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Avian Influenza H5N1: International Preparedness against a Future Influenza Pandemic

"We had three pandemics in the last century – there is no reason to believe there won't be one in this century." (123 p. 404) These words of Dr. Klaus Stöhr, coordinator of the Global Influenza Programme (GIP) at WHO from 2001 to 2006, expressed the position of the organization's leaders regarding the risk of a human influenza pandemic. The poultry outbreaks in different Asian countries, the occurrence of human cases, and the international spread of the disease raised concerns in the worldwide health community from 2004 to 2005. Compared to the SARS disease, an influenza pandemic could multiply the casualties, as well as put pressure on health systems for a longer period of time and generate significant social disruptions and enormous economic costs.

The avian influenza virus A (H5N1) resurged in February 2003 in Hong Kong, raising the risk of a human influenza pandemic at the same time as the SARS outbreak began. It became of international concern when the zoonose spread from Asia to Europe, the Middle East and Africa in December 2004. In other words, this virus A (H5N1), which infects domestic animals such as poultry, ducks, and even pigs, is susceptible to evolving into a highly pathogenic human form that could easily contaminate humans and efficiently transmit among them. A human influenza pandemic originating from a virus against which populations are not immune could have a significant worldwide impact in terms of human lives lost and burdens on public health systems, as well as causing social disruptions and economic costs. The Spanish influenza of 1918–1919 that generated over 40 million deaths worldwide, (124 p. 39) as compared to the estimated 20 million deaths due to World War I, is

N. Brender, *Global Risk Governance in Health*

often cited as the most striking example of a virulent influenza pandemic consequence.

This chapter focuses on the analysis of the avian influenza H5N1 from its resurgence in 2003 up to the end of 2008. Avian influenza H5N1 in humans remains rare, but is highly lethal. While the total number of human cases at the end of 2008 was limited to 393 in 15 countries, out of which 248 deaths occurred, (125) the case fatality ratio is high at approximately 63%.[1] For comparison purposes, after more than ten years, WHO registered 650 human cases, out of which were 386 deaths, resulting in a case fatality ratio of 59%. (126) Neither a vaccine nor effective drug treatments have been developed, although oseltamivir drugs (for example, Tamiflu) have shown some efficiency in certain circumstances. Between 2003 and 2009, a total of 63 areas and 15 countries reported H5N1 avian influenza in domestic poultry and wildlife to the OIE, out of which 50 countries have reported avian influenza only in domestic poultry. (127) From January through March 2004, more than 120 million poultry birds in Asia died of flu or were slaughtered to stop the avian influenza outbreak. (128 p. 406) Experts at the United Nations estimated that nearly 140 million domestic poultry either died or were destroyed. (129) In 2005, the losses of the affected countries were estimated at over USD 10 billion.[2]

In 2005, the international awareness of the risk of an influenza pandemic and the weaknesses in the countries', international organizations', and companies' preparedness to face this eventuality reached spheres beyond the international public health and scientific communities. The editors of *Nature* dedicated their May 26, 2005, issue to the avian influenza with this title: "Avian Flu: Ready for a Pandemic?" The *Nature* authors raised a red flag, and the information published was rapidly relayed in the media worldwide as well as on multiple websites, provoking debates and anxiety. The current H5N1 outbreak that originated in 1997 in Southern China, with a presumed interruption (no cases were reported during the interval 1997 to 2003) and resurgence in 2003, has been closely watched by health experts and members of the relevant national health institutions and international organizations as a potential source for an influenza pandemic. It finally reached an international public place, capturing the international audience's attention.

In 1997, Hong Kong authorities applied drastic measures to stop the epidemic. Within three days, Hong Kong's entire poultry population, estimated at around 1.5 million birds, was culled; (131) and sanitation and vaccination measures were implemented, such as hygienic measures for the cleaning and disinfection of market places, mandatory rest days, and the launch of a vaccination program for all local chicken farms.

Biosecurity and hygienic measures also were implemented on farms, as well as stricter import controls. This outbreak was considered to be the first alarm of an avian influenza with direct transmission to humans, causing severe illness with high mortality. The result was significant coverage in the Asian media, which increased the level of attention from influenza experts worldwide regarding the risk of an influenza pandemic. The swift reaction of Hong Kong authorities has been credited with reducing the risk of a human influenza pandemic, especially Director of the Hong Kong Department of Health, Dr. Margaret Chan.[3] After her appointment as Director, Communicable Diseases Surveillance and Response, as well as Representative of the Director-General for Pandemic Influenza, in June 2005, she was named Assistant Director-General for Communicable Diseases in September 2005 and will be coordinating WHO activities to face the risk of a human influenza pandemic of avian origin. No outbreak of the virus A (H5N1) occurred again until 2003; three incidents of human infection with other avian subtypes, namely H7N7 and H9N2, were documented in 1999 and 2003, but each only caused mild illness and resulted in only one death (131).

This alert reminded populations that twenty-first-century societies remain vulnerable to infectious disease epidemics, regardless of medicine's progress. The SARS outbreak was still present in people's memories and raised concern about the spread of infectious diseases worldwide. SARS, which had the potential to develop into a pandemic, probably originated in bats and then had to be transmitted to civet cats before infecting humans. The origin of the H5N1 influenza, like SARS, can be found in animals. Zoonoses have been watched and studied as they can develop into highly pathogenic human diseases and easily and rapidly spread worldwide. In particular, avian influenza viruses have the potential to mix with seasonal influenza viruses to result in pandemics. As the incubation period is longer for influenza, as compared to SARS, and is not associated with any visible symptoms (SARS could be detected during the incubation period as it was often associated with fever), early detection of the disease is compromised.

The influenza pandemic risk was largely debated in terms of the definition of an event, its likelihood of occurrence, and its potential impact. First, in order to result in a pandemic, an influenza virus must fulfill three conditions. A new virus emerges against which the population has little or no immunity. Then, this virus must be able to replicate in humans and cause disease, and, finally, it must be easily transmissible among humans. In summary, influenza pandemics arise when a "novel" influenza virus emerges, infects humans, and spreads efficiently and sustainably among them. No H5N1 human flu pandemic has

occurred currently as the three above-mentioned conditions have not been fulfilled yet. Some argue that the H5N1 virus is a novel virus that can create disease among humans, but that its sustainability and easy transmission from human to human have not yet occurred. Based on this approach, which is shared by WHO leaders, no pandemic exists, as the third condition is not met. In other words, WHO consider that "the emergence of an H5N1 strain that is readily transmitted among humans would mark the start of a pandemic." (132) Others insist that none of the three conditions are fulfilled at the present time since the human virus that would originate from the avian flu virus H5N1 and potentially cause a pandemic remains unknown. Based on this approach, none of the three conditions that give rise to a pandemic are currently fulfilled.

Since the resurgence of the virus A (H5N1), WHO has engaged in pandemic preparedness activities, cooperating with leaders of other organizations and member states. These activities are considered useful in preparation for the next pandemic, be it of an avian influenza H5N1 source or of another origin, as well as for new infectious diseases. The prepandemic phase 3[4] still allows for preparation and prevention, as the disease does not transmit easily from human to human. Dr. Margaret Chan,[5] Assistant Director-General for Communicable Diseases, emphasized that "for the first time in human history, we have a chance to prepare ourselves for a pandemic before it arrives." (134) In addition, these preparedness activities were declared useful as preparation for a microbiological attack. In an international post-September 11 and post-SARS context, this combination of arguments enhanced active international cooperation as well as national initiatives. Preparedness against this pandemic gave rise to unprecedented investments in surveillance of zoonotic diseases. According to the World Bank, donors contributed USD 3.9 billion to respond to H5N1 avian flu from 2005 to 2010 (135).

Finally, the risk of a human influenza pandemic moved to the top of the international agenda in 2005–2006 in relation to the significant sanitary, political, and economic consequences it may have worldwide. At WHO, pandemic issues were under the direct responsibility of the Director-General, who was directly involved in addressing this risk. In September 2005, President George W. Bush announced the International Partnership on Avian and Pandemic Influenza in New York. The two first objectives of this partnership consisted of fostering international cooperation to protect the lives and health of people and promoting timely and sustained high-level global political leadership to combat avian and pandemic influenza. (136) The avian influenza issue was also on the Group of 8 (G8) agenda in 2006, an organization whose leaders recognized that priority efforts should focus on the

early detection and control of the H5N1 strain of avian influenza at its source, as well as on the prevention of and preparedness for a potential human influenza pandemic. The G8 leaders reaffirmed their support of the WHO-administered GOARN, to FAO and OIE, as well as the UN System Influenza Coordination Office (UNSIC) and international financial institutions in addressing this global threat (137).

The resurgence of the virus A (H5N1) in 2003 in Hong Kong and the subsequent outbreaks in Asia in 2004 have made this virus the strongest candidate for a human influenza pandemic during the period of time under study (2003–2008) and after. Therefore, describing how H5N1 avian influenza has emerged as a global risk and the way it has been addressed at the international level is important.

3.1 H5N1 avian influenza risk analysis

The two alerts that were raised regarding the resurgence of the H5N1 avian influenza virus among humans happened within the surveillance system of WHO. Human cases were reported by member state authorities, first by officials in Hong Kong in February 2003 and then by those in Vietnam and Thailand in January 2004. In parallel, poultry outbreaks were also reported in the Republic of Korea in December 2003 and in Vietnam, Thailand, Cambodia, and Laos in January 2004.

3.1.1 First alert: Hong Kong (February 2003)

In February 2003, two human cases of avian influenza A (H5N1), a father who would die from the disease, and his son, were reported in Hong Kong. This family had traveled to the Fujian Province in China, where their 8-year-old daughter died from an undiagnosed respiratory infection. The outbreak of a strange pneumonia in the Guangdong Province, combined with the confirmation of these two human cases of avian influenza H5N1 in Hong Kong, alerted WHO officials. At that time, researchers were not sure whether the two Hong Kong patients had the same illness as those in Guangdong (138 p. 1504), as the SARS outbreak was occurring simultaneously and was first believed to be influenza.

As of February 19, 2003, results from two laboratories confirmed the presence of an avian influenza virus in a boy who had hospitalized in Hong Kong since February 12. On February 19, WHO officials, believing that the world might be facing an avian influenza outbreak, went on alert and mobilized the Global Influenza Surveillance Network to investigate the source of infection, (139) only to discover later that a new disease had emerged, SARS. While the SARS outbreak put the world on

alert and the disease was contained by July 2003, authorities in neither Hong Kong nor other Asian countries reported additional human cases of avian influenza H5N1 during 2003. However, outbreaks of H5N1 avian influenza in poultry hit the Republic of Korea beginning in December 2003, followed by outbreaks in Vietnam, Japan, Thailand, Cambodia, and Laos in January 2004.

3.1.2 Second alert: Asian regional outbreak (December 2003–January 2004)

The spectrum of an influenza pandemic resurged in January 2004, with human cases of avian influenza H5N1 that were reported in Vietnam and Thailand. On January 13, 2004, WHO published disease outbreak news regarding the avian influenza H5N1 in Vietnam, and on January 23, in Thailand, as well as an avian influenza fact sheet in the meantime. A travel advisory was issued on February 6, 2004, that did not impose travel restrictions but recommended that people limit contact with poultry when traveling in countries affected by animal and human outbreaks. (140) No global alert was issued, but WHO leaders sent investigation teams to study the transmission pattern of the disease in Vietnam and Thailand. According to WHO investigators, direct contact with infected poultry (or birds) was the primary source of infection, followed by exposure to an environment that may have been contaminated by feces from infected birds. However, the possibility of direct human-to-human transmission could not be completely eliminated. The WHO investigators' actions have continued since then, and they intensified in 2005 when people in Cambodia, Indonesia, and China were affected as well. From 1997 to 2004, the virus A (H5N1) had become more pathogenic, more lethal, and more resistant to drugs. Based on tests performed by WHO in Vietnam in 2004, the virus had become resistant to some antiviral drugs and could survive up to six days at 37°C, compared to two days in 1997 in the same test environment. (141 paragraph 3) Knowing the capacity of the influenza virus A to reassert itself or to mutate to infect humans probably in conjunction with seasonal influenza, WHO and its experts confirmed the risk of a worldwide A (H5N1) influenza pandemic.

Although the first two H5N1 human cases of the ongoing outbreak occurred in 2003, the analysis starts with the cases identified and reported in Vietnam in January 2004. These human cases, combined with avian influenza outbreaks in poultry in Japan and South Korea, initiated the risk analysis at WHO. These cases also corresponded to the end of the SARS outbreak that had mobilized most resources up until July 2003 and in the fall of 2003 to draw lessons from the SARS outbreak.

3.1.3 Method and legitimacy

WHO jointly applied four different layers of risk assessment methods for the avian influenza case. First, WHO used its risk assessment framework to assess the risk of an influenza pandemic based on the resurgence of the H5N1 virus in humans. Second, the avian influenza event was reported and evaluated under the EPR method using the "Guiding Principles for International Outbreak Alert and Response." (42) Third, it used the notification instrument that would become Annex 2 of the revised IHR for event detection, verification, and risk assessment. Finally, the influenza pandemic preparedness plan, in both the 1999 version and the revised version of 2005, prescribed the performance of a risk assessment to determine the level of alert ("pandemic phase").

