Risk Wise

Epidemics

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Foreword

Despite rapid advances in controlling infectious diseases like influenza, tuberculosis and malaria, the world is constantly threatened by the possibility of an epidemic. With the eradication of smallpox in 1980, optimism ran high about humankind's ability to make sure other infectious diseases would no longer pose a threat to human health. But as diseases like HIV/Aids, cholera, hepatitis, malaria and influenza continue to devastate communities, that optimism is beginning to look misplaced.

Infectious diseases do not respect geographical boundaries — they can devastate families, communities and entire countries, and if unchecked, they can take on global proportions. For the affected communities, they place sudden and intense pressure on health systems, and in addition to their morbidity and mortality, they disrupt countries' activities and development, making it difficult for affected areas to recover both socially and economically.

Prevention and preparedness for epidemic disease is a fact of life that must be acknowledged by every country. Every organization, whether public or private, must work together to enable the coordinated response that is needed to rapidly identify and contain public health emergencies, reduce panic and minimize disruption to trade, travel and communities.

Risk Wise Epidemics has been created to help civil administrations understand the threat posed by infectious diseases in societies of all kinds, and how they can work to minimize that threat. *Risk Wise Epidemics* is intended both to inform and to inspire steps towards the prevention and eradication of current and future epidemic and pandemic events. It brings together voices from all sectors of civil society, urging all nations to take the necessary measures to prepare for present and future infectious health threats.

Published in May 2009 to coincide with the 62nd WHO World Health Assembly, *Risk Wise Epidemics* can be used as a companion guide for civil administrators who are serious about improving the world's defences against infectious disease.

The publication represents the cumulative work of a wide spectrum of organizations and corporations with a collective desire to prevent, prepare for and mitigate future pandemic events.

Our deepest thanks go to all the UN agencies, regional and national governments, academic institutions and private sector organizations that have given so generously their time and resources to create this unique publication.

We trust that this latest title in the *Risk Wise* series of development publications proves a useful addition to your knowledge base, and we look forward to receiving your comments and requests for future editions.

Jacqui Griffiths
Tudor Rose

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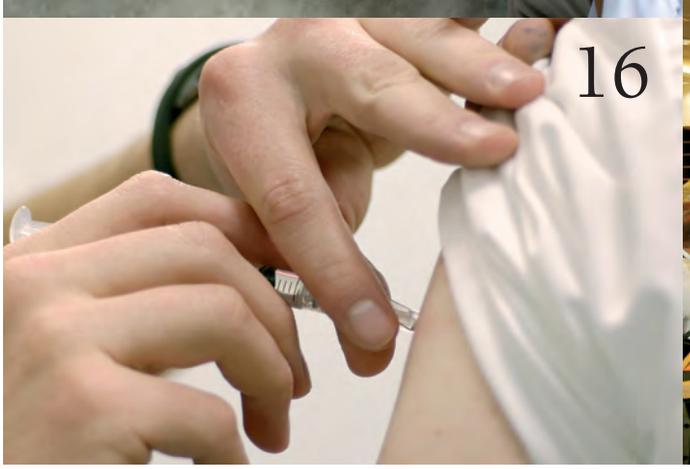


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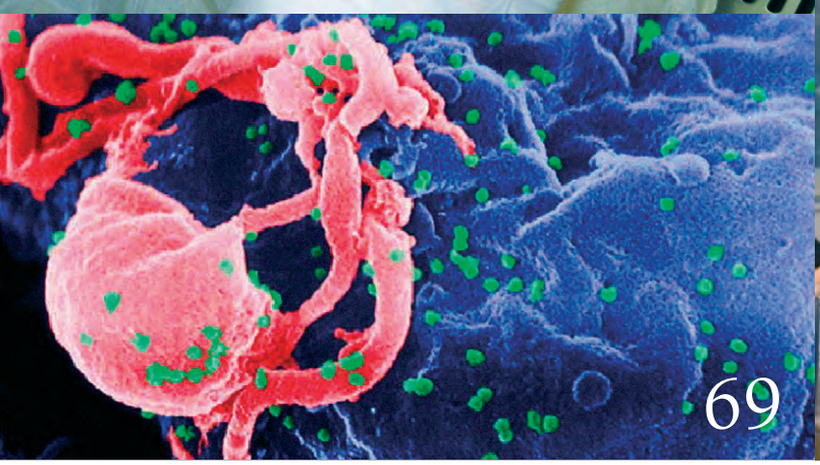
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79
Antigen A/Indonesia/5/2005 (H5N1), 3.75 µg
Content: not less than 2,5 ml Antigen suspen
reconstitution with adjuvant (final volume
corresponding to 10 doses for healthy a
Storage and transport at +2°C to +8°C. Do
Do not use for injection if not reconstitute
Manufacturer: GlaxoSmithKline Biologicals
See www.swissmedic.ch
Antigen for pre-pandemic


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Influenza pandemic: overcoming global issues

David Nabarro, UN System Influenza Coordinator for Avian and Human Influenza (UNSIC), and Iain Bald, UN Office for the Coordination of Humanitarian Affairs (OCHA)

There is now worldwide recognition of the need to prepare for an influenza pandemic. This is a significant achievement considering that only five years ago the world was largely unaware of and unprepared for the threat.

A high mortality influenza pandemic is as serious a threat for human security as it was in 2005 when the subject first received high-level attention from public health ministers and the media. Because of the interdependency of global systems and the speed with which people, goods and information can move around the planet, we can expect that the consequences of a pandemic today might be worse than ever before. As of 2009, more than half of humanity lives in urban settings, often characterized by high population density, widespread reliance on public means of transport, and dependence on 'just-in-time' delivery of products and services. In today's world, a pandemic may well show us that our interconnected society's degree of complexity and sophistication is also a significant vulnerability.

While an influenza pandemic will of course initially affect the health sector, there will be far-reaching consequences for all sectors due to the impact of absenteeism on labour, critical networks and international trade. The World Bank estimates that in addition to causing millions of deaths, the next influenza pandemic could well be a global catastrophe with an overall cost to the world economy of up to US$2 trillion.[1] This impact can be reduced if people and their governments are properly prepared. The only option is for all countries to remain vigilant so that they can identify early signs of a possible pandemic, and work together so that all communities

Image: UNSIC

Participants at the UN Country Team pandemic simulation held in Cairo, Egypt on 10-11 February 2009

can reduce the impact of this pandemic on people, livelihoods and society.

What member states are doing to strengthen their capacity to withstand the next pandemic

Previous influenza pandemics have been caused by novel viruses that are the result of change in the genetic material — either through mutation or reassortment — of viruses that circulate and cause disease within animals. One highly pathogenic influenza virus that has caused widespread concern is the influenza A virus H5N1. Since 2004, hundreds of thousands of people throughout the world have been working hard to contain the spread of this virus in poultry and to reduce the number of humans infected with the virus. Led by their national governments, and following strategies developed by the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) they have initiated changes in farming practices so as to upgrade hygiene in livestock production and markets, improve veterinary services and disease surveillance, immunize poultry with billions of doses of vaccine, limit infection rates through restricting movement of birds and cull those in the immediate area of outbreaks, and compensate persons whose birds or property were destroyed as part of the control effort. Progress has also been made in sensitizing the media and educating the public of the threat posed by H5N1, and in promoting behaviours that improve hygiene and bio-security so as to protect birds and humans from the virus. Many more countries have increased the speed and effectiveness with which they can respond to H5N1 outbreaks with improvements in surveillance and diagnostic systems. Indeed, several countries that detected HPAI infections or re-infections in 2007 and 2008 have now succeeded in eliminating infection thanks to the implementation of effective surveillance, prompt detection and rapid responses.

Image: UNSIC

Laboratory tests provide support to rapid containment and response to public health emergencies

The H5N1 virus has not, so far, changed in a way that permits continued human-to-human transmission and an influenza pandemic. Intensive efforts to date have without doubt led to a reduction in the likelihood of the next influenza pandemic being caused by the H5N1 virus. However, the risk of a pandemic from a change in H5N1 or other influenza A viruses remains. The global picture is one of an H5N1 virus that — despite all our collective efforts — is not yet fully under control and is likely to continue to cause both avian influenza in poultry and sporadic human cases in countries throughout the world. Much more remains to be done to contain H5N1 and to prevent the emergence of other animal diseases that endanger the health of humans. The world's people rely on local, national and international organizations to maintain continuous vigilance to detect and assist countries in responding to such threats.

Ideally, an emerging pandemic could be aborted through early containment by public health services. In case this is only partially successful however, national authorities need to be ready to limit human, social and economic consequences of a pandemic. But while there has been worldwide progress with development of pandemic preparedness plans, there are also great disparities in preparedness between countries. Whereas wealthier, industrialized countries have developed and deepened their pandemic preparations in sectors beyond health, many middle-income countries have yet to prepare for the continuity of essential services. Unfortunately, many low-income countries have not, during the past year, had the resources needed to advance their level of pandemic preparedness.

There are many components of pandemic preparedness, some of which will not be feasible to implement in all countries due to competing priorities and challenges, though more limited programmes can still be highly effective in mitigation of morbidity and mortality.

Of course, the health sector must be prepared to handle the consequences of any pandemic of infectious disease; but other sectors must be engaged as well given the necessary depth and breadth of the response. This requires a focus on all-of-government — indeed all-of-society — preparedness. In particular, national authorities should ensure that essential services critical for society will be able to continue to function under the stress of pandemic conditions.

United Nations assessments reveal an overall increase in planning for the continuity of vital infrastructure in 2008 compared to 2007. But while some individual countries have made concrete progress, this area of planning is still very limited in most countries, and correlates clearly with countries' income levels. The engagement of civil society and the private sector is still relatively minor, despite their importance for sustainable multi-sectoral planning. And although some governments have provided guidance and tools to assist businesses with pandemic and business continuity planning, few

Image: UNSIC

Discouraging children from treating poultry as pets is a difficult task

have actively engaged with the private sector on planning assumptions, responsibilities and expectations, or provided practical support for their application and followed up on implementation.

So far, cross-border pandemic preparedness has not been addressed sufficiently. As a pandemic will have cross-border impacts, transparent and collaborative cross-border preparation is needed to achieve interoperability during a pandemic. Border closures and travel restrictions could also have wider-reaching socio-economic impacts. There is also little evidence that national planning efforts are addressing the rights and interests of economically and socially disadvantaged groups, despite the likelihood that these groups will be disproportionately affected in a pandemic. Strategies to assess and cope with the impact on ethnic minorities, refugees and displaced persons are absent in most plans.

But planning itself is not sufficient. The preparedness required goes beyond sharing ideas, or even joint planning; it calls for the testing of assumptions, interdependencies and systems for directing and managing actions when undertaken by a range of different authorities. This can only be achieved by conducting simulations and reviewing the results to identify areas where there are overlaps, gaps or difficulties. In the most recent UNSIC-World Bank Progress Report, which gathered input from 148 countries, 53 per cent of national authorities reported that their plans had been tested during the past 12 months, but only 25 per cent reported having done this both at the national and local level; and only 38 per cent reported having incorporated lessons learned into plan revisions.[2] Indeed, evidence available to the UN indicates that the majority of national pandemic plans are still neither truly institutionalized nor operationalized — in that policies and laws have not been instituted, and that crisis response plans and procedures have not been rigorously tested.

To date, nearly US$3 billion has been pledged towards efforts to control the spread of highly pathogenic avian influenza (HPAI) and to address the pandemic threat. But the gap between the amount of external assistance required for those activities and the amount pledged each year by bilateral donors and multilateral development banks has increased since 2005. This means that the funds available are well below the amount needed. Although there has been continued support from major donor nations, the number of pledging donors has declined. There is a risk that this decline in resources pledged, especially for countries with the greatest remaining needs, could undermine the sustainability of the investments made thus far. In order to build on the initial response and successes achieved to date — both in responding to outbreaks in infected countries and in building capacity in all countries — there is a need to meet the longer-term funding needs and gaps.

What the UN system is doing to prepare

The UN system as a whole has invested substantially in getting ready for an influenza pandemic. It takes this threat very seriously, especially given that the UN must stand ready to sustain its existing life-saving operations regardless of circumstances. Doing so may prove extraordinarily difficult under pandemic conditions, as we expect even our normal operations to be drastically complicated by factors such as access to vulnerable populations, absenteeism, potential spikes in fuel and food prices, unpredictable financial circumstances, and other constraints.

The UN system has dealt with the threat in a coordinated fashion, devising a Consolidated Action Plan[3] to not only help limit the spread of H5N1 but also ensure that, collectively, we are able to mitigate the impacts of a severe influenza pandemic — and indeed other major disasters with profound social and economic consequences. The UN's approach to pandemic preparedness is built upon three pillars: ensuring staff health and safety; maintaining operational continuity of life-saving programmes; and supporting host governments' preparedness and response efforts. One of the strengths of the UN's approach is its operational bent: there is widespread preparedness practice within UN Country Teams, peacekeeping operations, and other parts of the system — working with local and central government, disaster responders, humanitarian groups, and with other parts of civil society and the private sector, as well as with all inter-governmental bodies represented at country level. We have also seen the useful development of a joint Concept of Operations that shows how the different parts of the UN system are going to work together in a pandemic. UN agencies such as the World Food Programme have organized training and simulation exercises to prepare logistics personnel for the delivery of humanitarian services in a pandemic. The World Health Organization (WHO), as the UN technical agency

Image: UNSIC

Participants at the tabletop simulation exercise held on 23 October 2008 under the auspices of the One UN System in Kigali, Rwanda

responsible for the health aspects of pandemic preparedness and response, has prepared guidance for its member states, the UN system and non-governmental organizations (NGOs). These kinds of initiatives help ensure that key personnel are informed and prepared, and will ultimately help save lives in a pandemic.

It is also clear that the broader humanitarian community will have a critical role to play, as academic research suggests that upwards of 95 per cent of deaths due to a pandemic will occur in developing countries, and that vulnerable populations there will suffer most. In light of this, 23 organizations involved in the delivery of humanitarian aid — including the Red Cross/Red Crescent Movement, international NGOs and UN agencies — signed a declaration on 29 October 2007, pledging to work together to get ready to respond to the consequences of an influenza pandemic on vulnerable populations. Two subsequent inter-agency simulation exercises were held in 2008, helping organizations identify gaps and inconsistencies in their respective pandemic plans; further joint activities are planned in 2009.

At the 2008 Sharm El Sheikh International Ministerial Conference — the sixth in a series of intergovernmental meetings on avian and pandemic influenza since 2005 — more than 120 countries and 26 international and regional organizations collectively reaffirmed their determination to continue efforts for multi-sectoral, multi-level and multi-country pandemic preparedness.

It has been recognized that emerging infectious diseases are significantly correlated with socio-economic, environmental and ecological factors, and thus in turn require coherent and connected approaches to prevention and control across many sectors, including animal and human health and wildlife. This coordination and collaboration underlies the principle of 'One World, One Health' developed by the Wildlife Conservation Society in 2004 and a strategic framework launched in 2008 by WHO, FAO, OIE, UNICEF, UNSIC and the World Bank, which have the aim of achieving better prevention of, preparation for and response to the health, social, economic and political impacts of infectious diseases emerging at the animal-human-ecosystem interface.[4] The successful use of the 'One World, One Health' concept in planning and implementation of programmes will contribute significantly to the overall goal of protecting the world from emerging infectious diseases of animal origin. Strengthening of laboratory, epidemiologic and public health response capacities (part of the One World, One Health concept) will in turn increase the ability of countries to identify and respond to pandemic influenza.

Conclusion: vigilance is vital, complacency dangerous

Over the last several years, substantial and significant progress has been made in pandemic preparedness worldwide. The number of countries that have developed a pandemic preparedness plan has steadily increased, and more countries have conducted simulation exercises of their plans. Nevertheless, many plans remain unendorsed at the highest political level and lessons from simulations are not being included in plan revisions, indicating that many plans are neither legally nor logistically feasible.

It is imperative that all countries and international organizations continue to devote resources to be better prepared to save lives and minimize socio-economic disruption in a pandemic. It is now important to consolidate achievements in pandemic planning, and make plans operational by further advocating, endorsing, testing and systematically reviewing plans with lessons learned. National authorities need to ensure that logistical and legislative provisions are made for effective non-pharmaceutical measures including (at a minimum) isolation of cases, quarantine of close contacts of cases and social distancing, and that pharmaceutical control strategies, such as use of anti-viral drugs for treatment and prevention of infection in certain groups, and vaccines, are implementable as far as possible. Since successful pandemic preparedness increases the resilience of national institutions in the face of other emergencies, national authorities should strive to integrate pandemic planning into national disaster management structures so as to increase its sustainability and broaden its benefits. It is also essential that national pandemic preparedness efforts be undertaken jointly by all stakeholders — including representatives of public sector bodies, private entities, civil society and Red Cross or Red Crescent societies, media organizations and faith groups. No country or region should prepare for pandemic in isolation — hence the absolute need for nations to work within the context of intergovernmental agreements and means for joint working at regional and global levels.

We must avoid being complacent given that a pandemic is such a major threat to the security of the human race. We have an opportunity to be ready now, and we cannot afford to miss it.

Limiting the impact of pandemic influenza through community-level actions

Jim Catampongan, Avian and Human Influenza Coordinator, Asia and Pacific, International Federation of Red Cross and Red Crescent Societies

Influenza pandemics are rare but recurring events. Ten pandemics have been recorded over the last 300 years, with starting points ranging from 10 to 49 years apart. In the 20th century, pandemics occurred in 1918, 1957 and 1968. Considered one of the deadliest disease events in human history, the 'Spanish influenza' in 1918 claimed more than 40 million people worldwide. By any calculation, that outbreak killed more people in a year than the Black Death of the Middle Ages killed in a century; it killed more people in 24 weeks than Aids has killed in 24 years.

According to Robert Kaufman, head of the International Federation of Red Cross and Red Crescent Societies' (IFRC) programme for avian and human influenza: "There are usually as many as three pandemics per century. Four decades have now passed without a pandemic and the alarm bells are ringing."

Although no one can predict when the next pandemic will occur, both scientists and policy makers around the world have acknowledged that another one is inevitable.[1] Since 1968, all prerequisites for the start of a pandemic have been met, except that the virus has not yet readily and sustainably spread among human beings. Nevertheless, the highly pathogenic avian influenza (HPAI) H5N1 virus has already caused widespread outbreaks in wild birds in over 60 countries[2]; it has also claimed the lives of 256 people from 15 countries[3] and presents a 63 per cent death rate, high by any measure.

Image: IFRC

Basic education in proper hand washing techniques in countries like Cambodia can go a long way to preventing the transmission of influenza

Considering that the virus is now endemic in countries in Asia and that outbreaks have recurred despite aggressive control measures, the next pandemic may just be a matter of time. The World Health Organization (WHO) notes that neither its timing nor severity can be predicted with any certainty; however, it is estimated that 20 - 40 per cent of Earth's population will become ill because a pandemic virus is new and human beings have no pre-existing immunity.[4] It is feared that the burden of the next influenza pandemic will be overwhelmingly focused in the developing world, where public health systems are weak and resources for preparedness and readiness have to compete with other pressing priorities.[5] It is also expected to bring devastating effects on the socio-economic, educational and health condition of the entire population across the world. Entire transportation systems and public utilities including water supply systems, schools, colleges, industries, banks and government offices may be forced to close during outbreaks.

Community preparedness and individual resilience is essential

Many national governments have already developed and rehearsed pandemic influenza preparedness and response plans. As these plans focus primarily on health sector response at the central and national government level, additional effort must be dedicated to integrating non-health sector, non-state and non-government components into the plan, as well as further defining response at community level. This necessity rests at the heart of the role the IFRC will play across Asia and around the world.

"Red Cross and Red Crescent Societies will save the most lives and prevent the spread of infection most effec-

Image: IFRC

Red Cross and Red Crescent H2P projects are developing trainings and materials that enable volunteers, like these in Bangladesh, to share simple messages that prevent or mitigate the transmission of influenza in households and communities

tively by working on the ground within communities," stresses Kaufman. "Volunteers and community leaders must first be well-trained – and we're doing this now – and then we need to be ready to implement specific, well-planned community-based interventions when a pandemic surfaces."

Considering that nearly everyone in a given community will be affected in an influenza pandemic, communities need to anticipate that there may be no outside help even though material resources for response may be available. As a result of severe illness due to influenza and other causes, health facilities may be overwhelmed, there may be shocks to livelihood and businesses due to high absenteeism, and lifelines may collapse. Communities may be left to respond on their own.

In an effort to survive a pandemic influenza wave, communities need to develop plans that involve all sectors to ensure that influenza infection is controlled, and that the delivery of essential services is continued to maintain basic functions of society – namely health, food, water and sanitation, energy, public security and order, finance, telecommunications and transportation.

The Red Cross and Red Crescent approach to community pandemic influenza preparedness

Red Cross and Red Crescent National Societies based in 37 nations throughout Asia and the Pacific, and 186 nations worldwide, are ideally positioned to support community preparedness for pandemic influenza. They have independent status and formal auxiliary relationships with national authorities and government ministries, coupled with expertize and capacity to reach the most vulnerable in the community. These societies have massive networks of branches and volunteers, and have extensive experience and knowledge in disaster planning and public health, and in responding to disasters and infectious disease outbreaks with life-saving goods and services.

Through those branches and community volunteers, Red Cross and Red Crescent National Societies will develop detailed plans for responding to a pandemic and disseminate simple but effective prevention and mitigation messages for households and communities. These include promotion of non-pharmaceutical interventions such as proper hand-washing, sneezing or coughing practices, avoiding gatherings and social distancing among children and adults, and voluntary isolation of ill household members.

National Societies can also augment the human resource needs of communities in the delivery of health and other services. Experience in community health programming will allow National Societies to provide home and community care to people who have influenza and other illnesses, and to refer ill community members to health facilities. Volunteers may also be enlisted to support the distribution of food and non-food items, management of dead bodies, provision of psychosocial support, or collection and reporting of information received from the community.

At the same time, because the actual occurrence of a pandemic remains a big uncertainty, over-preparing community volunteers now who are already heavily involved in the implementation of existing public

Image: Rob Few/IFRC

Throughout Asia, volunteers are engaged every day in promoting healthy habits. These Philippines National Red Cross volunteers may one day play a vital role in responding to a pandemic

health and other programmes would be inappropriate. While generic infectious disease messages and guidelines can be distributed at any time, it is believed that pandemic influenza-specific tools and materials can be given to volunteers at the ideal moment through 'just-in-time' trainings.

What is thought to be appropriate in the current circumstance is the preparation of simple, easy-to-use tools, guidelines and materials for community leaders and volunteers, and their pre-positioning close to communities. These may include culturally-sensitive and acceptable Information, Education, and Communication (IEC) materials for print and broadcast distribution that contain prevention and mitigation messages. Guidelines for volunteers identified to distribute food and non-food items can be put in place, and masks, gloves, aprons and other protective materials can be distributed for volunteers who may be caring for sick individuals.

To ensure that these tools, guidelines and materials are delivered to community volunteers when risk has increased — such as when WHO declares that human-to-human transmission has occurred — a cadre of trained district officials from National Societies and partners will be prepared to deliver those tools and materials to communities. A countrywide rollout plan will outline trigger mechanisms for national society response and coordination arrangements for working with partners during pandemic will be made clear. Simulation exercises will be conducted to test the effectiveness and completeness of these plans.

National Societies have recognized the fact that, despite their experience and knowledge in disaster management and public health emergencies and their extensive networks of chapters and branches, they must work with partners. Due to anticipated absenteeism during a pandemic wave, preparing township or district officials from various organizations will be important in the rollout of tools and guidelines. Working with partners will also maximize geographical coverage and ensure that as many communities as possible receive essential support.

Next steps for the IFRC

With the aim of contributing to increased household and community level response and preparedness to limit the impact of pandemic influenza, the IFRC has embarked on a three-year Humanitarian Pandemic Preparedness (H2P) programme to achieve the above-mentioned outputs in at least 25 countries. Host National Societies will play the primary role in implementation of this programme. In Asia Pacific, the Nepal Red Cross began implementing a 20-month community pandemic preparedness project late last year, while the Red Cross Societies of India, Indonesia, Laos, Philippines and Viet Nam will implement similar projects beginning in the first half of 2009.

These projects are being carried out through the support of the US Agency for International Development (USAID), which leads and funds the H2P Initiative. The Initiative also consists of partners that have established competencies relevant to pandemic preparedness:

UN agencies such as WHO, WFP, UNHCR, UNSIC/OCHA and IOM, constitute the normative group through the development of relevant global guidelines, and are supporting governments in the preparation of national pandemic preparedness and response plans.

The CORE Group, which leads the public health working group, is responsible for the development and design of guidelines and materials related to care for the ill, reduction of transmission and lowering of excess mortality from common non-influenza illnesses in a pandemic. It also seeks opportunities to stimulate country-level coordination of NGOs.

AI.COMM, managed by the Academy for Educational Development (AED), is the principal partner in behavioural change and communication. In addition to the development of communication materials, it leads formative research.

InterAction will take responsibility for communication with the private voluntary organizations (PVO) sector. It will also map out international non-governmental organizations (INGOs) and their partners' programmatic capacities at national levels that may be mobilized for response. InterAction will also coordinate three major regional meetings aimed at introducing the Initiative on a larger scale in Africa, Asia and Latin America.

The IFRC serves as the coordinating agency for the initiative. It also provides technical and financial support to Red Cross and Red Crescent National Societies to implement pandemic preparedness activities. It will hire or oversee experts, consultants and technical working groups tasked to develop appropriate tools and protocols in public health, food security and livelihoods. The IFRC will also facilitate coordination between partners in keeping the wider Red Cross Red Crescent Movement informed on H2P progress.

Experience and credibility in pandemic preparedness and response

Pandemic influenza is not new to the Red Cross and Red Crescent. During the 1918-1919 Spanish flu, Red Cross and Red Crescent National Societies were requested by governments to provide volunteers to care

Image: IFRC

An Afghan Red Crescent trainer supervises a community volunteer as she demonstrates proper hand-washing techniques. H2P projects will also develop guidance for volunteers on what they need to do differently during an influenza pandemic to protect themselves through infection control measures

for the sick and dying. The word influenza was also mentioned prominently in the written history of the IFRC, which was founded in May 1919 within a few months of the peak death rate of the Spanish flu.

Since then, the IFRC and its member National Societies have been in the forefront of delivering effective response to disasters and public health emergencies through health and care services, enhancing resilience and coping mechanisms, and reinforcing and complementing weak national health care systems. During the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003, national societies in Southeast and East Asia made it possible for volunteers and members to reach out to a large number of people with preventive measures, such as information and education materials, hygiene kits and other supplies, community-based health workshops, advocacy and volunteer training.

When the first highly-pathogenic avian influenza H5N1 was reported in early 2004, Red Cross and Red Crescent Societies were quick to help communities in raising awareness on the risks of exposure to sick or dead birds, poultry and animals, and how to avoid such risks. This was done through health and hygiene education, reinforcing good practice in the management of sick or dead animals, distribution of IEC materials, supporting social mobilization, case detection and referral, and strengthening communication.

Over the last 90 years the IFRC and its member National Societies have responded to the most urgent, life-threatening needs. Today, in preparing for an influenza pandemic that WHO estimates could risk 70 million lives, the IFRC continues to rely on its enormous volunteer network while it develops new tools and methods to respond to an evolving threat, so that vulnerable communities are prepared for and can respond to emergencies.

Updating laws for pandemics and other disasters

The IFRC is working on another important aspect of pandemic preparedness — ensuring that countries have the best legal frameworks in place to contain and respond to potential outbreaks. Three 'Legal Preparedness Projects' are currently underway in Cambodia, Laos and Viet Nam to review existing laws and policies for communicable disease emergencies and other disaster situations, and to make recommendations for legislative improvement. The Legal Preparedness Projects are funded by the Pooled Fund of the Greater Mekong Sub-region Communicable Disease Control Project of the Asian Development Bank, and are conducted in close collaboration with different government ministries, Red Cross and Red Crescent National Societies, WHO and other key organizations in each country.

Among the challenges of pandemic preparedness, and indeed preparedness for other major disasters, is ensuring that national laws, plans and systems are compatible with regional and international prevention and response mechanisms. Thus, a major objective of these projects is to improve the implementation of relevant international laws and standards and ensure that domestic legal systems facilitate international cooperation. In this regard, there are two international instruments of central importance:

Guidelines for the Domestic Facilitation and Regulation of International Disaster Relief and Initial Recovery Assistance of 2007 (IDRL Guidelines)
The IDRL Guidelines are a set of recommendations for governments on the legal requirements needed to receive international assistance in the immediate wake of a disaster that exceeds national capacities. They cover issues such as rapid customs clearance for relief goods and medications, the issuing of visas and necessary legal status to incoming humanitarian organizations, coordination of relief and recovery efforts and the monitoring of quality and accountability standards. Although non-binding, the IDRL Guidelines were adopted by governments at the International Conference of the Red Cross and Red Crescent in 2007 and have been recognized by a number of other international forums. Their principles are drawn from a large number of pre-existing treaties, resolutions and other international standards.

International Health Regulations of 2005 (IHRs)
The IHRs are a legally binding instrument, adopted by the World Health Assembly in 2005 to prevent and control the international spread of disease. They include a number of measures relating to disease surveillance, alerts, prevention, containment and response activities. A number of these measures require the development or amendment of laws to allow authorities to undertake necessary activities, such as the inspection and quarantine of goods and travellers, vaccinations and decontamination, the management of international borders and the exchange of information to assist international prevention and response. Additionally the IHRs seek to ensure that all such measures are consistent with human rights obligations and minimize disruption to international trade and travel.

It is hoped that the findings and recommendations from these Legal Preparedness Projects will provide valuable assistance to governments in identifying and resolving the most pressing legal issues which stand in the way of their readiness to respond to potential pandemics and other disasters.

Influenza: how to blunt the Damocletian sword

Professor Albert Osterhaus, DVM, PhD, Head, Department of Virology, Erasmus MC, Rotterdam

Influenza in humans comes in three different forms: seasonal, avian, and pandemic influenza. Although these three human disease entities are all caused by infection with an influenza virus, there are principle differences in their causative agent, disease manifestation and degree of spreading from human to human.

Annually recurring seasonal influenza is caused by an influenza virus of the A or B type and besides being responsible for a huge burden of disease, causes the deaths of about 400,000 people worldwide every year. Avian influenza in humans is caused by sporadic zoonotic transmissions of avian influenza A viruses from birds to humans. The highly pathogenic avian influenza A virus of the H5N1 subtype (HPAI-H5N1), that currently circulates in many areas of Eurasia and Africa in an unprecedented way, has caused the deaths of more than 60 per cent of the more than 400 reported sporadic human cases to date. Avian influenza is not or very rarely transmitted from human to human. If however an avian influenza A virus does acquire the possibility to efficiently spread from human to human, it becomes a real human pandemic virus and an influenza pandemic becomes reality: the virus spreads worldwide within a relatively short period of time.

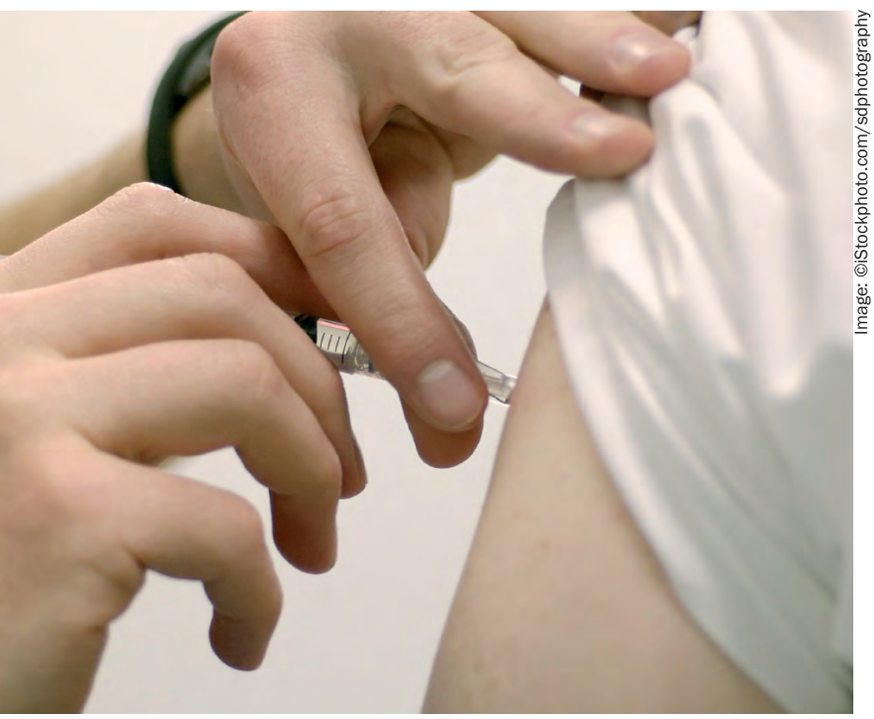

Image: ©iStockphoto.com/sdphotography

Vaccination is the most cost-effective medical intervention to combat seasonal influenza

Influenza pandemics in the 20th century varied from severe to moderate with the 1918-1919 pandemic ('Spanish flu') alone killing more than an estimated 50 million people. The subsequent influenza pandemics of 1957 ('Asian flu') and 1968 ('Hong Kong flu') were less severe, but still have each killed millions of people. Although the three influenza pandemics of the last century together have cost the lives of 50 to 100 million people, it should be realized that the cumulative number of deaths caused by the annually recurring seasonal influenza epidemics worldwide is in the same order of magnitude. So, it may be estimated that the different forms of influenza have cost the lives of more than 100 million people in the past century.

Probably the most intriguing question today is whether the world will face another influenza pandemic and if so, when will it happen, what avian influenza virus will be at its basis, and how severe will it be? The answer to the first question is that the re-emergence of an influenza pandemic is just a matter of time and should therefore rather be considered a matter of when than of if. This is based on the current knowledge of the mechanisms underlying the development of pandemic influenza viruses.

To become a pandemic virus, an avian influenza A virus should not only be pathogenic to humans, but should also transmit efficiently from human to human. The pathogenicity of a future pandemic virus will to a large extent be determined by the avian virus that will be at its basis. After crossing the species barrier to humans, an avian influenza virus may acquire transmissibility between humans by either of two mechanisms. The first is the result of combining genetic material of the avian and a mammalian influenza virus that is already present in humans or other mammalian species. The second mechanism is the result of sequential mutation of an avian influenza virus that repeatedly crosses the species barrier from birds to humans. The former mechanism was at the basis of the last two pandemics, the Asian flu and the Hong Kong flu, whereas the latter was probably involved in the generation of the Spanish flu virus. There is absolutely no reason to believe that the generation of yet another pandemic influenza virus by either of these two mechanisms will not happen again, and the frequently reported zoonotic transmissions of avian influenza A viruses of different subtypes to humans in the last decade, often with fatal consequences, clearly highlights

this risk. Avian influenza A viruses are repeatedly crossing the avian-mammalian barrier, but have so far not succeeded to become efficiently transmissible from human to human. Unfortunately it is impossible to predict with current knowledge when it will happen and which virus will be involved.

