaret Chan, who will take up her post as WHO Director-General on 4 January. "And while we hope that we never have to make a claim, we also know that whatever investment we make now in strengthening global public health infrastructures will have benefits for our responses to all future infectious disease threats." Chan speaks from personal experience of battling both H5N1 and SARS as Hong Kong's director of public health and, since 2003, in her work at WHO.

Influenza vaccines are no magic bullet. Work on a pandemic vaccine continues in several countries, but the true efficacy of a vaccine would become apparent only when used. Supply is also an issue: clinical trials suggest that current vaccine production would be unable to provide enough doses for the global population in the event of a pandemic.

Also, H5N1 vaccine strains show a lower production yield than usual seasonal vaccine strains, explained Dr

Marie-Paule Kieny, director of WHO's Initiative for Vaccine Research: "Moreover, H5N1 split or subunit-inactivated vaccines seem to be less immunogenic than their seasonal counterparts. Therefore, research efforts should be invested into understanding the basis for these differences, and into development of strains which do not have these two disadvantages".

Vaccine or no, the problem and solution are at the animal level. "If we can get a good handle on control in animals then the human threat disappears but there is still a long way to go towards achieving this, with many unanswered questions," said Peiris.

The most tantalizing question of all is whether an outbreak of pandemic avian flu could be stamped out at its source, as the 1997 Hong Kong H5N1 outbreak was. "It's never been attempted before and it's immensely complicated because the broadness of possibilities is so wide," said Fukuda. "The single most important lesson from the last decade is that emerging infectious disease threats such as this virus are tenacious and won't go away, and we need to be just as tenacious in response." ■

Jane Parry, *Hong Kong SAR*

Dilemma over live-donor transplantation

Organ transplants save thousands of lives each year, but put many live donors at risk due to an unregulated organ trade that exploits the vulnerable in developing countries and complicates legitimate organ donation efforts. Countries face a dilemma: how they can increase the supply of organs in a manner that is ethical and humane.

In rural Pakistan, Haleem Bibi had no choice but to support her family after her husband's hand was severed in a work accident. To make ends meet in February last year, the mother of seven sold one of her kidneys for about US\$ 1500 to a clinic serving overseas clients, who pay up to US\$ 40 000 for an organ transplant.

Months later, Bibi's family, who live in Jandala village in eastern Pakistan, remained mired in debt and her health worsened after receiving no post-operative care, a common feature of commercial organ harvesting. "The money has all been spent and now I have to work all day, which is very tiring," Bibi told the *Bulletin* in a recent interview.

Bibi's story is echoed by thousands more in Pakistan and other countries, where the neediest are often exploited by a thriving market for organs.

About 10% of the 63 000 kidney transplantations carried out annually worldwide involve payment of non-related donors of different nationalities, according to the World Health Organization (WHO). Globally, at least 200 000 people are on waiting lists for kidneys, and many more have no access to transplantation or dialysis services.

In industrialized and developing countries, kidney transplantation wherever possible is preferable to dialysis, which is physically taxing on patients and more costly than transplants. Every year, a million people develop end-stage renal disease, said Dr Luc Noël, coordinator of WHO's clinical procedures team, but only a fraction of those receive any kind of renal replacement therapy, and even fewer receive kidney transplants.

Different approaches are being taken to meet the demand for organs and halt transplant tourism, which is growing due to an increase in kidney disease and renal failure.

"There are two prevailing concepts of transplantation. One relies on money and leads to increased inequality, besides putting a price on the integrity of the body and human dignity. The second is based on solidarity and the

donor's sole motivation to save a life," Noël said. "We should seek a common global approach to donation and transplantation characterized by respect for the donors, so that they are proud of what they have done."

Donating a kidney holds some risks for the living donor, even though kidney donation is a widely recognized procedure. Careful selection of donors is vital to avoid renal failure later in life. The nephrectomy — removal of a kidney — procedure has risks, such as haemorrhage, as well as delayed and chronic recurring pain. The risk that the donor could die due to surgery has been put at one in 3000.

Scientists are investigating alternatives to human-to-human transplantation, such as human cell and tissue engineering and the use of animal organs. Pre-clinical studies in which pig hearts and kidneys were transplanted into baboons show promise.

At the same time, more preventive medical care is needed to stop people from developing conditions, such as renal failure, that make them seek new organs in the first place. But none of these approaches is expected to satisfy

the need for human organs for transplantation in the next five years.

In 1991, the World Health Assembly endorsed the WHO Guiding Principles forbidding organ sales, which state: "The human body and its parts cannot be the subject of commercial transactions. Accordingly, giving or receiving payment (including any other compensation or reward) for organs should be prohibited." The assembly, in 2004, further resolved to make countries accountable for transplant activities by calling on member states to protect the most vulnerable from transplant tourism and the sale of tissues and organs.

WHO advocates increasing the supply of kidneys from deceased patients, followed by those from living related donors in national, noncommercial and ethical programmes governed by legal frameworks.