WHO developed a two-way approach in order to assess the risk of a disease outbreak. On the one hand, it applies a "bottom-up approach" that relies on countries reporting, such as Hong Kong officials who reported human cases of avian influenza H5N1 in 2003, as well as officials in Vietnam and Thailand in January 2004. On the other hand, it can use a "top-down approach" based on the IHR resolution adopted by the World Health Assembly on May 28, 2003, that authorizes WHO to use nonofficial sources as a starting point for its outbreak verification process. (48) In the avian influenza case, WHO's risk analysis process in the first instance of the disease mainly consisted of a bottom-up approach that relied on the IHR identification and verification process for outbreaks of diseases.

3.1.3.1 Annex 2 of the IHR (2005)

Although the revised IHR was adopted in 2005 to come into force in 2007, WHO proceeded to a first analysis of the situation and a preliminary evaluation of the human influenza pandemic based on the IHR "Decision Instrument for the Assessment and Notification of Events That May Constitute a Public Health Emergency of International Concern" (46 pp. 45–48) that became part of Annex 2 of the revised IHR 2005. This method was documented as a process flowchart that is accompanied with explanations on how to apply this risk assessment process, and questions that need to be answered to evaluate the magnitude of the risk based on preestablished criteria. This document was meant to be a guideline for states' officials and WHO for the assessment and notification of events that might constitute a public health emergency of international concern. This notification instrument was available to WHO and state members since 2002, and the IHR working paper that was submitted for regional consultations in January 2004 included a preliminary version of that document that became part Annex 2 of the revised IHR. (142 p. 28)

At that stage, the concept of "Events That May Constitute a Public Health Emergency of International Concern" (PHEIC) prevailed, while the final version also included a systematic notification for a predefined list of diseases (in the box on the left) and a list of events involving specific diseases for which the decision instrument should be used (in the box on the right). Figure 3.1 below, represents this risk assessment flow chart as stated in Annex 2 of the revised IHR.

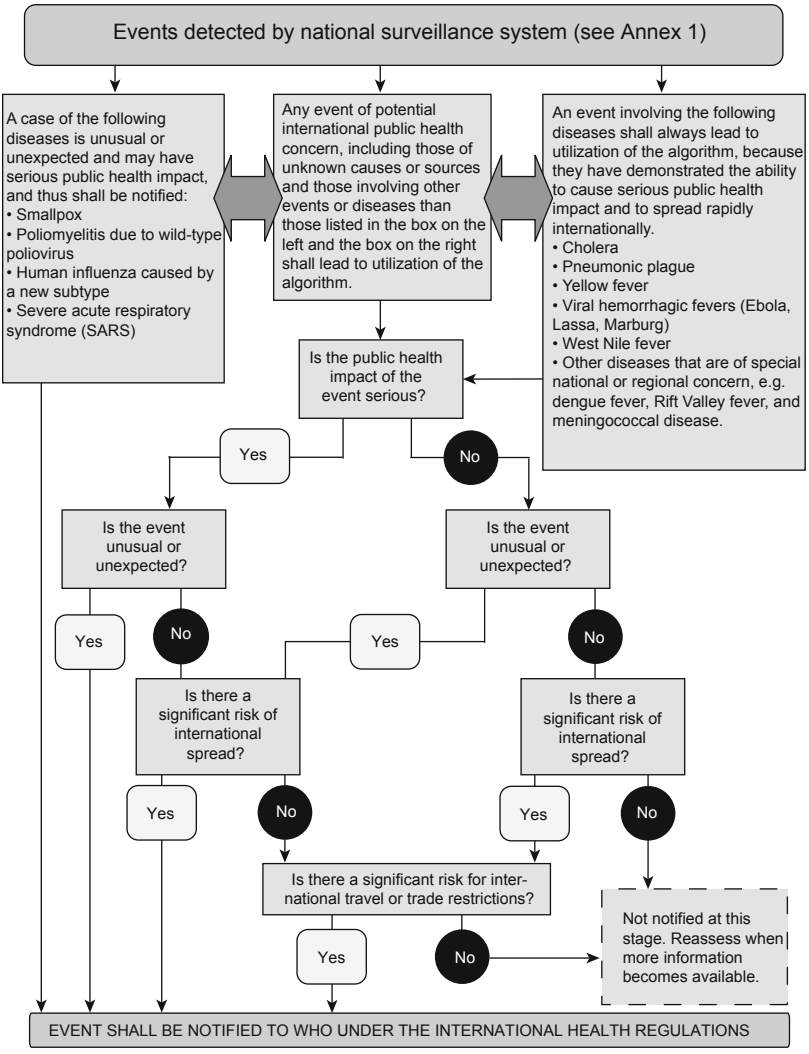

Figure 3.1 Annex 2 of the International Health Regulations (2005)

H5N1 avian influenza met the four criteria to be considered as a public health emergency of international concern: seriousness of the disease in terms of public health impact (high mortality); unexpectedness (unusual character of the disease that could result in an influenza pandemic); international spread (regional spread in 2004 and intercontinental spread in 2005); and risk of international travel and trade restrictions (travel precautions recommended and possible impact on poultry trade). If two of these criteria are met, state parties shall notify WHO under Article 6 of the IHR. The determination of a PHEIC is a key element of the risk assessment, as it is the triggering event for WHO to activate its network and organize an international response. In its first public statement of January 13, 2004, WHO already had expressed its concern about the regional outbreak in poultry in Asia, the human cases detected in Vietnam, and the instability of the virus, which could change into a form transmissible to humans and to which humans would not have immunity. (143) The resolution of the World Health Assembly of 2006 clearly referred to the concept of PHEIC to follow up on human cases of avian influenza. (144) Provisions that were contained in the "International Health Regulations Working Paper for Regional Consultations of 2004," including its Annex 2, were applied during the avian influenza outbreak. Based on a proposal made by Thailand to the Executive Board of WHO in May 2005, a resolution regarding the early application of selected IHR 2005 provisions on a voluntary basis was adopted during the World Health Assembly of 2006, which reinforced the application of this risk assessment procedure and the use of this notification instrument (144).

3.1.3.2 Pandemic preparedness plan and pandemic phases

The influenza pandemic preparedness plan 1999 (44) included a risk assessment of the pandemic level. However, the revision process of that plan was started already when the avian influenza H5N1 outbreak occurred and resulted in an acceleration of its revision process and the publication of the WHO Global Influenza Preparedness Plan in the fall of 2005. (145) The objectives of both plans were twofold. On the one hand, they provided WHO with a risk assessment method to evaluate an influenza event in terms of the potential to result in a pandemic and to decide at which "phase" the world is during each stage of the evolution of knowledge about the disease. On the other hand, these plans were meant to be guidelines for states in preparing their own influenza national preparedness plans. The WHO global influenza preparedness plans provided minimum standards to be achieved by states in order to

ensure adequate control and protection measures in the case of a human influenza pandemic.

3.1.3.3 Legitimate basis for action

Until the early adoption of the IHR in May 2006 or the entry into force on June 15, 2007, the formal legal basis for action remained the IHR 1969, and the resolution on IHR of May 2003 that was limited in scope. During that period, the provisions of the draft of the revised IHR were used as the basis for action and were generally accepted by states.

The IHR 1969 did not apply to the H5N1 avian influenza for the same reasons it did not apply to SARS. The resolution on the revision of IHR, (48) adopted by the World Health Assembly in May 2003, provided a legal basis for WHO action, but did not cover the whole range of activities as prescribed in the revised IHR project in 2002. While states' officials are urged to establish focal points and ensure collaboration with agencies involved in animal care, they do not have the obligation to notify WHO of the avian influenza disease. Under this resolution, WHO can use nonofficial sources of information that report outbreaks, issue alerts in the case of a serious threat after having informed the government(s) officials concerned, collaborate with national authorities in assessing the severity of the threat and adequacy of control measures, and conduct on-the-spot studies to ensure that appropriate control measures are being employed. This resolution provided a limited formal legal basis for action until April 2006, when the World Health Assembly adopted a resolution (144) on the early and voluntary application of the IHR (2005) to strengthen pandemic preparedness and response, in particular in surveillance, reporting, information sharing, and the setting up a National IHR Focal Point. The revised IHR were adopted in May 2005 (IHR 2005) to come into force on June 15, 2007. Early adoption was applied by states willing to do so, and on June 15, 2007, the IHR 2005 came into force and provided the formal legal basis for WHO actions.

In practice, the provisions included in the draft of the revised IHR that was submitted to the WHO Executive Board in January 2004 and that circulated during the year to result in a final draft in the fall of 2004 were applied in regard to the outbreak of avian influenza. Although the final version of IHR included some changes in scope and procedure, such as the joint use of a list of diseases and the concept of an event that can consist of a PHEIC, the provisions remained essentially similar. While the revised IHR 2005 did not contain the possibility of on-the-spot studies, as mentioned in the resolution on IHR, authors of the IHR 2005 linked the notification with the possibility of seeking assistance from

WHO as an incentive for states to report an outbreak. Annex 2 in its generic form, which pertained to a concept and not a list of diseases, was available to state officials for assessment and notification.[6] In fact, in the case of the avian influenza, national authorities of affected areas spontaneously reported the outbreaks and the number of cases to WHO, which initiated the verification and assessment process in return. The importance of timely and transparent reporting might have been influenced by the SARS experience. For Vietnam, it was also a way to seek assistance and have investigations on-site about the transmission of the disease in 2004.

In addition, avian influenza required more cooperation among institutions than did the SARS outbreak, due to the important impact on animal health. WHO's cooperation, mainly with FAO, OIE, and the World Bank, found its legitimate basis in Article 2 of the WHO Constitution, which grants competence to WHO "to establish and maintain effective collaboration with the United Nations, specialized agencies, governmental health administrations, professional groups and such other organizations as may be deemed appropriate." (146) The health mandate provided to WHO from its member states, therefore, allows the organization to cooperate and develop partnerships in order to address health issues efficiently at an international level.

3.1.4 Expertise organization

The diversity of the background and the international track record of the experts who were involved in the risk assessment and their capacity to apply the latest research into WHO protection measures characterize the pandemic preparedness activities.

3.1.4.1 Background diversity

WHO organized its expertise around three poles: the institutional expertise organized through the "traditional" consultation procedure in place at the WHO (member states consultation and international meetings); the combination of field experts internal and external to WHO – a new procedure implemented especially to address the risk of an H5N1 influenza pandemic; and the creation of a specific "task force" within the WHO that was fully dedicated to the avian influenza issue. The diversity of background of the expertise will be evaluated in terms of multidisciplinarity, geography, and institutional representation.

Member states' consultation. The first pole of expertise relies on the regular consultation procedure that was in place at WHO. Each text

that was prepared by WHO experts internally was reviewed by official representatives of governments of WHO member states. For example, the *WHO Global Influenza Preparedness Plan* that was reviewed and published in 2005 was developed according to this procedure. A group of experts tasked by WHO and consisting of approximately 15 persons, in consultation with WHO regional and country offices prepared the *WHO Global Influenza Preparedness Plan*. This plan had been in preparation for about ten years (a first version had been published in 1999) and was reviewed by regional offices of WHO and representatives designated by the ministries of health of member states. Similarly, the "WHO Checklist for Influenza Pandemic Preparedness Planning" was developed during a meeting of approximately 15 experts called by WHO. Finally, the measures found in "Responding to the Avian Influenza Pandemic Threat: Recommended Strategic Actions" were elaborated by WHO experts and reviewed by WHO regional offices. The WHO risk analysis and measures to be taken to reduce a risk were contained in these documents that were prepared by a combination of operational, strategic, and review dedicated persons. Dr. Klaus Stöhr and his team played a critical role in initiating the documentation preparation process and coordinating the review and the issuance of these documents that formalized the position of the organization regarding the risk of an influenza pandemic. We found no evidence regarding the diversity of backgrounds of the experts involved in that process.

International meeting (November 7 to 9, 2005). From November 7 to 9, 2005, WHO jointly convened an international meeting on avian influenza and human pandemic with FAO, OIE, and the World Bank that was held at WHO headquarters in Geneva to assess the risk to human health. The meeting was unprecedented in its design, attendance, and the scope of the work. More than 600 experts from over 100 countries gathered, agreed on the importance of the risk, and designed priority actions to prevent the emergence of a pandemic virus (or to delay its initial international spread) and to prepare countries to cope more effectively with a pandemic (147 p. 2).

During these two days, representatives exchanged information about avian influenza and discussed the latest research findings and countries' challenges in dealing with the outbreak or implementing pandemic coping capacities. The commitment of the organizations was evidenced by the presence of top-level managers and the decision to follow up with another conference in Beijing in January to address the financial needs for carrying out the proposed actions.

The meeting resulted in an action plan in six major areas: control at the source in birds; surveillance; rapid containment; pandemic preparedness; integrated country plans; communications. (148) These actions were summarized in the "WHO Strategic Action Plan for Pandemic Influenza 2006–2007," which serves as a reference for the international response in four categories of actions: reducing exposure to the H5N1 virus; strengthening of the early warning system; intensifying rapid containment operations and building the capacity to cope with a pandemic; and coordinating research. (149) An additional point raised in the meeting was included in the research section and relates to the timely and sufficient availability of vaccines and drugs.