With the advent of modern scientific insights and novel technologies it is possible in principle, to efficiently combat all forms of influenza, including pandemic influenza. Besides non-medical intervention strategies, like the implementation of hygienic measures and social distancing, which both may significantly reduce viral spreading, there are three medical intervention strategies which, especially when used in combination, may reduce the burden of seasonal, avian and pandemic influenza drastically: influenza surveillance, as well as the use of influenza virus-specific antiviral and vaccination strategies.

Surveillance of influenza in humans and animals

By far the best surveillance system for any infectious disease in humans is the global surveillance network for seasonal influenza. This was initiated over 50 years ago by the establishment of an ever-increasing collaborative network of national and regional collaborative influenza centres, established and maintained under the auspices of the World Health Organization (WHO). It is based on the regular reporting of seasonal influenza activity and characteristics of the human influenza viruses that continuously spread around the globe. It forms the basis for the bi-annual selection of influenza virus strains that should be represented in the seasonal influenza vaccines.

The recent implementation of mathematical modelling of the data as they emerge and the associated antigenic cartography, has recently added an important and novel dimension to the functioning of the network. It contributes to the identification of novel vaccine virus strains, and also provides novel insights in the way in which these viruses spread geographically over time. In spite of the major achievements of this network, it should be realized that there are still significant gaps in its global geographical coverage. As this surveillance network also currently plays a role in following the spread of avian influenza viruses in humans and in the characterization of these viruses, it will also function as an early warning system for an emerging pandemic influenza virus. This makes the issue of geographical coverage even more important, since in several areas where this could reasonably be expected to happen, this coverage is far from satisfactory. Influenza surveillance should not be limited to surveillance in humans, but should also include surveillance in birds and other animals, as they play an important role in the emergence of pandemic influenza viruses.

In several geographical areas like North America, Eurasia and Africa, combined activities between virologists, ornithologists and data managers have been started in the past decade to map the spread of avian influenza A viruses in waterfowl and the threat they may pose to other wildlife, domestic poultry, other domestic animals and eventually mankind. The value of these activities besides the mapping of the spreading and the associated risk is that it generates a large and continuously updated repository of avian influenza A viruses. This may allow the continuous development of an updated repository of seed viruses for eventual pandemic vaccine production, which will save precious time in developing a vaccine when the next pandemic emerges.

Stockpiling and use of antivirals

Currently there are two groups of specific antiviral drugs against influenza, which specifically interfere with the replication of the virus in the body: the adamantanes and the neuraminidase inhibiters, which have different working mechanisms. The first group, to which the drugs amantadine and rimantadine belong, has been known and used to treat seasonal influenza for a long time. These drugs however have some major limitations and disadvantages. They cause considerable adverse effects (less so for rimantadine), are not effective against influenza B viruses (the cause of part of seasonal influenza) and most importantly, influenza viruses rapidly develop resistance against them.

The neuraminidase inhibitors, to which the drugs oseltamivir and zanamivir belong, have been developed more recently and were introduced in the last decade. These drugs cause less side effects, are also effective against influenza B viruses and limited or no resistance development was observed initially when they were used clinically to prevent or treat influenza. In cell culture and in animal models it was demonstrated that they were also active against avian influenza viruses. Oseltamivir has been used so far in a limited number of patients with severe symptoms of avian influenza (HPAI-H5N1). Since the antiviral drugs have to be used as early as possible during infection for the optimal effect, and for seasonal influenza definitely before 48 hours, the actual therapeutic effect of the neuraminidase inhibitors in avian influenza of humans cannot be estimated to date. On basis of the preclinical data it may be expected that the neuraminidase inhibitors may indeed be effective against an emerging pandemic influenza virus. Consequently several countries have now stockpiled oseltamivir and some have complemented this stockpile with that of zanamivir.

While oseltamivir is currently the most widely used antiviral drug against seasonal influenza, oseltamivir resistant viruses were found at a low rate and the resistant viruses did not replace the sensitive viruses in the population. Also in patients treated with oseltamivir against avian influenza (HPAI-H5N1) resistant viruses were shown to emerge, without further spread of these resistant viruses. In the past year the situation with respect to oseltamivir resistance has changed considerably, when it became apparent that one of the seasonal influenza A (H1N1) viruses had developed resistance against this drug. This was first noted in Europe where in spite of very limited use of the drug, the resistant virus largely replaced the sensitive influenza A (H1N1) virus.

Subsequently in the winter season of the southern hemisphere and in the following winter season in North America, the oseltamivir resistant influenza A (H1N1) virus also replaced the sensitive one. Fortunately the oseltamivir resistant H1N1 viruses still proved to be susceptible to zanamivir, the other neuraminidase inhibiter and to amantadine. Since the use of antiviral drugs against influenza viruses may be life saving for high-risk

patients, the use of combinations of drugs may have to be considered in these patients from the start of symptoms. These events also raise questions about the risk that a future pandemic influenza virus could become resistant to stockpiled antiviral drugs. Therefore stockpiling of more than one antiviral drug would be advisable for pandemic preparedness plans.

Vaccination and stockpiling of influenza vaccines

Vaccination is the most cost-effective medical intervention to combat seasonal influenza.[1] More than half a century ago classical vaccines against seasonal influenza were introduced and ever since vaccination coverage for seasonal influenza has increased. The first influenza vaccines were produced by inoculating embryonated chicken eggs with the virus strains of choice and harvesting the allantoic fluid from which the virus was partially purified and inactivated. This basic method of producing inactivated seasonal influenza vaccines has essentially remained unchanged. These vaccines are updated biannually for the northern and southern hemisphere, based on epidemiological data collected by the abovementioned WHO-led influenza surveillance network.

Currently the total global production capacity for seasonal influenza vaccines has increased to more than 400 million doses of trivalent vaccine per season. In spite of all the technologic advances that would allow for newer methods of influenza vaccine production, current practice is still entirely dependent on the use of embryonated chicken eggs. The formulations for these vaccines include whole inactivated virus, split virus, viral subunits or surface antigens and live attenuated virus (LAIV).

In the context of a pandemic, seasonal influenza vaccine production capacity would have to be used for the production of a pandemic vaccine. This results in three major problems that would have to be solved: the long response time, the limited production capacity and the lack of efficacy of vaccines produced with the current platform used for seasonal vaccine production. In addition, safety issues and regulatory processes would have to be addressed in advance. The current response time between the seasonal influenza virus strain selection and production of the first vaccine doses is more than six months. This would be too long in the situation that a pandemic virus starts to spread globally. The overall world seasonal influenza vaccine production capacity is approximately 700 million doses of trivalent vaccine and with the current production platform using split vaccine, more than ten times the amount of vaccine would need to be administered in a two-dose regimen to induce adequate protection. Thus, the implementation of techniques that allow dose sparing have become a major priority in the field of pandemic vaccine development.

These considerations have prompted academic groups and influenza vaccine manufacturers to develop new generation vaccine formulations and production technologies that would solve these problems. Among the smaller changes that are relatively easy to implement are the development of novel cell culture based production systems, as well as improved methods to prepare vaccine seed viruses. Novel production systems based on the use of continuous cell lines, rather than embryonated chicken eggs would make the production systems more flexible, although it should be realized that the continued availability of these production substrates should also be planned well in advance. Furthermore, it should be realized that if LAIV pandemic vaccine could be produced, the vaccine production capacity would increase dramatically, since lower viral vaccine doses could be used.

In the field of vaccine virus strain selection considerable progress has been made over the past decade. Novel mathematical techniques of antigenic mapping that were originally developed to determine the best seasonal influenza vaccine strain candidates can now also be employed for the measurement of differences between newly emerging avian influenza A viruses that infect humans, like the HPAI-H5N1 viruses. This will have important and direct consequences for the identification and preparation of the best matching seed virus, using a repository of recently collected avian influenza A viruses and state-of-the-art molecular techniques.

In the past few years, considerable progress has been made in the improvement of the efficacy of influenza vaccine candidates, by using novel adjuvants, without a major negative impact on their safety profile. An adjuvant is a substance that is added to a vaccine to stimulate the immune system in a non-specific way, in addition to the specific stimulation provided by the vaccine proper. Thus the adjuvanted vaccine may induce a more potent and broader protective immune response than the non-adjuvanted vaccine.

The first adjuvanted avian influenza A vaccine has now been licensed, and has demonstrated promise for an avian or pre-pandemic influenza vaccine by allowing vaccine sparing and by inducing broader immunity. It may be expected that the registration of several adjuvanted vaccines for pre-pandemic use will follow and that such vaccines will also form the basis for the eventual use of pandemic vaccines that will be prepared with the actual pandemic seed virus strain. Finally, the use of several novel molecular techniques has shown great promise by yielding candidate vaccines inducing broad protective immunity in relevant animal models. It may be expected that influenza vaccines based on these technologies will also enter into clinical trials soon and that these approaches may also result in the use of novel generations of human vaccines to combat seasonal, avian and pandemic influenza.

Conclusion

Facing the burden of disease currently caused by seasonal influenza and the pandemic threat that looms like a sword of Damocles over humanity, the real question today is how to use the currently available tools most efficiently to reduce the future impact and disease burden of influenza on mankind. The use of vaccines and antivirals against seasonal influenza is currently limited to a small fraction of people in the high-risk groups who would benefit from it the most. Therefore too many people are unnecessarily suffering and dying from seasonal influenza every year. Finally, although we now have the tools to prepare the world to efficiently combat a future influenza pandemic that may be imminent, most countries have so far failed to develop effective pandemic preparedness plans, leaving their populations unprepared for such a major catastrophe that will cost the lives of many millions of people.

Preparing for the next influenza pandemic

Stephen C. Redd, US Centers for Disease Control and Prevention

A severe influenza pandemic has the potential to be one of the most catastrophic health events in history. This future pandemic will happen when an influenza A virus circulating in birds or other animals undergoes a genetic change that allows it to be transmitted efficiently from person to person. This genetic change can occur through a series of mutations or through a process called reassortment, which occurs when a person or animal is infected simultaneously with an animal influenza virus and a virus that already has the capability to be readily transmitted among people — some subsequent descendent viruses could have genetic material from both viruses. Should such a new virus emerge that can be readily transmitted from person to person, the world would be on the verge of a pandemic. Susceptibility to such a virus would be universal, the illness it would produce could be severe, and without effective control measures, transmission would be widespread. With increasing global interconnectedness, an infection with the characteristics of influenza — respiratory spread, initial non-specific clinical manifestations, and a short incubation period – has the potential to spread around the world in short order. Unmitigated, a severe pandemic could cause tens of millions of deaths worldwide, disrupt civil society, and lead to trillions of dollars of economic losses over a period of months.

Image: US CDC

The H5N1 influenza virus spread rapidly in poultry and wild birds during 2004-2006

In late 2004 and through 2005 and 2006, the world braced for an influenza pandemic caused by the H5N1 influenza virus. This virus had spread in poultry and wild birds over the course of months through Asia and into Europe and Africa, and although H5N1 was not readily transmissible from person to person, there was widespread concern regarding increasing chances that a series of random mutations of the virus in an infected bird, or genetic reassortment with an influenza virus better adapted to human transmission, would ignite a pandemic.

In the face of these dire possibilities, modern science and public health have expanded the repertoire of tools available to reduce the impact of an influenza pandemic since the last influenza pandemic in 1968. These tools include the capability to diagnose novel influenza virus infections specifically and quickly, availability of anti-influenza drugs, the technology to produce large quantities of vaccine well matched against a pandemic influenza virus, and, although not new, traditional public health measures to reduce exposure of susceptible persons to infectious persons. The global challenge is to marshal these interventions into a rapid, seamless, worldwide response for an inevitable event, but one where the timing and severity are unpredictable.

The United States is working in partnership with other national governments, numerous international organizations, and internally, to prevent and prepare for the next pandemic. In short, this work translates to planning and training to use the full range of interventions available. Because the next pandemic will almost certainly arise from an existing animal influenza virus, monitoring such viruses and attempting to control or eliminate them from animals is the first line of defence.

In the years since 2004, largely as a response to the H5N1 threat, individual countries and the global community have achieved a substantial level of pandemic preparedness. Sustaining and improving preparedness is now at risk because of complacency with the H5N1 situation — the virus has not become more transmissible from person to person — and because the global economic climate favours dealing with current problems rather than preparing for future ones. Nevertheless, the current H5N1 threat is undiminished, and the risk of a novel influenza virus, whether H5 or another type, spawning a global pandemic is ever present. Preparing for an influenza pandemic is an ongoing effort, and the global community must be ever vigilant to reduce the risk and prepare to mitigate the consequences of the next influenza pandemic.

Image: US CDC

Although influenza viruses are natural pathogens of migratory waterfowl and shorebirds, exposure to infected poultry appears to be more important in human cases of H5N1

Virology

Because of its widespread distribution and somewhat greater capability to infect and cause serious disease in a variety of mammals compared with other avian viruses, the H5N1 influenza A virus has to be considered the greatest current threat for the next influenza pandemic. This virus has occasionally infected humans and continues to have a mortality rate above 60 per cent. In rare instances limited person-to-person transmission has likely occurred, but these events have not been accompanied by changes in the make-up of the virus that signal a greater capacity for person-to-person transmission. One aspect of pandemic risk assessment involves detailed molecular examination of each novel influenza virus isolated from a human case, to determine whether it has changed so as to make person-to-person transmission more likely. This virologic risk assessment remains a critical component of preparedness.

Although H5N1 is considered the greatest threat, other novel influenza viruses also pose risk. The three pandemics of the 20th century all occurred as a result of mutation of a low pathogenic avian virus or mixing of a low pathogenic virus with different influenza viruses with genetic components better adapted to human transmission. H2, H5N2, H6, H7, H9, and, possibly, swine H1 viruses all have the potential to cause the next pandemic. As a consequence, virus tracking cannot be limited to H5N1.

Influenza in animals and pandemic risk

Controlling influenza in animals is the only way to truly prevent an influenza pandemic, but because influenza viruses are natural pathogens of migratory waterfowl and shorebirds, these interventions cannot be 100 per cent effective. Following H5N1's emergence as a major pathogen of poultry in 2004, outreaks in poultry or wild birds spread southward and westward through 2005 and 2006 until few countries of Asia or Europe were unaffected, and several countries in Africa had identified outbreaks. Although transmission from wild birds to domestic birds has probably occurred, it seems likely that the trade in poultry, sometimes illegal, was the more important pathway for expansion.

Since 2006, the epizoology of H5N1 has changed with the end of the rapid geographic expansion, and the development of endemic foci in the Nile delta, Indonesia, Southeast Asia, and possibly other locations. Backyard, small-scale holdings with limited biosecurity initially appeared to pose the greatest risk. In several countries, H5N1 appears to have infiltrated commercial poultry operations — including wet markets where live birds are sold and slaughtered — increasing the economic impact of avian influenza, but theoretically making control easier to implement as concentration of ownership could make centralized control efforts more effective.

Countries such as Viet Nam and Thailand and regions such as Hong Kong have effectively controlled avian influenza through programmes including aggressive culling, vaccination, and tight surveillance for possible reintroduction of the virus. Although these measures have been successful, they require intense, ongoing vigilance to identify and control reintroduction. For example, Viet Nam had no avian outbreaks or human cases during 2006, but experienced both in 2007, 2008, and 2009.

Avian influenza in humans and pandemic risk

Every case of avian or other novel influenza A infection in a human is potentially the start of the next pandemic.

Image: US CDC

It is important to minimize the likelihood of susceptible people coming into contact with an animal carrying a virus that can transmit from human to human

In the case of H5N1, human cases appear to follow exposure to infected birds or live poultry markets. The ability to retrospectively identify such exposures among human cases is highly dependent on the intensity of the investigation. Given the number of infected poultry and the rarity of human infection, few exposures result in human infection.

Since 2006, in parallel with the declining number of affected countries, the reported number of persons infected with H5N1 each year has declined. The overall mortality rate has remained above 60 per cent since 2005. Early treatment with antiviral drugs appears to improve the chances of survival and young children appear to have better survival chances than older children and adults. Country to country variation in mortality might have more to do with early detection and treatment than with any inherent virus properties.

While the decline in new H5N1 human cases is encouraging, changes in the intensity of surveillance for human cases may also explain some of the decline. As the expected H5N1 pandemic has failed to materialize, there is a natural sense that the risk of person-to-person transmission developing has diminished, despite the lack of scientific evidence of any change in the risk.

Reducing risk and mitigating the impact of pandemic influenza

The best strategy to reduce the likelihood of pandemic influenza is to reduce the likelihood that an animal carrying a virus that has developed the capability to transmit from human to human will come into contact with a susceptible person. As influenza viruses are constantly mutating, control of influenza in animals, particularly poultry and swine, is essential. Surveillance for novel influenza A viruses in domestic animals and swift action — investigation and laboratory confirmation followed by culling infected flocks or herds — is a constant requirement.

Once a possible human infection with a novel influenza A virus has been identified, rapid investigation and laboratory assessment is mandatory. Current guidelines recommend antiviral drug therapy for contacts of an infected person or of a documented outbreak of animal influenza. This scenario has played out repeatedly in countries with H5N1 disease in poultry and may be responsible for preventing transmission of the virus. Clusters of human cases of novel influenza A virus infection are an especially important target for surveillance as these could represent person-to-person transmission. As called for in the International Health Regulations, every country must have the capability or access to the capability to identify and report novel influenza A virus infections — as a public health emergency of international concern — and to take measures to reduce transmission. These steps are as vital to protect the population of a country where such an emergency occurs as they are to protect the rest of the world from the global threat of a pandemic.

Based on the results of mathematical modelling, mounting an intense intervention to extinguish of person-to-person transmission of novel, readily transmissible influenza virus appears justified if it is logistically feasible and if transmission is not widespread. This intervention, a containment operation, would include active surveillance for new infections supported by laboratory testing, treatment and prophylaxis with antiviral drugs, isolation of infected persons and their contacts, strict, time-limited entry and exit screening protocols for the area experiencing person-to-person transmission (the containment zone) and, depending on the virus, use of

Image: US CDC

Better understanding and control of animal influenza is vital to reduce the risk of a pandemic

vaccines prepared against animal viruses that might offer some protection against the mutated potentially pandemic strain. Extensive, detailed planning and training will be required for this strategy to have the best chance of extinguishing transmission. Whether these measures could successfully interrupt transmission and forestall a pandemic cannot be known with certainty and will depend on the unknown characteristics of a virus that has not yet been identified.

Actions following widespread transmission of a novel influenza A virus

Once infection with a novel influenza A has become established in human populations, several public health measures must be brought to bear simultaneously. These efforts include characterizing the clinical and epidemiologic features of the disease, developing a well-matched vaccine, communicating effectively and fully, implementing measures to reduce exposure to infected persons – including isolating those who are ill and encouraging their household contacts to stay home to prevent transmission beyond the household, and working to assure the continuation of vital societal functions. As these measures are implemented, policy makers have to be particularly sensitive to assuring that scarce resources are allocated in a just and ethical manner. Although specific implementation plans will naturally vary among countries and resources available, the general outline applies to all countries.

Detailed planning, exercising of plans, and revising and refining plans are the processes to assure that the public health interventions are valid and executable. Situations where the plans can be tested in real-life public health emergencies are an even better way to test and identify shortfalls in plans — risk communication efforts, for example, can be honed in responses to other emergencies. Given the unique features of an influenza pandemic, actual events cannot supplant exercises for some parts of the response.

Benefits of preparing for a pandemic

Because an influenza pandemic is such an all-encompassing emergency, preparedness efforts inevitably improve the capabilities required to respond to other public health emergencies. Decision-making processes, internal data collection and communication procedures, and risk communications expertize are all transferable to other responses. In addition to improving responses to public health emergencies, many of the elements of preparing for an influenza pandemic also improve and refine the tools for control of seasonal influenza. For example, the capability to quickly measure vaccine effectiveness, measures to reduce the impact of the bacterial complications of influenza, and increasing the supply of seasonal influenza vaccine are all by-products of pandemic preparedness.

Better understanding and control of animal influenza is vital to reduce the risk for an influenza A pandemic. When a cluster of human cases of a novel influenza virus is identified, intense, rapid efforts to suppress transmission offer the possibility to extinguish transmission and prevent a pandemic, even if the characteristics of the virus are such that it has the potential to cause a pandemic. If such containment efforts are not feasible or do not extinguish all chains of transmission, the full range of public health measures must be implemented to reduce the impact of a severe pandemic. The global cooperation and progress to prepare for a pandemic achieved since 2005 must be sustained even in the face of the current economic uncertainty. The risk of not being ready is simply too great.

Cell culture (Vero) derived pandemic influenza vaccines

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Efficient vaccine production requires the growth of large quantities of virus produced with high yields from a reliable, available, safe host system. Conventional methods for producing influenza vaccines are based on the growth of the viruses in embryonated chicken eggs. This is a cumbersome process in which each egg must be sterilized, candled, inoculated with virus and incubated before harvesting small volumes of allantoic fluid from each egg and pooling before purification. Between one and two eggs are typically required for one dose of seasonal trivalent influenza vaccine and the supply of eggs for seasonal influenza vaccine production requires up to six months to scale up. There is, therefore, a concern that there could be a major shortfall in the case of a major pandemic, when there would be the need for large quantities of vaccine to be produced rapidly, possibly in a situation where chicken flocks have been depleted by infection with highly pathogenic influenza virus.[1]

There is also evidence that selection of human influenza viruses for high yield growth in eggs is associated with the selection of antigen variants, which may be sub-optimal for inducing protective antibodies to wild type virus circulating in humans. In contrast to influenza viruses grown in eggs, virus propagated exclusively in mammalian-derived tissue culture has been reported to be representative of the natural virus. Studies in ferrets have also demonstrated that an inactivated influenza vaccine grown in Maden-Darby canine kidney cells (MDCK) induced higher mean serum haemagglutination inhibition and neutralizing antibody titres than did egg-grown vaccine, and induced superior protection against subsequent challenge with infectious virus grown in either cell type.

These reports demonstrated the possible superiority of a mammalian cell-derived vaccine and emphasise the necessity for a mammalian cell line that could be used to replace chicken eggs in the production of influenza vaccines. Consequently, the development of inactivated, cell-derived influenza vaccines grown at an industrial scale using a variety of continuous cell lines (CCLs), specifically, Vero, MDCK and PER.C6 cells, is well advanced.

Although a number of CCLs are being considered for production of influenza and other viral vaccines, Vero cells are the most widely accepted CCL by regulatory authorities for manufacture of viral vaccines. Vero cells were first used for human vaccines with the production of IPV by Montagnon and colleagues at the Institute Merieux, Lyon, France in the early 1980s, and this was followed by its use for an inactivated rabies vaccine. Vero cells have also been used for many years for the production of live oral poliovirus vaccine.

As such there is over 25 years experience with Vero-derived human vaccines with hundreds of millions of vaccine doses being distributed worldwide.[2] This experience has provided substantial evidence supporting the safety of this cell substrate and has provided encouragement to further explore the use of this cell line for a range of different viral vaccines including influenza.

Another major advantage of the Vero cell line for vaccine production is that it can be grown and infected on microcarrier beads and cultivated in fermenters to allow the large-scale production of vaccines. These developments were pioneered by Anton Van Wezel, who first demonstrated the high-density cell growth on microbeads for the production of polio and rabies virus vaccines. This microcarrier technology has been further developed to allow large-scale production of a number of vaccines using a serum-free medium. Such processes have been developed to allow amplification of a single one-millilitre ampoule of cells to achieve a fully confluent microcarrier culture at a 6,000-litre scale within eight weeks. This upscaling can be carried out without loss of cell productivity or viability with extremely consistent results.

Advantages associated with cell culture derived pandemic influenza vaccines

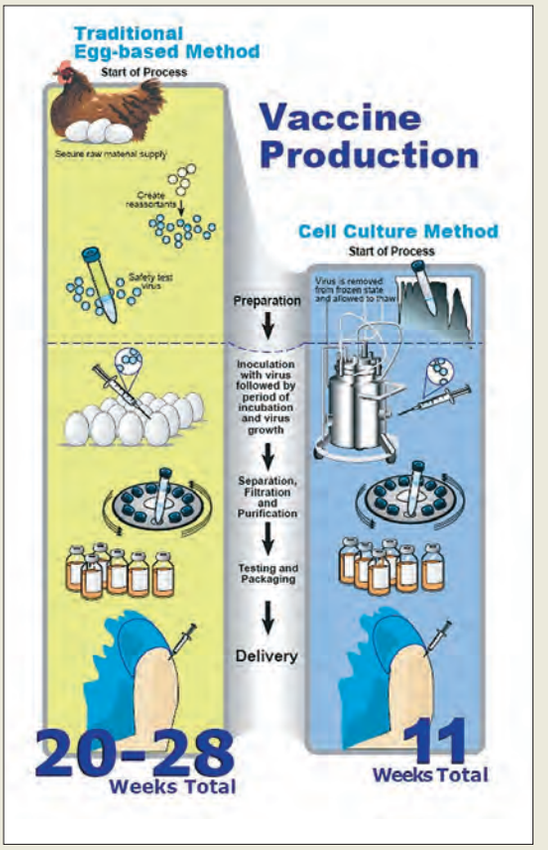
Most pandemic H5N1 vaccine candidates tested to date were manufactured using attenuated reassortant viruses. These reassortants are generated using the haemagglutinin (HA) and the neuraminidase (NA) genes of the circulating wild-type (WT) virus and the six remaining genes of the H1N1 influenza strain A/PR/8/34 (6:2 reassortants), which usually confer high growth properties in embryonated hens' eggs. This reassortant virus is also attenuated by removal of the polybasic cleavage site of the HA which is associated with high pathogenicity.[3] These reverse genetics (RG)-derived reassortants are then subjected to extensive safety testing before distribution to the influenza vaccine manufacturers. This procedure is essential to allow use of the virus under the biosafety level two enhanced, which is the highest safety level available in egg-based manufacturing facilities, and to generate the potential high-growth phenotype required for adequate vaccine antigen yield. However,

Cell culture (Vero) facility

Used for manufacture of H5N1 vaccine in Bohumil, Czech Republic

Source: Baxter Bioscience

Vero cell culture comparison



Comparison of Vero cell culture with embryonated eggs with respect to process and timelines

Source: Baxter Bioscience

this derivation of new reassortants requires several weeks, resulting in significant delay in the delivery of a new pandemic vaccine. In addition, the vaccine may provide an optimal antigenic fit with the WT circulating virus only with respect to the HA and NA genes and not with respect to the rest of the genes including the nucleoprotein and the matrix genes which are derived from the A/PR/8/34 virus.

A novel strategy was developed to avoid the delay and potential antigenic mismatch associated with vaccine production using egg-adapted, reverse genetics-derived reassortant virus. This involves use of wild-type virus to produce vaccine antigen in Vero cell culture, one of the most advanced cell culture systems for production of influenza viruses. For vaccine production, the virus harvest is inactivated using a highly stringent procedure involving two separate steps, formalin and UV treatment. Formalin alone was sufficient to achieve total inactivation with a large safety margin, as confirmed by safety (passage) assays of the bulk vaccine in two highly susceptible cell systems, that is Vero and chicken embryo cells. Double inactivation was chosen to enhance the safety margin. The inactivated virus is then purified by continuous sucrose gradient centrifugation followed by ultra/dialfiltration steps prior to formulation. Re-sequencing of the HA gene of both strains at the production level confirmed that virus grown in Vero cells did not result in the selection of antigenic variants.[4]

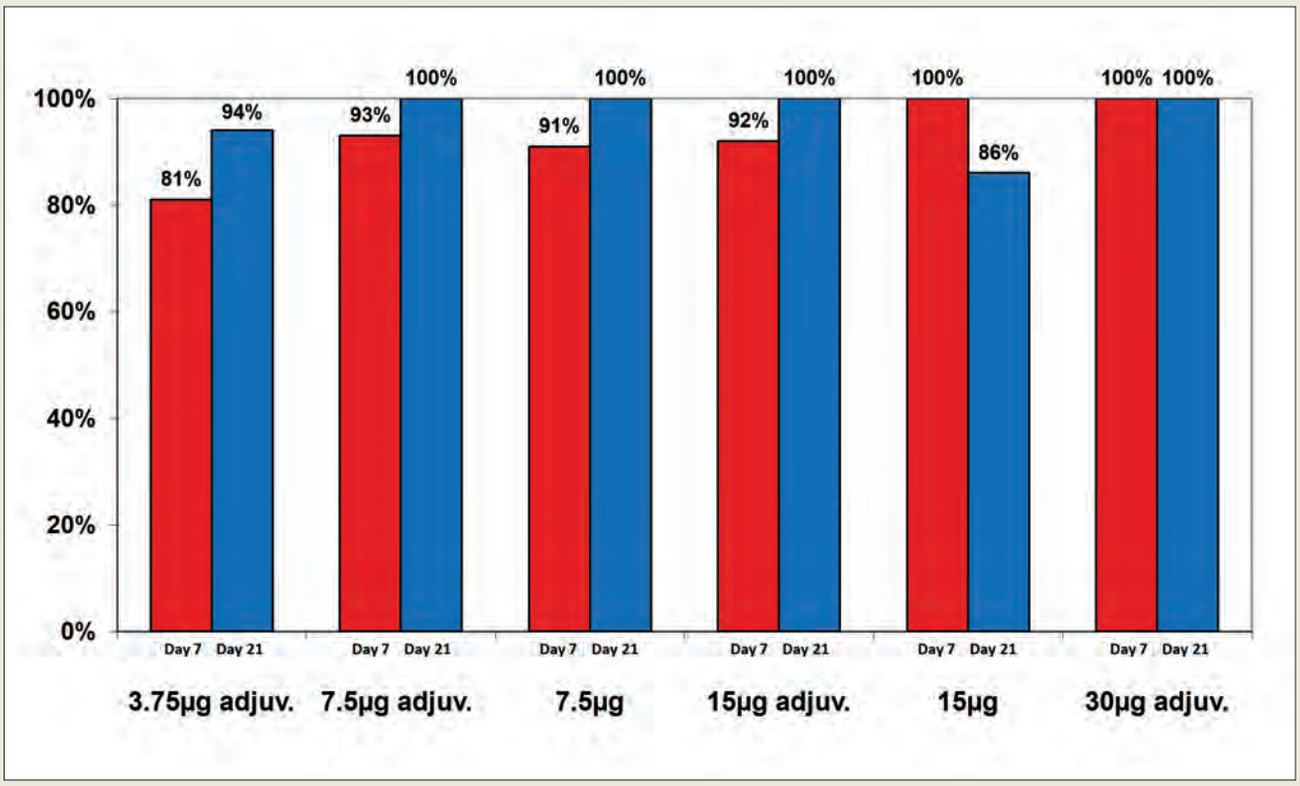
This process can result in the first batches of vaccine being available approximately 11 weeks after receipt of the pandemic vaccine strain. This contrasts with a lag time of 20-28 weeks, which is required for production of vaccine based on RG-derived attenuated virus in embryonated eggs.

Safety and immunogenicity of Vero cell derived whole virus H5N1 vaccines

In addition to vaccine supply, the other critical issues in the event of a pandemic are vaccine efficacy and safety. The H5N1 virus has diverged into three distinct lineages or clades (0, 1, 2) and multiple subclades within clade 2. Therefore production of pandemic vaccine can possibly only be initiated once the exact candidate strain is determined, if the protection induced by a vaccine is clade or subclade-specific. Ideally, an H5N1 vaccine would protect not only against the virus strain used for vaccine manufacture but also against viruses, which have undergone antigenic drift. However, traditional inactivated split and sub-unit H1N1 and H3N2 influenza vaccines induce relatively strain-specific serum antibody and are ineffective against antigenically drifted viruses. In contrast, studies with the Vero cell culture derived whole virus H5N1 vaccine have demonstrated that it is capable of inducing broadly cross-reactive neutralizing antibodies against a range of H5N1 clades and subclades.[5] Immunization studies in guinea pigs have demonstrated that two immunizations with a clade 1 A/Vietnam/1203/2004 strain vaccine resulted in induction of high titre neutralizing antibody responses to a clade 0 (A/Hongkong/156/1997), a variety of clade 1 (A/Vietnam/1203/2004, A/Vietnam/1194/2004, A/Thailand/83/2004), clade 2.1 (A/Indonesia/05/2005), clade 2.2 (A/turkey/Turkey/1/2005, A/chicken/Egypt/03/2006) and clade 2.3 (A/Anhui/1/2005) strains.

Although whole virus vaccines are reported to be more immunogenic in immunologically naïve individuals than split or sub-unit vaccines, they are considered to be associated with enhanced reactogenicity, partic-

Percentage of subjects with neutralizing antibody response to the booster vaccine (MN titer>20)



Source: Baxter Bioscience

ularly fever, when used as trivalent seasonal vaccines. All clinical studies to date (on around 4,000 subjects) have demonstrated that the Vero cell derived whole virus vaccine was well tolerated in adult and elderly populations. Data from paediatric studies is not yet available.

The data available from clinical studies confirmed the excellent immunogenicity seen in pre-clinical animal studies.[6] Clinical studies carried out with A/Vietnam/1203/2004 or A/Indonesia/05/2005 demonstrated that doses as low as 3.75 micrograms or 7.5 micrograms resulted in induction of seroprotective levels of neutralizing antibody in more than 70 per cent of subjects after two immunizations. This immunization regimen also resulted in induction of a substantial cross-reactive antibody response. In these studies, neutralizing antibodies were also induced against a clade 0 strain and, to a lesser extent, to a clade 2.1 strain, after immunization with a clade 1 strain vaccine. With this immunization schedule, the highest neutralizing antibody response was obtained 42 days after initiation of immunization and required a two-dose schedule.

However modelling of pandemic spread has shown that induction of an immune response to a pandemic strain in a significant proportion of the population within two weeks after initiation of an outbreak is critical in order to interrupt virus transmission. Therefore, conventional strategies requiring two vaccinations 21 days apart at the onset of a pandemic are unlikely to result in a rapid protection of the population. Alternative strategies would be required to ensure rapid induction of immunity in the population. Such a strategy would be the concept of pre-pandemic priming immunization with an existing available H5N1 strain, which may not necessarily be a complete match to an emerging H5N1 strain. Boosting would then be carried out with a single dose of the optimally or closely matched pandemic strain vaccine.

This concept has been investigated in a study where subjects were primed with two doses of a Vietnam (clade 1) strain vaccine in dosages ranging from 3.75 micrograms to 30 micrograms. Formulations with and without alum adjuvant were included in the priming immunization regimen. Approximately 18 months after priming, the subjects were then boosted with one dose of a 7.5 microgram non-adjuvanted formulation of an Indonesia strain (clade 2.1) vaccine, as a model for the pandemic strain vaccine. The collected data demonstrated that 81 per cent to 100 per cent of the subjects developed a seroprotective neutralizing antibody titre to the booster strain vaccine as early as seven days after the booster immunization. This prime-boost strategy, which requires only a single dose of vaccine in the event of a pandemic, would also result in a substantial increase in the availability of vaccine, in addition to the more rapid induction of protective immunity in the population early in a pandemic. The use of Vero cell technology, which allows more rapid and robust vaccine supply together with use of such prime-boost immunization strategies, would have significant impacts for global public health in the event of an influenza pandemic.