Noël praised models such as Spain's national programme, which maximizes donations from deceased individuals by using professionals to identify potential donors in hospitals and discuss the concept with their relatives.

In addition, Noël said that altruistic donation from live donors is acceptable when it is ethical; that is, when donor-informed consent is obtained without coercion, donor safety is ensured and donors have access to medical follow-up.

Given the shortage of deceased-donated organs, there is a growing lobby in favour of increasing the num-



Live kidney donors show the scars caused by operations to remove their kidneys in Lahore, Pakistan, in 2004. They were demanding financial help from the Pakistani government to help them pay off their debts, which they could not pay off even after selling a kidney.

Keystone/AP Photo/K.M. Chaudary

ber of living donors, including those who are not related to the transplant patient. Writing in the *British Medical Journal* in November 2006, Amy L Friedman, a transplant surgeon from the United States, argued that payment of live unrelated donors — which is forbidden under the WHO Guiding Principles and illegal in most countries — should be legalized to increase organ supplies and eliminate a black market in organs, thus making such procedures safer for all involved.

A law passed in Saudi Arabia in October envisages just this: that the government pays a monetary “reward” of 50 000 riyals (US\$ 13 300) and other benefits, including life-time medical care for unrelated organ donors in a system regulated at the national level. The law’s supporters said it would stop Saudi citizens from travelling to China, Egypt, Pakistan, the Philippines and other countries to receive organ transplants.

Noël argued, however, that such “rewards” were likely to attract the poorest segment of the Saudi population, such as migrant workers: “Involving money in the procurement of organs for transplantation, even if the word ‘sale’ is not used, confers a price on the organ and opens the way to brokers in the country and internationally.”

Some 400 kidney transplants take place in Saudi Arabia annually, but about 600 Saudis still travel abroad to buy them in countries such as China, Egypt, India and Pakistan, according to Dr Faissal Shaheen, director-general of the Saudi Center for Organ Transplantation, speaking from the Saudi capital, Riyadh.

At a WHO meeting on 26 and 27 November 2006 in Kuwait, transplantation experts and representatives from Saudi Arabia and 13 other countries from WHO’s Eastern Mediterranean Region pledged in the *Kuwait Statement* to oppose commercialism in organ donation.

After the meeting, Shaheen said the Saudi authorities were looking at how to regulate live unrelated organ donation without a commercial transaction. “We are thinking carefully how to make this new agreement purely altruistic, so this 50 000 riyals would be given as full medical insurance for the donor, plus compensation for days off work and other benefits like discount



The emergency ward at Dr Syed Adibul Hasan Rizvi’s Sindh Institute in Karachi.

Paul Garwood

on airfares, priority in work applications, so the donors will not have cash but rewards.”

Noël said it was essential that donors should be respected by society for what they have done and not be stigmatized, unlike the situation in the Islamic Republic of Iran, where many paid live donors are ashamed and do not seek or receive follow-up medical care.

Few poor people in developing countries have access to transplants. In Pakistan, the Sindh Institute of Urology and Transplantation in Karachi is regarded internationally as a model for altruistic transplantation. Its founder and director, Dr Syed Adibul Hasan Rizvi, said his institute performs 130 to 140 free transplants annually between living relatives.

“Our motto is ‘free with dignity,’” said Rizvi, whose institute accounts for 20% of Pakistan’s annual kidney transplants. He said the vast majority of the rest are performed by clinics run on a commercial basis.

“Pakistan has become a factory for regional transplant tourism,” Rizvi said in an interview with the *Bulletin*. Recipients travel to Pakistan, where the temptation for money and greed is great.”

Pakistan has no law regulating transplantation, but that may change soon. Draft legislation drawn up with Rizvi’s help and based on WHO’s guiding principles has been before parliament for 15 years. However, in early December 2006, the Pakistani

newspaper *Dawn* reported that the enactment of the organ donation bill “was assured” and President Pervez Musharraf put his weight behind the law in a statement saying: “... legislations will soon be in place to discourage illegal trade in human organs”.

Rizvi said most Pakistanis who donate kidneys do so because they have few other options to make money and extricate themselves from “bonded labour”, a system under which they are tied to property owned by landlords.

Prospective recipients from Australia, Europe, the Middle East and the United States who visit Pakistani clinics providing human organs pay up to US\$ 40 000 for a kidney, he said. The donor receives a small fraction of that, about US\$ 1000 to US\$ 2000.

Experts like Dr Francis Delmonico said the world is gripped by a crisis when it comes to organ failure — particularly kidney — and that this has resulted in limited supplies of organs and exploitation of the poor through organ trafficking.

“We have a global epidemic of kidney failure evolving associated with some 180 million diabetic patients,” said Delmonico, director of medical affairs for the Transplantation Society.

“The real solution is preventing people from having kidney failure with good medical care in the first place,” said Delmonico, Harvard Medical School surgery professor and a member of the WHO Expert Advisory Panel on Transplantation. ■

Paul Garwood, *Islamabad*