Experts Consultation: Containment protocol. The second pole of expertise was organized in a multistakeholder consultation. The preparation of the "WHO Interim Protocol: Rapid Operations to Contain the Initial Emergence of Pandemic Influenza" in March 2006 was the first application of this new procedure. The meeting's aim was for participants to design the bases for responding to avian influenza outbreaks and containing them to avoid a pandemic, and organization leaders gathered experts from different backgrounds in order to work on a document that was drafted by WHO internal experts. The participants were selected based on their field of expertise, professional background, activity, and organization in order to address as many aspects of the issue as possible and propose the most appropriate and comprehensive response. These working groups included international subject matter experts who were recognized for their contributions to the field of infectious diseases and work for various institutions (such as research institutes, universities, laboratories, and centers for disease control), independent experts, WHO internal experts, WHO regional representatives, officers of other international organizations (such as the International Migration Organization) or UN agencies (such as FAO), and representatives from the private sector (such as the Roche Group).

The formation of this protocol followed a completely different process than the influenza preparedness plan. It was prepared and reviewed through technical meetings and focused on technical issues and operations. This protocol was prepared by subject matter experts more than country representatives and was associated with a clinical meeting on how to use drugs and treat human cases. It was also based on a review of the literature that was performed by three specialists, who analyzed the relevancy and soundness as well as reliability of the material to be used in the drafting process. A first draft of the "WHO Pandemic Influenza Draft

Protocol for Rapid Response and Containment" was ready on January 27, 2006. (150) This draft was updated to serve as the basis for the work of the Global Technical Meeting on Early Containment Protocol for Pandemic Influenza that was held in Geneva from March 6 to 8, 2006 to discuss a influenza pandemic containment strategy.[7]

The purpose of that meeting was to reach a technical consensus on rapid detection, assessment, and response to the signs that were showing a development of the avian influenza virus toward more transmissibility among humans. (151) The meeting gathered 72 participants, of whom 19 were external experts. The participants were dispatched into three working groups: Operations; Surveillance and Epidemiology; Public Health Measures for Containment and Control. Experts in these groups reviewed and modified the entire draft to ensure the relevance and completeness of the measures proposed. The meeting resulted in the publication of the "WHO Pandemic Influenza Draft Protocol for Rapid Response and Containment" on the WHO website on March 17, 2006.[8] At the end of March 2006, and to complement the work that was being done, WHO organized two additional technical meetings on preparedness for the impact of pandemic influenza on refugee and displaced populations and on social mobilization to reduce the risk of avian influenza.

The composition of the expertise was intended to cover most of the technical and institutional aspects in the containment of an influenza pandemic. Information was missing about the area of expertise for eight participants who were all working for WHO. Table 3.1 shows the breakdown of participants by area of expertise.

Table 3.1 also shows that areas of work were largely diversified (more than 25 different areas of expertise) among external experts and WHO participants. It also indicates a predominance of epidemiology (25%), followed by public health (8%), emergency action, and surveillance (4%). This meeting included experienced staff from WHO headquarters, regional, and country offices who specialized in operational planning, outbreak response, logistics, epidemiology, laboratory diagnosis, infection control, ethics, social mobilization, and public and media communications.

Figure 3.2 concentrates on the 19 external experts (representing 26% of the participants) who attended this global technical meeting. It also shows a predominance of epidemiology (26%), followed by logistics, occupational health, immunology and vaccines, and public health (all at 11%). These external experts came from 17 different institutions, including universities, state agencies, agencies or programs of the United

Table 3.1 Breakdown of participants by fields of expertise, WHO global technical meeting on early containment protocol for pandemic influenza, March 6–8, 2006

Field of expertise	Number of experts	Percentage
Epidemiology	18	25.0%
Not available	8	11.1%
Public Health	6	8.3%
Surveillance	3	4.2%
Communication	2	2.7%
Infection Control	2	2.7%
Logistics	2	2.7%
Virology	2	2.7%
Biosafety	1	1.4%
Emergency Aid	1	1.4%
Emergency Aid, Food Assistance	1	1.4%
Emergency Disease Control	1	1.4%
Epidemiology and Public Health	1	1.4%
Epidemiology & Clinical Research	1	1.4%
Ethics	1	1.4%
Expert Adviser	1	1.4%
Global Migration and Quarantine	1	1.4%
Health Action in Crisis	1	1.4%
Health Technologies	1	1.4%
Human Resources	1	1.4%
Immunology	1	1.4%
Interagency Coordination	1	1.4%
International Health Regulations	1	1.4%
Medicines Policy	1	1.4%
Microbiology and Laboratory Systems	1	1.4%
Microbiology and Vaccines	1	1.4%
Nursing	1	1.4%
Occupational Hygiene	1	1.4%
Pandemic Contingency Planning	1	1.4%
Partners Network	1	1.4%
Procurement	1	1.4%
Research on Influenza	1	1.4%
Training	1	1.4%
Vaccines	1	1.4%
Veterinary	1	1.4%
Virology and Vaccines	1	1.4%
Virology and Zoonotic Diseases	1	1.4%
Grand Total	**72**	**100%**

Nations (FAO, United Nations Children's Fund [UNICEF], World Food Programme [WFP], and United Nations System Influenza Coordination [UNSIC]), the International Federation of Red Cross and Red Crescent Societies (IFRC), centers for disease prevention and control (United States

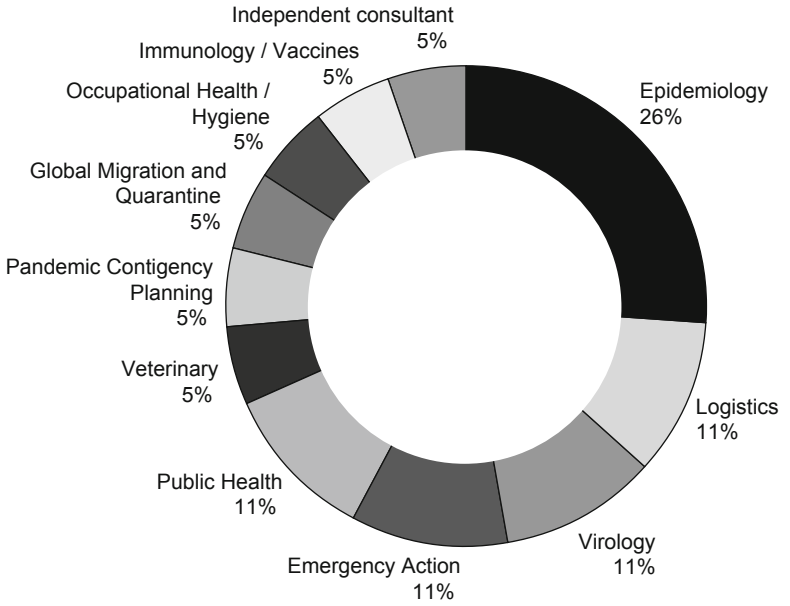

Figure 3.2 Breakdown of fields of expertise for external experts, WHO global technical meeting on early containment protocol for pandemic influenza, March 6–8, 2006

and Europe), one independent consultant, and one logistics experts from the Roche Group. The presence of a representative of the Roche Group was a completely new occurrence in such consultations. He was there to discuss drug stockpiling and distribution aspects after the Roche Group donated a stockpile of 3 million courses of oseltamivir (Tamiflu) (150 p. 13) to WHO to carry out the containment plan and dispatch these drugs at the source cluster. In addition, these experts had previous experience in containing infectious diseases, such as SARS or Ebola.

The expertise for the preparation of this protocol was broad-based geographically, with a multidisciplinary background in terms of the large variety of disciplines represented, as well as a diverse and international institutional representation. The experts from organizations both outside of WHO and within WHO represented institutions located in 12 countries from all continents. The financial, logistics, and legal fields were also represented, but were not numerous, and all came from WHO. While more social science aspects were included in the governance of avian influenza compared to the analysis of SARS, expertise remained underrepresented in the field of the social sciences.

Avian influenza task force and decision-making. The third pole of expertise was composed of a fully dedicated avian influenza task force that was formed at WHO. Since the beginning of the H5N1 outbreak, Dr. Klaus Stöhr, Global Influenza Programme, had been responsible for setting up and coordinating the work of an influenza pandemic task force on the model of the Emergency Committee prescribed in the IHR.[9] This task force was institutionalized by the World Health Assembly resolution on early adoption of the IHR 2005 on May 26, 2006, and officially organized in September 2006. The task force acted as a temporary mechanism until the IHR 2005 came into force to provide advice at the request of the Director-General of WHO, in particular on key changes to the pandemic alert phase and declaration of a pandemic, and on the appropriate response measures to be recommended. (153 p. 1) Members of the task force might also provide technical advice when requested by the Director-General of WHO on other relevant matters relating to avian and/or pandemic influenza (153 p. 2).

This task force included personnel who worked on SARS, and the leading individuals were the same. From a legal standpoint, its activities relied first on the draft of the revised IHR and later on the revised IHR that went into force on June 15, 2007. The draft of the "WHO Pandemic Influenza Draft Protocol for Rapid Response and Containment" that was submitted to the Global Technical Meeting of March 6 to 8, 2006, as described in the previous sections, details the composition and the activation of this task force. This task force is an independent multidisciplinary advisory body to the Director-General of WHO that will be convened upon receipt of a signal of emergent pandemic influenza. (150 p. 11) The document also described the activities and responsibilities of the task force as well as its relationship to the Director-General of WHO. The use of this task force was retrieved from the protocol by the experts during the meeting of 2006.

However, the task force was active before its formal approval by the adoption of the resolution for the immediate application of the IHR (2005) on a voluntary basis by the World Health Assembly on May 26, 2006. This resolution, considering the risk posed by avian influenza and pandemic influenza, requested that the Director-General of WHO "use the influenza pandemic task force as a temporary mechanism until entry into force of the International Health Regulations (2005) in order to advise the Organization on the response to avian influenza, the appropriate phase of pandemic alert and the corresponding recommended response measures, the declaration of an influenza pandemic, and the international response to a pandemic." (144 p. 4) This Influenza Pandemic Task

Force (IPTF or "the Task Force") met for the first time on September 25, 2006, in Geneva in order to organize the Task Force and appoint its members and to plan for any emergency and other relevant advice that may be required of it. (153 p. 1) It was constituted and acted as the future emergency committee prescribed in Article 48 of the IHR 2005, its role and activities were comparable.[10] The WHO Director-General selects experts who provide advice on whether an event constitutes a PHEIC and its termination, as well as recommendations to address the risk. The IHR "emergency committee" (the committee of experts or the influenza pandemic task force in the case of the avian influenza) provides advice, but does not create policies, which is the responsibility of the World Health Assembly and the Director-General. The task force was composed of a group of experts who worked on the avian influenza and provided advice to the WHO about measures to be taken. Experts are selected for their discipline expertise and excellence. They should have different relevant backgrounds such as clinical expertise, epidemiology, virology, or anthropology and constitute a geographically representative group of experts available and able to work under tight time constraints.

Field missions. Mission teams of investigators were sent to probe outbreaks, assess risk, and provide assistance to affected areas. In January 2007, WHO recorded nine missions with the GOARN and 30 joint assessment missions of WHO officers and national authorities. (154) The missions, run jointly by WHO and the GOARN, also included representatives of FAO and of OIE when infection control measures and the culling of animals were required, and with other institutions, such as the joint mission with the Asian Development Bank to Vietnam. Field missions were not only diverse in terms of backgrounds of experts but also in terms of organizations represented. WHO sent team missions to areas affected by the H5N1 avian influenza, among which were Vietnam, Thailand, Turkey, Azerbaijan, Indonesia, and Egypt. Based on the list of participants published in Annex 3 of the Turkey mission report (155) issued by WHO, we built Table 3.2, overleaf, which illustrates the multidisciplinary aspect of the expertise involved. The area of work was not indicated for one expert, but this has a negligible impact on our analysis.

The mission was divided into coordination and field teams, which partly explains the majority of WHO officers in the mission, with a representation of 41%. The WHO officers came mainly from the WHO Regional Office for Europe and headquarters and included high-level officers. Veterinary experts (15%) included three representatives of FAO,

Table 3.2 Breakdown of fields of expertise for WHO avian influenza H5N1 field mission in Turkey, 2007

Field of expertise	Number of experts	Percentage
WHO officers	16	41%
Veterinary experts	6	15%
EU Representatives	5	13%
Epidemiology	3	8%
Technical Officers	3	8%
Medical Officers	2	5%
Public Health Specialists	2	5%
Laboratory Specialists	1	2.5%
Not Available	1	2.5%
Total	**39**	**100%**

which shows the interagency collaboration between human health and animal health institutions. The European Union representatives (13%) also provided personnel in agriculture and public health. The mission was also broad based, with 14 different institutions, including the European Commission, United Nations bodies (such as FAO or UNICEF), centers for disease control, research institutes, and state public health agencies located in nine countries. While a communications officer was available to lead interviews in the field, no economic and legal officers to address the financial aspects of the outbreak or the compliance with the IHR and local rules were part of the group.

International track record. Both experts from WHO and external experts in charge of the risk assessment of the outbreak presented an international track record in their areas of expertise. Most of them also had practical experience in the field in managing infectious disease outbreaks, including the SARS outbreak in 2003. International track records were assessed mainly using publications in peer-reviewed journals such as *The Lancet* or the *New England Journal of Medicine*. The research of references was enlarged to the Medline database available through the *Lancet* search engine, (156) in which evidence was found of international track records for the members of the WHO Influenza Pandemic Task Force and the participants in the Global Technical Meeting on Early Containment Protocol for Pandemic Influenza held at WHO headquarters in Geneva from March 6 to 8, 2006.