Australian aid programme initiatives to combat emerging infectious diseases

Australian Agency for International Development

Australia is a leader in the response to pandemic and emerging infectious disease threats in the Asia Pacific region and contributes to other regions through the global programmes of multilateral agencies. The Australian Government's aid agency, the Australian Agency for International Development (AusAID), administers an AU$150 million package to support the response to pandemic and emerging infectious diseases.

AusAID and emerging infectious diseases

Australia's aid programme is centred on Asia and the Pacific, where at least 640 million people live in extreme poverty and at least 2 billion live in poverty. These figures are expected to increase when the impact of recent food and fuel prices and the global economic crisis are felt. An avian influenza epidemic could undo years of development, weaken economies and even be a trigger for social instability. Through the Australian aid programme, we help partner countries to prepare for, prevent and control avian influenza epidemics while assisting with strengthening national systems for animal and human health.

Some of our near neighbours are at significant risk of emerging infectious diseases, particularly Indonesia, Papua New Guinea and East Timor. These countries face major challenges and constraints because of weak systems of animal and human health surveillance and gaps in their capacity to respond to pandemics. Parts of the Mekong have experienced several outbreaks of avian influenza in birds since 2003, and there have been human cases and fatalities. Pacific island countries could be severely affected by a human influenza pandemic as they were in the Spanish 'flu outbreak of 1918–19. These countries have limited capacity to respond to emerging disease threats.

Australia's approach

Australia takes a broad approach in its assistance to combat pandemics and emerging infectious diseases in the region:

Flexibility — We are flexible so that we can respond to changing needs and priorities and even to sources of pandemics other than avian influenza. Our assistance is provided in ways that will yield longer-term benefits regardless of whether or when a pandemic occurs.

Participation — Our bilateral assistance is guided by partner governments' preparedness planning and needs assessments. Our contribution to regional and multi-donor initiatives helps meet country needs while reducing duplication.

Partnerships — AusAID works closely with other Australian Government departments and agencies such as Agriculture, Fisheries and Forestry, Health and Ageing, and the Australian Animal Health Laboratory. These departments have close links with equivalent national agencies and other relevant organizations in the Asia-Pacific region.

Policy coherence — Our assistance for emerging infectious diseases and pandemic preparedness is consistent with the Australian Government's broader foreign and domestic policy approaches and commitments. We engage in international and regional forums on these issues, including through the International Partnership on Avian and Pandemic Influenza and UN agencies.

Regional responses

Australian assistance is delivered through regional and single country programmes. We fund and support several major multilateral institutions such as the World Bank, the World Health Organization (WHO), the United Nations Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE). By funding the placement of epidemiologists into WHO country offices we help national health authorities to build up skills to detect and respond to human communicable diseases. Our support for the OIE helps government veterinary services in the region to meet international standards.

Population growth, climate change and consequent ecosystem changes contribute to the emergence of new diseases such as Severe Acute Respiratory Syndrome (SARS) and new strains of avian influenza. We need to improve our understanding of the drivers of these diseases and to develop effective ways of dealing with them. AusAID and Canada's International Development Research Centre are therefore developing a joint program to support research into emerging infectious diseases in the Asia Pacific region.

Australia also works with regional organizations such as APEC, the Association of South East Asian Nations (ASEAN) and ASEAN +3 on joint cooperation for disease control and planning. This includes simulation exercises and small-scale regional capacity building activities that provide opportunities to share experiences and lessons.

The Pacific region has particular challenges relating to distance and small land size. The Pacific Regional Influenza Pandemic Preparedness Project is implemented by the Secretariat of the Pacific Community and WHO, and supported by AusAID and New Zealand Aid.

Image: CARE Laos

Village-level training on avian influenza in Vientiane, Lao PDR

This is building the capacity of Pacific island states to deal with the potential threat of an influenza pandemic and other emerging diseases in line with regional and international guidelines.

Bilateral programmes

The largest bilateral programme on emerging infectious diseases funded through Australian aid is in Indonesia. We also assist Papua New Guinea with surveillance, reporting and rapid response, and East Timor with bio-security strengthening. In the Philippines we are helping build government health networks while in Burma we are supporting WHO and FAO programs to combat avian influenza. We have a strong presence in other countries of the Mekong as well.

Indonesia

Australia was one of the first countries to respond to Indonesia's avian influenza challenge, committing over AU$30 million in three phases since early 2004. The first phase provided emergency funds to WHO to assist in detecting and managing human cases and reducing the risk of a pandemic. By 2005 it was apparent that the disease had become entrenched in poultry, and further funding was provided to assist in diagnosing the virus and preventing and controlling the disease in birds. The third phase began in 2007 and will finish in 2010. This phase continues earlier activities, with additional funding for a broader Animal Health Support project for South and West Sulawesi. Our support targets three priority areas: coordination at the national level; prevention and control of the epidemic in animals; and surveillance, investigation and management of the disease in humans.

AusAID funding enables Australia's national science agency, the CSIRO, to employ two veterinary epidemiologists within the FAO programme to help expand the country's Participatory Disease Surveillance and Response Program to South and West Sulawesi. One veterinarian, Emma Watkins, is based in the South Sulawesi port city of Makassar which serves the whole of eastern Indonesia. "Large numbers of chickens or chicken products sent to Maluku or Papua or other parts of Sulawesi come through Makassar," says Watkins. "It is also a big centre for commercial chicken production." Watkins helps to train veterinary officers and animal health staff to help villagers identify and report diseases in poultry. "Many chickens here die from diseases other than avian influenza and the deaths are not reported. Our aim is to make sure that all diseases are reported and the information sent to Jakarta to give officials a national picture of what is happening."

The animal health workers make routine visits to villages where, through village heads or groups such as women's organizations, they work with local people to control and prevent the spread of avian influenza.

Image: Garry Smythe/WHO

Epidemiologist Gina Samaan monitoring poultry in East Java, Indonesia

However, as Watkins acknowledges, there are no short-term fixes. "We could simply go to villages and tell people that viruses spread in particular ways. But people often have their own ideas about how diseases spread. Long-term change is likely to be more effective if communities find their own solutions to the problem. Many people here own chickens — they get their protein and make extra cash from them — so if they can stop their poultry from becoming sick they stand to gain a lot."

AusAID funding is also at work in Indonesia helping WHO and the Indonesian Ministry of Health (MOH) to track and monitor trends of human cases of avian influenza. WHO field epidemiologist Gina Samaan accompanies the MOH from the most densely populated centres to remote locations around the country to investigate cases. She and the MOH team establish the circumstances that led to an infection and try to determine the cause. "We try to find out whether human infection was caused by a sick bird, a dead chicken or even possibly fertiliser," says Samaan. "We also want to know whether a death has been caused by late access to treatment and whether the virus has acquired the ability to transmit between humans. Unfortunately there is a stigma attached to having avian influenza in the same way there was with HIV/Aids in the 1980s, which means people can be reluctant to report an illness or seek help."

Samaan and the MOH team feed their findings into a national tracking system to help build an overall picture of trends and clusters and to see under what circumstances the virus passes from human to human. "At present infections are directly from infected birds to humans," says Samaan. "The MOH tries to make sure that family members living in close proximity to human cases remain healthy, since they are the ones with closest contact to a case and they may share a common genetic susceptibility to the virus."

The ability to conduct investigations will be stronger now that the Field Epidemiology Training Program is being revitalized. A group of 20 students has been selected to do Master's degrees by fieldwork in Applied Epidemiology. They will be trained to conduct independent investigations of avian influenza and other outbreaks of emerging diseases to an expert level.

The Mekong

The countries of the Mekong region remain high-risk areas for avian influenza outbreaks. The human, technical and health system capacities of these countries to address disease outbreaks, particularly at the village and district levels, are weak. The shared porous borders allow unmonitored movement of people and animals, which increases the risk of an avian influenza pandemic.

AusAID funds the non-government organization CARE Australia to establish a community-based Avian Influenza Risk Reduction Program in high-risk communities and districts across Lao PDR, Myanmar, Vietnam and Cambodia. The programme has piloted approaches to teach people to recognize, report, control and prevent the spread of emerging infectious diseases.

Image: Pham Thi Bich Nga

Children in Phu Luong Secondary School in Bac Ninh Province, Vietnam take part in a hand-washing competition. The child that properly washes its hands to effectively kill bird flu virus is the winner

In Cambodia, CARE organized Village Surveillance Teams (VST) — composed of the village chief, village health worker and village animal worker — to serve as the focal point for prevention, surveillance, control and reporting of avian influenza at the village level. The VST teaches local people how to identify and report avian influenza and encourages preventative practices such as hand-washing and proper food preparation.

Most households in the villages targeted by CARE have less than ten head of poultry and these roam freely in their surroundings. The VSTs have set up demonstration farms to promote bio-secure poultry raising practices such as proper pen size and distance from a house, segregation of new and sick poultry, vaccination, pen hygiene and proper waste disposal. These demonstration farms encourage the use of local materials such as bamboo and palm for pen construction, and provide technology for growing alternative poultry feed such as earthworms or water spinach. The demonstration farms show that poultry raised under bio-security practices are less at risk of diseases and have better weight upon maturity. If sold, these poultry command a higher price, which means more income for a family. Avian influenza coordinator Jacquelyn Pinat says the VSTs are key to prevention of the disease at the community level as they not only promote but also practice proper poultry-raising and personal preventative habits.

In Vietnam, CARE complements the national Government's general awareness programmes on avian influenza by targeting key behaviours and related messages to particular audiences to encourage behaviour change. CARE runs discussion groups with backyard farmers, poultry sellers and restaurant staff on bio-security and bio-safety practices. People are encouraged to use protective equipment such as gloves and masks when handling poultry or disinfecting cages, to wash clothes and motorbikes after transporting chickens to markets, and to use separate cutting boards for poultry in restaurants.

Theatre plays, games and poster competitions are used to teach children the importance of hand-washing and better hygiene practices. Avian influenza coordinator Lieve Sabbe says every effort is made to reach people in villages: "At the provincial level we work on a strategy, selecting messages based on the habits and cultures of a village. Then we move to the district level and identify how we can best work with target groups to give people information on avian influenza risks in poultry and humans. A communication plan for a village is developed over six weeks. People are interested, but it's hard when they have strong cultural practices and it takes time to change people's behaviour with things like hand-washing."

Conclusion

Australia's approach to emerging infectious diseases can be summed up by the old adage, 'better safe than sorry.' We know that, once unleashed, avian influenza has the potential to wreak havoc on the lives of individuals, families, communities and economies. A strong and determined emphasis on prevention and preparedness will help avoid outbreaks.

Thwarting the secondary enemy

Hassan Ahmad and Siti Sayadi, Mercy Relief, Singapore

The occurrence of natural disasters has risen distinctly over the last two decades. Hydrometeorological hazards such as floods and windstorms have contributed largely to the increase of rapid-onset natural hazards. The United Nations (UN) Under-Secretary General for Humanitarian Affairs characterized the high incidence of this type of disaster as a 'mega disaster' linked to climatic change.[1] Less predictable geological hazards such as earthquakes, volcanic eruptions and tsunamis have also seen an increase due to rapid urbanization, environmental degradation and weak governance. Such hazards are likely to have an even greater human cost.

The under-management of social issues like improper water use and sanitation, hygiene practices and limited healthcare awareness, mostly due to lack of funds, has led to a lack of knowledge and understanding of health issues such as diseases in both disaster-stricken and poverty-stricken areas.

Measures towards the prevention, mitigation and eradication of infectious diseases require a holistic approach in the following areas.

Risk of epidemics in disaster areas

In their manuscript *Epidemics after Natural Disasters*, Watson, Gayer and Connolly highlighted the issue of displacement as a primary concern that would lead to disease transmission.[2] They mentioned that "the risk for communicable disease transmission after disasters is associated primarily with the size and characteristics of

Image: Ernest Goh/ Mercy Relief

Evacuated survivors from Banda Aceh return home from non-affected towns like Medan because of unfamiliar conditions at the new locations. Such migration activities posed high risks of transmission of diseases

the population displaced, specifically the proximity of safe water and functioning latrines, the nutritional status of the displaced population, the level of immunity to vaccine-preventable diseases such as measles, and access to healthcare services." Mercy Relief's (MR) experiences in the aftermath of recent major disasters such as the tsunami in Aceh; the earthquake in Pakistan; and the war in Afghanistan support their assertion.

MR's modus operandi for acute emergency relief is to assess and evaluate firsthand the situation and basic needs for survival of the victims such as food, water and shelter in the affected areas. A team of medical personnel is usually included in the reconnaissance party to assess the medical and healthcare needs of the survivors, and at the same time provide support to local healthcare units in managing casualties. The objective of the subsequent medical relief missions is to attend to trauma cases — directly treating the patients or referring them to a more advanced institution.

Experiences and lessons drawn from various MR humanitarian relief missions have repeatedly brought to attention the compounded medical and social problems that could have been prevented if a proactive approach had been implemented to address the issues, both pre- and post-disaster.

Case Study I: Indian Ocean tsunami — Aceh, Indonesia, 2004

Tens of thousands of homes in Aceh were destroyed by the monstrous waves of the tsunami. The heavily crippled local government had to grapple with unprecedented displacement issues and burgeoning concern over the health conditions of the affected population. With hospitals and health institutions badly damaged or affected by the impact of the waves, major aid agencies faced the uphill tasks of obtaining relevant pre-disaster health data to determine the immunization status of the affected population.

MR deployed 17 medical teams to Meulaboh and Banda Aceh in the two months after the disaster. The local authorities there requested that MR send its medical teams to an isolated community of thousands of internally displaced persons (IDPs) at Secata camp in Mata-I, about 45 minutes away from the main town Banda Aceh.

While treating trauma cases directly resulting from the disaster, as well as diarrhoea due to contaminated food sources, a multitude of alarming discoveries surfaced in and around the overcrowded camps. Numerous pools of stagnant water left by the waves, coupled with the hot and dry weather, became convenient breeding grounds for mosquitoes and rodents. Mosquito nets distributed to the IDPs earlier were hardly effective when it came to overcoming the risk of vector-borne diseases. Fortunately, MR chanced upon a Korean non-governmental organization (NGO), which focuses

Image: Mercy Relief

Survivors welcoming food packs distributed during the emergency phase to address their most basic survival needs

Image: Mercy Relief

Aid agencies deploy liaison officers to allay anxieties by facilitating communications between evacuated patients and relatives on the ground

on fogging and spraying stagnant water to prevent mosquito breeding.

Another major issue was the improper use of clean water. Despite the availability of water purification units, the threat of water-borne diseases remained real. Upstream contamination of interconnected water sources was detected and the community in Secata continued their daily routine of using the spring water for bathing, washing and even consumption. Together with Oxfam, which was providing adequate water containers designated for different household purposes, MR conducted workshops to create awareness on proper and hygienic water use. To control the looming sanitation problems at the camps, Oxfam also set up cubicle toilets to prevent faecal contamination from the overflow of latrines. In Calang, east of Mata-I, a rapid health assessment conducted two weeks after the disaster found that all survivors continued to drink from unprotected wells, and at that time, 85 per cent reported having diarrhoea.

Given the crowded living conditions, there was also an apparent need for measles vaccination. While a higher immunization coverage level was needed to prevent any outbreak, MR could only effectively conduct opportunistic vaccination for children who came voluntarily to the medical centre where the teams operated. Secata's remoteness posed logistical problems in maintaining the cold chain to transport vaccines, creating further setbacks to the medical personnel whose mobility was already limited by the lack of transportation that hindered them from reaching more victims and conducting a mass-scale outreach programme. The World Health Organization (WHO) reported that clusters and sporadic cases of measles, including 35 reported cases in North Aceh district, were common despite mass vaccination campaigns conducted elsewhere by other agencies.

During MR's two-month operation at Mata-I it was also observed that many of the IDPs had low immunity levels, as they were only eating plain rice. MR therefore initiated a food distribution programme to boost their nutrition intake.

Case Study II: South Asian Earthquake — Muzaffarabad, Pakistan, 2005

Mountainous terrains, limited accessibility and severe climate posed early challenges to MR's initial team, which went to Abbotabad and subsequently settled at the UN base camp in Muzaffarabad. In an effort to extend medical aid there, MR partnered with Pakistan's largest medical NGO, the Pakistan Islamic Medical Association (PIMA). Complementing each other's strengths, the collaboration involved working together in the organization and set-up of a field hospital at Neelum Valley. Operations at the field hospital were stretched to capacity as the medical personnel had to attend to inpatients and outpatients, many of whom

Image: Terence Teo/ Mercy Relief

The field hospital in Muzaffarabad was overcrowded with patients and visitors, which meant medical personnel had to be vigilant in identifying and isolating communicable disease cases to prevent any spread within the ward

suffered injuries from impact and experienced some degree of post-traumatic stress disorder. There was also an influx of diarrhoea cases suffered by the IDPs from nearby camps. Before adequate water and sanitation facilities were provided at the IDP camps, an outbreak involving more than 750 cases of acute watery diarrhoea occurred in the unplanned, poorly equipped camp of 1,800 persons.

Despite the modest infrastructure MR operated in, the field hospital was well set up with an ambulatory consultation area, an operation theatre and a fully stocked pharmacy. A systematic registration and triage system was kept to record patients' data. It ended up becoming the referral hospital for WHO and the Pakistani Army, bringing in patients who had been evacuated from the surrounding mountain villages. In many of these referral cases, doctors were greeted with cultural revelations on the affected community's traditional injury management practices. In her report, *The Lure of Pakistan: A Humanitarian Relief Experience in Muzaffarabad*, Mercy Relief's team leader Dr Fatimah Lateef documented the ingenious way these patients coped with their injuries.[3] The Kashmiris typically "covered their wounds with turmeric powder, a spice believed to have antiseptic properties. Some also used locks of their own cut hairs to pad their fractured limbs, before bandaging with scarves or towels." For such occurrences where difficulties of immediate access to health facilities and delayed presentation of acute injuries occurred, the risk of wound infection and tetanus cannot be overly emphasized.

It was repeatedly documented in WHO's *Weekly Morbidity and Mortality Report* during the emergency period that illnesses and deaths from tetanus had occured due to contaminated wounds, partly due to the low vaccination coverage among the affected population.[4] As supplies of vaccines were limited due to logistical constraints during the time of MR's operations there, MR only managed to administer the first of three doses needed for the treatment of tetanus. Under-treatment of tetanus had contributed to the controversies surrounding the efficacy of vaccination efforts during the acute emergency period. Fortunately, PIMA diligently continued administering the remaining doses to the patients. The medical personnel also had to shoulder the task of educating affected communities on the functions and benefits of vaccination.

In the management of severely injured patients, medical personnel struggled with decisions to evacuate or isolate infected victims as this effort risked further trauma to the victims and their dependents. In cases where mothers were infected with tetanus and needed to be quarantined, it proved to be a problematic arrangement for the patients and their children, who required their mothers' continual presence and attention.

Image: Tay Mia Hiang/ Mercy Relief

In Afghanistan Mercy Relief's medical personnel mass-wash children with antiseptic soaps as part of its personal hygiene programme

Medical personnel were also faced with a space dilemma. The need to quarantine patients with infectious diseases at the field hospital required additional space in an already congested setting, which may otherwise have been used to cater for additional beds for patients with other conditions.

Case Study III: Armed Conflict — Afghanistan, 2002

MR worked alongside several other foreign NGOs at a medical centre in Spin Boldak, South Afghanistan. The main objective was to treat patients for common ailments and wounds. However, relief agencies seeking to extend medical aid in Afghanistan also had to combat tuberculosis (TB), which was already an endemic disease that pervaded in the war-torn country before the peak of its devastation.

There were many challenges in controlling the spread of TB and its subsequent treatment, which takes around six to nine months. If treatment falls short of the standard protocol, there is a risk of developing resistant strains of the bacteria. Thus, there is the continued risk of TB becoming a potential pandemic caused by bacteria. Apart from the mandatory three-weeks quarantine period imposed on the patient, there is the problem of providing the complete course of three drugs needed to treat the disease. If treatment is not done properly, patients may develop resistance and without proper X-ray facilities, the doctors can only clinically diagnose patients. Given the lack of resources, the doctors faced the dilemma of whether or not to treat the patients. Patients need to be educated extensively on the recovery process. While they may feel better after two weeks, they still need to be on medication for an extended period of three to four months under direct observation. Treatment of TB is a tedious process; therefore prevention of an outbreak would save valuable resources.

Working with the local government health office, MR embarked on a health education programme by first targeting children, primarily infants — the most vulnerable group to infectious diseases. Medical researchers have typically acknowledged the hypothesis that infants who are not breastfed are more vulnerable to infection and diarrhoea. In order to build up the infants' immunity levels, MR executed the programme with a conscientious aim to create a conducive and sustainable environment that encourages frequent breastfeeding for children.

Driven by the misconception that milk powder has superior nutritional value to breast milk, Afghani mothers became persistent in asking for milk powder. This had a reverse effect on relief agencies' efforts to

increase milk powder supplies for emergency situations to avoid malnutrition in affected children. To dispel the misconception, health talks were conducted to educate the mothers on the benefits of breast milk. The programme was expanded to promote appropriate child feeding and caring practices, including diversifying diets and improving hygiene, as even with adequate nutrition, poor hygiene could still aggravate the spread of diarrhoeal diseases. In response to this MR conducted a bathing exercise to educate parents on the need to keep their children safe from diseases.

Lessons learned

There is a need to establish cooperative networks with partner agencies and local authorities — No single agency can be fully self-sufficient in its operations and work independently from other NGOs. NGOs must be open to collaborations with more experienced or bigger partners to tap into their resources, network and expertize to supplement their deficiencies. For example, in order to provide efficient and effective medical aid, relief agencies must be well equipped in other resource areas like logistics, manpower and telecommunication amenities. These resources facilitate proper planning and coordination in the midst of operational chaos. The goodwill established with trusted networks during peacetime will pave the way for successful cooperation when disasters occur.

There is a need for a holistic approach — Basic needs for survival required and expected by the affected communities are interconnected. Effective aid cannot be extended in a piecemeal manner.

Local cultural sensitivities need to be understood — In making recommendations for the prevention or management of diseases, relief workers need to be sensitive to customary practices and social beliefs that may create psychological barriers to the local community's acceptance of proposed treatments. Within a relief team, able and knowledgeable leaders should be appointed in the field to take charge of operations and be accountable for decisions.

Operations in ground situations need to be adaptable — Relief workers must be adoptable and adaptable to ground situations. Medical aid workers cannot expect to duplicate the same working conditions that exist in an urban peacetime setting or impose their own standard practices on their local partners and co-workers.

MR believes that healthcare is but one of the five key components for effective and sustainable development in disaster-stricken and impoverished rural communities, the other four being shelter; water and sanitation; education; and livelihood opportunities. The five components are intimately connected, hence the need to address them in a holistic fashion. Immediate and tangible benefits appeal more to these communities.

Immediate subjective wants versus gradual objective needs

Having worked in 19 countries over the last six years in disaster-stricken and impoverished rural areas, the common thread that runs through these communities is that the targeted communities' chief motivation stems out of immediate subjective simple personal wants, which prevail over gradual objective comprehensive communal needs.

Livelihood opportunities and their sustainability are paramount to any household. Water is quintessential to the immediate survival and sustainable development to these affected and disadvantaged communities. A development project, which provides immediate and sustainable sources of food and income — for example potable water and water for farming — is virtually certain of winning over the wills and minds of the targeted communities.

Macro issues such as the threat and spread of avian flu and HIV, or environmental degradation, are least proximate to these communities in terms of consciousness and conscience.

Parallel to developed communities, people become interested in insurance only after they have reached a certain level of comfortable income and lifestyle. This psychological block is motivated by the limited social bandwidth and the anxiety of immediate personal survival. Such phenomena accurately explain the rural or affected communities' disinterest towards immunization. For disaster-stricken communities in rural areas, given the trauma and devastation around them, the survivors will not be motivated to adopt any revolutionary health procedures that would not compensate them for the loss of their families and properties.

In addition, culture and religion are known to influence the ways people define health, express pain, select treatment options and deal with grief. These characteristics of the affected communities represent yet another challenge to the international aid community. Relief workers cannot underestimate the influence such beliefs bring in shaping rural communities' understanding of medical treatment and the myths created surrounding the spread of modern medical theories.

Conclusion

Poverty increases vulnerability and, as such, immunization programmes should be implemented in impoverished and developing communities during peacetime. However, it must also be taken into consideration that efforts to eradicate an epidemic after a major disaster require extensive resources, thus causing significant financial strain on the affected country. To avoid this, a holistic preventive strategy to combat diseases needs to be implemented proactively before an epidemic occurs. In addition, the need for education to encourage practice cannot be overemphasized and this needs to be done during peacetime.

Essentially, any aid agency that wishes to embark on the formulation of a pandemic contingency plan must be able to appreciate the concerns, outlook and culture of the targeted communities. Only then can the communities be won over effectively.

A general increase in the number of large-scale natural disasters requires an international response — hence the need for an effective network of NGOs (of diverse capabilities) for better coordination, maximizing on each other's strengths and avoiding duplication of efforts. This would allow for greater efficiency in the allocation of resources and better services to the targeted communities. Regional capacities to respond to disasters should be developed and relevant institutional relationships strengthened. This would include existing regional organizations, the UN regional offices, and the national disaster management agencies and health agencies of countries prone to natural disasters.

European Medicines Agency: influenza pandemic preparedness

Ragini Shivji, Scientific Administrator and John Purves, Head of Sector, Quality of Medicines Sector; and Patrick Celis, Principal Scientific Administrator, Regulatory Affairs and Organizational Support Sector, European Medicines Agency (EMEA)

The European Medicines Agency (EMEA) is a decentralized body of the European Union (EU). Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. All medicinal products for human use derived from biotechnology and other high-tech processes, including advanced-therapy medicines and products for some clinical uses, must be approved via the centralized procedure. EMEA carries out significant work on human medicines, including dealing with applications for marketing authorizations for influenza vaccines.[1]

The EMEA is responsible for the scientific evaluation of applications for European marketing authorization for medicinal products (centralized procedure). Under the centralized procedure, companies submit a single marketing authorization (licence) application to the EMEA. The EMEA conducts a single evaluation and adopts a scientific opinion, recommending or refusing the granting of a centralized (or 'Community') marketing authorization to the European Commission. Once granted the marketing authorization is valid in all European Union and European Economic Area (EEA) states (Iceland, Liechtenstein and Norway).

The safety of medicines is monitored constantly by the agency through a pharmacovigilance network. EMEA takes appropriate actions if adverse drug reaction reports suggest changes to the benefit-risk balance of a medicinal product.

Six scientific committees, composed of members of all EU and EEA states, conduct the main scientific work of the agency. For vaccines authorization, the main committees are the Committee for Medicinal Products for Human Use (CHMP), and the Paediatric Committee (PDCO). These committees are also supported by a number of working parties, such as the Vaccine Working Party (VWP).

The agency brings together the scientific resources of the EU medicines national competent authorities (NCAs) in 30 EU and EEA states in a network of European experts. It contributes to the EU's international activities through its work with the European Pharmacopoeia, the World Health Organization, US Food and Drug Administration and the ICH trilateral (EU, Japan and US) conferences on harmonization, involving other international organizations.

As part of its remit, the agency has been undertaking, for several years, work in the area of influenza pandemic preparedness. There follows some background regarding the influenza viruses causing disease and an overview of the history and current status of EMEA pandemic preparedness activities.

Influenza viruses and influenza pandemic

Influenza viruses that cause human disease are divided into two groups: A and B. Influenza A has two subtypes which are important for humans: A(H3N2) and A(H1N1), of which the former is currently associated with most deaths. Influenza viruses are defined by two different protein components, known as antigens, on the surface of the virus. They are spike-like features called haemagglutinin (H) and neuraminidase (N) components.

The genetic make-up of influenza viruses allows frequent minor genetic changes, known as antigenic drift, and these changes require annual reformulation of influenza vaccines. Three times in the last century, the influenza A viruses have undergone major genetic changes mainly in their H-component, resulting in global pandemics and large tolls in terms of both disease and deaths. The most infamous pandemic was 'Spanish flu', which affected large parts of the world population and is thought to have killed at least 40 million people in 1918-1919.

Most recently, limited outbreaks of a new influenza subtype A (H5N1) directly transmitted from birds to humans have occurred in Hong Kong Special Administrative Region of China in 1997 and 2003. Although H5N1 is presently the virus of greatest concern to become a pandemic influenza virus, other avian influenza viruses known to infect humans could also cause a pandemic.[2]

Early EU/EMEA pandemic preparedness activities

WHO has been leading pandemic preparedness activities for a number of years. However, in 2001 the Health and Consumers Directorate General of the European Commission (DG SANCO, Health Threat Unit (HTU)) initiated the development of pandemic preparedness plans in all EU member states that had not already prepared pandemic plans.[3] This work has continued in recent years, also in association with the European Centre for Disease Prevention and Control (ECDC). All EU member states now have a national influenza pandemic preparedness plan.

During this initial work into pandemic preparedness, to which EMEA contributed, it was recognized that the

Image: EMEA

EMEA delivers guidance and stimulates debate with the vaccine industry

unique nature of a pandemic meant that novel mechanisms would need to be developed to deal with such a situation. One of the conclusions was that in the event of a pandemic, new regulatory approaches to facilitate the rapid manufacture, regulatory review, authorization and supply of pandemic vaccines would be required while maintaining high standards of quality, safety and efficacy.

For pandemic influenza vaccines, the vaccine strain can only be identified — and therefore vaccine may only be produced — after the onset of the pandemic. Vaccine development and authorization is a process that ordinarily takes many years. It should be noted that in the event of a pandemic, it is likely to be a minimum of three months before any vaccine is available to be used for the prevention of disease. Even when vaccine does become available, there will be several months before sufficient doses are available to immunize all citizens of the EU. During this period of time, it is likely that antivirals would be used.

'Mock-up' pandemic vaccines

To speed up the review of applications for marketing authorizations, EMEA developed the concept of a 'mock-up' pandemic influenza vaccine that mimics a future pandemic influenza vaccine in terms of its formulation, manufacturing and control methods. However, because the virus strain which might cause a pandemic is not known, the mock-up vaccine contains a novel strain with 'pandemic potential' — that is, a strain that has never previously circulated among humans, such as H5N1. Apart from the specific pandemic virus strain, which can only be identified after the onset of the pandemic, most other scientific and technical aspects of the vaccine dossier may be evaluated in advance of the pandemic, and clinical experience (immunogenicity and safety data from vaccine use in healthy volunteers) can be gained with such mock-up vaccines. In addition, the documentation submitted in the application contains a 'risk management plan' that describes how the safe use of the vaccine would be monitored during a pandemic.

This approach reduces the resource and time requirements from both the manufacturer and regulatory authorities during the emergency pandemic period, which could impact on the provision of a safe and efficacious vaccine of good quality, in advance of an emergency situation. Following the onset of a pandemic and identification of appropriate pandemic strains, the mock-up vaccine dossier may be updated to include the required influenza strain by means of a variation to include this strain. The decision on who should receive the vaccine, and when it should be given, will be made by the governments in each EU member state.

Image: EMEA

EMEA is a decentralized body of the EU

The guidance and procedures for the generation of mock-up vaccines was developed at EMEA in 2003-2004. The principles incorporated in these guidelines are also widely accepted by the international regulatory community such as the WHO and non-European authorities such as Japan and Australia. These guidelines define scientific 'dossier' requirements and procedural steps for such applications via the centralized procedure.

The European vaccine manufacturers (EVM), and individual influenza vaccine manufacturers were involved in the development of these guidelines and EMEA has developed its own Pandemic Influenza Crisis Plan. In this context, EMEA has well-established links with the influenza vaccine manufacturers — Joint-EMEA Industry Task Force (JEIF) — and has initiated regular meetings to facilitate preparedness. This has stimulated debate and allowed industry, regulators and experts to discuss a variety of topics of importance for the development of both pandemic and pre-pandemic vaccines.

In 2007 the first mock-up vaccine, Daronrix®, was authorized. Since then, three further mock up vaccines have been authorized: Focetria®, Pandemrix® and Celvapan. European Public Assessment Reports for all these can be found on the EMEA website.[4] Other manufacturers are developing mock-up vaccines, too.

EMEA Pandemic Influenza Crisis Management Plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals

The EMEA Pandemic Influenza Crisis Management Plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals (EMEA Pandemic Influenza Crisis Plan) outlines the management structures and detailed procedures that will support the various activities to be undertaken in the event of an influenza pandemic. This and other pandemic EMEA documents are published on the EMEA website.[5]

The primary objective of the plan is to define and implement the EMEA policy and, consequently, the strategy for the rapid and efficient handling of actions required by the EMEA Secretariat related to pandemic influenza vaccines and antivirals, in liaison with CHMP, competent authorities of the member states, the European Commission (DG SANCO and DG Enterprise), ECDC and the vaccine marketing authorization (licence) holders, or applicants. The plan is underpinned by a series of detailed work instructions and SOPs (see EMEA website[6]). Since an influenza pandemic would have far-reaching consequences to the work of EMEA, the agency has also developed its Pandemic Business Continuity Plan, including specific issues and precautions for staff during an influenza pandemic.

WHO would identify the start of the influenza pandemic. This information would be provided to the commission (DG SANCO), which would notify EMEA. A procedure has also been developed on surveillance and how the start of a pandemic would be recognized and communicated, such that the EMEA crisis management plan could be initiated, even when imminent WHO/DG SANCO announcement of pandemic activities is expected.

In these initial stages of a pandemic, antivirals would be the only treatment for the disease. With this in mind, on the request of the European Commission, in 2007 EMEA (CHMP) conducted and updated a review of quality, safety and efficacy aspects of antivirals, which can possibly be used in the case of a pandemic. Procedures are currently being developed on how to react to any safety signals arising from the use of non-centrally authorized antivirals or from the use of bulk active substance of centrally authorized antivirals. A strategy is under discussion for the use of antivirals during a pandemic, specifically regarding the collection and evaluation of safety data. This will allow authorities to react promptly to emerging safety signals during the pandemic should they arise.

Once the EMEA pandemic plan is initiated, marketing authorization holders would begin development work on the identified pandemic strain such that it could be included into the mock-up vaccine, to create a pandemic vaccine. As this was being done and the manufacture and control of the vaccine was being progressed, there would be active collaboration and discussions between EMEA and associated experts, and the vaccine manufacturers. This process would result in the 'rolling review', which has been introduced to further facilitate the development and availability of pandemic vaccines. This approach provides the opportunity for manufacturers to submit data as it becomes available, and obtain an EMEA regulatory view on an ongoing basis.