The Influenza Pandemic Task Force was composed of 11 WHO officers and 20 external experts. The WHO officers group included Dr. Heymann (Acting Assistant Director-General), Dr. Ryan (Director Epidemic and

Pandemic Response), Dr. Rodier, and Dr. Fukuda[11] (Coordinator Global Influenza Program), who also worked on SARS, and who had written approximately 90 publications, while the group of external experts had written approximately 600 publications. The 19 external experts of the containment protocol meeting had written over 150 publications, out of which approximately 20 were from the international organizations' experts. The 72 members of the WHO staff had over 550 publications.

3.1.4.2 Research

The coordination of international research and the quality and transparency of this research are essential to enhancing the risk analysis in order to shape the most adapted measures to address the risk. The prolific research activity and production of scientific articles about virology, clinical management, epidemiology, and economic and social aspects of the avian influenza and the pandemic risk have been undertaken during the period under analysis and still continue. Global coordination of research by WHO essentially covers two situations: research during the preparation phase and research during the pandemic itself. (149 pp. 17–19) Research during the pandemic itself will be organized in the same manner as for SARS in virtual networks of experts to gather epidemiological data in real time. (157 p. 20) These data will be used in predictive models in order to adjust the measures to be taken. Studies of the virus and, in particular, the tracking of its changes in virulence will be used to predict the severity of the disease in the next waves. Studies about drugs' effectiveness will also have to be performed to detect resistance or alternative treatments. We primarily focused our analysis on research about virology and epidemiology during the preparedness phase as the pandemic was not declared during the period under study.

WHO had as an objective to coordinate international research on avian influenza and organized it around the following structures: international conferences to share information; technical meetings to work on specific issues and produce guidance (such as the containment protocol described in the previous section); telephone conferences when necessary. WHO formed its group of experts based mainly on the influenza network (as in the case of SARS), which resulted in the involvement of similarly renowned experts in the management of the avian influenza. The influenza network that includes national centers and collaborating centers has a long history and experience in analyzing viruses due to its yearly work on seasonal viruses. This network was also a major provider for laboratory expertise in the H5N1 avian influenza case. Article 47 of the revised IHR 2005 prescribed the creation of a roster of experts

in all relevant fields of expertise. The WHO Director-General appoints the members of this roster in accordance with WHO Regulations for Expert Advisory Panels and Committees and shall appoint one member at the request of each state and one for relevant intergovernmental and regional economic integration organizations. This roster of experts could reach 300 to 400 people and should be multidisciplinary and international, but in December 2008, 56 experts (158) were designated by states (not even 30% of state parties participated). In addition, an informal preliminary version of the emergency committee that was provided for in the revised IHR 2005 was set up to advise WHO leaders in decision-making. The exact composition of this committee was not disclosed, but it included experts who are internationally recognized in the field.

Research on changes in the virus and its ability to cross barrier species has been key to the development of recommendations in clinical management and in preparedness activities. The virus has been known since 1997, and its resurgence in 2003 and 2004 has been closely watched, in particular, to determine if it had the ability to easily infect humans and become transmittable among humans. A first study performed on ten human cases in Vietnam showed that human transmission could not be excluded. (159) This gave rise to the inclusion of additional precautions to protect health-care workers in the clinical management of patients. Hygiene campaigns were carried out during field missions to prescribe how to handle dead poultry and how to limit possibilities for infection in households among members of a family. In addition, researchers in the WHO Global Influenza Surveillance Network studies found some genetic similarities between the 1918 virus and the H5N1 virus circulating in 2005, which raised the level of alert within WHO. One field of investigation was also the possible transmission from human to human. Research conducted in Thailand evidenced that transmission from a girl to her mother and her aunt probably occurred during close contact without protection in September 2004 and established that the virus was not a new variant, but did not confirm the mode of transmission as the index seemed not have been in contact with poultry. (160 p. 338) These results were reflected in the WHO document "Avian Influenza: Assessing the Pandemic Threat" (161) that synthesized the state of knowledge and assessed the risk of a human influenza pandemic. This risk assessment included as a temporarily reassuring element the fact that human-to-human transmission was rare, and an element of concern was the fact that the H5N1 virus presented similarities to the Spanish influenza virus. (161 pp. 8–18) These elements gave rise to further surveillance recommendations and the pursuit of studies about

the virus's evolution, as well as research to develop new methods for detecting the virus in environmental samples to better understand the relationship between animal and human disease (130 p. 7).

Another example of how virology and laboratory research provided valuable input into the risk assessment to issue recommendations is the "Influenza Research at the Human and Animal Interface: Report of a WHO Working Group," (162) which was published based on the work done by a group of 22 laboratory directors and senior scientists gathered in Geneva on September 21 to 22, 2006. This report integrated the results of the latest studies that showed that virus shedding patterns were changing and that the virus had acquired the capacity to transmit back to wild birds from poultry, which explained certain spread trends and which was an additional source of concern for a pandemic. Culling infected poultry remained the strategy based on Japan and Korea successes in containing the animal outbreaks and in avoiding infection in humans. However, culling is costly and disruptive; therefore, the experts recommended to countries with fewer resources to vaccinate poultry, such as Vietnam did. This approach is not without risk and should be watched carefully, as Hong Kong did in 1997, as it can disseminate the virus.

The early containment strategy that was developed for avian influenza H5N1 was primarily based on research results and included past experience with avian influenza in Hong Kong in 1997 and the Netherlands in 2003 (H7N7 virus), and with SARS in 2003. According to two mathematical modeling studies by Ferguson et al. (163) and Longini et al., (164) published in 2005, the combination of public health measures in the region where the pandemic virus emerged, along with the administration of antivirals, could possibly contain the outbreak before it spreads internationally. Ferguson et al. showed that prophylactic and social-distancing measures, combined with antiviral treatment, would be effective if the reproduction number is below 1.8. (163 p. 213) Longini et al. came up with similar conclusions for a reproduction number below 1.6 by using a model for rural Southeast Asia. Targeted antiviral prophylactic, quarantines, and prevaccination would be essential to contain the new virus at its source. (164) They also envisaged that WHO's stockpiling of 120,000 treatment courses in 2005 could possibly be sufficient to contain the disease, while they advised a stockpile between 100,000 to 1 million. (164 p. 1087) Ferguson et al. suggested stockpiling 3 million or more courses of oseltamivir. (163 p. 213) Detection, rapid identification of the cluster to deliver the cures, availability of sufficient stockpiles, population cooperation for social distancing measures,

and international cooperation would be essential in order to succeed. (163 p. 213) If the containment strategy cannot prevent the pandemic, it is expected the development of the pandemic would slow for a few weeks or months, which would allow for some time to develop vaccines. Officials from the Roche Group committed to giving WHO 3 million courses of oseltamivir (Tamiflu) (165) for one of the main measures of pandemic containment.

Professor Ferguson was one of the advising experts to WHO regarding avian influenza, and he also published papers on the transmission dynamics of SARS. (73) His two studies were used as the basis for developing the containment protocol and were quoted on page 8 of the March 3, 2006, draft of the "WHO Pandemic Influenza Draft Protocol for Rapid Response and Containment." (150) Professor Ferguson participated as one of the experts in the technical meeting of March 6 to 8, 2006. The updated containment protocol published ten days later clearly refers to the stockpiling of 3 million courses of oseltamivir that Roche donated to WHO in 2005, half of which will be stored in the United States and half in Switzerland. (150 p. 13) Further research will be done on effectiveness of different measures and on Tamiflu as well due to resistance arising in certain patients in different countries such as Egypt.

3.1.5 Risk assessment process

The avian influenza risk assessment process consists of a series of steps that should lead to the adoption of risk management measures that are issued by WHO. Demonstrating that WHO experts proceeded to a risk analysis, showing that a risk assessment process was in place in the avian influenza case, is important. The presence of an observation system and risk assessment mechanisms and the realization of a cost benefit analysis constitute the three major components of the risk assessment process.

3.1.5.1 Observation system

Avian influenza surveillance is mainly based on the Global Influenza Surveillance Network, which is described in the section on observation systems in Chapter 2. Previously in this chapter, the successive alerts and activation of the Global Influenza Surveillance Network in 2003 for the Hong Kong cases and in January 2004 for the Vietnam cases were mentioned. Officials in affected countries notified WHO of outbreaks through this network. While accuracy and completeness were questioned in the Egyptian reporting, Indonesian officials openly opposed WHO in not reporting outbreaks and not sharing viruses (166).

Virus analysis and development of vaccines was a central point of the preparedness activities. In response to the risk of H5N1 pandemic, in 2004, WHO established the WHO H5 Reference Laboratory Network as an ad hoc component of the WHO Global Influenza Surveillance Network (GISN). (167) The four WHO Collaborating Centers for Reference and Research on Influenza, the WHO Collaborating Centre for Studies on the Ecology of Influenza in Animals, and other laboratories with internationally recognized expertise in avian influenza are part of this network. Major tasks of this WHO H5 Reference Laboratory Network are to collect virus specimens that are made freely available to WHO laboratories working on the development of vaccines, perform antigenic analyses, participate in the WHO process to select, develop, and distribute candidate vaccine viruses of H5N1, and provide WHO with surveillance data.

3.1.5.2 Risk assessment mechanisms

Risk assessment mechanisms included the completion of the risk assessment method, evaluation of the pandemic phase with the support of the task force, and uncertainty reduction. The determination that the H5N1 avian influenza outbreak qualified as a PHEIC based on Annex 2 of the IHR was a key driver in launching an international response. Due to the high level of uncertainty, estimates of the risk vary significantly in regard to the epidemiological assumptions, which are reflected in the evaluation of the cost of a pandemic.

The WHO risk assessment process was based on the Global Influenza Surveillance Program as the main observation system, and the risk assessment mechanisms included the application of the overall risk assessment framework jointly with Annex 2 of the revised IHR 2005 and the "Guiding Principles for International Outbreak Alert." In addition, the risk assessment mechanism contained in the 2005 global influenza preparedness plan was applied in making a decision about the pandemic phase. WHO carried out risk assessment activities regarding the risk to human health and made joint recommendations with OIE and FAO to reduce the avian influenza spread among animals. WHO officials cooperated closely with both organizations in order to remain informed about the evolution of the disease in the animal population, as the control of the disease among animals was represented as a precondition to the reduction of the risk to humans.

Pandemic phases risk assessment. WHO initially activated the "Influenza Pandemic Preparedness Plan of 1999" in January 2004 to assess the risk

and declare the corresponding pandemic phase. The revision process of the influenza pandemic preparedness plan was accelerated, and its draft served as the basis for the reassessment of the phases until 2005. The "WHO Global Influenza Preparedness Plan" (145 p. 2) of 2005 provided a classification of an influenza pandemic in six phases that was summarized and published on the WHO website, as shown in Table 3.3 below:

Table 3.3 Classification of influenza pandemic phases, WHO global influenza preparedness plan of 2005

Inter-pandemic phase	Low risk of human cases	1
New virus in animals, no human cases	Higher risk of human cases	2
Pandemic alert	No or very limited human-to-human transmission	(3)
	Evidence of increased human-to human transmission	4
New virus causes human cases	Evidence of significant human-to-human transmission	5
Pandemic	Efficient and sustained human-to-human transmission	6

The distinction between the phases depends on risk assessments based on the latest current knowledge about the risk. (145 p. 6) The adoption of one phase triggers a series of measures to be undertaken by WHO and member states in order to prevent an influenza pandemic from arising or to handle it once it occurs. Inter-pandemic Phases 1 and 2 correspond to the suspicion or the evidence of a new virus strain in animals that could result in human infection. The assessment evaluates the risk of human infection and includes factors such as pathogenicity in animals and humans, occurrence in domesticated animals and livestock or only in wildlife, geographic spread, and virus characteristics. Preparedness measures (promoting global surveillance and contingency planning) and public health measures to protect persons at risk (measures to reduce risk of infection, vaccine development, availability of antiviral drugs) should be put into place.

For phases 3, 4, and 5, the risk of a pandemic is assessed by evaluating the rate of transmission, geographical location and spread, severity of illness, presence of genes from human strains (if derived from an animal strain), and other scientific parameters. For Phase 3,

measures are needed to detect, notify, characterize, and prevent the spread of disease, but the disease remains essentially not transmissible from human to human. These measures include states' guidance and laboratory confirmations, information and communication actions, and recommendation of measures for affected and nonaffected areas, such as infection control measures (wearing face masks) and social distancing measures (confinement). Phase 4 is characterized by limited human-to-human transmission and triggers measures to contain the disease within limited foci or to delay its spread to avert a pandemic and to gain time to implement measures. Phase 5 corresponds to a substantial risk of pandemic with larger clusters of localized human-to-human transmission that would lead to an intensification of the measures in Phase 4. Finally, Phase 6 would be the pandemic, which is characterized by increased and sustained transmission in the general population. WHO's actions would aim to minimize the impact by closely monitoring epidemiological, virology, and clinical features of the disease and its global impact and assessment of the effectiveness of measures. These actions would also include mitigating the impact in affected countries by promoting increased production of vaccines and antivirals, and optimizing patient care.

Based on the assessment of the risk of an H5N1 influenza pandemic, WHO declared the world to be in Phase 3. (133) Phase 3 is characterized by human infection(s) with a new subtype, but no human-to-human spread or, in most rare instances, of spread via a close contact. (145 p. 7) WHO provided guidance to national authorities regarding risk assessment and risk response, country assistance, and laboratory testing. It fostered collaboration to collect strains, established case definitions, and published avian flu-related information. WHO officials also promoted vaccine development and antiviral stockpiles.

The world remained in Phase 3 during the period under study (it is currently in the "alert" phase (168), according to the Pandemic Influenza Risk Management – WHO Interim Guidance published in 2013), which implied the continuous assessment of the risk to change phases, the adoption of preparedness measures, and risk communication activities. The level of risk and the measures to be taken are reevaluated on a regular basis regarding the evolution capacity of the virus to transmit among humans. Phase 4 would be declared based on a risk assessment performed once a new human virus appears and transmits easily among humans. Although transmission among humans was recognized in specific clusters (e.g., in Vietnam and Thailand), WHO officials considered that these sporadic cases in different countries did not constitute

an increased human-to-human transmission. As a consequence, the pandemic alert was not upgraded to Phase 4. However, as the H5N1 virus is still circulating among animals and humans and causing illness and deaths, and the risk of an influenza pandemic remains present, Phase 3 was not downgraded to Phase 2.

The WHO Director-General is ultimately in charge of declaring that the world is in a specific pandemic phase and of deciding on a change of phase. The Director-General's decision was based on a written recommendation that was issued by a committee composed, at the time of the outbreak, of the Assistant Director-General for the Communicable Diseases cluster (Dr. Margaret Chan), the Director of the EPR team (Dr. Mike Ryan),[12] the Global Influenza Programme leader (Dr. Klaus Stöhr), their regional equivalents, and selected experts. A teleconference was organized to discuss the avian influenza evolution, and before or during this conference, the participants could ask for epidemiologic complements of information in order to give their opinion on the current situation. Such teleconferences usually result in recommendations that are drafted by the reporting person and take the form of a "Note for the Record" that is transmitted to the Director-General as support for the group's decision.

Risk assessment method implementation. The "Guiding Principles for International Outbreak Alert" (see risk assessment mechanisms in Chapter 2) was applied with the general risk assessment framework and in the general frame of the global influenza surveillance program. The implementation methods included detection, verification, and communication of the avian influenza cases, as well as risk assessment steps. Detection followed the specific procedures established within the Global Influenza Surveillance Program. In this risk assessment, WHO considered elements such as context, the fact that the disease was known, its regional and then intercontinental spread, its potential serious health impact (high mortality rate), its transmission capacity (from animal to human), its potential impact on travel and trade (impact on poultry trade), and the capacities of infrastructures and health care to handle the disease, in order to make a first decision on how the event should be handled (in pandemic Phase 3, the number of cases is limited).

The alert regarding the resurgence of the H5N1 virus in February 2003 was given through the normal routine surveillance activities of the WHO Global Influenza Surveillance Network. Influenza surveillance follows preestablished procedures that have a long history of practice. The first human case of avian influenza H5N1 was reported in Hong

Kong in February 2003. This case, as well as a second case identified in Hong Kong, followed the general routine procedure established for the surveillance of influenza. The first examination of the patient at the hospital detected a flu virus of type A, generating the performance of further laboratory analysis to determine the virus identity and whether it was of A (H5N1) type. A representative in one of the WHO reference centers located in Hong Kong confirmed the presence of the influenza virus A subtype H5N1 in the first sample analyzed. The usual influenza surveillance procedure prescribes that a hospital representative should communicate the results of the analysis to an official in the ministry of health, who will transmit them to the WHO regional office. The WHO regional office will then inform the WHO headquarters in Geneva, which is what happed in that case. Simultaneously, officials in the ministry of health of the concerned country can also inform WHO headquarters, which was also the case for these two avian influenza cases. The same procedure will apply for other cases reported in other countries later in the process. Once the cases are verified, WHO will publish a report on its website.

The identification of these two human cases coincided with and was related to the strange pneumonia cases (later known as SARS cases) that were reported in China, Hong Kong, and Vietnam during the same period of time and led to the publication of a disease outbreak report. This report explained that avian influenza H5N1 had been detected among a family that had traveled to South China and that the WHO Global Influenza Surveillance Network was put on alert. (139) Even after the risk of an avian influenza pandemic was ruled out in order to focus on the new disease, SARS, these two cases of avian influenza H5N1 remained a concern for Hong Kong authorities, based on the precedent of 1997. The H5N1 virus was a strong candidate for a human influenza pandemic due to its virulence and its capacity to mutate or to reassort. The WHO officials follow up on infectious disease outbreaks during regular technical meetings held every morning at the WHO headquarters while avian influenza officers meet weekly or on an ad hoc basis, specifically, or more frequently if deemed necessary. Past experience with the Spanish flu, the flu of 1957, and the flu of 1968 also raised concern among experts. A pandemic was expected to be more devastating due to the intensification of international trade and travel, but the capacities to respond to such diseases have also improved worldwide.

In terms of application of the overall risk assessment framework, the situation is different from SARS due to the fact that H5N1 avian influenza is a known disease for which the causative agent is identified and

characterized. On February 19, 2003, the results from two laboratories confirmed the presence of the influenza virus A subtype H5N1 in one of the two patients reported by Hong Kong authorities. The causative agent was identified and was similar to an influenza outbreak in Hong Kong in 1997 that had been detected in 18 patients, causing 6 deaths. The high pathogenicity of the virus A (H5N1) already was established in 1997. At that time, the systematic culling of the entire poultry population in Hong Kong and the closing and disinfection of animal markets, as well as the implementation of sanitary days was the key to eradicating the virus in Hong Kong and are considered to have averted a pandemic.

Animals are the principal vector of the disease. The disease probably found its source in waterfowl and has propagated among chicken and ducks. The virus has crossed the species barrier, infecting pigs and feline animals. As animals, in particular poultry – and in some cases pigs – are the main vectors of the disease to humans, the reduction of the risk to human health is conditioned by the reduction of the risk to animal health.

In 2003, further investigations were performed, as other members of the family were sick, and one daughter had died on February 4, 2003, in Fujian Province, China. Hong Kong authorities pursued laboratory and epidemiologic investigations to determine the source of infection as no outbreaks of avian influenza had been reported in Hong Kong, but the investigations were put on hold due to the SARS outbreak and the absence of other cases reported. Outbreaks in Korea and Vietnam could be traced back to the same agent, and on August 8, 2004, epidemiological research traced the first human case in China to November 25, 2003, which was misidentified as a SARS case in Beijing. This case became the first confirmed case of the avian influenza outbreak of 2003–2004.

In addition, the cause-effect relationship became known, as well as the lethal capacity of the virus. The exposure assessment consisted of estimating how humans could become exposed to the virus and with what effect. If the H5N1 virus origin was clearly identified in all Asian countries that were affected in the first months of 2004, the exposure conditions and the populations at risk were more difficult to estimate. Investigation missions were led in Vietnam and Thailand to learn more about the modes of transmission of the disease from poultry to humans. These studies led to the conclusion that the disease was transmitted through close contact with infected poultry and that in Thailand, the disease may have had other symptoms than those initially observed. Initial research done on ten patients in Vietnam identified close contact (holding, killing, or preparing food) with infected poultry as the

probable source of infection in eight out of nine patients for whom a clear history could be taken, but could not completely rule out human-to-human transmission within two family clusters. (159) This study also referred to previous research done based on the 1997 outbreak of H5N1 influenza in Hong Kong, where limited human-to-human transmission was evidenced, but could not be sustained. The authors also reminded readers that previous evidence has been found that this virus has the ability to jump and cause devastating illness in humans.

The circulation of the avian influenza virus H5N1 within East Asian countries, and later in the Middle East, Europe, and Africa, has increased the risk of an influenza pandemic by multiplying the sources of a potential outbreak of human influenza originating in the H5N1 avian influenza animal reservoir. The sources of the risk have been identified as wild birds that have traveled along the migration roads, contaminating ducks and poultry, as well as pigs in certain circumstances. The different virus strains have been identified and analyzed in order to produce vaccines and watch the evolution of the virus, so as to anticipate a mutation or a reassortment that could affect humans more easily and intensively. The risk of a human influenza pandemic mainly relies on the capacity of the virus A (H5N1) to reassort or mutate into a new virus more – or equally as – pathogenic than the virus A (H5N1) that would transmit easily and efficiently among humans. A human pandemic may also originate in another virus, but the H5N1 represents a potential source for a human pandemic. First, the virus is highly pathogenic and lethal both for animals and humans. Second, the virus probably is of Chinese origin, has spread internationally, and has developed among domestic poultry that live closely with humans and therefore constitute a risk for humans to catch the disease. Third, the disease has been present for a certain period of time among animals and has become endemic in some parts of the world, affecting poultry and other animals such as pigs. This is a reason why experts have been evaluating the risk of human influenza derived from avian influenza H5N1 as likely and, in particular, in a mutated or reasserted strain of virus A (H5N1).

The dose-response or cause-effect assessment relates to the amount of exposure necessary to cause the disease. The virus also became more lethal in 2004 and could survive longer in the environment, (169) but direct contact with infected poultry, or surfaces and objects contaminated by their feces, is considered as the main source of infection. The groups at risk are rural populations that keep small poultry flocks around their house and poultry farm workers. Cooked food is without risk, but consuming raw poultry or eggs in affected areas should be avoided. In

1997, as in 2003 and early 2004, the identified human cases were linked to close contacts with animals and, in some cases, to ingestion of raw poultry food or blood, but the disease has not been easily transmitted from human to human. Isolated cases of human transmission have occurred, but have not resulted in easy and effective transmission from human to human. Finally, risk characterization should result in the calculation of a risk, such as the number of people who could catch the avian influenza in a particular population. This phase can give rise to a quantitative result mostly in the form of a probability or a qualitative result expressed by scenarios. Modeling studies were used as a basis to produce different scenarios, usually a mild and severe scenario (sometimes with a middle-range scenario). The results varied significantly based on the method applied, the data used, and the assumptions made.

Controversies arose about the probability of the occurrence of a human influenza pandemic and the severity of its consequences. The position of WHO is that a human influenza pandemic is certain and will occur in the twenty-first century. Therefore, its probability of occurrence is 1, and compared to previous pandemics, its impact is expected to be significant worldwide. WHO worked on only this scenario, acknowledging as uncertain the timing of this pandemic and the virus (the source of the novel virus could be H5N1 or another virus). Professor Robert Webster, a world-renowned and influential virologist at St. Jude Hospital and an expert at WHO, has constantly warned the world about the occurrence of an influenza pandemic for approximately 30 years. More nuanced opinions, such as that of Professor Edwin D. Kilbourne, who retired from New York Medical in 2003, considers it "possible" that a virulent virus such as the agent of the Spanish influenza of 1918–1919 could confront the world again, and that "probably" medical technology and competence (including vaccines, antivirals, and antibiotics) could control it. He insists that no one knows whether there will be another Spanish influenza. (170 pp. 38–39) No definitive consensus exists among scientists about the certainty and the timing of an influenza pandemic of virus A (H5N1).

However, the risk of an avian influenza pandemic or another pandemic that may find its source in animal diseases is considered as real by a majority of scientists. Professor Robert Webster, borrowing the terms from Dr. Malik Peiris,[13] has qualified the risk of an influenza pandemic of H5N1 origin as "low probability, high impact." (171 p. slide 83) If the H5N1 becomes easily transmissible among humans and its case fatality ratio stays above 50%, the world would face a catastrophe. Although other influenza viruses have the potential to evolve into a pandemic

virus, the H5N1 virus has particularly worried WHO and its experts. First, there is the existence of an H5N1 panzootic (a pandemic among animals), which constitutes a significant reservoir for infecting humans. Since the resurgence of the virus in the beginning of 2003, it has spread westward to affect Russia, Kazakhstan, Turkey, certain parts of Europe, and even Africa. It has also become endemic in parts of Asia and, more recently, in Africa. Second, the virus is highly lethal among animals and humans. Its case fatality ratio, both in birds and humans, is over 50%. Once an influenza outbreak starts and reaches a certain level of local or regional spread, continued worldwide spread of the virus is considered inevitable. Therefore, this pandemic could be particularly harmful, considering the fact that little or no immune protection has been developed against this H5N1 virus in the human population. Third, the H5N1 virus has the capacity to change in unpredictable ways, which would allow the new virus to spread efficiently and sustainably among people.

While experts mostly agree that the risk of a human influenza pandemic exists, the severity of its impact in terms of human lives is debated. This debate and its outputs were critical, as the estimated number of deaths is a central element for preparedness activities. An influenza pandemic could affect 20% to 50% of the population, with an unknown mortality rate, offering a wide range of possibilities for estimating the risk. Based on past pandemics, WHO communicated that up to 25% of the worldwide population, which represents about 1.5 billion people, may be affected by an influenza pandemic. (115 p. 47) During the meeting of November 25 to 26, 2004, held in Bangkok, that gathered representatives from WHO, ASEAN, and three countries, Dr. Klaus Stöhr, project leader of the GIP, publicly communicated WHO's first estimate of 2 to 7.4 million deaths due to an influenza pandemic. The WHO experts based their estimate on the model used by data produced by Martin Meltzer,[14] a health economist from the US CDC in Atlanta, whose model was based on the "mild" pandemic in 1968 (172).