At the end of the rolling review procedure, the marketing authorization holder of a mock-up dossier vaccine would then formally apply for a variation (a change to the marketing authorization of the vaccine) by supplying full information to CHMP on the vaccine including the new pandemic influenza strain. This variation would be processed quickly — normally within a few days — as most of the data would be comparable to that generated for the strain, which was reviewed during the assessment of the mock-up vaccine and the new data reviewed during the rolling review. Once the variation had been approved by the European Commission and a commission decision given, the vaccine would be available for use.

In the event of a pandemic, the public will be aware of the situation in a similar timeframe to the commission, member states and the agency; thus, the handling of communications will become crucial especially when public confidence is at risk. An EMEA pandemic communications policy on this aspect is in place to deal with the matters within its remit, taking care of the interface and roles and responsibilities of other interested parties, including the commission, ECDC and member states.

Pre-pandemic vaccines

Further to the first authorizations of mock-up vaccines in 2007, it became clear that European public health authorities were considering alternative uses of these vaccines, such as for prime-boost strategies (for example, priming poultry workers) in the pre-pandemic phase. They also wanted to stockpile the mock-up vaccines for use when the pandemic is declared and before the actual pandemic vaccine becomes available. Given that the mock up vaccines were authorized with the condition that they would only be used following the introduction of the actual pandemic strain after pandemic onset, an alternative approach was required. To address this issue, in 2007 the guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier (that is, not mock-up vaccine) context ('pre-pandemic vaccines') was developed.

A pre-pandemic vaccine has subsequently been authorized by EMEA/European Commission. Since pre-pandemic vaccines can be used at any time after the marketing authorization has been granted, a more extensive clinical testing programme, including a larger safety database for all ages and risk categories, has to be established before licensing.

Future approaches for pandemic influenza vaccines

Seasonal influenza vaccines are composed of three circulating seasonal influenza strains (two A subtypes and one B strain). At present, mock-up vaccines only contain one influenza strain. Both seasonal and pandemic influenza vaccines contain inactivated influenza virus, which is grown and inactivated before being purified/processed to various extents depending upon the product. Traditional production methodologies have relied on the use of hens' eggs for manufacture, the availability of which, especially during a pandemic, is more difficult to assure. A few manufacturers do now have procedures in place to manufacture influenza vaccines using cell culture technology, which is more easily controlled.

Live attenuated influenza vaccines are composed of an attenuated (non-pathogenic) strain containing the antigen from the virulent disease causing strain (seasonal or pandemic circulating strain) which has been engineered to grow at lower temperatures, such as that of the human nose. This concept appears to have several advantages, not least the ease of administration (nasal spray) rather than injection. It is also easy to grow; although, it does still utilize hens' eggs. There are already seasonal live attenuated influenza vaccines authorised outside of the EU.

Other vaccines are also being developed, namely recombinant subunit influenza vaccines, containing the antigenic components (haemagluttinin or neuraminidase) of the seasonal/pandemic influenza strain, grown by recombinant DNA technology. DNA vaccines are also under development, whereby the H gene would be injected into humans who, using their own cellular machinery, produce H protein against which an immune response would be elicited. These technologies have potential advantages in eliminating the need for hens' eggs and markedly increasing production capacity.

Tetravalent vaccines are a combination of the three seasonal strains plus one strain with pandemic potential (such as H5N1). This approach might seem promising for allowing priming of a large part of the population.

Conclusions

EMEA has been actively delivering guidance and stimulating debate with the industry, resulting in marketing authorization applications for mock-up pandemic and pre-pandemic influenza vaccines. During this period there has been, and continues to be, good cooperation with European vaccine manufacturers. EMEA has also identified the need and put in place a system allowing the agency to undertake its role fully in the event of an influenza pandemic. To strengthen the plan, we have also looked at more general operational aspects in the form of business continuity planning and training, and organized appropriate meetings both internally and at the European level, to address these issues.

Finally, EMEA continues to work in close collaboration with the EU national competent authorities and other colleagues involved with pandemic preparedness (European Commission, ECDC, member states). EMEA also collaborates internationally in this area with WHO, US FDA, Health Canada).

The views expressed in this article are the personal views of the authors and may not be necessarily understood or quoted as being made on behalf of or reflecting the position of the EMEA or one of its committees or working parties.

Pandemic preparedness in South Eastern Europe

Michala Hegermann-Lindencrone, Maria Haralanova, Altin Malaj and Caroline Brown, WHO Regional Office for Europe and Silvia Bino, Institute of Public Health in Albania

The World Health Organization (WHO) Regional Office for Europe has held the secretariat function for the South Eastern European[1] (SEE) Health Network (HN) since 2001.

In 2002 a specific project on surveillance and control of communicable diseases was established, which includes strengthening of pandemic preparedness and response within the framework of the SEE HN. This work is supported by the Communicable Diseases unit (CDS) of the WHO Regional Office for Europe through the provision of technical support and guidance in SEE countries.

Strengthening pandemic preparedness in SEE

The majority of the national pandemic preparedness plans in SEE were drafted in 2005 under the project of strengthening surveillance and control of infectious diseases. It was also in this year that the WHO Regional Office for Europe, together with the European Commission (EC), organized the first joint workshop on pandemic preparedness for the (at that time) 52 Member States in the WHO European Region. Since then, an additional three joint workshops held by the WHO Regional Office for Europe the EC and the European Centre for Disease Prevention and Control (ECDC) on pandemic preparedness have taken place and representatives from all SEE countries have been attending. The areas being addressed at the workshops have changed as pandemic preparedness in the countries has developed.

Specific workshops in the framework of the surveillance and control of communicable diseases in SEE countries have also addressed pandemic influenza, beginning in 2006 at the fifth and sixth SEE HN regional workshops, 'Strengthening surveillance and control of communicable diseases in SEE', which were organized by SEE project and the WHO Regional Office for Europe in Sofia, Bulgaria and Belgrade, Serbia. The subject was on the agenda again in 2008 at the SEE HN's eighth regional workshop, 'Strengthening surveillance and control of communicable diseases in SEE', where pandemic preparedness was the focus. This workshop was organized jointly by the WHO Regional Office for Europe, ECDC and SEE HN.

In the period between the workshops, all countries in the SEE region worked to strengthen their preparedness for the next influenza pandemic. In 2008, within the framework of the SEE HN project addressing pandemic preparedness, the WHO Regional Office for Europe with participation of SEE regional experts carried out assessment visits to all countries within the region to evaluate their level of preparedness, identify how to help them further improve and to provide technical input on areas of pandemic preparedness identified by the country. Assessment visits to the candidate countries in the EU were carried out jointly with the ECDC, while the two EU countries in the SEE region were visited and assessed in 2007 by ECDC, the WHO Regional Office for Europe and the EC.

Image: Silvia Bino

Assessment mission to Serbia

Pandemic preparedness assessment visits in SEE

The country visits followed a methodology applied in EU Member States in 2006-7, which was developed by the WHO Regional Office for Europe and ECDC and has resulted in the ECDC pandemic preparedness assessment tool.[2]

Each country was visited by an international assessment team, which also included an expert from a neighbouring SEE country to enhance interoperability in the region. Assessment team members were all experienced experts across the field of pandemic preparedness. The assessment of pandemic preparedness was made in association with a national focal point who was responsible for developing the agenda of the visit in collaboration with the external assessment team and who accompanied them during the mission. Within a week, meetings were held with all relevant stakeholders such as pandemic and general emergency planners at ministerial level, national institutes of public health, laboratories and hospitals. Also, planning at regional and local level was addressed through meetings with local governments and regional institutes of public health. Through these meetings, information was obtained about the pandemic preparedness situation in each country, and challenges and opportunities for further development and implementation of pandemic preparedness were discussed.

An essential part of the visits was to gather all stakeholders on the first day of the visit for a briefing about the assessment visit and the expected outcome, as well as the relevance of each stakeholder's involvement. Similarly, stakeholders were convened on the last day of the visit for a debriefing about the findings and recommendations made by the assessment team. This gave them an overview of the situation in other areas of pandemic preparedness, and provided an opportunity to discuss future work across agencies and administrative levels. After each visit, a report was prepared and submitted to the ministry of health in the assessed country, which contained recommendations about future work on pandemic preparedness. A SEE status report will be published based on observations made during the pandemic preparedness assessment visits to the countries involved.

Pandemic preparedness was the main focus of the assessment visits, but seasonal and avian influenza was also addressed. The main areas of pandemic preparedness addressed during country visits were planning and coordination; communication; situation monitoring and assessment; health system preparedness; pharmaceutical and non-pharmaceutical interventions; general society preparedness; local level preparedness planning; interoperability; and pandemic exercises.

Current status of pandemic preparedness in SEE

The current status of preparedness in pandemic planning in the SEE region has been identified as far as a week's worth of assessment in each country visited can achieve this. The following status of pandemic preparedness is presented as a general description of main observations made during the country assessment visits.

Seasonal influenza — in general, the seasonal influenza vaccination coverage is low in SEE countries, some of the reasons being the apparent lack of technical and financial support for national vaccination programmes and insufficient campaigning. Seasonal influenza surveillance takes place in all countries, although in some clinical data reporting is not supported by laboratory testing. Five out of nine countries have WHO-recognized national influenza centres (NIC) and report to the European influenza surveillance platform (EISS) as well as to the WHO Global Influenza Surveillance Network (GISN). The remaining four countries are in the process of establishing laboratory capacity as well as weekly reporting to the EISS platform. It has been agreed that a regional centre for influenza surveillance will be established in the NIC in Bucharest, Romania.

Pandemic planning and coordination — all countries in the SEE region have pandemic preparedness plans, most

Image: Nicholas Phin

The pandemic preparedness team in the former Yugoslav Republic of Macedonia

Image: André Jacobi

Pandemic preparedness is discussed during the visit to Bosnia and Herzegovina

of which were developed in 2005 and 2006, but have not been subjected to thorough revision since. These regional plans tend to focus on the response to avian influenza outbreaks rather than a full-blown pandemic. Despite this, avian influenza contingency planning is an essential part of pandemic planning, as it provides a good basis for developing national capacity and pandemic preparedness.

One of the main obstacles to improving pandemic preparedness is a general lack of resources dedicated to pandemic preparedness planning. With other public health issues taking priority over planning for a pandemic, there is a lack of human as well as financial resources available to develop and implement pandemic preparedness plans, thus having a significant impact on the progress made. Furthermore, there is a need for better government understanding of the concept of pandemic preparedness (versus avian influenza preparedness) and awareness of the importance of pandemic preparedness planning. It was also observed in most countries that government endorsement is necessary from the highest level down to each municipality and hospital, to emphasize the need to start planning for a pandemic now.

With one or two exceptions, there are not yet operational pandemic preparedness plans in the SEE countries. Current plans are strategic documents containing broad statements of intent, not operational documents ready for implementation. Most countries express the intention to update their pandemic plan with the publication of the new WHO guidance document in 2009. Revising the pandemic plan according to the new WHO guidance will include a shift in focus from plans focused exclusively on the health sector to an inclusion of other essential sectors in society, the so-called 'whole-of-society' approach. Some countries in the region have already started to consider how to expand pandemic preparedness to include non-health sectors, but at the moment there are no written plans for non-health sector preparedness in the SEE countries.

Communication — up until now, communication strategies in SEE countries have generally focused on seasonal and avian influenza. For avian influenza, training sessions have been held by the United Nations Childrens Fund in at least four countries. As well as this, many countries have distributed information material to the population, including specially developed material for children, the Roma population and occupationally exposed groups, on avian influenza and how to deal with issues such as dead poultry. Nearly all countries have developed sensible means of communicating with the general public on seasonal or avian influenza, which includes advertising at bus stands, distributing leaflets in public places or attaching them to newspapers. At least one country reported that since not all inhabitants have Internet access, it had to think of other means of communicating with the public. An actual pandemic communication strategy was not seen in any country. Some countries had mixed seasonal, avian and pandemic communication strategies, but a closer look at these strategies made it clear that work still needs to be done on a specific strategy for pandemic influenza. In two countries, communication material from other countries had been used and translated into the local language and, to some extent, adapted to the national culture. In at least three countries it was reported that the seasonal influenza strategy needed updating to address the need for increasing the uptake of seasonal influenza vaccinations, particularly in risk groups.

Monitoring and health system preparedness — all countries visited had outbreak investigation teams in place for outbreaks of avian influenza. At least five national influenza laboratories in the region have the capacity to detect H5 in clinical specimens and other laboratories are in the process of establishing the necessary capacity to do so.

SEE countries have invested in educating and informing healthcare workers about human cases of avian influenza, including training of healthcare workers, distribution of information leaflets and case management guidance. Most countries, however, have not yet addressed the education of healthcare workers and development of hospital preparedness plans for pandemic influenza, and in general the hospital staff/management that were visited were not aware of the need to develop such plans. In several countries, the reason for this was that it was unclear who should initiate the process. Hospital staff/management, for example, expected the initiative to come from regional level administration, while regional level administration expected hospital staff/management to be aware that they needed to develop a pandemic plan.

Additionally, lack of resources among hospital staff to develop and test hospital plans and to educate and train staff contributes to the low priority given to hospital preparedness so far in some countries. Until now, funding has mostly been made available for improving preparedness against outbreaks of avian influenza in humans and animals. A general trend in the SEE region is that preparedness in the primary healthcare services has not yet been addressed. As primary healthcare facilities may be the first point of contact with the healthcare system for patients during a pandemic, it is essential to address the handling of an excessive number of patients.

Pharmaceutical and non-pharmaceutical interventions — all countries in SEE have procured antivirals for outbreaks of human cases of avian influenza, but for the moment

Image: André Jacobi

A preparedness discussion in Bosnia and Herzegovina

Image: Andreas Gilsdorf

Bosnia and Herzegovina

countries have not stockpiled antivirals for use in a pandemic. The existing stockpiles are due to expire in the coming years and countries need to decide whether to renew the stockpiles with the manufacturer. Stockpiles of antibiotics for a few months' use exist in several SEE countries, which is considered an advantage for their pandemic preparedness.

Several SEE countries have previous experience with non-pharmaceutical interventions like school closure and banning mass gatherings during epidemics of seasonal influenza and have the legislation to support these interventions. However, these issues are still to be addressed in the context of a pandemic.

Pandemic preparedness outside the health sector is not yet apparent in SEE. According to the observations made during the country visits, initial thoughts have been made on this topic in a number of countries but planning as such, and involvement of essential sectors other than the health sector has not yet begun.

Pandemic planning at local and regional level — planning at local and regional level has predominantly concentrated on human cases of avian influenza in most countries. For many of the visited countries it was observed that there has been no message from higher administrative levels that pandemic planning should be initiated. Lack of sufficient resources was also described as one of the main reasons, but it was also observed that in many cases the regional or local plan for outbreak of avian influenza was interpreted or misunderstood to be a pandemic preparedness plan for the region or municipality. Nevertheless, the avian influenza contingency plans that have been developed at local and regional levels will provide an important basis for developing pandemic preparedness at subnational level due to the experience of going through a planning process and the overlap in some of the technical issues.

Interoperability — the network of strengthening surveillance and control of communicable diseases in SEE HN, which has existed since 2002 under the Stability Pact for South East Europe, has shown to be a good framework for collaboration between countries in the region. Until now, collaboration on pandemic preparedness has been mainly through the workshops organized under the SEE HN in collaboration with the WHO Regional Office for Europe and sharing of information among their public health institutes. Also, all countries agreed and signed a declaration for regional collaboration on implementation of the revised International Health Regulations, under which pandemic preparedness is an important component. A few countries reported that they have initiated some informal collaboration with a neighbouring country on some aspects of pandemic preparedness.

Pandemic preparedness exercises — none of the countries reported that they had undertaken pandemic preparedness simulation exercises. All countries had carried out exercises on outbreaks of avian influenza and have in this way strengthened their response to outbreaks significantly. In particular, six SEE countries were involved in an inter-country exercise in Albania in 2008, which tested their avian influenza contingency plans.

Main achievements since 2005

Observations from country assessment visits and the recent workshop on pandemic preparedness have made it clear that a great deal of work has been done and much progress has been made. A number of achievements have been realised including:

- Strategic national pandemic plans have been developed in all SEE countries
- There is better understanding and awareness of pandemic influenza and the requirements for preparedness
- Pandemic planning committees/working groups in all SEE countries have been established
- There is good collaboration between countries under the SEE HN framework

- Preparedness for outbreaks of avian influenza in humans is in place and information material has been distributed to health care facilities in many countries
- Initial preparations have been established on whole-of-society preparedness
- Unicef outbreak communication training has been undertaken in many of the SEE countries
- Avian influenza exercises have been undertaken in several countries and an inter-country exercise was undertaken in 2008. Experience from these exercises is useful for future pandemic preparedness exercises in and between countries
- All countries have been provided access to the EISS platform (www.eiss.org) to report seasonal influenza and currently five countries are reporting to the weekly bulletin.

Next steps

Although progress has been made on pandemic preparedness in SEE, there are still several areas of pandemic preparedness that have not yet been addressed and areas that need to be revised and strengthened.

Based on assessment visits to countries, the recent SEE workshop on pandemic preparedness and the new WHO guidance document, countries are encouraged to revise and update their plans and make sure that they are operational. By implementing country-specific recommendations and following the new WHO guidance, pandemic preparedness in SEE will grow stronger in the coming years. Stronger pandemic preparedness will have an impact on the countries' general emergency preparedness and defence against communicable diseases other than influenza, as well as contributing to the implementation of the International Health Regulations.

In addition to the overall recommendation to revise pandemic plans following country-specific recommendations and the new WHO guidance, the main areas of pandemic preparedness which countries are encouraged to address in the coming year are:

Preparedness beyond the health sector — countries are encouraged to initiate pandemic preparedness planning in sectors other than the health sector in order to ensure the continuity of essential functions in society during a pandemic. To initiate this process, it is vital that one ministry (typically the health ministry) takes the lead in informing other ministries about the importance and relevance of their involvement in pandemic preparedness planning. This topic will be addressed in the new WHO guidance on pandemic preparedness.

Planning at regional and local level — planning is not simply a matter of having a good national preparedness plan. It is essential to build capacity at lower administrative levels and to involve all levels in the planning process. Municipalities will need to develop pandemic plans and hospitals, power plants and water and food suppliers will need to develop business continuity plans to ensure that they can continue their essential functions throughout a pandemic. It is also important to coordinate pandemic preparedness with general emergency plans within a country.

Strengthening interoperability in SEE — countries are encouraged to collaborate on pandemic preparedness planning and through joint planning efforts, create a strong regional preparedness. Countries are also recommended to review pandemic plans of neighbouring countries and to learn from each other. Interoperability was addressed during the assessment visits as well as during the recent SEE workshop and, as a result, a SEE working group on regional interoperability in pandemic preparedness will be created.

Exercises — pandemic plans need to be tested in exercises, to ascertain that they are sufficient and realistic. This is an important component of preparedness planning and needs to be done at a national as well as a local level. Testing plans is a useful way to identify gaps and to harmonize plans with existing outbreak response or emergency preparedness plans. Plans should be updated according to lessons learned during the exercise. In addition to in-country exercises, international exercises are also considered beneficial, and could be considered for SEE when all countries have well established national pandemic plans.

The SEE HN

The SEE countries have experienced drastic changes in the past 20 years. War, and economic and political tumult led to periods of civil unrest, political crises and in many areas a cessation of community services. This has led to a number of difficulties including adverse impacts on health care, which threatened their populations in many ways.

In 2001 the SEE HN was established and a commitment was made by the signatories of the Dubrovnik Pledge to improve health in the region. SEE ministers of health agreed to work together and implement nine regional public health projects (mental health, communicable disease surveillance, food safety and nutrition, blood and blood components safety, tobacco control, maternal and neonatal health, health information systems, medical emergency services, and public health services). The governments of Belgium, France, Greece, Slovenia, Sweden, Switzerland and the United Kingdom support the projects both technically and financially.

The SEE HN has become a political forum of regional cooperation in public health of the highest level. SEE countries will assume full ownership of this cooperation in 2009 by establishing a new SEE HN Secretariat and regional health development centres on the specific technical areas of cooperation as outlined by the Dubrovnik and Scopje pledges.

In 2002 the project of strengthening surveillance and control of communicable diseases was started and all countries are committed to collaborate and establish a network of experts. A number activities within the project such as training on applied epidemiology and surveillance, establishing and assessment of surveillance systems, seasonal influenza and the International Health Regulations took place throughout 2002-2008 and others are scheduled in 2009 and beyond.

Most of the activities related to pandemic preparedness are supported by the Belgian Government. The project management office is in Tirana, Albania. For further information please contact the SEE HN Secretariat. Contact information can be found on the WHO Regional Office for Europe website: www.euro.who.int/stabilitypact as well as http://cdsinssee.org.

Conclusion

To date, countries as well as external partners have focused their efforts on strengthening avian influenza contingency plans, which is a crucial step in enabling detection and, if possible, containing the spread of a new human influenza virus. Significant achievements have been made in this field and countries have developed their capacity to respond to outbreaks of avian influenza in animals as well as humans. It is now time for involved stakeholders, national as well as external, to focus more on strengthening preparedness against a pandemic.[3]

Hepatitis A virus: its vaccines and global epidemiology

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The seminal isolation and propagation of hepatitis A virus (HAV) in cell culture *in vitro* reported by P. Provost and M. Hilleman at Merck and Co. in 1979 invited the development of vaccines against HAV infection according to the paradigms applied successfully for the national and global control of poliovirus by formalin inactivated and live attenuated virus vaccines. The subsequent report of the exquisite immunogenicity of a single dose of formalin inactivated alum adsorbed vaccine reported by Merck and Co. in 1989 encouraged the notion that future HAV vaccines could be delivered conveniently as a simple one-dose prime and one-dose boost regimen. Indeed, the demonstration of protective efficacy of even a single priming dose in children in Monroe, New York, US supported the licensure of the formalin inactivated alum adsorbed VAQTA® in 1995 by Merck and Co. In parallel, industrial development at GlaxoSmithKline, Aventis Pasteur and Berna Biotech led to licensures in the US and Europe of HAVRIX®, Avaxim® and Epaxal® respectively.

The manufacture of the four licensed inactivated hepatitis A vaccines is in many ways similar. All four vaccines are prepared with HAV adapted to cell culture grown by serial propagation in the substrate and serum dependent primary human diploid fibroblast cell line MRC-5, and the HAV is purified to varying extents before inactivation by formalin. The general industrial manufacturing dependence on the MRC-5 cell substrate dictates the economic realities of inactivated HAV vaccine cost of goods, and will have significant implications for any eventual attempts at global control of HAV. Unlike the inactivated polio virus vaccines first developed by Jonas Salk and brought to large-scale commercial manufacturing consistency and practicality by Sanofi Aventis, VAQTA, HAVRIX and Avaxim are adjuvanted by adsorption to alum, whereas Epaxal is adjuvanted by association with virosomes, unilamellar liposomal structures with the hemagluttinin (HA) of influenza A Singapore virus embedded in PE.

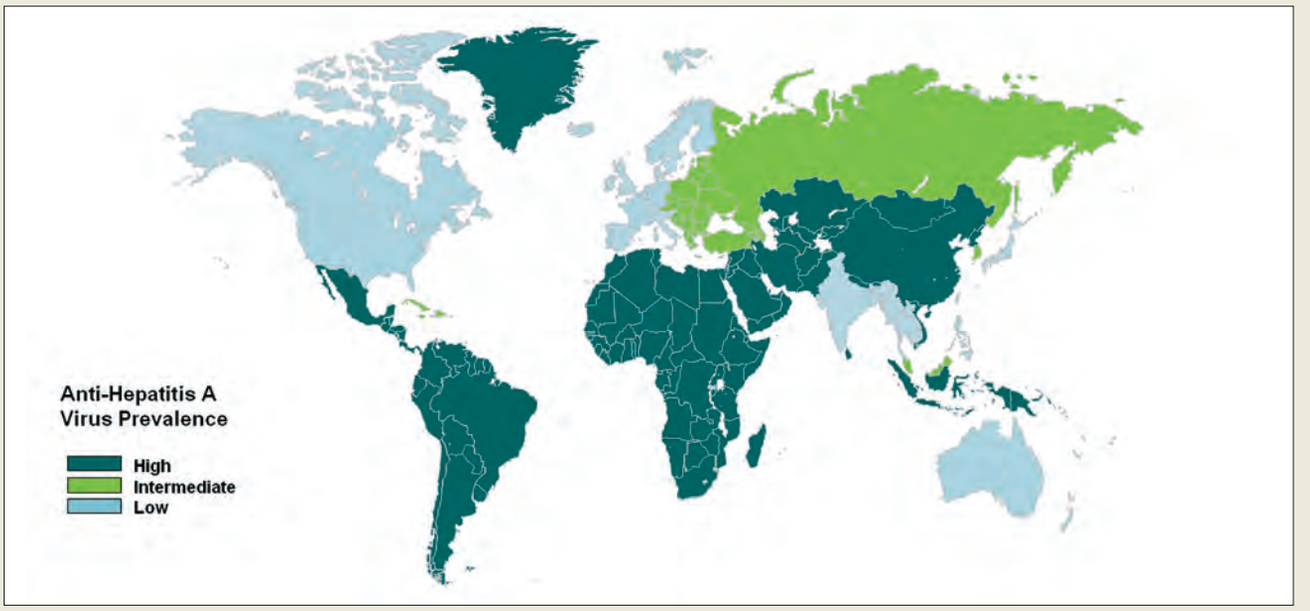
These vaccines have been demonstrated to be very safe, and in many ways similarly immune potent, inducing more than 85 per cent seroconversion of paediatric and adult recipients. However, studies suggest that the rapidity with which the virosomal Epaxal induces seroconversion makes it especially attractive for those travelling or deployed on especially short notice to regions where HAV remains endemic. These vaccines can be used essentially interchangeably for adults, priming with the vaccine product of one manufacturer and boosting with the vaccine product of a second. The interchangeability of paediatric dosing in the US is restricted to VAQTA and HAVRIX. Avaxim is yet to be licensed with a paediatric formulation.

At the time of writing, the use of HAV vaccines in a two-dose regimen has led to the accumulation of nearly 15 years worth of data on the long-term persistence of humoral immunity, demonstrating by direct assay a level of protective neutralizing antibodies, which extend over ten years and, from those titres, inferred levels of protection for nearly 20 years. These findings have prompted debate over the necessity of a boosting dose, a discussion which centres on the contribution of immunological memory to long-term protection. These long-term persistence data are of course valuable to discussions of the health economics of inactivated vaccine use in developed nations. Perhaps of even greater value to global control would be data on the protective efficacy of a single priming dose in paediatric recipients in an endemic setting. From that it might be reasoned that the priming dose would dispose the vaccinee to a vigorous response to wild type HAV infection conferring in the paradigm established for poliovirus, both an especially durable humoral and cell-mediated immunity with value to the vaccinee as well as community control of HAV.

In the US, the Advisory Committee on Immunization Practices (ACIP) recommends a universal childhood immunization with the standard course of a single priming dose followed by a boost dependent on vaccine at 6-18 month intervals. Epidemiological studies of the effects of these recommendations, both in community-based vaccination studies and in routine vaccination, find the incidences of HAV to be greatly reduced by these interventions, though those countries free of endemic disease continue to be liable to outbreak in seronegative populations. This is down to the importation of HAV by travellers or foodstuffs imported from countries where HAV is endemic. An outbreak in the US of food-borne HAV in November 2003 from green onions sourced in Mexico led to more than 600 cases, of which 125 were hospitalized with a case fatality rate of 0.5 per cent. These incidences can be expected to continue in the western hemisphere until the time that universal immunization is ultimately realized.

As expected, the inactivated HAV vaccines, since their licensure in the US and numerous other countries worldwide in 1995, have little altered global patterns of endemicity of HAV infections. In the western hemisphere only the US and Canada remain free of endemic disease, as do most countries in Western Europe and Australia. By contrast, HAV remains a globally distributed infectious disease pathogen with nearly four billion persons at risk worldwide resulting in nearly 1.5 million cases of clinical hepatitis annually. The transmission of HAV by the faecal

Anti-Hepatitis A virus prevalence



Global rates of hepatitis A antibody seroprevalence reflecting endemic distribution of hepatitis A virus

Source: Adapted from: CDC http://wwwn.cdc.gov/travel/yellowBookCh4-HepA.aspx

oral route ensures its endemicity in developing nations, imposing a serious burden on human health and economic development owing to the duration of the infection and its capacity for environmental spread. The distribution of HAV in China is particularly striking, where rates of infection exceed 90 per cent in those over 35 years of age. Uneven standards of public sanitation in China, as well as in other developing parts of the world, establish areas relatively free of HAV infection in childhood making possible outbreaks of enormous scale. Such an example of this occurred in Shanghai in early spring of 1988, when more than 300,000 cases of HAV disease were reported owing to the consumption of raw clams contaminated with sewage. Of the 47 fatalities recorded in this well studied epidemic, an elevated rate of mortality was observed in patients who were HBeAg positive, a serological indicator of ongoing disease. The Shanghai experience has not since been reported on a similar scale, but it serves as a lasting paradigm for the consequences of emerging economies and HAV epidemiology, as developing nations emerge with significant urban populations surrounded by rural endemic diseases.

The significant burden of HBV disease in China, estimated to exceed more than 30 million persons affected by chronic HBV disease as well as the burden of HCV infections and their special vulnerability to HAV infection, has imposed a particular sense of urgency in the country to control HAV disease. To this end, the findings of Mao Jiangsen and his colleagues at Zhejiang University and the biotechnology capability of Zheijiang Pukang Biotechnology Institute have been especially notable. Over a period of ten years or so, building on the precedent of P. Provost and M. Hilleman at Merck who in 1984 reported the attenuation of the HAV CR326F strain for replication in humans, they carried forward the isolation of the H2 strain from a Chinese clinical specimen, its attenuation by serial passage at reduced temperature in KMB17 human diploid fibroblasts and its development as a candidate live virus vaccine. The H2 vaccine is reported to be safe at doses of greater than 106 TCID50, promoting seroconversion to protective levels of humoral immunity within 21 days post-immunization, without liver enzyme elevations or other serious adverse events. The vaccine has been widely distributed in China since its licensure in 1995 and is held responsible for significant reductions in the rates of HAV disease.

Clearly the benefit/risk equations established for the H2 vaccine reflect the endemicity of the HAV disease and the real probabilities of infection of vaccine recipients in the absence of immune prophylaxis. The details of the deployment of this vaccine including those related to vaccine shedding, reversion of the attenuated phenotype, as well as details of the manufacturing and formulation of this vaccine at the scales required for significant impact on HAV endemicity in China, are not widely detailed in western scientific literature and would be a welcome addition to the vaccine bioprocess literature. The details would of course be additionally of interest, as other developing countries will need to structure and organize their own national containment programmes for HAV to confront evolving circumstances of endemicity. In concept the control of HAV, a picornavirus like polio with a faecal oral mode of transmission and no animal reservoir, should be vulnerable to the same strategies that have brought global poliovirus to bay using the Sabin live attenuated vaccines in the Global Polio Eradication Initiative. The extent to which the live attenuated H2 vaccine or similar products of biotechnology can be enlisted solely, without dependence on inactivated vaccine for final closure, will depend largely on the issue of reversion of the HAV attenuated phenotype and the degree of vaccine virus shedding noted above. In this regard it is of interest to note that Chinese science continues to publish on HAV vaccine development, especially on several of their own efforts to develop an inactivated HAV vaccine using Vero cell substrate, in an attempt to expand the biotechnology options for vaccine production.

Hepatitis B virus: its vaccines and global epidemiology

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For thousands of years hepatitis has been one of the most serious diseases to affect human beings. According to several reports epidemic jaundice, one of the representative symptoms of hepatitis B, was described as early as the fifth century BC by Hippocrates. Much scientific investigation throughout the ages has also focused on identifying the etiological agent of the disease. In 1965 Baruch Blumberg identified the Australian antigen, HBsAg (hepatitis B surface antigen) in the serum of patients suffering from hepatitis. Shortly after in 1970, Dane identified the complete hepatitis B virion (HBV) causing hepatitis B, thereafter known as the Dane particle. Saul Krugman subsequently clarified the epidemiology of hepatitis B and its prevention. In 1971 he conducted tests on humans — they and chimpanzees are the only species to host HBV — which involved giving them heat-inactivated crude HBV-infected serum. From the results it was proven that giving the boiled HBV-infected serum to humans was immunogenic and partially protective. Based on Krugman's experiments, Maurice R. Hilleman at Merck developed the first plasma-derived subunit vaccine against HBV infection in 1975.

Acute and chronic infections

HBV is a partially double-stranded, enveloped DNA virus belonging to the hepadnaviridae family that replicates in the liver. When humans are infected by HBV, it can result in either acute or chronic infection. Generally, in the case of acute infection, its clinical manifestations are highly age-dependent. Newborns commonly do not show any clinical symptoms, but adults are highly symptomatic. Occasionally, acute infection can lead to a fatal fulminant hepatitis in the proportion of one to two per cent. The risk of developing a chronic infection, defined as the presence of HBsAg in serum for over six months, is inversely age-dependent. Infants infected in the perinatal period have a 90 per cent chance of developing chronic infection, whereas older children and adults are at a much lower risk with just a six to ten per cent chance. It is reported that there are at least 200 million chronic carriers around the world, approximately 15 per cent of whom will develop chronic hepatitis and roughly 25 per cent of whom will die of either cirrhosis or hepatic cancer. Furthermore, chronic infection by HBV results in up to an 80 per cent chance of contracting hepatic cancer. Accordingly, HBV is one of the most serious viruses resulting in fatality and vaccination against it is particularly important.