The number of deaths has remained a controversial issue, due to the high level of uncertainty around the characteristics of the future influenza pandemic, including the novel virus's pathogenicity and virulence. Dr. Klaus Stöhr, project leader of the GIP from 2001 to 2006, estimated in the fall of 2004 that in a few months, a human flu pandemic could cause 20% of the world's population to become ill, about 28 million people to be hospitalized (if enough beds are available), and 7 million to die. (173 p. 2195) In comparison, the Spanish influenza pandemic of 1918–1919, against which all modern pandemics are measured, resulted

in approximately 20% to 40% of the worldwide population's becoming ill and over 20 million deaths.[15] The WHO experts considered that the Spanish influenza was such an exceptional event that it should not be used as a benchmark for modeling the spread, morbidity, and mortality of the potential H5N1 human influenza pandemic. In addition, WHO argued that better nutrition and health conditions in 2004 compared to the period in which the Spanish influenza occurred, are positive factors to include in an analysis. (175) The WHO officials' announcement of a possible pandemic was controversial and put the organization in a difficult position. In the past, WHO had announced pandemics that did not occur. WHO may have used this cautious approach in order to safeguard the organization's credibility in the face of skeptical governments (176 p. 124).

However, experts such as Dr. Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, considered the estimate of 2 million to 7.4 million deaths too cautious and responded to this estimate on November 25, 2004, saying that a 1918-like pandemic could kill at least 72 million. (172) In 2005, he published his conclusions about possible higher casualties, ranging from 180 million to 360 million deaths globally, based on the rate of death of the Spanish influenza. (177 p. 1842) On November 29, 2004, Dr. Shigeru Omi, director of WHO's Western Pacific Region Office in Manila, in response to this contestation of WHO's estimate, publicly said that the number of deaths could be as high as 20 million, 50 million, or "in the worst case," 100 million. (172) On December 8, 2004, WHO published a statement recognizing the scientific grounds of the different estimates and providing a range of 2 to 50 million deaths, in which the 7 million deaths were presented as a best-case scenario. (175) WHO justified the significant differences in estimates by the high level of uncertainty about the characteristics of the disease and the difficulties in making extrapolations from past pandemics. First, the proportion and the categories of the population that would be affected by the disease as well as the pathogenicity of the virus remain unknown. Second, the pandemics that were used as references for extrapolations presented different characteristics and incomplete or disputed data. Finally, extrapolations from past pandemics should take into account changes in the environment and the level of preparedness. While certain experts, such as Dr. Osterholm, still considered WHO's revised estimate as insufficient and lacking in leadership, others considered it an improvement and a recognition of the uncertainty surrounding this issue. (172) Various estimates were produced by different experts,

including a worst-case scenario based on extrapolation on the lethality of GenZ of the 2004 H5N1 virus that reached an estimate of 1 billion deaths (176 p. 126).

Beyond the fight over numbers, this debate shows the difficulty experts may face in reaching a consensus in situations involving a high level of uncertainty and how the measures proposed could vary as a function of these estimates, such as contingency planning for health infrastructures and drug stockpiling. The WHO experts' assessment presented the risk of an influenza pandemic as certain and realistic, and emphasized the unprecedented opportunity to prepare for it. (178 p. 478) This risk assessment was associated with two unknowns: the time frame, and the virulence of a subsequent pandemic virus. (178 p. 478) The WHO experts justified their estimates by the fact that pandemic viruses present great variations in mortality, severity of illness, and patterns of transmission. In the fall of 2005, having considered the potential and the evolution of the H5N1 virus among animals and humans worldwide, WHO declared the world in Phase 3 of the pandemic classification: "a new influenza virus subtype is causing disease in humans but is not yet spreading efficiently and sustainably among humans." (133) Since that date, WHO has regularly confirmed that the world remains in the prepandemic Phase 3. In the fall of 2008, during the 2008 Wright Colloquium, Professor Webster underlined the fact that the H5N1 virus may not become the next pandemic virus due to its evolution so far, but that preparedness remains essential in facing the next virus that will come within the next 10 to 15 years and is useful in fighting seasonal influenza, as well (171).

Uncertainty reduction. Uncertainties essentially are related to the pandemic timing and its severity. The virulence of the pandemic virus cannot be known in advance, although comparisons can be made with previous pandemic viruses or the H5N1 2004 strain. No one can predict with certainty when a pandemic will start, although an increase in the number of animal cases and human cases, combined with the appearance of seasonal influenza virus periods, increases the possibility of a pandemic occurring during these periods. The severity remains a highly debated issue, as explained in the section above. Scenario-building provides the possibility of reducing uncertainty, but the sensitivity to changes in parameters, such as the reference event (e.g., Spanish influenza or 1957 flu) or the infection rate, produces very different results that complicate the preparedness activities. Experts in the United States established a moderate scenario based on the 1958–1968 pandemic and

a severe scenario based on the Spanish influenza. (179 p. 18) While in both scenarios they assume that 30% of the population would get sick (90 million), out of which 50% would need medical care (45 million), hospitalization (including intensive care and mechanical ventilation) as well as the number of deaths varies significantly. In the moderate scenario, they predict 865,000 hospitalizations and 209,000 deaths, compared to 9,900,000 and 1,903,000 in the severe scenario. Planning for these extreme scenarios is difficult, as even an event such as the moderate scenario involves significant loss of human life and a high burden on health care. As a comparison, worldwide seasonal influenza epidemics result in about 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths (180) each year. European Union officials' summary of the main national plans considered that in the absence of any intervention, during a period of 9 to 15 weeks, 30% of the population would get sick, with an average of 0.37% deaths among infected people, (181 p. 4) which would result in about 150 million persons infected and 550,000 deaths. Based on these figures, case fatality ratios – understood as the proportion of deaths among ill persons – are respectively 0.23% and 2.1% for the American moderate- and severe scenarios and 0.37% for Europe, compared to the WHO conservative scenario of 0.49% (182 p. 71).

During 2004 to 2005, due to uncertainties regarding the disease's evolution among animals and its transmission to humans, and in rare cases among humans, precise computations of the risk remained difficult. However, experts agreed that a risk of a human influenza pandemic of H5N1 origin existed. In particular, the capacity of the H5N1 virus to cause severe outbreaks in humans was evidenced in Hong Kong in 1997. At this stage, WHO believed that the outbreak could be controlled through the elimination of the animal reservoir (mostly poultry) to reduce the risk of human infections by the current virus and prevent it from having opportunities to transform into a human influenza pandemic virus. Later, it will be shown that if specific culling helps reduce the spread of the disease in one localized context, it appears to be ineffective in the longer term to reduce the risk of pandemic. Table 3.4 summarizes the elements that were known during this initial period.

As the level of uncertainty remains significant in regard to the risk of a human influenza pandemic, the risk assessment has been a continuous process based on global surveillance and the work of experts who have relied on the latest experimental and empirical studies to increase their knowledge about the current avian influenza virus H5N1 and, in particular, about the different virus strains that circulated in the different

Table 3.4 Balance between known and unknown facts about an H5N1 influenza pandemic

Known	Unknown
Severe disease in humans caused by avian influenza virus A subtype H5N1	Pathogenicity and virulence of novel pandemic virus
Highly lethal – Case fatality ratio above 50% for animals and humans	Case fatality of influenza issued from pandemic novel virus
International spread of avian influenza H5N1	Rapidity and scope of international spread
Not easily transmittable – close contact needed with infected animals	Transmission modes – expected to be similar to those of regular influenza
Symptoms	Symptoms
Global impact	Magnitude of global impact
Drugs' effectiveness	Drugs' effectiveness

countries, transmission modes, symptoms, clinical management, and effective treatments. However, all this knowledge was accumulated regarding the avian influenza virus H5N1, while experts recognized that the disease that may ultimately result from it may present different features. Increasing knowledge about the H5N1 virus may not necessarily result in expanded knowledge about the novel virus, requiring that the process start again from a situation of a higher level of uncertainty. However, as the H5N1 is virulent in its current form, studying it and preparing for its sustainable transmissible version in humans appeared to the experts as a rational approach with which to start.

Although progress has been made on the knowledge spectrum since the virus subtype H5N1 appeared in 1997 in Hong Kong, uncertainty remains about the final virus that could come from the virus H5N1. One may consider the H5N1 disease in humans as a potential risk in 2004, and as the causative agent, the causal chain is known, as well as evidence about transmission by close contact. The H5N1 virus was clearly identified as provoking severe disease for humans. Knowledge about the avian influenza H5N1 in humans has progressed during the period considered here, mainly regarding the transmissibility of the disease, clinical features, and analysis and sequencing of the virus strains, but the risk is not completely known. Studies have shown that the virus develops in different strains – and these should be closely watched as one could give rise to a pandemic – and also that transmissibility among humans may occur in rare cases. Different models based on expert judgments to

formulate probabilities and potential damage in order to estimate the number of human deaths, as well as the social and economic costs, have been proposed and serve as a basis for discussion and analysis both at the international and the national levels.

Task force role in risk assessment. The Avian Influenza Task Force functioned as the emergency committee prescribed in the IHR 2005. In the case of the avian flu, the WHO collaboration with outside experts relied on the influenza network of laboratories and experts. For existing diseases referred to as "known risks," such as regular influenza, WHO was already working with a network of external experts. WHO officers already knew the personnel of focal points who were involved in the management of infectious diseases, but this information was not centrally documented and accessible within the organization. Dr. Stöhr, who was instrumental in setting up the multicollaboration center during the SARS outbreak, benefitted from his experience and contacts to organize this task force internally (WHO personnel) and externally (experts). Members of this task force provided advice to the Director-General, but did not constitute the only source of information for the Director-General. The Director-General also received information from other organizations, governments (and not only through their ministries of health), and personnel in other internal WHO programs.

The Director-General was directly involved in the management of the H5N1 avian influenza issue, with the support of senior experienced staff from WHO's headquarters in Geneva (in particular from the GIP and the Epidemic and Pandemic Alert and Response team) and from the regional offices. The advice of experts, including risk assessment results, was an essential aspect of the decision-making process. The Director-General had to balance expert advice with other information that came from ministries of health, for example, or other organizations (governmental or nongovernmental) or internally from WHO-related programs.

For example, in the case of the avian influenza, vaccination recommendations from experts were considered in light of the opinion of experts in the WHO vaccine programs that proved to work well and be effective over the past 40 years. The Director-General also relied on internal experience and skills to ensure the feasibility of a recommendation and to adjust it, if necessary. Lessons from the SARS outbreak could be used to improve action, in particular, in dealing with affected areas. Finally, political considerations also played a role, such as governments that expressed their worries about the impact of the avian influenza on their economies (e.g., tourism) or international trade (e.g., trade of

poultry or related food products). The Director-General had the final word on the measures to be adopted and communicated, such as the decision of the pandemic phase (see above). Any change in phase has to be decided by the Director-General of WHO, based on the risk assessment that is prepared within the organization and with the contribution of external experts.

3.1.5.3 Cost analysis

WHO included a cost analysis within the risk assessment, both with regard to human lives and in monetary terms. WHO's evaluation of human life losses was based on modeling studies, and the estimate initially used was largely debated. In summary, human life losses could range from 2 million to 1 billion. WHO undertook preparedness actions in any case, but the estimation of drugs and vaccine needed, for example, has to be based on an estimate. This estimate could be effective (matching the needs) or ineffective (excess of stockpiling or lack of drugs), both of which would generate costs to be compared to the initial estimates. We did not find evidence of such analysis.

Another critical aspect for the emergence of the avian influenza as an international issue is its impact on the economic system, in particular on trade and travel. Different studies were performed on the risks of the infectious diseases and their impact on the economies. While the US CDC estimated the loss from USD 71 billion to USD 166 billion for the US economy only, (183 p. 114) the global impact of an influenza pandemic ranges from USD 200 billion to USD 4 trillion, depending on the duration of the pandemic, its attack rate, and mortality. The epidemiological uncertainty is reflected in the uncertainty of the global economic impact.

Table 3.5 overleaf provides an overview of different estimates.

During the international "Meeting on Avian Influenza and Human Pandemic Influenza" (188) that gathered 600 delegates from over 100 countries, held on November 7 to 9, 2005, in Geneva by WHO, Milan Brahmbhatt presented the World Bank perspective on the economic impact of an influenza pandemic and the estimated cost of a human pandemic of USD 800 billion per year, (189) which corresponds to a 2% loss in the worldwide GDP. This estimate was higher than the cost of SARS, as World Bank experts considered the duration of an influenza pandemic would be longer than the SARS outbreak of 2003. In comparison, SARS resulted in a loss of 2% in the East Asian GDP over three months in 2003. WHO used the World Bank estimate as a reference already in 2005 in its summary report (147) of the November

Table 3.5 Estimates of global economic impact of an influenza pandemic

Source	Model	Mild scenario (GDP loss)	Ultra scenario (GDP loss)	Comment
Warwick McKibbin, Alexandra Sidorenko (2006). (184)	APG-Cubed Model	0.8% USD $330 billion	12.6% USD $4.4 trillion	Model applied to 20 countries
World Bank (2005). (185)	Oxford Economic Forecasting model (OEF)	2% GDP USD $800 billion per year	4%–5% USD $1.5–2 trillion. (186)	Mild scenario used by WHO as reference
Vanessa Rossi, John Walker, (94 p. 18) Oxford Economic Group (2005)	Oxford Economic Forecasting model (OEF)	USD $150–$200 billion	5%–6% USD $1–2 trillion	Extrapolation of SARS
Erik Bloom, Vincent De Wit. (187) (2005)	Oxford Economic Forecasting model (OEF)	2.3% USD $14.2 billion	6.5% USD $282.7 billion	Impact on Asian Economies

international conference and continued to use it repeatedly during the period under study (190).

The International Pledging Conference on Avian and Human Influenza that was held in Beijing, on January 17 to 18, 2006, for the purpose of addressing the financial needs expressed during the WHO meeting of November 2005, resulted in funds pledged of USD 1.9 billion. These funds aimed to cover WHO, FAO, and OIE strategies to reduce the risk of a pandemic. The FAO and OIE strategy aimed to control avian influenza in terrestrial poultry in Asia to reduce the risk of human infection and the risk of a pandemic virus arising. These funds do not include the funds allocated directly by the organizations in their regular budget. For example, in the risk assessment, WHO included a budget for pandemic preparedness, which constituted an improvement as compared to the SARS preparedness. Officials at WHO established a strategic two-year action plan covering 2006 and 2007 that described their strategy regarding an influenza pandemic, goals, actions to be undertaken and the expected results, as well as the estimated costs for these strategies. They presented an evaluation of the funding requirements to complete the two-year strategy and reach the expected results in terms of reducing

human exposure to the H5N1 virus, strengthening the early warning system, intensifying rapid containment operations, building the capacity to cope with a pandemic, and implementing global coordination of scientific research and development (157 p. 22).

In total, as illustrated in the Table 3.6, WHO needed a budget of USD 100 million to carry out this action plan, of which about one-third was allocated to the work that took place at WHO headquarters. These costs of USD 100 million should be added to the USD 1.9 billion pledge from donors, as well as costs from regular budgets of other organizations, and preparedness costs related to national investments requested to upgrade health infrastructures, to establish emergency plans, and to improve surveillance activities.

In the risk assessment, WHO experts referred to the World Bank mild scenario estimate of USD 800 billion per year as a justification to undertake costly actions for preparedness that could save future higher costs. Based on the SARS experience and modeling studies, WHO experts considered that the social and economic disruptions generated by an influenza pandemic will be more significant due to the interconnectedness and

Table 3.6 WHO strategic action plan budget, 2006–2007

	2006–2007 WHO Funding Requirements in USD Million							
Strategic action plan goals	**HQ**	**AFRO**	**AMRO**	**EMRO**	**EURO**	**SEARO**	**WPRO**	**TOTAL**
Reduce human exposure to H5N1	3.0	0.5	0.6	0.5	0.6	0.5	0.5	**6.2**
Strengthen the early warning system	5.0	3.0	2.0	2.0	3.0	3.5	3.5	**22.0**
Intensify rapid containment operations	10.0	3.0	1.1	3.0	3.0	3.0	3.0	**26.1**
Build capacity to cope with a pandemic	4.0	4.0	4.0	4.0	4.0	4.0	4.0	**28.0**
Coordinate national and international science & research	13.0	0.5	0.6	0.5	0.5	1.0	1.0	**17.1**
Total funding requirements	**35.0**	**11.0**	**8.3**	**10.0**	**11.1**	**12.0**	**12.0**	**99.4**

interdependency of trade and economic systems and the nature of the disease. (149 p. 3) In this context, the approximate USD 2 billion costs appear to be highly accurate. When referring to the World Bank estimate and the funds needed to carry out preparedness activities, WHO implicitly carried out the message that these costly actions would be inferior compared to the current estimated costs of a pandemic and that these investments to reduce the panzootic risk, to improve surveillance, and to reinforce coping capacities could possibly result in lower costs than estimated in the event that a pandemic arises.

3.2 Avian influenza H5N1 international response

The determination of whether a PHEIC exists was a key driver for the initiation of an international response. It generated early communication about the public health risk and, in particular, the risk of international spread. WHO issued statements of information and recommendations to guide states in their risk reduction activities.

The WHO response to reduce the risk of an influenza pandemic is articulated around six cornerstones that are addressed: (1) reducing the opportunities for human infection; (2) strengthening early warning systems; (3) building the capacity to cope with a pandemic; (4) containing or delaying the spread at the source; (5) reducing morbidity, mortality, and social disruptions; (6) coordinating scientific research. The first three activities are preparedness actions that take place prepandemic, while containment and reduction of the impact are launched when the virus emerges. While research activities are conducted in prepandemic periods to increase the level of knowledge about the risk of an influenza pandemic, during the pandemic phases, guiding the response and providing for corrective action are crucial. Scientific assessment of the epidemiological characteristics of an emerging pandemic, evaluation of the effectiveness of health interventions, and evaluation of medical and economic consequences of the pandemic will influence the allocation of resources. The main recommendations in relation to the six cornerstones mentioned above are described in the document "Responding to the Avian Influenza Pandemic Threat: Recommended Strategic Actions," (130) and were further developed in the "WHO Strategic Action Plan for Pandemic Influenza 2006–2007." (149) These two documents were used as the basis for our analysis as they synthesized the measures taken by WHO since 2004.

Between January 2004 and December 2008, WHO issued more than 50 guidelines, recommendations, and descriptions regarding the avian

influenza H5N1 (191) in the areas of diagnosis and treatment, food safety, infections control, vaccines and antivirals, and surveillance to address the outbreak and to prepare for an influenza pandemic. We analyzed how the risk assessment was completed once the H5N1 resurgence occurred as a general activity and focused on particular aspects to show how each aspect contributed to the issuance of these strategic actions. For more details about these actions, we referred to specific recommendations that were issued, as the study of all recommendations would not have been feasible due to time and scope constraints linked to this research. The global strategy for the progressive control of highly pathogenic avian influenza published in collaboration with United Nations' FAO and the OIE underlined human health and animal sector preventive measures that could be jointly implemented, such as surveillance of human cases and poultry outbreaks, which were used as an indication of the measures necessary to reduce the exposure of humans to the H5N1 virus. While WHO's preparedness activities for facing an influenza pandemic started before 2004 with the issuance of an influenza pandemic preparedness plan in 1999, they have intensified since the resurgence of the H5N1 virus in 2004. WHO accelerated the revision of this plan, which was made available in the spring of 2005 to serve as a guide for countries' authorities to organize their preparedness and contingency actions. This release contributed to building countries' response capacities. As containment is a key concept in use since 2002, we also analyzed the preparation of the containment protocol that will be a key instrument in delaying or containing the disease at its source. Research activities were addressed as an inherent part of the scientific risk assessment in order to determine how research results were included in the measures recommended by WHO.

The measures proposed were essentially preparedness measures, such as the reduction of possibilities of infection arising from animals, development of preparedness plans, reinforcement of health infrastructures and surveillance systems, development of vaccines, and the stockpiling of drugs. The WHO experts' strategy regarding avian influenza aims at reducing human exposure to the H5N1 virus, strengthening the surveillance system and early warning, containing the disease at its source or limiting its spread, building the capacity to cope with the pandemic, and coordinating international scientific research and development. (149) WHO coordinated a cooperative response and used adequate channels of communication in regard to the avian influenza H5N1. Coordination with other organizations, such as the United Nations and the World Bank, was necessary as one organization could not ensure

the totality of actions at the global level, and additional funds were required. Animal health being intertwined with human health, cooperative action with OIE and FAO was essential to ensure risk reduction in both areas. Cooperation was also achieved with the private sector in regard to the production and stockpiling of drugs. Finally, cooperation with other initiatives and institutions, such as the World Bank for the financing of the activities, was ensured.

3.2.1 Reduction of casualties

Casualties in terms of animal and human cases increased and peaked in 2006, but have decreased since then up to 2008. However, the avian influenza is endemic in certain countries, and the situation remains preoccupying as the virus could mutate and spread among populations.

WHO took measures to limit the exposure of humans to infection by issuing infection control measures and food safety recommendations and proceeding to information campaigns during field missions. In parallel (and jointly with WHO in certain field missions), FAO and OIE carried out culling operations to reduce the number of infected animals, therefore limiting the opportunities for human contagion. These measures contributed to the preservation of the collective interest by reducing the risk of an H5N1 pandemic, limiting the geographical spread of the disease among animals and humans, and reducing the number of cases. These measures were carried out during the entire period under study following the outbreaks in animals.

Table 3.7 shows an overview of the outbreaks in animals up to February 2009, the status of each area in terms of avian influenza among animals, and the correspondence with human outbreaks.

This table shows that in 2009, out of the 63 areas that reported avian influenza outbreaks among animals (domestic poultry and wild animals), only 8 reported new outbreaks in animals and 3 in humans. This illustrates a trend that the disease was coming under control, except in certain countries such as Vietnam, China, and Egypt, where it has become endemic. It also shows that officials in approximately one-third of the countries declared them to be H5N1 free, and one-fourth declared their outbreaks resolved. However, information about animal cases was not available for countries such as Indonesia, where the disease is entrenched, and for other developing countries. No evidence shows that these countries are H5N1 free or that the outbreaks have been resolved. Similarly, human cases may not be reported due to insufficient detection capacities or lack of resources to do the reporting.

Table 3.7 Outbreaks of avian influenza H5N1 among animals and humans by affected area

		Animal cases reported			Human cases reported			
H5N1 Avian influenza Affected areas	**Status at Feb 2009 of animal outbreaks**	**month**	**day**	**year**	**month**	**day**	**year**	**Reported cases 2009**
Republic of Korea	free	Dec	12	2003	None			No cases reported
Vietnam	***notified 2009***	***Jan***	***8***	***2004***	***Jan***	***11***	***2004***	***outbreak***
Japan	free	Jan	12	2004	None			No cases reported
Hong Kong	notified 2009	Jan	19	2004	None			No cases reported
Thailand	free	Jan	23	2004	Jan	23	2004	No cases reported
Cambodia	resolved	Jan	24	2004	Feb	2	2005	No cases reported
Lao PDR	notified 2009	Jan	27	2004	Feb	26	2007	No cases reported
Indonesia	not available	Feb	2	2004	Jul	21	2005	No cases reported
China*	***notified 2009***	***Feb***	***4***	***2004***	***Nov***	***25***	***2003***	***outbreak***
Malaysia	free	Aug	19	2004	None			No cases reported
Russia	free	Jul	23	2005	None			No cases reported
Kazakhstan	not available	Jul	29	2005	None			No cases reported
Mongolia	not available	Aug	10	2005	None			No cases reported
Turkey	free, resolved	Oct	6	2005	Jan	5	2006	No cases reported
Romania	free	Oct	7	2005	None			No cases reported
Taiwan	not available	Oct	20	2005	None			No cases reported
Croatia	not available	Oct	21	2005	None			No cases reported

Continued

Table 3.7 Continued

H5N1 Avian influenza Affected areas	Status at Feb 2009 of animal outbreaks	Animal cases reported			Human cases reported			Reported cases 2009
		month	day	year	month	day	year	
United Kingdom	resolved	Oct	23	2005	None			No cases reported
Kuwait	free	Nov	11	2005	None			No cases reported
Ukraine	free	Dec	2	2005	None			No cases reported
Iraq	not available	Feb	1	2006	Jan	30	2006	No cases reported
Bulgaria	not available	Feb	3	2006	None			No cases reported
Nigeria	resolved	Feb	8	2006	Jan	31	2007	No cases reported
Greece	not available	Feb	9	2006	None			No cases reported
Italy	not available	Feb	11	2006	None			No cases reported
Slovenia	not available	Feb	12	2006	None			No cases reported
Iran	free	Feb	13	2006	None			No cases reported
Germany	notified 2009	Feb	14	2006	None			No cases reported
Egypt	***not available***	***Feb***	***17***	***2006***	***Mar***	***20***	***2006***	***outbreak***
France	free	Feb	17	2006	None			No cases reported
India	notified 2009	Feb	18	2006	None			No cases reported
Austria	not available	Feb	18	2006	None			No cases reported
Bosnia-Herzegovina	not available	Feb	20	2006	None			No cases reported

Slovakia	not available	Feb	20	2006	None			No cases reported
Hungary	free	Feb	21	2006	None			No cases reported
Azerbaijan	resolved	Feb	24	2006	Mar	14	2006	No cases reported
Georgia	not available	Feb	24	2006	None			No cases reported
Niger	not available	Feb	27	2006	None			No cases reported
Pakistan	free	Feb	27	2006	Dec	15	2007	No cases reported
Serbia-Montenegro	resolved	Mar	1	2006	None			No cases reported
Switzerland	not available	Mar	1	2006	None			No cases reported
Poland	free, resolved	Mar	6	2006	None			No cases reported
Albania	free	Mar	7	2006	None			No cases reported
Myanmar	free	Mar	9	2006	Dec	14	2007	No cases reported
Cameroon	not available	Mar	11	2006	None			No cases reported
Denmark	resolved	Mar	14	2006	None			No cases reported
Afghanistan	not available	Mar	15	2006	None			No cases reported
Israel	free, resolved	Mar	16	2006	None			No cases reported
Sweden	resolved	Mar	16	2006	None			No cases reported
Jordan	free	Mar	23	2006	None			No cases reported

Continued

Table 3.7 Continued

H5N1 Avian influenza Affected areas	Status at Feb 2009 of animal outbreaks	Animal cases reported			Human cases reported			Reported cases 2009
		month	day	year	month	day	year	
West Bank/Gaza Strip	free	Mar	23	2006	None			No cases reported
Czech Republic	not available	Mar	27	2006	None			No cases reported
Burkina Faso	not available	Apr	3	2006	None			No cases reported
Sudan	free	Apr	17	2006	None			No cases reported
Côte d'Ivoire	resolved	Apr	19	2006	None			No cases reported
Djibouti	resolved	Apr	24	2006	May	12	2006	No cases reported
USA	not available	Aug	14	2006		None		No cases reported
Bangladesh	notified 2009	Mar	30	2007	May	28	2008	No cases reported
Saudi Arabia	free	Apr	2	2007	None			No cases reported
Ghana	resolved	Apr	12	2007	None			No cases reported
Togo	resolved	Jun	22	2007	None			No cases reported
Benin	resolved	Dec	5	2007	None			No cases reported
Nepal	notified 2009	Jan	16	2009	None			No cases reported

** Outbreaks in poultry announced on January 27, 2004. First case retrospectively dated November 25, 2003, confirmed in August 2006 as wrongly attributed to SARS.*

Table 3.7 is based on data through February 2009 reported by countries to WHO (192) and OIE. (193) The sections below are based on data reported by countries to WHO (192) and to OIE up to December 2008. Two OIE databases were used: the WAHID database (194) for data since 2005 and the HANDISTATUS II (195) for data prior to 2005.