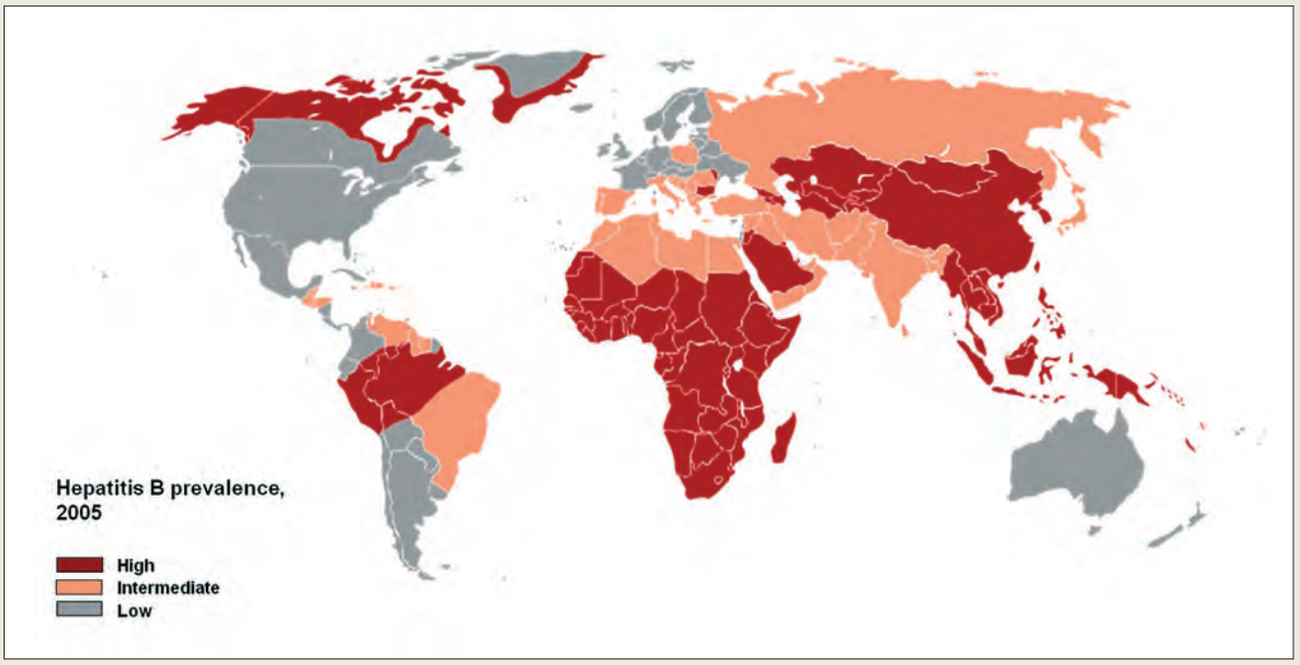
Importance of vaccination and development of recombinant subunit vaccines

During the neonatal period, vaccination against HBV with current plasma-derived or recombinant-derived HBsAg vaccines can protect at least 95 per cent of infants from HBV infection. Because of this ability, vaccination has been regarded as one of the best preventative methods against HBV infection.

It is estimated that there are approximately 100,000 new hepatitis B cases per year worldwide, and studies focusing on vaccine production technologies have to satisfy the demands of both developing and developed countries. Developed countries have been asking for advanced types of vaccines that provide greater safety, efficacy and convenience, yet many infections occur in developing countries where they face issues of low income, lack of medical infrastructure, and lack of cold chain facilities.

As indicated earlier, vaccination to prevent persons from being infected by HBV was initially conducted using a plasma-derived subunit vaccine developed with HBsAg particles derived from the plasma of chronic HBV carriers as an active pharmaceutical ingredient. However, the plasma-derived subunit vaccine had several drawbacks, including limitation of the blood supply, the risk of contamination with potential adventitious viruses, and a high vaccine price due to blood procurement. To overcome these drawbacks, a recombinant subunit vaccine using the S gene, which codes a small-sized HBsAg protein (S protein), was developed using S. cerevisiae in 1984. Later, in an attempt to significantly increase HBsAg productivity by circumvention of the yeast 'crab-tree' effect, commonly encountered in high cell density cultures of S. cerevisiae produced in fed-batch culture mode, host replacement with methylotrophic yeasts such as H. polymorpha and P. pastoris was applied to HepB vaccine production. A recombinant subunit vaccine based on M gene (preS2-S), which codes a middle-sized protein (M protein), was also developed using Chinese hamster ovary cells, and its protective efficacy is similar to that of the S protein based vaccine. Recombinant subunit HBV vaccines have many advantages in that they are independent of plasma procurement, their production cost is much lower, and their quality control is easier in terms of consistency when compared to plasma-derived vaccines containing a variety of HBsAg subtypes (primarily, adr, adw, ayr and ayw) and genotypes, as well as different sized HBsAg proteins (S, M and L protein) in the HBsAg particles. Due to these benefits, recombinant subunit vaccines with one subtype (primarily S protein) have become dominant in the market despite the fact that they have

Hepatitis B prevalence



Prevalence of chronic infection with hepatitis B virus

Source: Adapted from: CDC http://wwwn.cdc.gov/travel/yellowBookCh4-HepB.aspx

antigenic characteristics that may lead to Major Histocompatibility Complex (MHC) linked non-responsiveness in some individuals.

Development of novel HBV vaccines to combat non-responsiveness and increase convenience

In an attempt to overcome non-responsiveness towards the recombinant HBV subunit vaccine, a variety of adjuvants including unmethylated CpG motif, adenovirus and vaccinia virus vectors, and virosomal technology are being explored. One of the most promising approaches is the use of vaccines including an S protein-CpG motif conjugate capable of inducing a T helper cell-independent immune response against HBsAg, thereby bypassing class II MHC restriction. Indeed, during clinical trials this innovative recombinant subunit HBV vaccine showed a 100 per cent seroprotection rate even in seronegative seniors aged 40 to 70 years. These findings indicate that the CpG-conjugated HBV vaccine is effective in non-responders to alum-adjuvanted HepB vaccine and induces a better immune response in immunocompromised individuals. Moreover, development of efficient drug delivery systems such as sugarglass, skin patches that employ lymphotoxin beta, and modified dextran microparticles, may contribute to increased efficacy and improved quality of the HBsAg vaccine. Hence, it is believed that the introduction of the aforementioned newly-developed technologies to existing HBsAg vaccines not only increases efficacy but contributes to convenience and a decrease in the cost of goods, while enabling the production of HBsAg vaccines with improved safety and stability.

Supranational measures required for HBV prophylaxis in developing countries

Between 70 and 90 per cent of infants born from mothers with active chronic hepatitis B infection (positive for HBsAg and HBeAg) become infected by HBV, and roughly 90 per cent of these children will turn into chronic carriers. For those children born from mothers who are chronic carriers (positive HBsAg), approximately 20 per cent will become infected by HBV and roughly 90 per cent of them will become chronic HBV carriers. As approximately 25 per cent of chronic carriers generate serious diseases such as cirrhosis or hepatic cancer, vaccination of newborns to protect them from getting chronic HBV infection is of utmost importance.

The initiation of the Expanded Programme on Immunization by the World Health Organization (WHO) and the creation of the Global Alliance for Vaccines and Immunization (GAVI) — a grand coalition including WHO, UNICEF, PAHO, the Gates Foundation, Rockefeller Foundation, vaccine industries non-governmental organizations and many more — has helped in the battle against hepatitis B. Currently, in more than 100 countries, especially in highly endemic areas of Southeast Asia, China, the Pacific, the Middle East, Sub-Saharan Africa and India, children are vaccinated against hepatitis B, mostly using recombinant subunit HBV vaccine. The initiatives of the Developing Country Vaccine Industry in alliance with GAVI and its partners to provide a consistent and sustainable supply of affordable vaccines, recognizing the essential role of developing country vaccine producers, may contribute greatly to the control of the worldwide medical and economic burdens of HBV infection.

Combination of human monoclonal antibodies for post-exposure prophylaxis of rabies: leading the way in antiviral innovation

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The human immune system reacts when it encounters a virus with a polyclonal immunoglobulin response specific for that particular virus type. Most of these virus-specific antibodies are unable to keep the virus from infecting cells that carry the receptor for it, and are therefore able to replicate the virus. Some of these virus-specific antibodies coat the virus with a layer of antibodies. These cover the envelope of the virus and make it impossible for it to reach the cells in the human body that are able to multiply it. If such antibodies are effective, a limited and abortive infection occurs at the port of entry, but little or no virus production ensues. Such antibodies are present in a small but effective proportion of plasma in vaccinated individuals, and in individuals who cleared a particular infection.

In the early days of antiviral therapy, hyperimmune plasma preparations taken from vaccinated individuals or from people who cleared the infection were made and used to prevent and/or treat viral infections. Success with prevention of infection or disease was achieved for hepatitis A and B viruses, for RSV, for CMV, for VZV, measles, vaccinia and for rabies. Treatment success was obtained — albeit in some cases limited — for CMV, parvovirus, for enteroviruses and vaccinia. Most of these preparations were made from human plasma with the risk of transmission of viruses, like hepatitis B and C and HIV, that reside in blood. Experts uniformly promote this method, as long as the technology to isolate and produce monoclonal antibodies to be used to replace immunoglobulins comes into existence. Crucell's monoclonal mixture against rabies is the farthest ahead to reach this goal.

Post-exposure prophylaxis of human rabies

The original idea of Louis Pasteur was that following a bite by a rabid dog, fox or bat, vaccination could prevent the development of symptomatic rabies. In 1954 Marcel Baltazard, director of the Pasteur of Iran institute, published his findings of post-exposure prophylaxis exclusively using the rabies vaccine. Baltazard considered the results to be disastrous. Of the 186 individuals bitten in the head, 53 (28 per cent) developed rabies and died. From these data it may be assumed that rabies vaccination prevents about 50 per cent of rabies cases.

In 1954, Baltazard did a key experiment using a rabbit immunoglobulin preparation showing that the combination of antirabies hyperimmune serum with rabies vaccine was able to completely prevent rabies. Eighteen people were bitten in the head by a rabid wolf with proven rabies infection. Five received two inoculations of serum plus vaccine and all survived the attack; seven received one inoculation of serum and vaccine, and six of these survived; of the five individuals that only received vaccine, three succumbed to rabies. The one child whose scalp was bitten, and who received multiple local and systemic inoculations of serum plus vaccine, survived. Combined, these data underscored the importance of administering rabies immunoglobulin besides vaccine.

Karl Habel, working at the National Institutes of Health in the US, developed the first potency test for rabies vaccine and antibodies. Using the so-called Habel-test for potency, he showed convincingly in the 1960s that one could use a serum from a species that was identical to the challenged recipient or a serum from a non-matched species with the same effect. This test involved mice infected with the rabies virus. Later, a correlation of protection was established by the World Health Organization (WHO) using an in vitro test, the so-called modified rapid fluorescent focus inhibition neutralization test. This assay has allowed later studies to establish the protective dose of monoclonal antibodies.

The road to replacing immunoglobulin preparations by monoclonal antibody or combination of antibodies

Mouse monoclonal antibodies, as well as human monoclonal antibodies, have been shown to protect rodents from a lethal rabies virus challenge. One of the most potent of human antibodies neutralizing rabies was discovered and described by Bernhard Dietzschold of Thomas Jefferson University in Philadelphia. He subsequently included this in a cocktail of three antibodies, SOJA, SOJB and SO57. This cocktail protected mice effectively from a lethal dose of rabies virus. All three antibodies were subsequently licensed and entered the 2004-2005 rabies programme.

From the onset, criteria were established for a monoclonal antibody product; a single antibody was at no point considered because of the risk of escape from one antibody to another. After consulting the leading world experts on rabies it became clear that two antibodies should be included in an effective antibody mixture, which had to be of high quality. The inclusion criteria formulated were: the MoAbs should target distinct, non-overlapping epitopes; and preferably should not compete for binding to rabies

Rabies causes over 50,000 deaths each year in the endemic countries

Source: FX Meslin, WHO NECTM, Knobel and Tang et al EID, 2005; Zhang et al InfoRab 2005, APCRI data

Image: Embassy Czech Republic, Nairobi

Mt Kulal dogs, Kenya. Preventive vaccination against rabies. Despite efforts to vaccinate dogs against rabies, canine bites remain a major cause of rabies infection in high endemicity areas

virus glycoprotein. In addition, *in vitro* generated, antibody-resistant rabies virus variants selected using one antibody should be neutralized by the non-selecting other antibody in the cocktail and vice versa.

Subsequently, the variable heavy and light chain coding regions of the SOJA, SOJB and SO57 antibody genes were synthesized, introduced into a single human immunoglobulin G1 (IgG1) vector, and the IgG1 molecules in PER.C6 cells were expressed. This resulted in the antibodies CR57, CRJA and CRJB. Because CRJA had only borderline potency against rabies and CRJB competed for the same region on the rabies glycoprotein, only a single antibody was left for use in an effective anti-rabies cocktail: CR57. Next, the CR57 binding site as a linear epitope in antigenic site I was meticulously mapped and characterized, and a hunt ensued for a non-competing and complementary antibody. After selecting antibodies from the blood of a rabies-vaccinated individual by phase display, a complementary antibody (CR4098) was identified that recognized a distinct, non-overlapping epitope (antigenic site III) of conformational nature. On the one hand it shows a potency and breadth of protection similar to CR57; on the other hand it has the ability to neutralize 100 per cent of CR57 escape mutants. Reciprocally, CR57 neutralizes rabies virus mutants escaping CR4098 neutralization.

Sequence analysis indicated that only three out of 229 rabies isolates from different regions in the world had mutations in the CR57 epitope and five out of 123 isolates – all from central Africa – had mutations in the CR4098. No field isolate of rabies had both sets of mutations.

The making of the human monoclonal antibody mixture to replace HRIG

The human monoclonal antibody mixture differs in isotype and in antigenic recognition to hyperimmune anti-rabies immunoglobulin (HRIG), but is similar in potency and affinity. In collaboration with Charles Rupprecht of the Centers for Disease Control and Prevention (CDC) in the USA, the breadth of neutralization of the two individual antibodies as well as the mixture was assessed. The combination did neutralize all field isolates tested, and the few isolates that were not neutralized by one of the two anti-rabies antibodies in the mixture were always neutralized by the other.

Next, the CR57/CR4098 mAb cocktail and HRIG, the only available polyclonal human anti-rabies product, were compared head-to-head. In combination with the vaccine, the mAb cocktail protected Syrian hamsters against lethal rabies which they were exposed to 24 hours after being administered the vaccine and cocktail. The results were comparable with those obtained with HRIG and the mAb cocktail also did not interfere with the rabies vaccine differently to HRIG.

In September 2008 the first administration of the CR57/CR4098 mixture to humans (CL184) was reported. The studies included healthy adult subjects in the USA and India, and involved two-part testing. Rabies virus neutralizing activity was detectable from day one to day 21 after a single dose of CL184 20IU, the same dose as HRIG. All subjects had adequate protection levels against rabies when combined with the vaccine up to the end of evaluation, which was recorded at 42 days after the first injection of an antibody and vaccine.

The anti-rabies human monoclonal antibody mixture CL184 is on the way to presenting a replacement to old-fashioned immunoglobulin preparations, which are in short supply. Because supply constraints are removed by licensure and launch of the monoclonal mixture CL184, this product candidate has the potential to prevent most, if not all, of the current 55,000 deaths per year due to rabies in the world.

Responding to the spread of avian influenza H5N1: a wildlife conservation perspective

Rebecca Lee, Scientific Task Force on Avian Influenza & Wild Birds

Avian influenza is a highly contagious disease caused by influenza A viruses, affecting many species of birds. Avian influenza affecting poultry is classified into two recognized forms according to disease severity: low pathogenic avian influenza (LPAI) and highly pathogenic avian influenza (HPAI). LPAI viruses are generally of low virulence, while HPAI viruses are highly virulent in most poultry species, resulting in nearly 100 per cent mortality in infected domestic flocks.[1] The natural reservoir of LPAI viruses is in wild waterbirds — most commonly in ducks, geese, swans, waders/shorebirds and gulls — in which they cause few apparent clinical consequences.[2]

To date, influenza A viruses representing 16 haemagglutinin (HA) and nine neuraminidase subtypes have been described in wild birds and poultry throughout the world.[3] Viruses belonging to the antigenic subtypes H5 and H7, in contrast to viruses possessing other HA subtypes, may become highly pathogenic after having been transmitted in low pathogenic form from wild birds to poultry and subsequently circulating in poultry populations.[4]

Since it was first recognized in 1997, HPAI H5N1 has infected domestic and wild birds in more than 60 countries across Asia, Africa and Europe. Over 200 million domestic birds have died from disease or been slaughtered in attempts to control its spread. There have been serious human health consequences — by March 2009, the World Health Organization (WHO) had confirmed more than 400 human cases, over 60 per cent of these fatal — and there remains potential for the virus to adapt allowing for human-to-human transmission and the emergence of a human pandemic. In 2005 before the spread of the virus out of Asia, the Food and Agriculture Organization (FAO) of the United Nations estimated impacts on the economies of the worst affected countries in Southeast Asia of over US$10 billion.[5]

Prior to the emergence of the current Asian strain of HPAI H5N1, outbreaks of HPAI in wild birds were extremely rare. The spread of HPAI H5N1 from poultry into wild bird populations and the broad geographical scale and extent of the disease in wild birds is both extraordinary and unprecedented, and the conservation impacts of HPAI H5N1 have been significant. It is estimated that between five and ten per cent of the world population of Bar-headed Goose *Anser indicus* died at Lake Qinghai, China in April-May 2005. At least two globally threatened species have been affected: the Black-necked Crane *Grus nigricollis* in China and the Red-breasted Goose *Branta ruficollis* in Greece. However, the total number of wild birds affected has been small in contrast to the huge number of domestic birds affected, and many more wild birds die of more common avian diseases each year. Perhaps a greater threat than direct mortality are the indirect threats, including the development of public fears about waterbirds and misguided attempts to control the disease by disturbing or destroying wild birds and their habitats. Such responses are often encouraged by inflammatory and misleading messages in the media and the political need to show action is being taken.

This paper presents an overview of HPAI H5N1 and its impacts on wild birds, along with the international consensus on what should be done to reduce the spread of the virus, specifically where wild birds could be involved either as vectors or victims.

The emergence and spread of HPAI H5N1 via multiple vectors

The HPAI H5N1 virus almost certainly originated from the mutation of an LPAI virus on poultry farms in East Asia (a precursor to the virus was identified in samples from domestic geese that died in Guangdong, China in 1996). The virus then spread rapidly within and between farms, taking advantage of local practices in the feeding, housing, slaughtering and trade of domestic ducks, chickens and geese including practices at mixed live bird markets. Lack of hygiene, overstocking and mixing of different domestic animals greatly increases the risk of viral spread.

The role of Asian domestic ducks in the epidemiology of HPAI H5N1 has been closely researched and found to be central not only to the genesis of the virus,[6] but also to its spread and the maintenance of infection in several Asian countries.[7] Typically this has involved flocks of domestic ducks used for cleaning rice paddies of waste grain and various pests, during which they are exposed to wild ducks using the same wetlands. Research in Thailand demonstrated strong associations between HPAI H5N1 and abundance of free-grazing ducks.[8] Gilbert et al (2006), concluded that in Thailand: "wetlands used for double-crop rice production, where free-grazing duck feed year round in rice paddies, appear to be a critical factor in HPAI persistence and spread."

Image: Taej Mundkur

In Asia, the role of domestic ducks in the epidemiology of HPAI H5N1 has been found to be central not only to the genesis of the virus but also to its spread and the maintenance of infection in several Asian countries

Movements of people, such as farmers, veterinarians, and even journalists and tourists, as well as legal and illegal trade in poultry and caged birds are also factors in the spread of the virus. Globalization has led to massive and widespread movements of people, poultry and materials around the world at an unprecedented pace, providing greater opportunity for the spread of the virus. The outbreaks in Nigeria in early 2006 were most likely caused by the supply of infected live poultry from multiple sources, including East Asia and Turkey. Surveillance of 5,000 wild waterbirds in African wetlands in 2006 supports the view — since no evidence of HPAI H5N1 was found — that wild birds probably play a relatively minor role in the spread of highly pathogenic avian influenza. This view is consistent with the fact that the northward migration of wild birds from Africa to Europe between March and April 2006 did not cause any major outbreaks. Nor do wild birds seem to play a role in countries like Indonesia where HPAI H5N1 has been present in poultry for some years and where human cases have occurred. In February 2007, a HPAI H5N1 strain detected on a turkey farm in Suffolk, UK was shown to be almost identical to a strain discovered on a poultry farm in Hungary, pointing to a transmission route from poultry to poultry and not from wild birds to poultry. The outbreaks took place in a non-migratory period and at a site that was not adjacent to major wetlands, nor to areas used by significant numbers of waterbirds. So, wild birds were unlikely to have played a significant role during these outbreaks. The outbreaks in Central Europe between June and August 2007, where a number of dead wild birds infected with HPAI H5N1 were found in different parts of the Czech Republic, Germany and France, were linked to an HPAI H5N1 outbreak in a Czech turkey farm. Again, wild birds were unlikely to be the main factor spreading the virus since the outbreaks were observed in mostly non-migrant species and during a non-migratory period. Further, extensive surveillance of apparently healthy wild birds has found little evidence of infection in birds on migration or of their ability to carry the virus over long distances.[9]

While it is clear that trade in domestic poultry has been the crucial factor in the spread of HPAI H5N1, even for the transmission of avian influenza over long distances and across continents, indirect evidence suggests that wild birds may also play some role. Numerous species of wild birds, especially waterbirds, are susceptible to infection by the HPAI H5N1 virus. Close contact between domestic birds and wild birds can undoubtedly lead to cross-infection, from poultry to wild birds and from wild birds to poultry. Additionally, species that live in and around poultry farms and human habitations may serve as 'bridge species' that could transmit the virus between poultry and wild birds either by

direct contact between wild birds and poultry kept outside, or by indirect contact with contaminated materials. While there is no direct evidence that wild birds have carried the virus long distances on migration,[10] analysis of genetic sequences and other indirect evidence suggests that wild birds are likely to have contributed to the spread.[11] The relative importance of different modes of infection transfer, however, is unclear in the present state of knowledge.

Poor planning in response to ever increasing human populations and development pressures has led to the increasing loss or degradation of wild ecosystems, which are the natural habitats for wild birds. This has resulted in closer contact between wild populations, domesticated birds such as chickens, ducks, geese, and other domestic birds, and humans and has thus provided greater opportunities for the spread of HPAI H5N1.

The interplay between agriculture, animal (domestic and wild) health, human health, ecosystem health, and socio-cultural factors has been important in the epidemiology of the virus.

Minimizing the spread of HPAI H5N1

There is wide international consensus that attempting to control HPAI through responses such as culling or disturbing wild birds, or destroying wetland habitats is both unfeasible and diversionary, and thus should not be attempted, not least since it may exacerbate the problem by causing further dispersion of potentially infected birds. Resolution IX.23 of the Ramsar Convention on Wetlands states that: "The destruction or substantive modification of wetland habitats with the objective of reducing contact between domesticated and wild birds does not amount to wise use as urged by Article 3.1 of the Convention, and also may exacerbate the problem by causing further dispersion of infected birds." This statement is supported in Resolutions 8.27 and 9.08 of the United Nations Environment Programme's Convention on the Conservation of Migratory Species of Wild Animals (CMS) and Resolution X.21 of the Ramsar Convention.

Currently, wildlife health problems are being created or exacerbated by unsustainable activities such as habitat loss or degradation, which facilitates closer contact between domestic and wild animals. In the case of HPAI H5N1, healthy wild wetlands will limit the number of waterbirds that enter agricultural areas.

The key to the control of HPAI remains control and prevention in the poultry sector,[12] with long-term solutions being to separate poultry rearing operations and wetlands used by wild birds so as to avoid shared access and cross-contamination. Wild birds and poultry occurring in the same region should not use the same wetlands or have direct contact with each other. Runoff from domestic poultry operations should not pollute wetlands used by wild birds. Farmers can help to reduce the risks of direct transmission among poultry and cross-infection between wild and domestic birds, such as improving hygiene and biosecurity standards in farms and during the transportation of birds.

Many advocate the need to move to markedly more sustainable systems of agriculture with significantly lower intensity systems of poultry production so as to reduce the risk of avian influenza and other bird diseases. These need to be more biosecure, resulting in far fewer opportunities for viral cross-infection and thus pathogenic amplification. There are major animal and human health consequences (in terms of the impact on economies, food security and potential implications of a human influenza pandemic) of not strategically addressing these issues. However, to deliver such an objective in a world with an ever-growing human population, and with issues of food-security in many developing countries, will be a major policy challenge.

Risk of misinformation and adverse policies

The spread of HPAI H5N1 is of public concern and receives much media attention. Yet a widespread misunderstanding of the issue remains, especially regarding the different ways in which the virus might be spread. Misinformation has led to wild birds being automatically blamed, which creates public fear and thus political pressure for ill-advised and disproportionate policies such as the culling or disturbance of wild birds or the destruction of wetland habitats. The principal modes of transmission, such as the trade in poultry and poultry products, the trade in cage birds and human movements no doubt play a far more significant role in the spread of HPAI H5N1. In some cases, these modes of transmission have been underestimated and do not receive proportionate exposure in the media. We need to present an accurate and balanced view that acknowledges there are multiple vectors whose relative importance can change, depending on the area or outbreak concerned.

Direct action to reduce the risk of spread and infection in wildlife

Early detection is essential for the control or eradication of HPAI H5N1, hence rapid reporting of infection remains central to international and national control strategies. Comprehensive surveillance programmes including wildlife surveillance are essential for better understanding the disease, monitoring its development and contributing to early warning systems. Wild bird surveillance programmes should incorporate the results of risk assessments that have identified those species likely to be at higher risk of carrying HPAI H5N1, as well as the best strategic design (including optimal selection of sampling sites) and methods of sampling these species.[14] National veterinary services should be upgraded to the standards of the World Organization for Animal Health (OIE).

The development of global early warning systems, which incorporate the results of national and international surveillance programmes, should be a high priority, and aim for the following attributes:

- Open and transparent participation of relevant parties
- Targeted active and passive surveillance and other data-gathering
- Web-based output allowing the rapid dissemination of open-access data and information deriving from surveillance systems
- Integration of surveillance results with geographical and other data to facilitate integrated responses and risk management
- Meta-data allowing full analysis and interpretation of results in order to facilitate appropriate responses

GAINS instructors and students set mist nets during an avian influenza surveillance training course at Punta Rasa, Argentina. Extensive surveillance of live wild birds has found little evidence of infection in birds on migration or of their ability to carry the virus over long distances

(*inter alia*, information on type of surveillance (active or passive) and locations of sampling locations)
- Facilitation of timely and effective risk management. This implies clear warning triggers and targeted reporting.

Interest groups, such as hunters and birdwatchers, can play a vital role in surveillance programmes and the monitoring and reporting of outbreaks. Biosecurity needs to be enhanced so to reduce, as much as possible, the risks associated with contact between poultry and wild birds (or humans). It is clear, for example, that the strict biosecurity measures put in place throughout the European Union in 2006, in response to outbreaks in wild birds and poultry, were very effective in minimizing disease spread between poultry farms. When the presence or threat of avian influenza appears to warrant it, human activities causing disturbance to waterbirds and their habitats should be reduced, as there is a risk of the displaced birds taking the infection elsewhere; the birds moving to areas where they may become infected by other sources; and/or inadvertent human or vehicular transport of the virus to other areas. For similar reasons, destruction of wetlands and culling of waterbirds should also be avoided.

What conservation scientists are already doing

Significant efforts have already been made to try to understand the role of wild birds as vectors of HPAI H5N1, as well as the actual and potential impact of the virus on wild populations of conservation concern. Many countries have initiated or reinforced surveillance programmes aimed at determining the prevalence of the virus in wild bird populations. Existing data on movements of wild birds are being analysed, notably for those species considered more likely to survive the infection and to be able to carry the virus over significant distances. These efforts have already led to some important results, but remain insufficient to produce the detailed assessment of the role of wild birds in the spread of the virus needed for risk assessment. Preliminary analysis has also identified about 40 globally threatened wild bird species, the populations of which could be severely affected by HPAI H5N1.[15] Separate European research has identified 26 species potentially at higher risk of either catching or spreading HPAI H5N1.[16] These data are now available to help land managers in Europe respond to future emergencies.

What science needs to explore further about the role of wild birds

There is a need for targeted international ringing (banding), colour-marking and satellite telemetry programmes for waterbird species likely to be at higher risk of carrying HPAI H5N1, as well as improved international analysis of existing relevant data. This must

Image: Pablo Beldomenico

synthesise information on the routes and timing of waterbird migration, especially of poorly known intra-African migrants, and birds using Central Asian, Asia-Pacific and Neotropical flyways. We need to strengthen bird research worldwide, especially in areas where little or no ringing and counting schemes have operated in the past so as to provide a sound scientific basis for risk assessments. We need to publish the results of these studies and other relevant data in new flyway atlases made widely available and accessible on the Internet.

We need better and integrated data on trade in domestic poultry and other birds to build epidemiological models. Research into the following epidemiological and ecological aspects of HPAI H5N1 in wild bird populations should be increased:

- Prevalence of HPAI H5N1 in various wild bird populations
- Ecology of the virus in the environment
- Natural mortality rates in wild bird populations
- Identification of higher risk species, that is, those with high susceptibility to HPAI H5N1 and/or those that have a relatively higher risk of spreading it.

We need research on the behaviour and ecology of those migratory and non-migratory bird species living in close association with humans and poultry, which might act as a 'bridge' for the transmission of HPAI between waterbirds and poultry. Such research should aim to develop practical guidance on ways and means of reducing this risk.

Guidance on responding to HPAI H5N1

Responding to the perceived threat, as well as to outbreaks of HPAI H5N1, involves a wide range of activities from preparing contingency plans to sampling wild birds and dealing with the media. Additional complexity is added by the varying scales at which these activities must be completed, for example contingency plans are required at the international, national, subnational and site levels.

Since 2005, a large body of guidance on responding to the spread of HPAI H5N1 has been produced, including much material made available through FAO and OIE websites. This includes guidance related to surveillance, enhanced biosecurity, contingency planning and preparation, and responses to outbreaks of HPAI infection.

A guide to this guidance has been produced and is available as part of Ramsar Resolution X.21.[17] The guide consists of a framework, which provides a conceptual map; and a directory of materials, which organizes the guidance under a number of separate issues and provides source information including web links.

What governments are encouraged to do

Governments are encouraged to:

- Avoid unjustified and counter-productive measures such as culling of wild birds and destruction of the natural habitats on which they depend
- Undertake transparent, structured, science-based risk assessments making use of all available knowledge
- Establish and test emergency response strategies for various spatial scales incorporating lessons learned from associated responses
- Implement wild bird surveillance and research programmes
- Conduct comprehensive epidemiological investigations of HPAI H5N1 outbreaks and share resulting data with the global community
- Involve those with relevant scientific expertize including specialist ornithologists in developing such risk assessments and response strategies, as well as in designing wild bird surveillance programmes and conducting epidemiological investigations of outbreaks
- Cooperate internationally in the exchange of all relevant data and information
- Increase capacity where needed for wildlife disease surveillance and management
- Develop communication programmes aimed at promoting balanced understanding and awareness of actual risks and appropriate responses in all stakeholder groups, including poultry keepers, to reduce risks to human health and increase early disease diagnosis; the media, to improve accuracy and availability of messages; the public, to aid in public reporting for surveillance programmes; and habitat managers, to improve contingency planning. [18]

Thanks to Ruth Cromie and other members of the Scientific Task Force on Avian Influenza & Wild Birds who provided input.

The Argentine approach to pandemic preparedness

Dr Oreste Luis Carlino and Pablo Orellano, Pandemic Preparedness, Ministry of Health, Argentina

Virological, epidemiological and clinical influenza investigation has deep roots in Argentina. The first influenza laboratory investigations began in the 1960s, leading to certification of the effects caused by the influenza A (H3N2) pandemic during the years 1969-1970 in Córdoba province, Argentina. Up to the present date, there are three National Influenza Centers (NIC), located in the Instituto Vanella, Universidad Nacional de Córdoba; the Instituto Nacional de Enfermedades Infecciosas, (INEI ANLIS), Buenos Aires; and in the Instituto Nacional de Epidemiología (INE-ANLIS), Mar del Plata.

A Pandemic Plan was prepared in the national institutes as a response to the first World Health Organization (WHO) alerts regarding the need for preparedness for a possible influenza pandemic. This plan was presented at a Pan-American Health Organization (PAHO) meeting, on 19 December 2002, held in Chile.

During 2003, we kept working on the plan and added the development of the National System of Sanitary Surveillance (SNVS) and the Influenza Sentinel units, which contribute surveillance activity that is vital for the correct development of the plan.

Image: Min. Health Argentina

Córdoba flu pandemic drill: an emergency service physician informs his personnel of H5N1 confirmation at the beginning of a flu pandemic

The first national meeting of the DNPS and Dirección Nacional de Emergencias Sanitarias (DINESA) was held on 14 December 2004, and the plan was transferred to all the nation's provinces. Since then, the work has focused on three different axes:

1. Permanent updating of the plan
2. Local implementation
3. Development of rapid response teams.

To monitor the plan's local implementation, different simulations took place in the tabletop and drill fields.

The tabletop exercises have recreated scenarios of eventualities and allowed the exercise of the local, strategic intermediate and national levels of decision. These were held during 2005 in the nation's five regions.

The drills have been events that require a huge display of human, material and economic resources. They allow the impact that an influenza pandemic might have on the hospital structure, airports, security forces, transport, news and so on, to be measured with higher precision. In addition, they enable the identification of where parts of the plan can be improved, and where there are failures of the organizations involved.

In addition to conducting the drills, and in order to ensure preparedness for an influenza pandemic, a strategic stock of Oseltamivir was acquired during April 2006. Sixty per cent of this was distributed to the capital cities of Argentina, while 40 per cent is stored at the central level, in order to provide support for the first provinces affected. While in that instance, 75 milligram tablets of Oseltamivir were acquired for adult treatment, a strategic stock has now been provided for children with the purchase of Oseltamivir syrup and paediatric tablets. The strategy to avoid pandemic flu spread in Argentina is based on early detection and the immediate blockade of initial foci with Oseltamivir, and the immediate activation of national rapid response teams (NRRTs).

The WHO checklist is incorporated into the readiness tasks. In this context, work is being done with the different national ministries, and with private organizations, to spread pandemic readiness. At the legal level, the Sanitary Load Law has been enacted, which allows the rapid delivery of sanitary samples and biological material. This was a great contribution to the legal support, along with the Procedures Guide for Avian and Pandemic Influenza, which was created by

Influenza pandemic preparedness drills to date

Entre Rios, August 2005
Level: Operational

Subject: First Drill Field of avian influenza in birds

Organized by: National Secretary for Animal Health, the National Economy Ministry (SENASA) and the National Health Ministry.

Córdoba, December 2005
Level: Operational

Subject: Phase 6 – Overflow at the hospital, hospital procedure, and primary health attention in CAPS Villa Angelelli. Evolution from local avian influenza cases to phases 4-5.

Participants: National and Provincial Health Ministries, Ministry of the Interior, airport and international organizations.

The Influenza Pandemic Plan was tested, especially the first, second and third triage in San Roque Hospital, Córdoba. This involved the taking and sending of samples to NIC, Córdoba; H5N1 positive reporting; measures of infection control in emergency rooms and emergency situations at the hospital; management of resources for transfer of patients; resources for commitment at the hospital, external consultant awareness protocols; treatment and diagnostic services in CAPS, and domiciliary visits on the ground; and information management.

Misiones, August 2006
Level: Operational

Subject: Phase 3-4 – Passengers in a severe state and others with symptoms in a commercial aeroplane arriving at Iguazu Airport, from a country in phase 4; contact control with every passenger; and hospital overflow.

Participants: National and Provincial Health Ministries, Ministry of the Interior, airport and international organizations.

The Influenza Pandemic Plan was tested, especially triage on the passenger aeroplane; management of passengers affected at the airport; migration procedures; management of resources for transfer of patients; resources for commitment at the hospital; intensive therapy unit attention protocols; control of hospital infections; and information management.

Mendoza, September 2006
Level: Operational

Subject: Phase 5 – Passenger transport from a limited country with people from Southeast Asia (phase 5); hospital overflow; intensive therapy unit attention protocols.

Participants: National and Provincial Health Ministries, Ministry of the Interior, airport and international organizations.

The Influenza Pandemic Plan was tested, especially the management of resources for patient transfer; resources for commitment at the hospital; intensive therapy unit attention protocols; the control of hospital infections; and information management.

San Juan, November 2006
Level: Operational

Subject: Phase 5 – Passenger transport from a limited country with people from Southeast Asia (phase 5); hospital overflow; hospital procedure; isolation cell; disinfection of ambulances; and personal biosecurity.

Participants: National and Provincial Health Ministries, Ministry of the Interior, airport and international organizations.

The Influenza Pandemic Plan was tested, especially hospital procedure; hospital infection control; coordination with security forces; management of resources for patient transferral; resources for commitment at the hospital; and information management.

Buenos Aires, November 2008
Level: National Strategic

Subject: Phase 6 – Limitation of countries; Paraguay and Brazil in phase 6; beginning of phase 6 in Puerto Iguazu, Argentina; and pandemic diffusion.

Participants: A 'solitarity exercise' in conjunction with the Argentinean and Chilean armed forces.

the Ministry of the Interior with full participation of its dependent organisms (Dirección Nacional de Migraciones, Dirección Nacional de Protección Civil, Gendarmería Nacional Argentina, Prefectura Naval Argentina, Policía Federal Argentina and Policía de Seguridad Aeroportuaria). This guide supports other national organisms, including AFIP, Dirección Nacional de Aduanas, Ministerio de Salud, Dirección Nacional de Epidemiología; Dirección Nacional de Sanidad de Fronteras, and SENASA.

During 2007, an important breakthrough came with the creation, by Presidential Law number 644/2007, of the General Coordination Unit of the Integral Plan for Influenza Pandemic Prevention. This unit will be coordinated by the Ministry Cabinet Headquarters.

A further aspect of the current work is the update of procedures for the acquisition and delivery of wild birds, poultry and human samples; procedures for the disposal of corpses in an influenza pandemic situation; and the implementation of the PAHO /Centers for Disease Control and Prevention generic protocol of seasonal influenza surveillance adopted by Argentina. All of the capacity-building strategies and the implementation of surveillance, detection and response mechanisms for seasonal, avian and pandemic influenza planned up to 2011 are based on this protocol.

There is also a plan of action to advance preparation organized by priorities in the Influenza Pandemic Plan. Priority activities are: technical cooperation, responsibilities and execution dates. The most relevant subjects are: explicit definition of functions and responsibilities of people and organizations involved (POE) to take political decisions; POE for human resources management during

Image: Min. Health Argentina

Internal and external disinfection of an ambulance with bleach solution during the San Juan flu pandemic drill

Image: Min. Health Argentina

Patient care of severe acute respiratory illness (SARI) simulation during San Juan flu pandemic drill

emergencies; risk communications; technology implementation for rapid and continuous communication within the country; implementation of ethno-anthropologic potential impact (culture, language, beliefs); legal and ethical aspects; completing the legal aspects to include influenza in occupational diseases; revision and enactment of the plan by a bioethical commission; goals, indicators and responsibilities of the evaluation of the plan; preservation of basic services, development of eventuality plans for the maintenance of basic community services; planning for additional personnel to maintain basic community services during emergencies; protocols for volunteer capacity in key basic services; animal-human interphase, databases with epidemiological surveillance information for avian influenza; studies of risk evaluation of avian influenza introduction into the country; public health measures; evaluation and modification according to drill fields; social communication; development of rapid responses protocols.

Rapid response protocol development

The NRRT was created to respond opportunely to early events and unusual cases, clusters or outbreaks of severe respiratory infections caused by respiratory viruses, seasonal, avian or pandemic influenza, severe acute respiratory syndrome (SARS) or other biological eventualities. The team will respond whether these outbreaks are moderate or severe, seasonal or non-seasonal, and whether or not they affect at-risk populations.

The training programme is permanent in Argentina, with exclusive dedication during the first two weeks. After that, personnel must participate in two training courses, two simulations and two real outbreak studies every year. The objective of the NRRT is research and intervention as a tool for the pandemic influenza plan and other biological emergencies. NRRT trainees will have a specialized training in their original discipline, and are capable of developing tasks in the surveillance and response health system:

- Public health surveillance
- Public health and epidemiology research
- Public health interventions
- Situation analysis and health tendencies
- Risk management.

Main expertise of trainees

At the end of their training, personnel are ready to integrate with the NRRT as participants, where their main responsibilities are as follows:

- Be available for transfer to the emergency site within 24 hours after the NRRT call
- Use tools for epidemiological analysis
- Ensure rapid notification and research of outbreaks, in order to identify source and means of transmission
- Produce required information for effective social risk communication to population and media, in association with communication experts
- Propose effective prevention and control measures to avoid the spread or diminish its impact
- Propose effective public health measures for post-emergency rehabilitation.

There are several key indicators for the commencement of action:

- Rise in the number of acute respiratory infection (ARI) cases

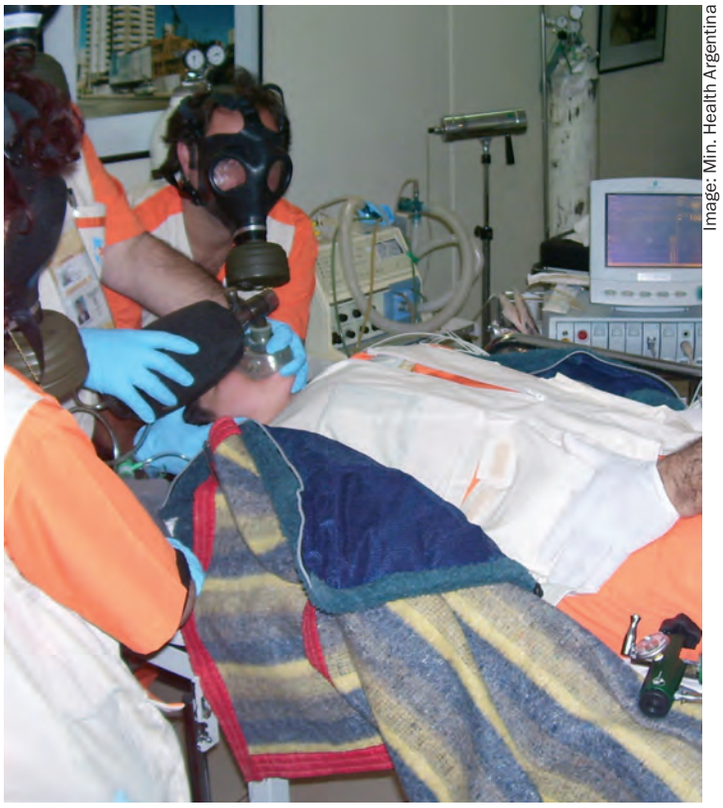


Image: Min. Health Argentina

Patient care within the shock room (alternative location for intensive care unit). Every attendant is using personal equipment for respiratory protection. Modality usually used during drills

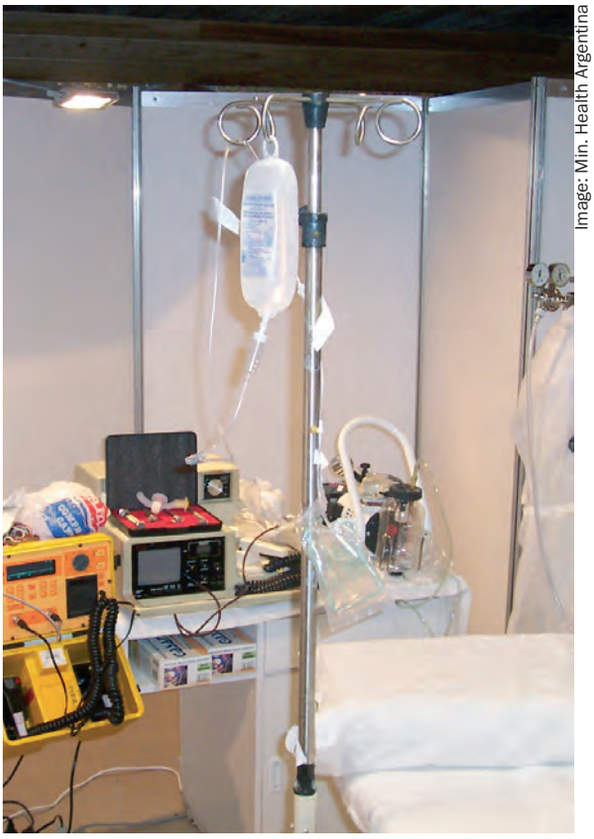


Image: Min. Health Argentina

Shock room for the first triage, showing all equipment required for the task

- Presence of clusters of ARI cases
- Close communities (such as prisons, military camps, schools) with suspected cases or related to animal exposure
- Rumours
- Others: epizootics, rise in influenza drugs sales, absenteeism in schools.

An economic evaluation has been developed in order to assess the cost benefit of rapid response teams intended to avoid the spread of influenza. This evaluation is intended to assess whether the cost associated with the creation, training and maintaining of rapid response teams is accompanied with a cost saving related to the avoidance of deaths and patient maintenance. Costs included within the study could be divided into direct costs (including patient treatment, hospitalizations, laboratory tests, transmission-blocking vaccination, physicians, epidemiologists and educational health campaigns), and indirect costs (loss of working hours, patient care and travel by relatives). On the other hand, benefits of the prevention strategy are taken into account, and for this matter 'willingness to pay' studies are considered, as a monetary representation of what a disease condition means for a patient. In order to compare and analyze different alternatives, decision-tree models are used to help in the classification of data and the assessment of several variables acting at one time. In this case, data was analyzed using a decision-tree analysis with TreeAge version 3.0.5 software.

The results showed that in the presence of an outbreak, without rapid response teams, the cost of facing the outbreak and associated costs rise to 750 international dollars per person, while the saving derived from avoiding the outbreak could be estimated in 550 international dollars per person. This means a saving of 1,302 international dollars per person in the general population, and identifies a value for the usefulness of this strategy. Nowadays, other cost benefit and cost effectiveness evaluations are being projected in order to continue the assessment of every strategy's efficiency. Among other issues, several should be highlighted:

- How much Oseltamivir or other drugs should be kept as strategic stock, taking into account medicament lost due to expiration?
- Should rapid response teams be maintained at national level and move during emergencies to each department, or should they be formed in every jurisdiction?
- What would be the right time for rapid response teams to leave the outbreak site and permit the local team to take care of the situation?
- Is it possible to form a regional rapid response team that could coordinate a response in regional outbreaks, and could be this strategy more efficient?

The answer to these and other questions would be very important for national and provincial ministries of health, in order to optimize and guide efforts. Basing these efforts on the experience of other countries is important in this early stage of planning development for Argentina, but local resources and possibilities must also be taken into account.

The importance of being prepared: the Austrian way against communicable diseases

Prof. Hubert Hrabcik, MD, Director General of Public Health and CMO, Federal Ministry of Health, Austria

Viral infection diagnosis and prevention has a long history, and the pandemic influenza threat, in particular, is changing the face of this discipline. The stark reality is that, through three influenza pandemics, between 50 million and 60 million people have lost their lives. In addition, these tragedies have had profound consequences for social structures.

There is a tremendous difference between the scientific-based possibilities of diagnosis and treatment. In the past, only symptomatic treatment was possible; but now, it is possible to follow sudden diagnosis with efficient methods of treatment. The most important innovation — the advent of effective antimicrobial agents — combined with principles and use of immunization, have ushered in a new era.

Let's not forget the exciting possibilities offered by today's information and communication technologies. Now, information and early warning really are faster than in previous years, when the spread of a disease was noticed by new cases first.

In Austria, as far back as the days of the former monarchy, it was well known that strong assessment and observation of communicable diseases are necessary for the social and economic stability of a country. A special epidemic law has existed since 1913, which both regulates the responsibilities of the various organizational levels, and authorizes public health officers to order public health associated measures.

Now, there is also a political sensibility of these needs. Since the European Commission (EC) and World Health Organization (WHO) announced the need of preparedness in the field of pandemic influenza, there has been a political commitment to work towards this.

In the first working period, Austria's health service officials had to decide on the quantitative and qualitative dimensions in which to establish the preparedness plan.

Image: Min. Health Austria

Effective communication is an essential tool in pandemic preparedness

From lessons learned, especially in Southeast Asia, it was clear that there was a strong connection between the spread of avian flu and a decrease in Gross National Product (GNP). Under the guideline 'health in all policies', we started our work primarily in the public health field. However, an accompanying crossover with essential services and trade was also announced. Strong cooperation between public health organizations at federal and regional levels resulted in the structuring of a federal guideline and regional realization plans.

From the beginning, all three medical universities were involved. A special scientific advisory board was created under the chair of the Director General of public health. We began working first to finalize a theoretical plan, and then to establish budgeting for it.

At the start, one important question was raised: what part of the population should be protected — all of it, or only a part? Following discussions with our acting minister it was decided that we want to support and protect a maximum of the population.

The second development was our decision to use antivirals and prophylactics, especially for all essential services. This had been acknowledged before, but had not been a practical option until recently.

Third, we wanted to ensure we had the best vaccine — that is, the most recently produced vaccine using the pandemic strain. However, the existing egg-based production techniques meant that these could not be produced in time. Now, though, the cell-culture based vaccine production technique gives us the opportunity to reach this target. Indeed, we are in a happy situation, because one of the two companies that can guarantee this technique is located in Austria.

Next, we explained our planning to all ministries and large industries, requesting specific additions to the health plan. The target was to secure public life and security throughout the country, in the event of a flu pandemic.

It is clear that all levels of society — public bodies, private industry, and families — need to work together to create an effective shield that will protect the population. In a nationwide effort, we offered a common purchasing of antivirals, and this was accepted by a large part of the industry. In cooperation with our defence ministry, we would be able to stockpile pharmaceuticals and facemasks. Of course, efforts towards such preparedness can never stop, and a constant updating of all planning is necessary.

Preparedness across Europe

These issues and measures should extend beyond a single country. A key requirement in preparing for future pandemics is the coordination and synchronization of preparedness measures Europe-wide. This was one of the lessons learned under the first EU-wide pandemic exercise.

Van Swieten

Van Swieten was the first Austrian national exercise to evaluate crisis management of a national emergency due to an infectious disease.[2] In general, the EU exercise 'Common Ground' was taken as a model for the national exercise concerning scenario, aims and objective. Additionally, the results of the evaluation of Common Ground were incorporated. The exercise took place in November 2006 and lasted for two days.

The aim of the exercise was to evaluate the communication and cooperation between national and regional levels during a pandemic situation. The exercise centre was located on national level. All public health officers on regional level were actively involved, while the involvement of the district level was voluntary. Furthermore, several hospitals asked for participation to test there internal crisis plans.

The objectives of the exercise were the evaluation of:
- Communication between the Ministry of Health (MoH), the nine regional health boards and the other involved ministries
- General preparedness for an influenza pandemic in Austria
- The interoperability of the regional plans.

Central elements of the exercise were therefore:
- Surveillance during a pandemic
- Counter measures such as use of antiviral medicinal products and the pandemic vaccine
- Logistic issues
- Trans-border issues such as 'health shopping' and travel restrictions.

The scenario of this two-day exercise was divided into three blocks and covered six months in real time. Each block was played in compressed time. In block one, players had to react according to pandemic phase 5 when clusters of human infections with a new influenza virus subtype appeared in Southeast Asia. In block two, players had to manage pandemic phase 6 with no availability of pandemic vaccine. In block three, the logistics for the use of the pandemic vaccine during the second pandemic wave (phase 6) had to be handled.

Van Swieten was evaluated by the same methods as used in the evaluation of Common Ground.[3] In the evaluation process the need for intensive work on several topics was disclosed:
- Continuous inter-ministerial cooperation concerning the issue border control/closure of borders, closure of airports and 'health shopping'
- Concrete plans for business continuity
- Planning presumptions (definition of triggers for certain situations).

However, one of the most important results was the need for strengthening the public health sector. A well functioning public health system is the backbone for successful crisis management in the field of infectious diseases, and thus needs to be supported concerning human and financial resources. Furthermore, public health officers need to have continuous access to training on high level. Therefore in 2006, the Austrian MoH started a special initiative to send key personnel of the regional health boards to international training seminars and workshops.[4] A group of well-trained public health experts will be established that can function as multipliers at regional level. Additionally, the MoH organizes crisis management training seminars at national level.

Another important element is the electronic reporting system for infectious diseases (EMS), which was implemented in Austria beginning in 2009.[5] The EMS allows for real-time surveillance and thus for immediate crisis management when needed. The EMS will be fully integrated in future exercises in order to optimize its functionality.

Image: Min. Health Austria

It is the ethical and moral duty of every country to prepare for potential pandemic

Under the key principle of protecting the whole population, several plans should be put into action:

- Use epidemiologically based measures
- Use antivirals for prevention
- Prepare an immunization programme for the whole population.

Realizing these plans also demands a budget. However, it is not easy to get money for only theoretical threats, where nobody knows the start time. In order to address this, we calculated the economic damage if the population was unprotected, comparing this with the expense of preventative measures.

We found a quotient of 1:10 in the comparison of expenses with damage, in addition to the enormous pain caused in society if it is unprotected. The ongoing discussion and political decision then went according to expectations. All Austrian ministries, and all regional governments had been involved, and a clear message emerged: it is not enough to show up your medical preparedness; cross-sectoral preparedness on health issues must be demonstrated in all policies.

We are now we are in the second phase of our preparedness plan, focusing on private industry, where we are trying to raise awareness and understanding that pandemic protection helps to guarantee economic survival.

On the regional level, there exists a lot of important planning. Never before have we tried to vaccinate our population in the shortest time as possible. But with more than 30,000 physicians preparing for prevention, this is now realistic.

A special need is medical education and training. Our first pandemic exercise, named 'Van Swieten', tested communication as a command post exercise, and also the quality of our preparedness plan. The next will be a bilateral exercise with one of our neighbouring countries.

Because we are now accustomed to the reporting of new HP-Influenza cases, it is necessary to maintain readiness, not only in the health field, but also on the political field.

One evaluation, done by the European Centre for Disease Prevention and Control, was very successful but also instructive in generating new ideas and perspectives.

Conclusion

With regard to the existing possibilities of prevention, diagnosis and treatment, it is an ethical and moral duty for each country to prepare for a pandemic. All fields of federal and regional responsibility should be involved from the very start, and each nation should have an epidemic law, and recognize the necessity of using antivirals and a pandemic vaccine. Creating a plan and investing money in pandemic preparation helps to guarantee the prosperity of a nation, ensuring that vital services and industry can continue in the event of a pandemic.

It is crucial to understand that success can only be achieved by involving all three levels of society in pandemic preparedness: the public, private industry and the family.[1]

Planning for the future — influenza pandemic preparation in Croatia

Vladimir Drazenovic, Spec. Virologist, Head of National Influenza Centre, Croatian National Institute Of Public Health

The role of the World Health Organization (WHO) in global preparedness for future influenza pandemics has been defined. Its activities are divided into stages of the pandemic and interpandemic period. The national pandemic influenza preparedness plan of Croatia equally takes account of these stages and WHO recommendations in its activities.

Croatia has a National Committee on Intrapandemic Planning (NCIP), which has few standing members who would enable the continuity of its operation. Yet if necessary, the committee could engage additional experts when there is need for their expertize.

Basing itself on the experiences of health organizations in crises, the Ministry of Health and Social Welfare has established a Ministry of Health Crisis Headquarters (MHCQ) by the health minister's decree. Structurally, the MHCQ has been shaped into a coordinating body to run the local self government units. For this purpose, it has set up health headquarters in all its counties. The MHCQ is made up of departments, one of which is in charge of preventive medical care (PMCD) and has been set up for the precise task of running epidemic control activities.

Organizationally, the MHCQ is a government administrative body for managing crises and catastrophes. It acts as a link between the existing governmental bodies, local self government and technical organizations with the view of meeting the challenges that present themselves. PMCD uses the Croatian National Institute of Public Health, Epidemiology service and WHO National Influenza Centre (NIC) as Croatia's central public health body, and county public health institutes (CPHIs) at local self-government level. This constitutes a primary link between governmental administrative authorities and local self government bodies, as well as reaching out to other technical health organizations.

Image: Vladimir Drazenovic

The public health web portal www.gripa.hr

NIC has an important role and coordinates a number of different activities for future influenza pandemic preparation.

The basic presuppositions on which activities for pandemic preparedness within the whole country are based are the infrastructural organization for seasonal influenza and the best preparation for a pandemic. In this sense, epidemiological, virological and serological surveillance of the dynamics of parameters related to influenza have been set up. While epidemiological surveillance encompasses the number of reported cases according to age groups, serological surveillance is oriented to the estimation of vaccine efficiency used that year. Virological surveillance of circulating strains of the influenza virus looks at the frequency of movement of particular virus strains and their presence in the population. It is also possible to conduct good monitoring of the dynamics of the epidemic itself in the form of a weekly real-time reporting scheme based on positive confirmations of the number of influenza cases. By using real-time polymerase chain reaction molecular diagnostics it is also possible to process a large number of samples in one day, which is a basic requirement in virological surveillance in the case of a pandemic.

Certainly one of the most important roles of NIC is in the collection of representative numbers of circulating influenza viruses and sending them to the Collaborative Centre in London to participate in vaccine strain selection. As long as vaccine production continues to be based on embryonated chicken eggs, its goal each year is to keep the virus isolated in that medium. This classifies NIC among only ten recognized laboratories in Europe that still regularly carries out this very important type of diagnostic.

Aside from surveillance of the above named parameters and other activities, seasonal vaccination coverage is of great importance in case of a pandemic. On average, around 100,000 seasonal influenza cases are reported in Croatia annually, even though the true number is actually larger. The cheapest and most efficient way to

Image: Vladimir Drazenovic

Harvesting of influenza viruses from embryonated chicken eggs

conduct public health services with the goal of lessening medical and economic losses is vaccination.

Survey data shows that the vaccination dose per capita in Croatia is 14.6 per cent and for target groups it is over 50 per cent. Based on WHO's recommendation, the goal is to cover 75 per cent of target groups by 2010. For the majority of the population for which vaccination is recommended, 650,000 free-of-charge vaccine doses are ensured by the Ministry of Health and Social Welfare and the Croatian Health Insurance Institute. Smaller numbers of vaccines by other producers are also available on the open market, which amounts to approximately 50,000 doses.

Vaccination is particularly recommended to persons at an increased risk of complication, those in close contact with risk groups, and health workers. Aside from persons above the age of 65 years, those of all ages (older than six months) suffering from diabetes, asthma, malignant diseases, chronic diseases, pulmonary and renal diseases, anaemia and a weakened immune system also fall under the risk group category.

Making an immunization strategy decision and recommending the size of a vaccination campaign is one of NCIP's first responsibilities in the case of a pandemic. Until the emergence of a new influenza virus subtype with a pandemic potential, no reliable prediction can be made regarding what other population categories could constitute risk groups for influenza pandemic complications and death. Health workers are essential personnel in the case of pandemic. Therefore, depending on the size of vaccine supply, health workers should come next to the priority group in receiving the vaccine. Services vital to the functioning of the state should also be covered by the vaccination, but it would be optimal for the majority of the population to be vaccinated.

In the sense of heightening vaccination coverage, a proactive approach with multidisciplinary activities has been taken. The first step in heightening vaccine coverage has been to fulfil the goal of having faster availability of vaccines during times of seasonal and also pandemic influenza. In cooperation with vaccine producers from Europe and the Croatian pharmaceutical company Institute of Immunology, a high-tech filling machine for immunological preparations (flu vaccine) has been purchased. This bridges the bottleneck in vaccination production by significantly shortening the time to prepare vaccinations. The syringe-filling machine has a maximum capacity of 8,000 syringes per hour, which amounts to 190,000 fillings in one day so that vaccines for a million persons can be prepared in five days. Also, studies have been launched for production of vaccines on cell culture. The inactivated flu vaccine is traditionally prepared with embryonated chicken eggs, which means the producer can face a number of difficulties such as an insufficient number of eggs and eggs of inadequate quality in the summer season. In the case of a pandemic when several hundred extra doses are needed, this is a major issue.

MRC-5 and Vero (WHO) are cell lines that WHO has approved for production of vaccines for human use. The Institute of Immunology is currently working on optimizing Vero cell growth in a bioreactor, the procedure of producing the vaccine itself and the selection of the virus of a high titre. Preliminary studies on Vero cells as a substrate for influenza vaccine production in Croatia have shown that the flu virus strains recommended for vaccine in the last three seasons are replicated best in cell culture and the achieved titre is comparable with those obtained when inoculating embryonated eggs. In 2009 the plan is to resolve remaining issues with analytical methods and process flow, to optimize parameters, to finish small-scale production and to make progress with documentation (standard operating procedures and so on).

Secondly, a great deal of effort has been put into the active education of health workers who deal with vacci-

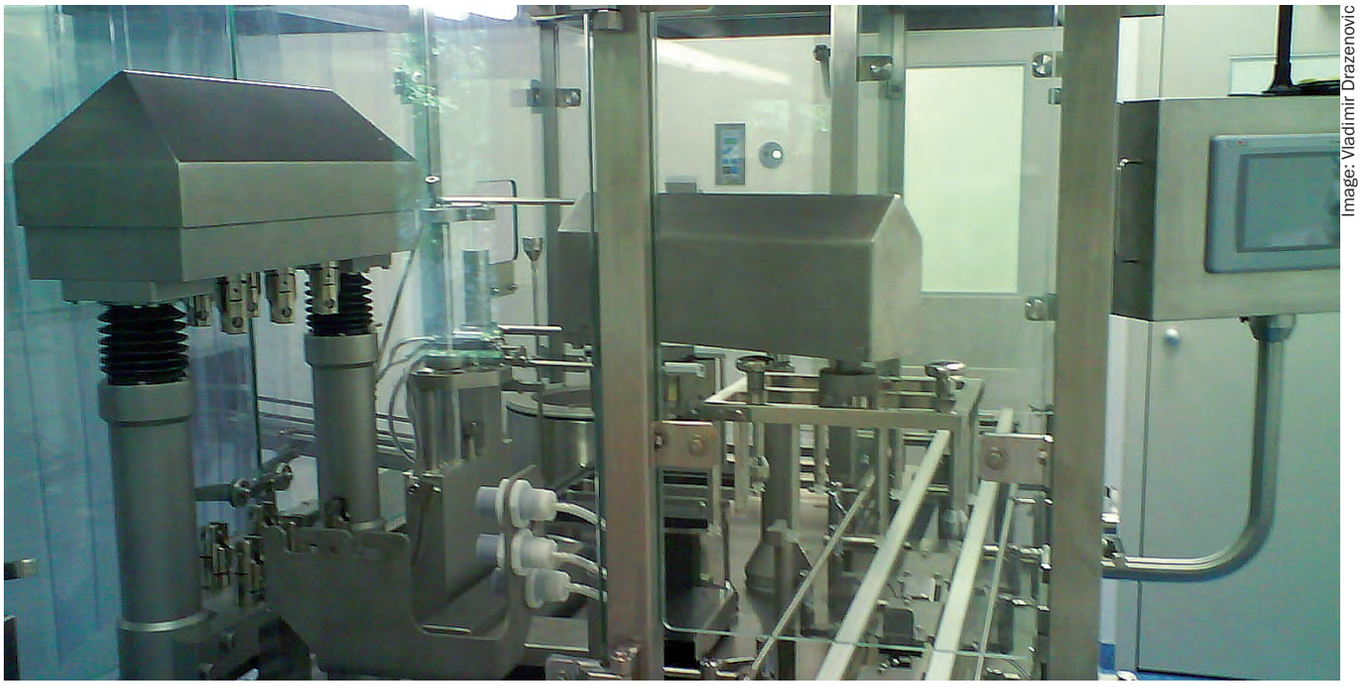


Image: Vladimir Drazenovic

The syringe-filling machine has a maximum capacity of 8,000 syringes per hour

nation and administration of antiviral medications. Related to this, lectures based on EU decisions — EU-27 on the central role of health workers in increasing flu vaccination coverage — have been delivered to 4,000 people, comprising around 30 per cent of all physicians in Croatia. Teleconferences on this subject have also been held in those areas which are more remote, including islands.

A third action has been to launch a public health web portal, www.gripa.hr, with the goal of increasing access to information on seasonal influenza, vaccination and preparations for possible pandemics. The portal was set up by the Croatian National Institute of Public Health and the WHO National Centre for Influenza. On it one can find credible information on influenza, its treatment and vaccinations. This improves communication between health experts and the general public with the goal of improving health and prevention. The launch of the portal was accompanied by promotional activities in public health institutions with the participation of leading health workers, the media and the name of the domain itself. The site has been approved by the Minister of Health of the Republic of Croatia.

There are several sections on the web page including: all about flu; vaccinations; FAQ; e-cards; ask the expert; news; useful links; and a weekly real-time report from the National WHO Influenza Centre. On the main page there are statements by the Director of the Croatian National Institute of Public Health and other top medical authorities who proactively support the policy of flu vaccination. Such activity has imposed itself as a necessity because of the significant number of questions asked by those affected by seasonal influenza (approximately 100,000 people) and because of the considerable number of vaccinations being carried out in Croatia (650,000). For those who want to find out more, the website also provides access to a translated version of a book about influenza, which over ten chapters gives a comprehensive view on the virus. The 300-page book is free to download in its entirety, and it is also possible to access links in its reference section where the author has referred to original texts. This totals around 2,000 pages worth of information dedicated to influenza.

The web portal is the best possible way of making information available to those who want access to it 24 hours a day, 365 days a year. Its interactive capabilities also enable users to ask question directly. The justification for such a public health activity is confirmed by an outstanding number of visits to the site — over 100,000 users per month were recorded in the first two months — and exceptionally positive comments from medical authorities and electronic and print media.

Until there is efficient availability of WHO's recommended vaccine, to further prevent the occurrence of an influenza pandemic Croatia has stockpiled anti-virals to cover ten per cent of its population. This amounts to 200,000 doses of Oseltamivir and 100,000 of Zanamivir, which will be renewed when they pass their expiry date.

Even though the efforts to establish an efficient system for cases of influenza pandemics are coordinated by the WHO National Influenza Centre, the Croatian National Institute of Public Health, the Ministry of Health and Social Welfare and the Veterinary Services and are based on WHO recommendations, there is still room for improvement. After all, a possible future influenza pandemic will hardly leave room for improvisation. Having this in mind, we have to be aware that only timely and accurate information available to everyone will make the general public and the media aware that any relaxation in preparation of pre-pandemic activities can lead to disaster.

It has been over 40 years since the last influenza pandemic and history records up until now show that a number of pandemics have occurred in each century. So, we can say with great certainty that with the passing of each year we are getting closer to a new pandemic.

Epidemiological surveillance: dynamic and long-term process

J.L. Castanheira, C. Gomes and J. Catarino, Department of Epidemiology and Health Statistics, General Directorate of Health, Portugal

Portugal is a Member State under modest development in the context of Organisation for Economic Co-operation and Development (OECD) — in 2007, gross domestic product per capita was EUR15,373.[1] The country is provided with a preparedness plan which seems to be adequate. Work undertaken in preparation for the anticipated pandemic has included the elaboration of a contingency plan developed in the following four axes:

- **Epidemiological surveillance**
- **Prevention/control measures**
- **Communication**
- **Evaluation.**

The most recent version of the Portuguese National Pandemic Plan[2] (March 2007) follows World Health Organization (WHO) guidelines, protocols, strategies and influenza activity periods and phases. The plan has received wide social recognition, and has been positively recognized by national and international entities. As epidemiologists, we believe this is due to the following:

- Because it is oriented towards action based on epidemiological evidence, the conceptual framework adopted is the most adequate
- Procedures are aimed at assuring a social dynamic appropriate for controlling situations and solving problems. Thus, from planning to evaluation, procedures are anchored in and facilitate the sustained, active and engaged participation of stakeholders
- The plan is rooted in an equitable and universal public health structure and is well articulated, from the frontline to rehabilitation, with the health care provision network.

Nevertheless, these features are not fortuitous; they are the result of favourable conditions (cultural, social and geographic) and of the natural evolution of policies aiming to control communicable diseases. We are proud of such policies, which have been systematically adapted since the nineteenth century and have been formatted according to an epidemiological surveillance system that has been in place for decades.

Main features

Portugal is a country of about 10.5 million inhabitants, with an area of 92,000 km² – three times the size of Belgium and almost a sixth of France. Portugal has been independent and unified country since the twelfth century, and has maintained its present borders for more than 700 years. An important colonial power since the sixteenth century, Portugal did not enjoy in any significant way the socio-economic impact of the nineteenth century's Industrial Revolution.

The recent history of public health in Portugal can be divided in three time periods: before 1971 (the sanitary period), between 1971 and 1979 (the 'health centre' period), and after 1979 (the post-NHS period).[3]

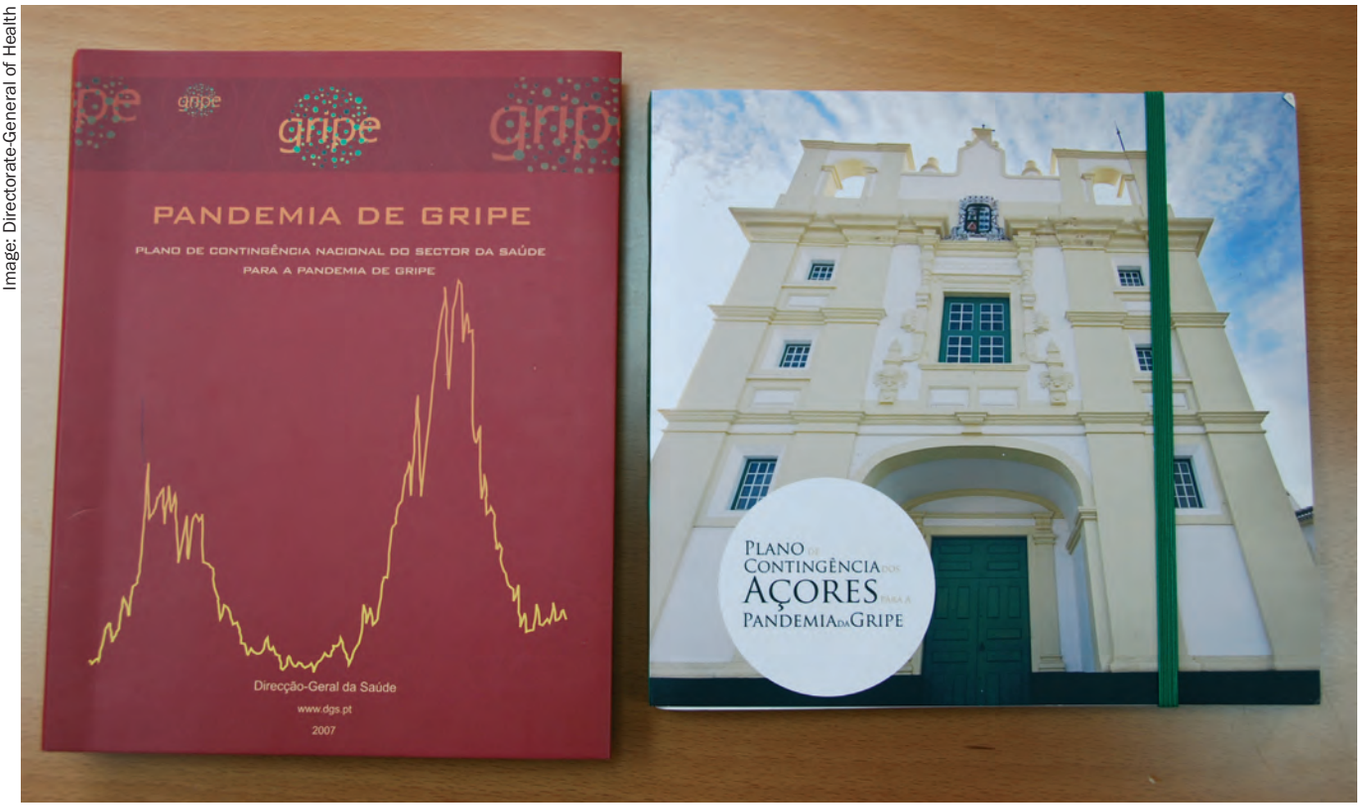
The network of health authorities was initiated during the nineteenth century based on about 300 municipalities. In 1898 it was enriched with a National Laboratory of Public Health, later nominated Instituto Nacional de Saúde Dr Ricardo Jorge. At local level, public health services performed both environmental and personal activities. These focused mainly on preventive programmes (such as immunization), care of specific health risk groups (for example, maternal and child health), and the control of endemics (such as tuberculosis).

In 1971, relevant legislation paved the way for changes in Portuguese public health, with the implementation of an extensive network of health centres and a career structure for health professionals, including a well-defined medical public health career. In fact, the Portuguese health centre experience pioneered the concept of health care systems based on primary health care.

Since 1979, the implementation and development of the National Health Service (NHS) have been influenced by different prevailing political models and management capabilities. It seems apparent that the Portuguese NHS brought about public health without a highly visible public health service, a consequence of the integrative logic adopted. Since then a key challenge and a critical issue has been how to foster a coherent public health philosophy, explicit public health policies, significant health promotion actions, and a steady development of public health training and research in the absence of a specific public health structure. However, private practice was never limited, and in order to face a health crisis or health management problems, efforts are likely to be seen that aim to involve all hospitals and ambulatory health care units, in public and private sectors. Nowadays, the NHS includes 21,024 medical doctors and 36,812 nurses, with 35 per cent of doctors and 23 per cent of registered nurses integrated in primary health care units.[4]

Epidemiological surveillance has been facilitated through mandatory notification of communicable

Image: Directorate-General of Health



Portugal has already published its own contingency plans for pandemic influenza

diseases. In 1926, a public health reform was carried out, and a legal document was published with the first list of diseases under mandatory notification. The legislation was updated in 1949, when the list of diseases was extended and the system improved.

In 1996 the Sistema de Alerta e Resposta Apropriada (SARA), a system of alertness, was implemented, maximizing communication technologies in order to improve public health practices of based on relevant knowledge. In 1998, an in-depth revision of the list of diseases under notification was performed, following which hepatitis C and HIV/Aids infection were included.

The National Vaccination Programme (NVP) was initiated in 1965 with a vaccination campaign against polio, which led to the virtual disappearance of the disease. The NVP is universal and free. It currently includes vaccines against 12 diseases: diphtheria, tetanus, whooping cough, polio, tuberculosis, measles, mumps, rubella, hepatitis B and infections by Hemophilus influenzae type B, Meningococcal type C and Human Papiloma Virus.

Saúde 24, a multichannel contact centre, is a new service provided by the Portuguese NHS, implemented in 2007. Through nurses trained in the system, Saúde 24 provides information both on clinical and non-clinical situations. The scope of such information includes mainly specific situations related to acute care and drug-related problems, public health topics and general information on the availability of health care units. Mainly, Saúde 24 intends to help people approaching the health care system, facilitating the choice of the most appropriate unit to provide care for the presumed condition of health. It may also redirect contacts to other call centres, namely to the Emergency Centre and to the Intoxication one. So far, this call centre has received more than 860,000 phone calls with an efficacy rate of 95 per cent.

Health authorities and epidemiological surveillance

Nowadays, an efficient network of public health units ensures that the epidemiological surveillance system is maintained through a network of healthcare providers based in hospitals, general practice clinics and long-term care units, whether public, private or public funded.

In the practice of public health in Portugal, it seems relevant to emphasize the following aspects:

- Health authorities are selected among medical doctors specialized in public health, after an internship
- The keystones are the local units, connected by a reliable communication network to hospitals and other health services, and to the health authorities at regional and national levels
- Among health authorities a chain of command is well defined, from the national level (Director-General of Health) to the regional and to local levels
- Local health authorities are located in primary health care units, leading multidisciplinary teams in public health services. Whenever needed, intersectorial cooperation with others is developed and participation in local Civil Protection councils is mandatory
- At municipality level, there is a long and well-established tradition of cooperation aiming to promote health and prevent diseases, particularly in the control of communicable diseases

Incidence of diseases prevented by vaccination in the first year of vaccination and in 2007

Disease	Number/Year	2007
Diphtheria	1,512 (1965)	0
Polio	297 (1965)	0
Tetanus	373 (1965)	9
Whooping cough	858 (1965)	21
Measles*	813 (1987)	0
Mumps	2,197 (1987)	191
Rubella	671 (1987)	6
Hepatitis B	1,234 (1993)	64
Haemophilus influenza type B	24 (1999)	8

*Vaccine introduced in 1974, but new cases known only since 1987

Source: Directorate-General of Health

- The network of public health laboratories, under the coordination and supervision of the National Institute of Health, is crucial
- Professional careers in public health for doctors and for registered nurses, an internship in public health and graduate programmes (MSc and PhD in Public Health and associate domains) carried out by the National School of Public Health and several universities, are relevant in influencing the practice, namely the performance of any surveillance system.

The Director-General of Health is the Portuguese Chief Medical Officer. The Directorate-General of Health (DGS), the technical entity sponsoring the national health authority, is entitled to release guidelines aiming to assure preparedness and to control diseases, namely to coordinate epidemiological surveillance. DGS is closely articulated to European Centre for Disease Prevention and Control (ECDC), being the Portuguese competent body for surveillance, health threat preparedness and control, training, communication and scientific advice.

Since 2005, DGS has developed a special unit aiming to support public health emergencies. Its main objective is to detect signals that may become, after proper validation, public health alerts. After detection of the alerts, the DGS unit related to the specific alert triggers the necessary measures for risk management. This Public Health Emergency Unit (UESP) also helps to achieve effective means of communication to enable adequate response, giving an essential contribution to the development of the epidemic intelligence concept and to the early detection of public health threats. This unit ensures the management of the information system on the utilization of emergency rooms, which has been developed since 2003.

International cooperation

During the last century and particularly after the Democratic Revolution of 1974, Portuguese public health entities and professionals were entitled to receive relevant support, namely:

- Technical aid from WHO, particularly in the implementation of primary health care policies and during the organization of the NHS
- Participation in multi-centre research projects, networks and working groups led by the European Commission
- Graduate programmes, platforms, study visits, cooperation of consultants and auditors, provided by the universities and public health agencies of other countries.

Throughout the years, Portugal has developed programmes of international cooperation within the health domain, especially with Portuguese speaking countries — Angola, Brazil, Cape Verde, Guine-Bissau, Mozambique, São Tomé and East Timor. These agreements include giving hospitals medical aid to evacuate patients; technical missions to be carried out in the respective countries by Portuguese health specialists (for example in domains such as medical imaging, public health, cardiology, paediatrics, pneumology and immunoallergics); missions to support the organization and operation of the health services in those countries; training of the respective countries' health professionals through training periods in Portuguese institutions; and projects of scientific research.[5]

Aiming to develop specific epidemiological surveillance systems and to facilitate pandemic preparedness, cooperation between Portugal and the Portuguese speaking countries may be reinforced, in line with WHO guidelines.

Final remarks

Epidemiological surveillance requires tools — from adequate communication technology to laboratory facilities, and appropriate and highly motivate professionals.

Pandemic preparedness requires political will and social commitment, plus adequate epidemiological surveillance system(s) and appropriate control mechanisms within a context of effective public health leadership.

Arnaldo Sampaio, one of the most distinguished Portuguese public health leaders, used to teach: "In public health, do not adopt — adapt." Not easy! One can adopt guidelines and recommendations, case definitions and technical procedures; one may even have a well-made plan, developed with the support and expertize of technical advisers. Probably, it will be almost nothing without the expertize, practical experience, social engagement and good will of professionals, particularly at community level.

Being prepared to face a public health crisis, each community — from local to national level — shall have a global and integrated (public) health system. It is with the *blood, sweat and tears* of professionals, mainly from those who work in the community and with patients, that the tasks and activities will be accomplished. From the recognition of needs to evaluation, and the emphasis of actions to control problems, the most important actors are the local people.

Pandemic preparedness cannot be reduced to a splendid discourse of politicians and public health officers. 'Be prepared' means motivation, competence and leadership in community action to solve problems. Public health is action, and requires social investments, sustainable efforts and continuous training.

HIV/Aids Vaccine Research — how many more false dawns?

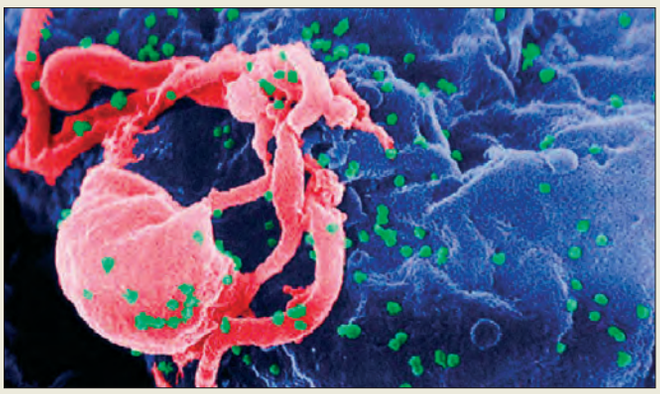
Dr Muhammad Ali Dhansay, Vice-President, Research, South African Medical Research Council

HIV remains a global health problem of unprecedented dimensions. Unknown 25 years ago, HIV has already caused an estimated 25 million deaths worldwide and has generated profound demographic changes in the most heavily affected countries. Sub-Saharan Africa remains the region most heavily affected by HIV, accounting for 67 per cent of all people living with HIV and for 75 per cent of Aids deaths in 2007.[1]

Globally, there were an estimated 33 million people living with HIV in 2007. The annual number of new HIV infections declined from three million in 2001 to 2.7 million in 2007. Overall, two million people died due to Aids in 2007, compared with an estimated 1.7 million in 2001. Southern Africa continues to bear a disproportionate share of the global burden of HIV: 35 per cent of HIV infections and 38 per cent of Aids deaths in 2007 occurred in that sub-region.

Women account for half of all people living with HIV worldwide, and nearly 60 per cent of HIV infections in sub-Saharan Africa. Young people aged 15-24 account for an estimated 45 per cent of new HIV infections worldwide. An estimated 370,000 children younger than 15 years became infected with HIV in 2007. Globally, the number of children younger than 15 years living with HIV increased from 1.6 million in 2001 to two million in 2007. Almost 90 per cent live in sub-Saharan Africa.

Scanning electron micrograph of HIV-1 budding from a cultured lymphocyte



HIV has caused an estimated 25 million deaths worldwide

Source: Cynthia Goldsmith, Centers for Disease Control and Prevention

Sub-Saharan Africa's epidemics vary significantly from country to country in both scale and scope. Adult national HIV prevalence is below two per cent in several countries of west and central Africa, as well as in the horn of Africa, but in 2007 it exceeded 15 per cent in seven southern African countries (Botswana, Lesotho, Namibia, South Africa, Swaziland, Zambia and Zimbabwe), and was above five per cent in seven other countries, mostly in central and east Africa (Cameroon, the Central African Republic, Gabon, Malawi, Mozambique, Uganda and the United Republic of Tanzania).

The estimated 5.7 million South Africans living with HIV in 2007 make this the largest HIV epidemic in the world. Meanwhile, the 26 per cent HIV prevalence found in adults in Swaziland in 2006 is the highest prevalence ever documented in a national population-based survey anywhere in the world.[2]

Despite increasing access to highly active antiretroviral therapy and community-based prevention initiatives, over the past decade at least 40,000 Americans have become HIV-infected each year. The Aids epidemic in the US is increasingly affecting African Americans, who comprise more than half of the new infections while constituting less than 15 per cent of the US population.

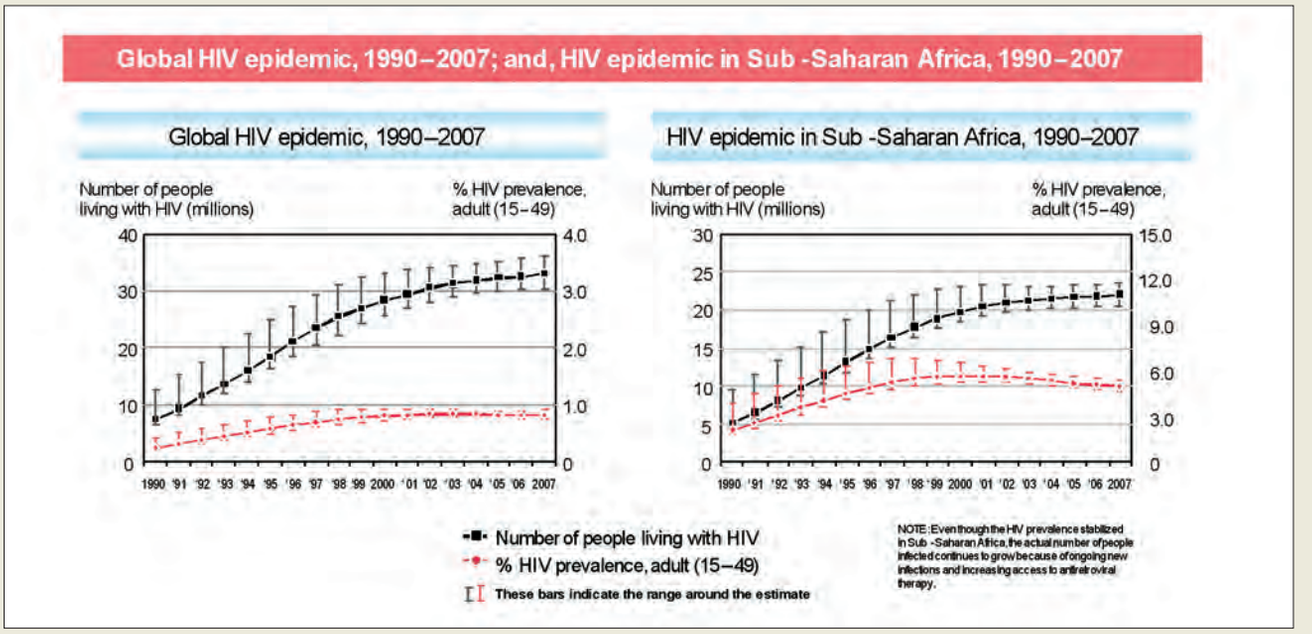
The response

Since the start of the global response to the HIV epidemic, prevention has been overshadowed by treatment. "We cannot treat our way out of this pandemic. For every two patients placed on antiretroviral drugs during 2007, five new HIV infections occurred. A renewed and revitalized movement for HIV prevention is now required," said an article in the Lancet. The reality is that the pandemic will not be defeated without effective, multiple prevention strategies — biomedical, behavioural, and structural interventions. The emphasis on prevention is an attempt to address the 2.5 million new HIV infections every year, together with the long-term consequences for children and communities. A safe and effective HIV vaccine would be an enormously valuable tool in the campaign to stop the spread of HIV.[3]

HIV vaccines

The development of an efficacious HIV vaccine is one of the world's greatest public health challenges. The

Estimated number of people living with HIV and adult HIV prevalence



Sub-Saharan Africa bears a disproportionate share of the global HIV burden

Source: UNAids Report 2008

absence of a known correlate of protection and the widespread genetic diversity of the virus pose substantial scientific hurdles, and this remains one of the greatest challenges in developing an effective HIV vaccine.

The vision of the African Aids Vaccine Programme (AAVP), an initiative sponsored by the World Health Organization (WHO) and the Joint United Nations Programme on HIV/Aids (UNAids), is an Aids-free Africa through an effective vaccine. The AAVP is a network of African HIV vaccine stakeholders committed to promoting HIV vaccine development for Africa through research, advocacy, partnership and contribution to capacity strengthening and policy development.

In southern Africa, subtype C accounts for over 95 per cent of infections (19-22). Subtype C is also largely responsible for the epidemics in Ethiopia and India, and accounts for over 50 per cent of HIV-1 infections globally. In response to the devastating subtype C epidemic in southern Africa, the South African Aids Vaccine Initiative (SAAVI), a lead programme of the South African Medical Research Council (MRC), in collaboration with the University of Cape Town and the US NIH, developed two subtype C HIV vaccines — SAAVI DNA-C2 and SAAVI MVA-C — to be employed together in a prime-boost protocol.

In light of the AAVP goals, it is heartening to note that the first Aids vaccine constructed and developed in Africa is currently being tested in the US — so much for being dubbed 'third-world'! This trial will examine the safety and immunogenicity of the candidate vaccines, in both a subtype C region (South Africa) and a subtype B region (US), as part of the scientific agenda of the HIV Vaccine Trials Network to find vaccines that will prevent HIV infections in adult and adolescent populations globally.

It is extremely important for developing nations, and especially Africa, to build the capability of manufacturing vaccines, since it is unlikely that stockpiles of critical vaccines will be made available to them should there be a global pandemic of, for example, avian influenza. The lessons learned from research and development in the Aids vaccine field will go a long way to help build this capacity. An example of this is the Biovac Institute, which has partnered with SAAVI and is also in talks with the Istituto Superiori di Sanità in Italy to support its vaccine manufacturing capability. The latter is part of the Italy-South Africa Programme to support the Ministry of Health of South Africa in the implementation of a national programme of global response to HIV and Aids.

Despair among HIV vaccine researchers

While an HIV vaccine remains the primary goal for a comprehensive strategy to curb the global HIV pandemic, the path to success is unknown and has become more complicated. In 1984 Margaret Heckler, Health and Human Services Secretary under US President Ronald Reagan, told Americans: "We hope to have a vaccine ready for testing in about two years." This was after scientists had identified HIV as the virus responsible for Aids.

Originally, vaccine research focused on identification of immunogens that would elicit neutralizing antibodies to prevent infection. Two phase-3 trials did not find any protection against HIV infection. Nonetheless, efforts to design vaccines that elicit antibody responses continue. The importance of T-cell immunity in containing HIV infection was influenced by studies of early infection in people and experiments on non-human primates.

The results of the recent failed vaccine clinical trial (Step Study), however, have profoundly affected the HIV vaccine development field. Participants receiving the vaccine, who had higher pre-existing levels of adenovirus

type 5 antibodies, had more HIV infections. A second phase-2 proof-of-concept trial of a T-cell vaccine candidate, the Phambili study in South Africa, was interrupted as a result of the findings of the Step Study. The failure of the T-cell vaccines has led to a re-examination of the HIV vaccine field, and the need to broaden research directed at answering fundamental questions in HIV vaccine discovery through laboratory, non-human primate, and clinical research was recognized.

The world's leading scientists have stopped talking about vaccine targets, instead favouring terms such as 'incremental advances'. The only timeframe mentioned with any confidence is 2031 — the end point for a United Nations Aids research programme, when a vaccine 'could be available'. But that does not mean that the quest for a vaccine, and the funding it requires, should be diverted in any way.

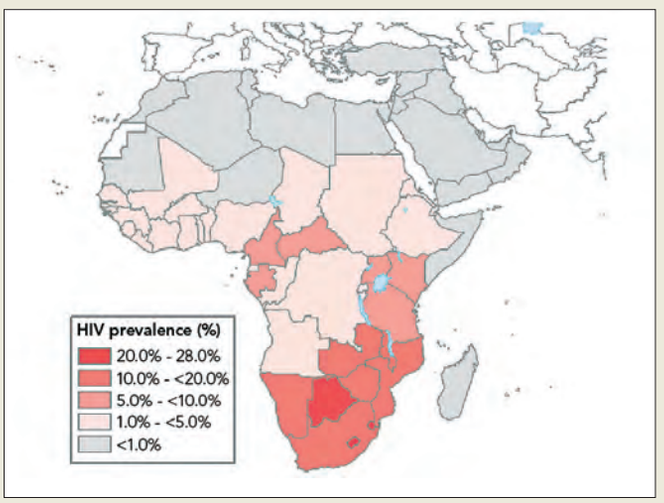
The development of a polio vaccine was decades in the making. In the 1930s claims of imminent success began to circulate, but polio continued to cripple thousands of children every year in industrialized countries. However, soon after the introduction of effective vaccines — OPV — in the late 1950s and early 1960s, it was practically eliminated as a public health problem in the western world.

Microbicidal gels could be the key to HIV control, but they will never have the blanket disease eradication power of a vaccine. A medication that relies on repeat applications by an individual remains open to considerable human error. The vaccine can generate herd immunity to the point where, with a single jab, whole populations can live free of the condition. It may take another 20 years, but it will be worth the wait; the historic success of vaccines argues that HIV vaccine research must be continued and accelerated.

Beyond the HIV vaccine

The Lancet editorial continues: "We must increase the health-systems strengthening element to our policy and practice. We must continue to argue for more funding. We need to rethink our approach to evaluating prevention. And we must find better ways to enhance coordination between international and national actors. The very distinction between treatment and prevention is false. Both are inextricably connected. Countries need to develop context-specific national preventive strategies, not off-the-shelf slogans dreamt up by donors. Prevention needs to embrace the political, economic and social determinants of risk too. The HIV/Aids community must be more honest about admitting its failures — the absolute amount of preventive practice and science has simply been too little. The mix of interventions has been wrong. Leadership and management of programmes to deliver these interventions have been weak. It is fair to say that, despite greatly increased resources, the state of the response to Aids is currently at a vulnerable moment. Implementation of prevention strategies has been, at best, uneven across countries — in too many instances, almost non-existent. There is still a risk of complacency. Even Aids activists have badly neglected prevention advocacy."

HIV prevalence (%) in adults (15-49) in Africa, 2007



Source: UNAids Report 2008

Twenty-five years after Aids was first reported, an institutional, commercial, professional, and even civil society industry now controls the global response to Aids. Each party, in good faith, has a position to defend, a strategy to advance, and probably someone to oppose.

It is time for new voices in Aids to ask questions, to disrupt axes of power, and to disturb the air.[4] The lessons learned over the past 25 years should be used to provide the foundation on which to build comprehensive, sustainable, nationally owned responses that are vital to the ultimate control of this pandemic.[5]

The question of rights of participants, access to standard of care and of possible research injury in HIV biomedical prevention trials[6] are relevant, considering the unfavourable results of HIV vaccine trials thus far and the risk of becoming HIV positive. The role of ethics committees, data and safety monitoring boards and community advisory boards in this context is therefore critical, where the participants are usually socio-economically deprived.

The South African HIV/Aids Research and Innovation Platform (SHARP) has recently been established by the Department of Science and Technology and is being managed by LIFElab. It has the objective of increasing the number and quality of South African developed products and services for the prevention and treatment of HIV/Aids through increased support for basic and applied research, development and innovation in the areas of anti-retrovirals, microbicides, vaccines and diagnostics.

"In recent weeks we have seen governments across the world working together to solve the global financial crisis," says Stephen Matlin of the Global Forum for Health Research. "No one country can ignore what has been happening, and by working together, governments know they have more chance of affecting real change. In the same way, the global community must act together to invest in health research and achieve global health gains." Similarly, the academic and biotechnology sectors globally need to partner and collaborate in seeking the elusive holy grail of a safe and effective HIV vaccine. Further, the recent USD100 million gift to create an institute to jumpstart the search for an HIV vaccine in Cambridge, USA, is a positive development in view of shrinking endowments and broke donors, as a result of the global economic slump.

Infectious disease control and emergency management: the Swedish approach

Dr Johan Carlson & Dr Anders Tegnell, National Board of Health and Welfare, Sweden

Sweden is a country of some nine million inhabitants in the north of Europe. It is administratively organized into 21 counties, which are responsible mainly for the health care, and 290 municipalities, which are responsible for most other services to the inhabitants.

The Swedish system for communicable disease control is decentralized to a very high degree. The major operational role lies within the 21 counties, varying in size from less than 100,000 inhabitants to more than two million. In some of the counties with small populations, the geographical area might be very large, with a dispersed population. Each county has a medical officer in charge of communicable disease control, who has a coordinating function regarding the operational activities in the area.

Image: Matton

National stockpiles of antivirals and antibiotics have been purchased to ensure that a variety of drugs is available whenever possible to deal with future changes in resistance among viruses and bacteria

At national level the National Board of Health and Welfare (NBHW) fills the national coordinating function, but also develops guidelines and directives and supervises activities in the counties. The Swedish Centre for Communicable Disease Control (SMI) is the national node for the surveillance system, and is tasked with developing the knowledge that forms part of the basis for the normative activities of the NBWH.

The general principle for the responsibilities for preparedness and the management of a crisis is that it should be in the hands of the same actor as the one who is in charge of them in peacetime. This means that responsibility for planning for healthcare and communicable disease control during a pandemic lies with the healthcare authorities, and in practice pandemic planning for healthcare is often an integral part of the hospitals' emergency plans. For emergency planning in other sectors the municipalities have a central responsibility, while coordination for a bigger geographical area lies with the county administrative boards.

Planning assumptions

Pandemic planning needs to be based on a concept of the effects that the pandemic will have on people and on the society. Several sources can be used to develop this concept, but the main source is the knowledge of previous pandemics and, to a certain extent, the yearly epidemics of seasonal influenza. However, these give only a possible scenario, and the likely variations are big. This is accepted in the Swedish planning process, and the solution is an adaptable planning were many details in the plan will have to be left for rather late adjustments. Things that might be adjusted are, for example, needs for hospital beds, risk groups that need special resources and others. However, some assumptions need to be made in case no better data becomes available. Swedish assumptions are that the pandemic will start somewhere outside Sweden and that it will resemble the Hong Kong or Asian pandemic rather than the Spanish influenza.

One assumption that has increasingly become a focus of the planning is that the pandemic will affect major parts of society. Many people will be ill at one time and there will be a lack of manpower in many of the functions of

society. The effect of this might be worse than in previous pandemics since many functions these days are manned by far fewer people than in the past. The consequence is that many, if not most parts of society need to plan for a pandemic, and especially how to deal with a loss of manpower.

Another difference with the past in Sweden is that the number of hospital beds and staff is less now than in the past, in spite of a larger population. Hospitals need to plan carefully for an increased demand for healthcare, especially since they might also lose manpower.

A third important aspect is that communication will be perhaps the most important task of the national actors. In today's world both the general public and many other agencies will have huge requirements for information about the pandemic and about how to act in their own individual situation. Failing to communicate relevant information in a timely and trustworthy way could harm the relations between the public and several supporting functions of society, and worse, could hinder the management of the outbreak. Once a crisis such as this is underway, there would be little time for preparation and coordination. Therefore, national agencies need to plan well in advance for strategies and action to meet the demands for communication.

Finally, a pandemic will be an international concern and collaboration between countries and with international agencies will be an important task. This will present an opportunity to share good practices about how to deal with the pandemic and thereby increase the possibilities for effective action. However, it will also mean that adequate resources must be allocated for this collaboration.

Planning activities so far and in the future

Planning for a pandemic in Sweden had taken place over the years, and plans did already exist in many of the counties on how to deal with the problem at local level. But the major national concerted effort took place in 2004 when the Government asked the NBHW to develop a national plan, which was delivered in early 2005. This planning process and the spread of H5N1 over the world showed that much more needed to be done before Sweden would have an acceptable capacity to deal with a pandemic. With a more detailed mission from the Government and some extra funds the NBWH could start a more coordinated effort to improve pandemic preparedness.

The planning has moved ahead in four major areas. The first has been to ensure the availability of medical measures that could be used to alleviate the effects of a pandemic — mainly vaccine, antiviral drugs and antibiotics. In spite of the counties having the responsibility to deliver healthcare, it was deemed necessary for the national state to take a responsibility in these areas to ensure an optimal preparedness. Early in the process it was unclear what would be the best strategy to ensure vaccine supply and a rather big effort was made to investigate if a national or Nordic production facility should be developed. However, when the big international manufacturers quickly improved global production, an advance purchase agreement was signed instead. National stockpiles of antivirals and antibiotics were purchased in an effort to ensure a variety of drugs would be available whenever possible to deal with future changes in resistance among viruses and bacteria. Recently the logistics of bringing these products to the people who need them during a pandemic has been

Image: Staffan Larsson

To support health staff in an already stressful pandemic situation, training materials are being developed, with the aim of helping in handling the situation at work and communicating on an inter-personal level

Image: Staffan Larsson

Management of a crisis shall be in the same hands as in peacetime. Planning for healthcare is often an integral part of hospitals' emergency plans

developed and even tested in an exercise involving two of the counties.

The main part of the operational activities in healthcare and communicable disease control takes place in the counties, and the first version of the plan already took this into account by developing a special guidelines document for local planning in the counties. It includes a number of technical documents focusing on different areas, among others the use of antivirals and hospital hygiene during a pandemic. Over the last two years, different kinds of assessment of Swedish pandemic planning have been carried out. While the European Centre for Disease Prevention and Control visited Sweden and made its assessment report in 2007, the national audit office examined various Swedish authorities and their work with pandemic planning. In 2008, the NBHW visited all the 21 counties in order to follow up the development of county plans. In the light of these findings, the national plan and the guidelines for local planning will once again be revised during the first half of 2009.

As mentioned above it has been realized that communications during a pandemic will be one of the major challenges. In collaboration with other national authorities, tools for these activities have been developed and to a certain extent tested during the recent avian influenza scare.

The measures being taken are aiming to satisfy needs within three main areas: to provide to the general public appropriate guidance and means to act according to the situation; to make clear to everyone involved the areas of responsibility of national and local agencies; and to prepare a system of cooperation and action for successful and trustworthy communication whenever needed. Some investigations on attitudes to the pandemic among the public and health staff, and their expectations of information during a pandemic, have also formed a basis for the strategies and materials that are now being developed. Great importance is attached to the role of healthcare workers. To support health staff in an already stressful pandemic situation, training materials are being developed, with the aim of helping in handling the situation at work and communicating on an inter-personal level among worried patients, colleagues and family. Measures also include information materials for the public on different areas of knowledge identified as important during a pandemic, such as basic hygiene measures and ways of transmission of influenza. National as well as international collaboration has been very useful in the development of strategies, messages and channels of information.

Finally, in collaboration with the Swedish emergency management agency there has been a major effort to improve preparedness in society as a whole, especially to keep essential functions running during a pandemic. A tool to identify these functions has been developed, and guidelines for how these functions should plan are available. A follow-up during 2007 showed that this is a difficult task but that many innovative efforts had been made that have considerably improved our preparedness.

Planning ahead

Swedish pandemic planning has evolved from a medical communicable disease perspective to a realization that a pandemic will affect all of society, and therefore all aspects of society need to be involved in preparedness. Swedish preparedness for a pandemic has improved during recent years. However, both according to our own evaluation and that of international reviews Sweden, like most other countries, still has some way to go. This can be achieved in Sweden as in other countries with the continued commitment — political and economic — of a broad collection of responsible actors from all parts of society. There will also be a need for coordination and support at international level.

Preparation for an influenza pandemic in Switzerland

Dr Patrick Mathys, Head of Pandemic Preparedness Section, Federal Office of Public Health, Switzerland

Although avian influenza is no longer making the headlines of the Swiss and European media, in Asia and Africa more and more people who are in close contact with infected poultry are becoming infected. The virus could mutate at any time and become easily transmissible between humans, triggering an influenza pandemic. As the situation has hardly changed since 2005, preparation for a pandemic remains a major task for the authorities. The updated Swiss Influenza Pandemic Plan was published early in 2009. Such preparation is not only up to the authorities of the federal government and the cantons — all levels of society, including private companies and the population must also contribute.

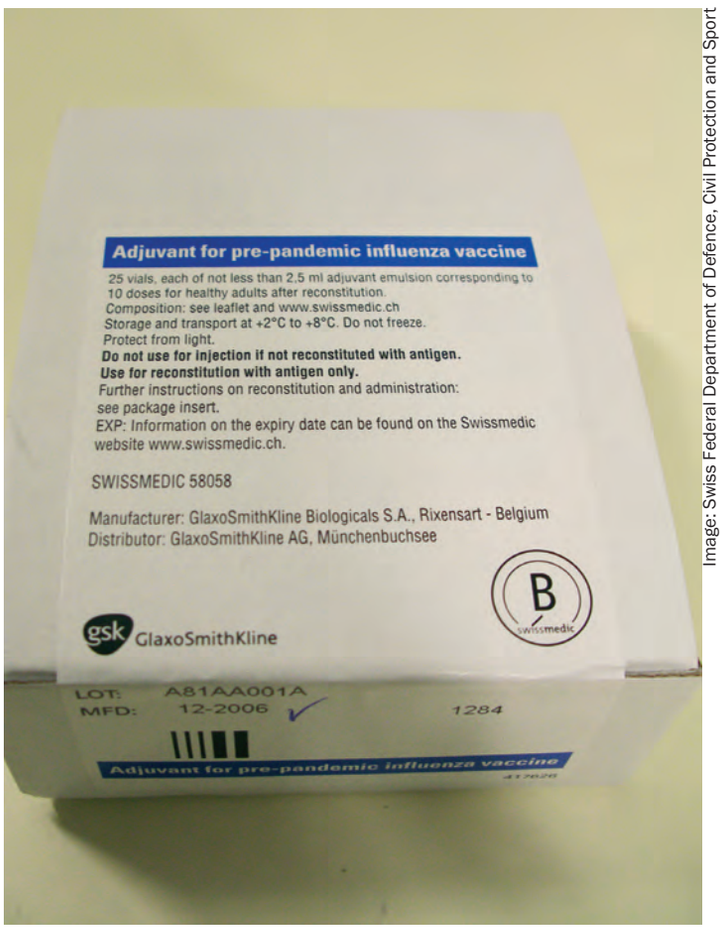


Image: Swiss Federal Department of Defence, Civil Protection and Sport

Adjuvants stored for prepandemic vaccination

The World Health Organization (WHO) considers the flu pandemic as one of the three major global threats, along with the food crisis and climate change. In her opening speech to the 61st World Health Assembly in May 2008, the Director General of WHO recommended that we remain vigilant and that preparations should not be reduced. Consequently, preparation for an influenza pandemic is still very important for the federal and cantonal authorities in Switzerland.

If pandemic flu broke out in Switzerland today, of the same strength as the 1918 Spanish flu, and if no measures were taken in the area of public health, then about two million people would become ill and about ten thousand would die.

Swiss Influenza Pandemic Plan — in brief

According to the legislation on epidemics, the federal government and the cantons are responsible for combating pandemics. At the federal level, the Federal Department of Home Affairs (FDHA) coordinates combating pandemics. On 27 April 2005, the Federal Council approved the Ordinance on Measures to Combat an Influenza Pandemic, through which the Influenza Working Group was set up. This extra-parliamentary commission was assigned the mission of advising and supporting the authorities on all matters connected to seasonal flu and the possibility of an influenza pandemic. The main task of the commission is to continue developing and regularly updating the Swiss Influenza Pandemic Plan. This work will be done in cooperation with the Federal Office of Public Health (FOPH), the Federal Commission on Vaccination Issues, the National Ethics Commission and experts called upon from time to time. The Swiss Influenza Pandemic Plan is based on the scientific data available, the recommendations made by WHO, and experience from previous pandemics.

The plan should first and foremost provide the strategic basis for early detection of an influenza pandemic and to combat its consequences. In the plan, measures are described which have been developed so as to react as quickly as possible. The plan also provides the cantons, companies and organizations in the private sector with basic information so they can develop their own contingency plans to combat pandemics.

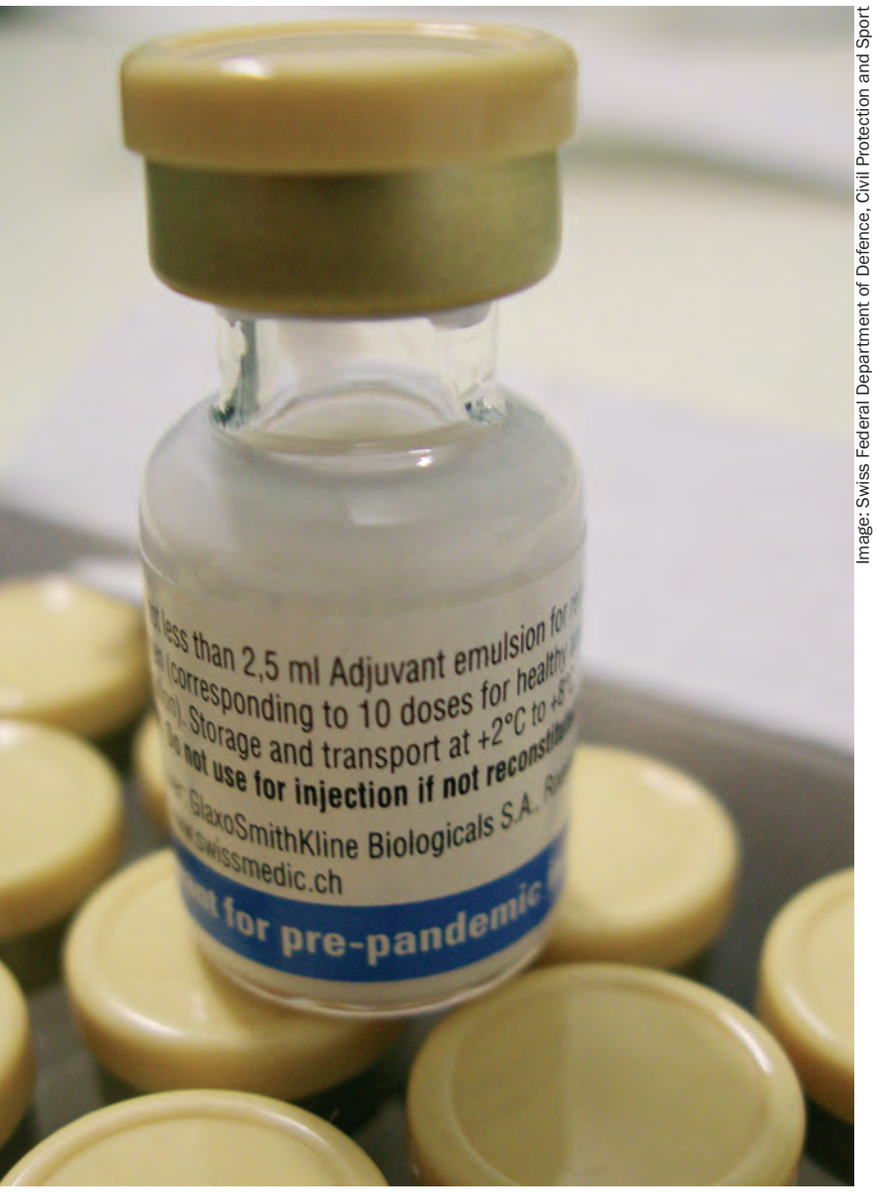


Image: Swiss Federal Department of Defence, Civil Protection and Sport

Adjuvants (GlaxoSmithKline) stored for prepandemic vaccination

The strategy is based on the following principles:

Preventing the virus from entering the country — If the monitoring systems for human and animal diseases in another country discover a new virus, then its introduction into Switzerland, and in particular contact with people and animals, must be prevented.

Prevention of adaptation of the animal virus to human beings — In the event of an animal infection, each focus of the virus has to be eliminated, secondary infections are to be prevented and situations must be avoided in which human beings would come in contact with the virus.

Preparation of the health system — All appropriate measures are to be taken in the area of public health to slow down and limit the spread of the virus between people and to ensure that the provision of healthcare runs smoothly.

Provision of specific medicines — The storage of antiviral drugs, antibiotics, vaccines and various sorts of protective equipment makes it possible to prevent a shortage of supply.

Vaccination of the population — The administration of a pre-pandemic vaccine and then of a pandemic vaccine are the most effective population-based measures to reduce the number of patients and the severity of the disease.

Ensuring the provision of basic services to society — Institutions and businesses have to continue to function, despite a high rate of absence.

Information for health personnel, the authorities and the population.

Development of the Swiss Pandemic Plan

The development of the Swiss Pandemic Plan entails four stages: monitoring, prevention, treatment, and non-medical measures, as outlined below.

Monitoring

Subtype H5N1 of the influenza A virus has been detected in various species of wild birds in Europe. Therefore, it cannot be ruled out that this subtype could again be brought into Switzerland by wild birds and spread here. To assess this danger in a more precise way, wild birds are monitored in two different ways: passive monitoring is mainly concerned with dead or sick birds, whereas active monitoring involves the investigation of live birds.

In addition to monitoring, Switzerland, Germany and Austria initiated a joint three-year research programme (2006-2008) in the region of Lake Constance (the 'Constance' research project). The objective was to improve our understanding of bird flu and the mechanisms by which it spreads, and to increase our knowledge in order to protect poultry and wild birds more effectively and in a more specific way from any possible introduction of bird flu.

In addition, the monitoring of birds also contributes to achieving the overall objectives of monitoring bird flu in Switzerland:

- Reduction of the risk of animal to human transmission, with immediate establishment of any transfers that could lead to the occurrence of a form of the virus completely adapted to human beings
- Prevention of infections in exposed people, for example personnel involved in combating epidemics in animals; or prevention of transmission to those surrounding a diseased person, such as medical staff in particular
- Prevention of the introduction of the virus by means of early detection of any sick people who have travelled to Switzerland, in order to limit or delay the spread of the virus.

In relation to the monitoring of human beings, during the pandemic alert period the emphasis is on early detection of cases of infection with a new HxNy influenza virus subtype that has pandemic potential. The objective is to halt the spread (phases 3 and 4) or at least to delay it (phase 5, beginning of phase 6). Hospital doctors and laboratories play an important part in this, and have the duty to notify the competent authorities within two hours.

Doctors working in hospitals must report suspected cases according to specific, clearly defined criteria to the competent cantonal authorities, which will transmit the notification to FOPH. Diagnostic laboratories must notify any confirmation of the new influenza virus subtype to the competent cantonal authorities and to FOPH.

For this purpose, FOPH has established an on-call service, according to the guidelines in the International Health Regulations (IHR).

Prevention

Vaccination is one of the most effective measures to limit the damage caused by an influenza pandemic. For this reason, on 18 October 2006 the Federal Council instructed the Federal Department of Home Affairs (FDHA) to procure eight million doses of pre-pandemic vaccine from GlaxoSmithKline (GSK), in order to protect the entire resident population of Switzerland. This is an H5N1 vaccine with an additive (adjuvant), which extends its effectiveness to virus strains related to the H5N1 virus currently circulating. This vaccine is stored in Switzerland. A clinical study evaluating the tolerability of the pre-pandemic vaccine in the working population and the simulation of a mass vaccination is currently ongoing.

In parallel with the purchase agreement for pre-pandemic vaccine, the FDHA has signed a reservation agreement for pandemic vaccine, to ensure rapid supply in the event of a pandemic outbreak. The pandemic vaccine will be more specific than the pre-pandemic vaccine, as it will contain the virus that caused the influenza pandemic. It can be expected that it would take about six months from the moment when a pandemic virus and its characteristics are well known until a vaccine can be developed and mass-produced.

The objectives of a pre-pandemic vaccine stockpile are as follows:

Minimize the spread of a mutated H5N1 influenza virus in Switzerland — Protective vaccination for the following risk groups (two doses of pre-pandemic vaccine):

- First line healthcare workers (HCW), laboratory personnel
- Persons in contact with infected poultry (poultry workers, veterinarians, cullers)
- Persons travelling to the affected countries in the framework of programmes to support them

Minimize the burden of disease during the pandemic — Priming of the population resident in Switzerland with one dose of pre-pandemic vaccine, after testing cross-reactivity with the new pandemic virus, followed by one dose of pandemic vaccine as soon as it becomes available.

Image: Swiss Federal Department of Defence, Civil Protection and Sport

Antigen (GlaxoSmithKline) stored for prepandemic vaccination

Treatment

According to the Ordinance on the Obligation to Store Reserves of Medicinal Products in April 2004, it became compulsory to store reserves of neuraminidase inhibitors (Tamiflu®). On 9 December 2005 the Federal Council decided to store enough Tamiflu so that 25 per cent of the resident population of Switzerland can be treated in case of an infection and about 250,000 health professionals who are directly exposed at work can be supplied with prophylaxis. This quantity meets the WHO recommendations. The Federal Office for National Economic Supply (FONES) is responsible for monitoring this obligation to store reserves and for organizing distribution to the cantons.

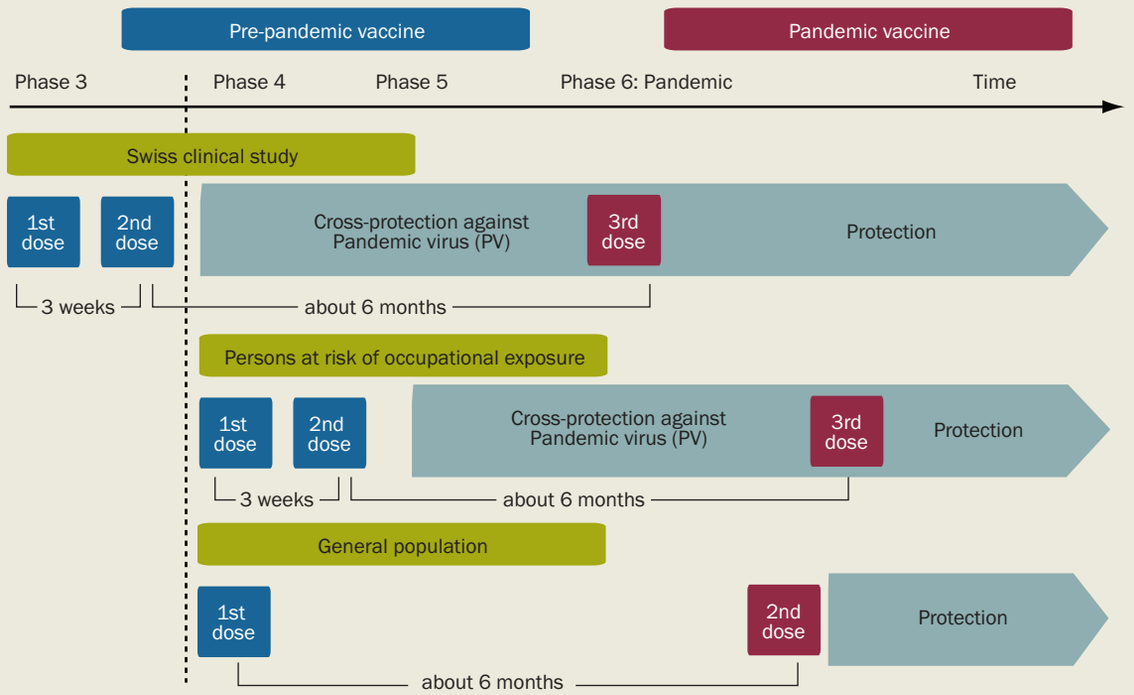
In addition, the federal government has stored an emergency reserve of 10,000 quickly available treatments, with FOPH responsible for managing and releasing the supply. This reserve is to meet any shortages of Tamiflu on the market, before release from the compulsory store.

During the last epidemic of seasonal flu, more strains of the influenza virus occurred that were resistant to Tamiflu. Therefore, an evaluation was started, including at the level of the European Union, to support a strategy for the use of antiviral drugs in case of a pandemic.

Non-medical measures

The following non-medical measures are envisaged, which are generally used to combat infectious diseases: isolation of patients; contact management and quarantine; social

Swiss strategy for pre-pandemic and pandemic vaccination



Source: Swiss Federal Office of Public Health

distancing (for example, limiting and banning national or international events, closure of schools); training on behaviour to provide personal protection (such as wearing face masks in certain situations).

FOPH has published recommendations for the population as a whole on personal hygiene in case of an influenza pandemic. These are part of an overall strategy, which includes further measures such as vaccination, the treatment of patients with antiviral drugs, and measures in the workplace. Personal hygiene measures can contribute to reducing human-to-human transmission of the influenza virus, thereby delaying or reducing the severity of the pandemic. They are mainly aligned with pandemic phase 6 according to WHO. They are directed toward members of the general public who are not occupationally exposed. The following measures are recommended:

Hand hygiene — Wash your hands regularly and thoroughly with soap and water.

Paper handkerchiefs — Hold a paper handkerchief in front of your mouth when coughing or sneezing. After use, throw the paper handkerchief in a waste bin. Then wash your hands.

Code of conduct in public — If possible, avoid close contact with other people. When speaking with other people, keep at a distance of at least one metre. When greeting people or saying goodbye, avoid handshakes, hugs and kisses.

Wearing a facemask in certain situations — The exact situations can only be determined after the appearance of the pandemic virus. However, members of the public are recommended to keep a supply of 50 facemasks (surgical masks), in order to prevent a shortage of supply. These masks are retailed.

As regards facemasks, there is a compulsory store supervised by FONES of about 250,000 FFP2/3 masks for medical personnel. Also, at the federal level, there is a supply of 30 million surgical masks. Ten million masks are for the federal administration personnel, and 20 million are to be used in case of an acute shortage of supply in the cantons, especially for health service provision or for people who have come into contact with sick people or who may be infected.

The State Secretariat for Economic Affairs (SECO), in cooperation with other partners, has drafted recommendations for companies, which are intended to provide them with support and guidance when planning measures in case of a pandemic. In particular there is a manual on how companies can prepare themselves, and a document answering the most frequently asked questions about the legal and economic aspects of preparing companies for a pandemic.

Evaluation by WHO

In October 2007, a delegation of experts under the leadership of the WHO Regional Office for Europe evaluated the preparedness of Switzerland for a pandemic. This audit showed that Switzerland is one of the best prepared countries in Europe. The evaluation pointed out the appropriate decisions taken by the Federal Council, and the efforts that have been made at various levels in Switzerland. In addition, it was recommended that the achievements be consolidated, that the motivation of the parties be maintained, and that the leadership role of the federal government be strengthened.

Progress report: the Taiwan pandemic flu vaccine R&D programme

Pele Choi-Sing Chong, Investigator and Director, Vaccine Research and Development Centre, National Health Research Institutes, Taiwan

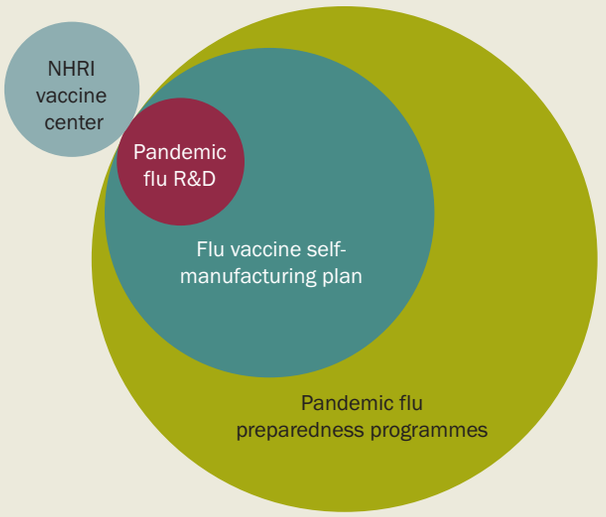
In early 2004, Professor Ih-Jen Su, the General Director of the Taiwan Centre for Diseases Control (CDC), invited experts from academic, private sectors and government agencies to a series of meetings and taskforces to gather opinions and suggestions for formulating a strategic plan for dealing with pandemic influenza. Three global strategic plans and policies were eventually recommended to the Taiwan Government: a policy preventing the introduction of highly pathogenic avian influenza virus (HPAIV) in Taiwan; the stock piling of anti-influenza drugs; and influenza virus vaccine self-manufacturing plans.

Under the current Director of Taiwan CDC, Dr Steve Kuo, the first two policies have been well implemented and no case of human infection has been reported so far. Taiwan CDC had purchased and stockpiled more than 2.3 million human doses of anti-flu drugs, Tamiflu® from Roche and Relenza® from GlaxoSmithKline (GSK) — sufficient to cover ten per cent of the Taiwan population. Taiwan has also built up self-manufacturing capability for Tamiflu. With the help of local county government agencies, the Department of Health created public awareness of HPAIV through media such as television, the Internet and a hotline (1922 flu Q/A hotlines). In addition, different levels of drilling exercises were performed in hospitals, ports of entry and poultry across the island during the last four years (2005-2008), to ensure each sector involved was prepared in the event of an influenza pandemic.

In late 2004, the taskforce for influenza virus vaccine self-manufacturing plans had several meetings and concluded that Taiwan needed a flu vaccine manufacturing plant to ensure self-supply of flu vaccine during a pandemic flu period. The goals of the Flu Vaccine Self-Manufacturing Strategic Plans were:

1. To become one of the world's top ten flu vaccine manufacturers within ten years
2. To have capacity for both a self-sufficient supply and an international health assistant programme of flu vaccines
3. To enhance Taiwan's biotechnology competitiveness.

Roles of vaccines in Taiwan pandemic flu preparedness programme

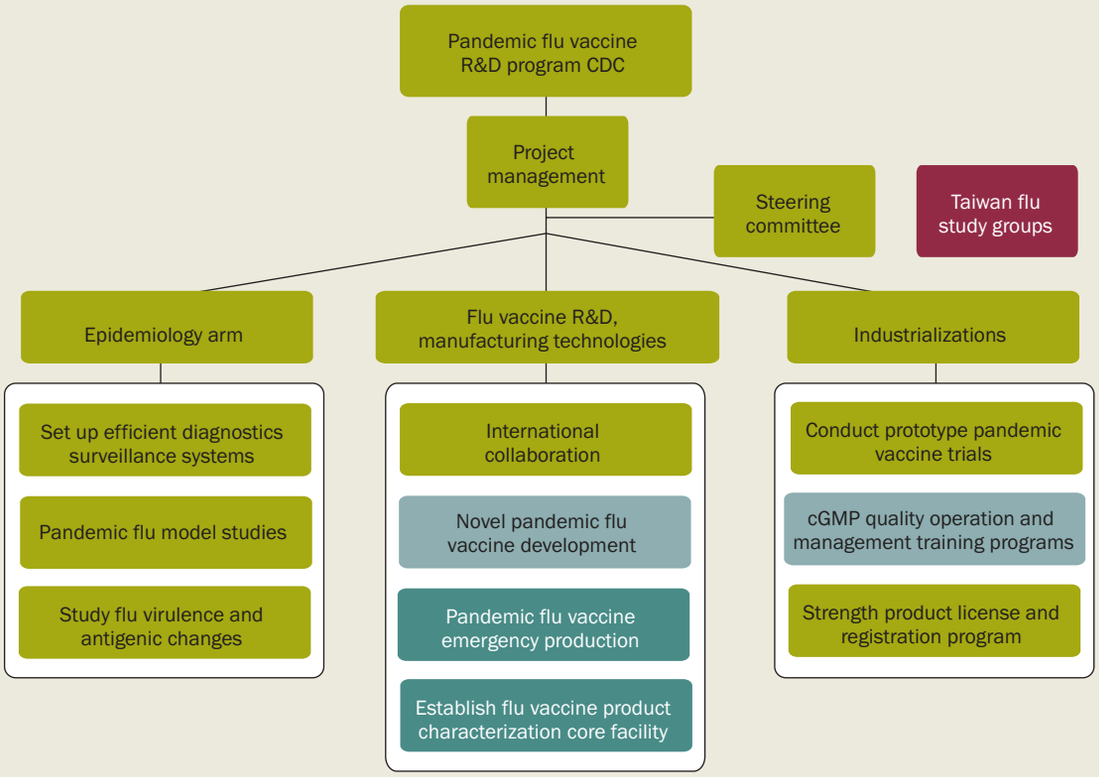


Source: Taiwan CDC and NHRI

The plans were approved by the Executive Yuan for funding from the Council for Planning and Development (CEPD). The Executive Yuan asked CDC to take the lead in implementing the strategic plans. In addition, President Lee of Academic Sinica proposed world collaboration at the APEC meeting, and the Taiwan Government was ready to contribute NTD600 million in research and development (R&D) for pandemic flu vaccines. In early 2005, Dr Steve Kuo invited Dr Chong of the National Health Research Institutes (NHRI) Vaccine Center to join CDC's pandemic flu working group meeting and asked Dr Chong to draft an R&D programme for pandemic flu vaccine to be reviewed by the Flu Vaccine Self-Manufacturing taskforces, and meanwhile to identify leading experts within Taiwan institutes to coordinate three areas of activity (epidemiology, international collaboration in vaccine R&D technology transfer, and industrialization).

Based on current scientific literature, when a flu pandemic occurs, 30 per cent of the population will be infected and 3-5 per cent of these patients will eventually die. The current anti-flu drugs (Tamiflu and others)

Strategies and direction for pandemic flu vaccine R&D in Taiwan



Source: Taiwan CDC and NHRI

will certainly play important roles in fighting the death rate, but pandemic flu vaccines must be available as soon as possible. Since we still do not understand the mechanisms by which pandemic influenza strains originate, the manufacturers currently do not know what the compositions of the vaccines should be, and cannot commit themselves to massive stockpiling of future vaccines. There is now capacity to manufacture about one billion doses of avian flu vaccine, but globally we need 6-12 billion doses. To minimize the risk of a shortage of vaccine supplies, the World Health Organization (WHO) urged that all governments should organize to implement regional flu vaccine manufacturing plans:

- To initiate and collaborate on a global pandemic flu vaccine R&D programme
- To assign a current Good Manufacturing Practice (cGMP) biological plant to develop flu vaccine emergency production
- If possible, to establish regional vaccine self-manufacturing facilities capable of producing 20 million doses.

To minimize the risk of flu vaccine supplies, the Taiwan Government has initiated plans:

- To purchase seasonal flu vaccine from different vaccine suppliers
- To establish a detailed competition purchase mechanism to control the cost of vaccines
- To implement an influenza vaccine self-manufacturing plan
- To initiate a pandemic flu vaccine R&D programme
- To assign NHRI/CDC to develop a flu vaccine production emergency plan.

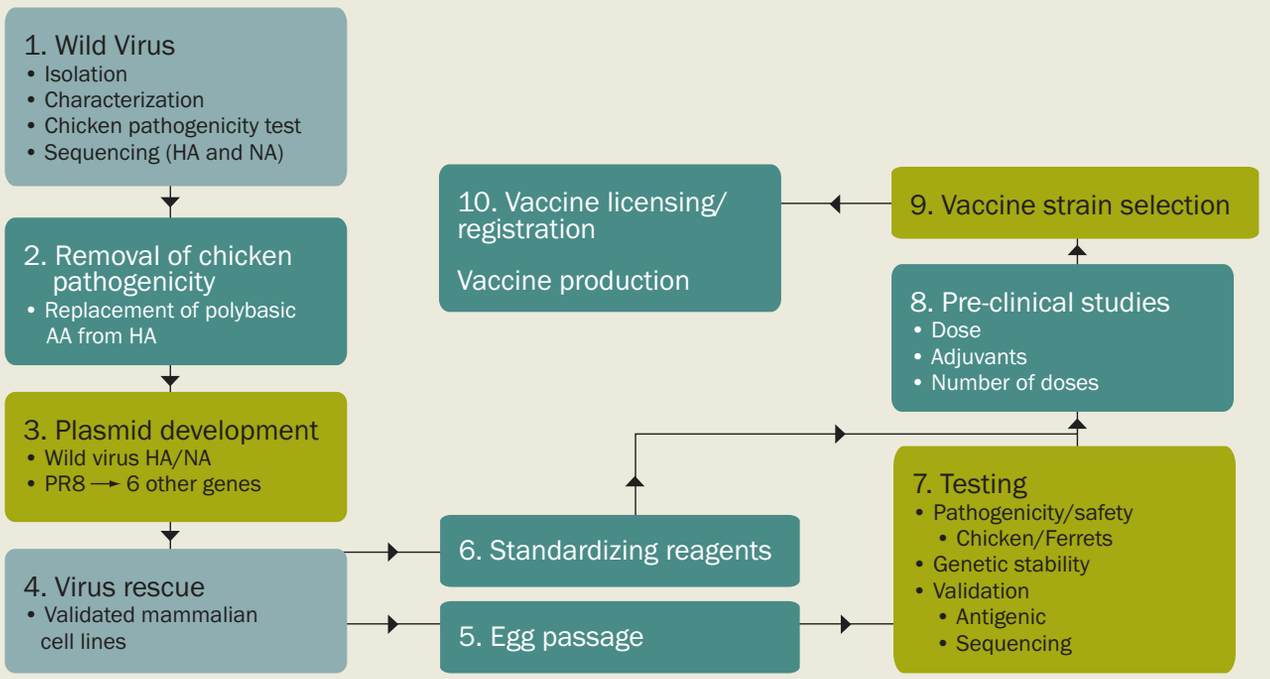
To develop a successful pandemic flu vaccine R&D programme and vaccine industry in Taiwan, the task-forces understand that we need all parties (academic, government and private industries) to work together with risk/profit sharing in mind. The NHRI Vaccine Center plays the transitional roles including pilot plants, cGMP-grade clinical materials production and cGMP quality management training, and initiates phase 1 and 2 clinical trials with Investigational New Drug (IND) submissions. Private industries invest to build manufacturing plants and take proven vaccine candidates to market by conducting phase 3 trials and developing global marketing strategies. Last but not least, the task-forces understand that government must provide long-term vaccine purchase policy and incentive packages. The three-year short-term R&D flu vaccine programme was initiated in 2006.

There follow some progress reports on the roles and achievements accomplished by this R&D programme to date.

Epidemiology

In order to ensure the creditability and critical mass to operate efficient surveillance systems for identifying novel influenza viruses and unusual clusters of respiratory infections in humans, an Influenza Epidemiology Steering Committee, headed by Dr Mei-Shang Ho of

Strategy for H5N1 vaccine development



Source: Taiwan CDC and NHRI

Academic Sinica, was organized to assist the Taiwan CDC Influenza Center.

Taiwan CDC has provided service contracts to Taiwan Institutes for analyzing the antigenic and genetic characteristics of influenza strains circulating in Taiwan for identifying the potential vaccine strains. The Taiwan CDC Influenza Center has been upgraded, and has developed efficient surveillance systems in data management and information documentation for the rapid identification of novel influenza viruses and unusual clusters of respiratory infections in humans. The surveillance systems currently provide easy access to raw data on flu viruses circulating in Taiwan, and biostatistical analysis for virus strain recommendation.

Taiwan CDC has initiated collaboration with WHO flu virus reference laboratories (in particular US CDC, Japan National Institute for Infectious Disease (NIID) and Hong Kong flu lab) by exchanging epidemiological data on influenza obtained from Taiwan regions.

A virus seed laboratory has been established to isolate, select and prepare master virus seeds for vaccine strains. To facilitate analyzing the antigenic and genetic characteristics of influenza strains circulating in Taiwan, CDC Influenza Center currently produces flu virus strain-specific ferret polyclonal antibodies. In addition, the flu centre has established a P3 research laboratory to produce pandemic flu virus mutations using reverse genetic reassortant technology.

In summary, the achievement of the Epidemiology team can be highlighted as follows. The surveillance team analyzed circulating seasonal flu viruses of the past three years (2004-2007) in order to:

- Identify and use regional circulating low reactor seasonal flu virus strains to prepare ferret antibodies as reference reagents
- Predict and suggest virus strains to the WHO vaccine strain selection committee
  - Poor children reacting to virus strains most likely to be circulating infectious virus in the coming season
  - Current information (2007) indicates one of the vaccine strains recommended by WHO would not match the coming seasonal flu virus
  - S.R. Shih and fellow authors indicated that the Asian strains circulated at least 18-24 months ahead of selected EU or US vaccine strains[1]
  - C.A. Russell and fellow authors found that if the trends observed during this period could be used to forecast each year based on the surveillance within E-SE Asia, this would enable consequent improvements to vaccine strain selection.

During this period, the Mass Immunization, Serology and Vaccine Strain Production team used seasonal flu immunization as a practice to establish mass immunization protocols:

- Established serology reference laboratories
  - Antigen-specific ELISA
  - Micro-neutralization assay
  - HI
- Used reverse genetic technology to create a vaccine strain based on H3N2-A/Taiwan/641/2006 virus strain in 45 days.

International collaboration in vaccine R&D and technology transfer

To ensure we will have a self-sufficient pandemic flu vaccine supply tomorrow, the flu vaccine self-manufacturing strategic plans provided financial assistance to the NHRI Vaccine Center, so it has the most technically competent staff and a cGMP pilot plant facility to manufacture prototype pandemic flu vaccine during times of emergency.

Through an R&D grant from the National Science Council and Department of Health Vaccine Center, NHRI has successfully:

- Collaborated with the Japan NIID for technology transfer, in particular flu QC tests
- Established a P2+ facility for emergency MDCK cell-based flu virus vaccine production at 100,000 doses capacity
- Developed bioprocesses to characterize potential virus seeds with both growth profiles and master seed files
- Implemented a cGMP pilot plant with a scale of 250,000 doses per three months for pandemic flu vaccine development.

NHRI has also:

- Established a collaboration agreement for international prototype pandemic flu vaccine clinical trials to be performed in Taiwan
- Assisted Taiwan vaccine manufacturer(s) to negotiate and obtain flu vaccine manufacturing technology transfer (cell-culture based vaccine production)
- Assisted Taiwan institutes in negotiating and obtaining intellectual properties for reverse genetic technology to generate pandemic flu mutant strains for vaccine production.

The NHRI Vaccine Center has achieved the following:

- Completed the MDCK master cell bank and RG-14 H5N1 virus seed validation
- Developed MDCK cell-based processes for emergency production of H5N1 vaccine candidates
- Completed pre-clinical toxicology studies
- Completed preliminary stability studies on the storage condition for vaccine bulk and alum-absorbed vaccine candidate
- Made ready more then 10,000 doses (based on 15ug of HA) of vaccine bulk for emergency use
- Implemented and validated essential QC tests
- Formulated the NHRI H5N1 vaccine candidate in alum, which could elicit protection against wild type H5N1 challenges in mouse models.

Industrialization

The Flu Vaccine Self-Manufacturing Task Forces had considered how to assist Taiwan CDC in drafting a long-term flu vaccine supply contract as the incentive plan for investors to build a flu vaccine self-manufacturing plant in Taiwan. The following terms of incentives have been put forward:

- A ten-year contract to supply four million doses of flu vaccine
- Technical assistance to build a flu vaccine manufacturing plant with a 16 million dosage capacity for seasonal flu vaccine
- Provision of flu vaccine marketing analysis and foreign financial assistance
- Technical assistance for the Taiwan Vaccine Company to negotiate and obtain intellectual properties for reverse genetic technology to generate pandemic flu mutant strains for vaccine production
- Technical assistance for flu vaccine manufacturing plants to set up cGMP QC lab for product release tests
- Technical assistance for flu vaccine manufacturing plants to produce clinical lots and initiate IND submission for phase 1, 2 and 3 trials.

Nobody knows when a pandemic flu will happen, but everyone knows that there will be a shortage of flu vaccines in the world. Vaccine stockpiling is one option that the Taiwan Government has taken. The question is how many doses we should keep each season, since flu vaccine have only a one-year expiry date. If we keep too much it will be very expensive. Some flu vaccine companies are working on antigen-sparing using adjuvants. For emergency cases during pandemic flu in Taiwan, we should have 0.3 to 0.5 million doses of current-year flu vaccines stockpiled. This is based on the adjuvant vaccines that are normally 10-50 times better than non-adjuvanted vaccines. Therefore, 0.3 million could be converted into three million doses. In this case, Taiwan CDC has supported those vaccine companies currently conducting antigen-sparing clinical trials, so we can have first-hand information on whether this type of vaccine will work for Taiwan's people.

During the vaccine development process, one of the major bottlenecks is the evaluation of IND and clinical trials approval. To fast-track flu vaccine (pandemic or normal flu vaccines), the Taiwan Government understands that this is a good opportunity to financially assist the Taiwan FDA and Center for Drug Evaluations to build up infrastructure to enhance vaccine evaluation and licensing processes, in particular the IND and clinical trials protocols approval. To this end, CDE and Taiwan FDA have completed flexible policies for pandemic flu vaccine approval for clinical trials and product registration.

Conclusion

To minimize the risk of vaccine supplies, the Taiwan government has successfully organized and implemented regional flu vaccine manufacturing plans. The Taiwan CDC and NHRI Vaccine Center have initiated and collaborated on a global pandemic flu vaccine R&D programme. NHRI Vaccine has established a P2+ GMP biological plant for H5N1 flu vaccine emergency production. The Taiwan Government has initiated a build/operate/own incentive package for a regional vaccine self-manufacturing facility with the capability of producing 16 million doses of seasonal flu vaccines.

Notes & References

Overcoming global issues of tackling a potential influenza pandemic

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