3.2.1.1 Spread limitation

International spread continues but to a lesser extent. Risk reduction can be expressed by the number of affected countries remaining stable or decreasing during the period. The risk of an influenza pandemic is linked to the avian panzootic. Therefore, and although WHO focused on measures to protect humans, WHO, FAO, and OIE assisted countries in decreasing the risk of a human influenza pandemic by reducing the presence of the H5N1 virus among animals. Massive culling campaigns took place in Asia, and carcasses were destroyed, which should result in outbreaks being stopped or even resolved. One limitation of this approach is the completeness and reliability of data, as reporting is essentially based on spontaneous notifications of H5N1 outbreaks to OEI as well as an indication of the number of cases, the number of deaths, and the number of animals destroyed. We have considered the cases of avian influenza (and not the suspected cases that are also reported to OIE) to remain closer to the approach used for human cases, which are confirmed laboratory cases. The total number of deaths refers to the birds that died from the avian influenza, while the total number of animals destroyed is the result of the killing and destruction of carcasses. These data were gathered by country[16] and aggregated for the purpose of this analysis.

Spread in humans. Between 2003 and 2008, 393 human cases of avian were reported to WHO by officials in 15 countries. Table 3.8 overleaf, illustrates the chronological progression of the avian influenza disease in humans worldwide and provides the number of cases by country and by year with an indication of the first reporting date for each onset.

This table shows that avian influenza among humans has spread as of 2008, recording one new country affected by the disease, Bangladesh, during that year. It also highlights the fact that from 2003 to 2005, the disease remained regional and mostly affected East Asian countries (China, Vietnam, Thailand, Cambodia, and Indonesia). It moved to the Middle East and Africa in 2006, and continued to affect countries in Asian and African continents into 2008. If Europe has been affected by avian influenza among animals, no human cases have been reported.

Table 3.8 Number of human cases of avian influenza H5N1 per country and per year of onset

Reported	Country	2003	2004	2005	2006	2007	2008	Total cases
Nov-25-03	China	1		8	13	5	4	**31**
Jan-11-04	Viet Nam	3	29	61		8	6	**107**
Jan-23-04	Thailand		17	5	3			**25**
Feb-02-05	Cambodia			4	2	1	1	**8**
Jul-21-05	Indonesia			20	55	42	22	**139**
Jan-05-06	Turkey				12			**12**
Jan-30-06	Iraq				3			**3**
Mar-14-06	Azerbaijan				8			**8**
Mar-20-06	Egypt				18	25	8	**51**
May-12-06	Djibouti				1			**1**
Jan-31-07	Nigeria					1		**1**
Feb-26-07	Lao PDR					2		**2**
Dec-14-07	Myanmar					1		**1**
Dec-15-07	Pakistan					3		**3**
May-28-08	Bangladesh						1	**1**
Total of cases		**4**	**46**	**98**	**115**	**88**	**42**	**393**

Note: China's first case retrospectively confirmed in 2006. Vietnam's first cases occur in December 2003 and are reported in January 2004.

In addition, North and South America, as well as Australia, have been spared, both from animal and human cases.

Thailand, Turkey, Iraq, Azerbaijan, and Djibouti did not record any avian influenza cases among humans in 2007 and 2008. Although it may be too early to declare these areas free of avian influenza, this reflects the effects of the measures that were implemented. In other countries, avian influenza became endemic, such as in China, Cambodia, Vietnam, Indonesia, and Egypt. In Egypt and Indonesia, the situation remains seriously preoccupying. Indonesia is the most affected country, and officials in that country did not succeed in controlling the disease. The quality of the surveillance system and the reliability of the reporting system in Egypt were questioned, as well as the absence of measures taken by government officials.

In fact, the incidence of the disease among humans depended on the level of the avian influenza outbreak among animals, in particular in poultry, and the presence of backyard flocks in households. Massive culling was one effective measure in controlling the outbreak among poultry in 1997 in Hong Kong, as well as improved sanitary measures in markets. Hong Kong officials have not reported any other human

cases since 2003, although some infected wild birds were found and an outbreak in commercial poultry occurred in December 2008. The next section provides information about the spread in animals.

Spread in animals. The avian influenza H5N1 outbreak that started in China has affected 63 areas in total, reaching a peak of 54 areas affected in 2006. Table 3.9 shows the areas affected in the years from 2004 up to February 2009. The "1" indicates that the H5N1 avian influenza has been found in that country but not the numbers of outbreaks, as some countries have experienced numerous outbreaks. This table shows that a peak occurred in 2006 in a number of affected countries, which is also reflected in the number of reported human cases. This trend reflects the risk of infection of humans in dealing with sick poultry. In general, outbreaks in animals precede human cases. If outbreaks can be detected immediately and destruction measures taken rapidly, a chance exists to reduce the risk of human contamination.

3.2.1.2 Human life impact

The threat to human life on a worldwide basis can be measured through the evolution of the number of human cases of avian influenza per year worldwide and in the most affected countries. Between 2003 and 2008, a total of 393 human cases of avian influenza resulted in 248 deaths, with a case fatality ratio of about 63%.[17]

Avian influenza cases among humans. Figure 3.3 overleaf shows the yearly evolution of the total number of the human cases of H5N1 avian influenza in the world from 2003 to 2008.[18]

The number of avian influenza cases increased up to 2006, with a peak of 115 cases, and then decreased steadily up to 2008. This decrease occurred after the increased surveillance, protection, and infection control measures were put into place, including massive culling of birds in affected areas. Officials of WHO started communicating these measures in 2004 and 2005, and have continuously updated the guidelines and recommendations. A major set of measures was issued in 2005 and early 2006. These measures were associated with funds delivered in different key areas for the surveillance and control of an influenza pandemic and produced effects in the years up to February 2009. However, this positive trend of the reduction of human cases of avian influenza worldwide should be considered with caution.

First, the situation remains of concern in developing countries where efforts have been made to improve surveillance and the detection of

Table 3.9 H5N1 avian influenza affected areas as reported to OIE

Countries	2004	2005	2006	2007	2008
Cambodia	1	1	1	1	1
China	1	1	1	1	1
Hong Kong SAR	1	1	1	1	1
Indonesia	1	1	1		
Japan*	1			1	1
Korea Rep. of*	1		1	1	1
Laos	1		1	1	1
Malaysia*	1		1	1	
Thailand	1	1	1	1	1
Vietnam	1	1	1	1	1
Croatia		1	1		
Kazakhstan		1	1		
Mongolia		1	1		
Romania*		1	1	1	
Russia*		1	1	1	1
Turkey*		1	1	1	1
Ukraine*		1	1		1
Afghanistan			1	1	
Albania*			1		
Austria			1		
Azerbaijan			1		
Bosnia Herz.			1		
Bulgaria			1		
Burkina Faso			1		
Cameroon			1		
Czech Rep.			1	1	
Denmark			1		
Djibouti			1		
Egypt			1		1
France*			1	1	
Georgia			1		
Germany*			1	1	1
Greece			1		
Hungary*			1	1	
India*			1	1	1
Iran*			1		1
Iraq			1		
Israel*			1		1
Italy			1		
Ivory Coast			1		
Jordan*			1		
Myanmar*			1	1	
Niger			1		
Nigeria			1		1
Pakistan*			1	1	1

Continued

Table 3.9 Continued

Countries	2004	2005	2006	2007	2008
Palestinian Aut. Terr.*			1		
Poland*			1	1	
Serbia & Montenegro			1		
Slovakia			1		
Slovenia			1		
Spain			1		
Sudan*			1		
Sweden			1		
Switzerland			1		1
United Kingdom			1	1	1
Bangladesh				1	1
Benin				1	
Ghana				1	
Kuwait*				1	
Saudi Arabia*				1	1
Togo				1	1
Nepal					
Number of affected areas by year	**10**	**13**	**54**	**28**	**23**

Notes: Hong Kong and Palestine are considered as separate reporting entities by OIE. Data were not available for Taiwan and Nepal outbreak occurred in January 2009.

* Countries self-declaring freedom from highly pathogenic avian influenza (HPAI) after outbreaks of H5N1 avian influenza in domestic poultry.

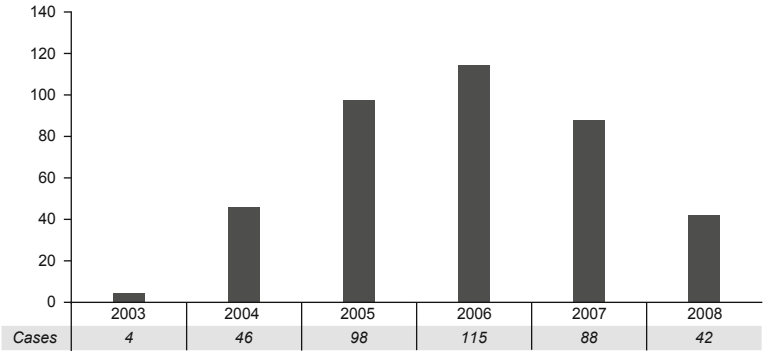

Figure 3.3 Human cases of avian influenza H5N1, 2003–2008

cases. Experts find it difficult to estimate the influence of the implementation and improvement of an avian influenza surveillance system, as well as the introduction of detection tests in poultry in a number of cases. Improvement in the detection and reporting of cases may contribute to an increase in the number of cases, while insufficiently developed or absent systems will result in underestimating the data. For developing countries, on the one hand, surveillance systems are costly and difficult to implement, and on the other hand, the reporting of human cases of avian influenza may constitute a lower priority level for these countries that are affected by other recurring and more lethal diseases.

Second, H5N1 avian influenza symptoms can be attributed to other diseases such as regular influenza or pulmonary infectious diseases. If suspected cases are not confirmed with further laboratory analyses, the identification and reporting can be impacted.

Third, not only is the number of cases an important indicator, but also the capacity of the virus to transmit easily from human to human is a key factor in the generation of a pandemic. Although the number of human cases has decreased and remains limited, a pandemic can still emerge if the virus becomes easily contagious among humans. Studies have confirmed that transmission of H5N1 avian influenza from human to human has occurred in rare situations, among family members, for example. However, the virus has not yet acquired the ability to transmit easily and efficiently among humans.

Avian influenza cases among animals. Up to February 2009,[19] avian influenza among animals affected 63 areas, with about 27 million bird cases, resulting in 9 million deaths and 112 million birds destroyed. The data are based on reports to OIE of the number of cases, the number of deaths, and the number of animals destroyed. These data do not include outbreaks other than H5N1 that have occurred (for example, the outbreak of H7N3 in Canada that resulted in nearly 14 million birds culled and the outbreak of H7N7 in the Netherlands that resulted in around 30 million birds culled). "Birds" mainly refers to poultry; some wild bird cases were reported and not retrieved from the computation as they had an immaterial impact on the figures. Figure 3.4 shows that the pattern of HPAI cases in bird populations is similar to the trend in human cases, with peaks of cases and numbers of birds destroyed in 2006.

Avian influenza eradication campaigns have relied on the massive culling of poultry populations, as well as the implementation of infection control measures, from disinfection of places and material to hygiene measures for individuals who come into contact with poultry.

In certain cases, biosecurity measures have been implemented, as well. As shown by Figure 3.5, significant eradication campaigns were undertaken in 2004, although their success depended on the compensation scheme that is offered to poultry owners. Most of the cases occurred in small poultry flocks, and inciting the populations to identify (if possible) and to report the disease was difficult, especially when it constituted the poultry farmers' main subsistence source.

3.2.1.3 Economic cost

One element that shows that the international response was appropriate in the case of avian influenza consists in comparing the effective economic cost of the actions taken in the case of avian influenza to the estimated global cost. In terms of costs, expenses for actions undertaken

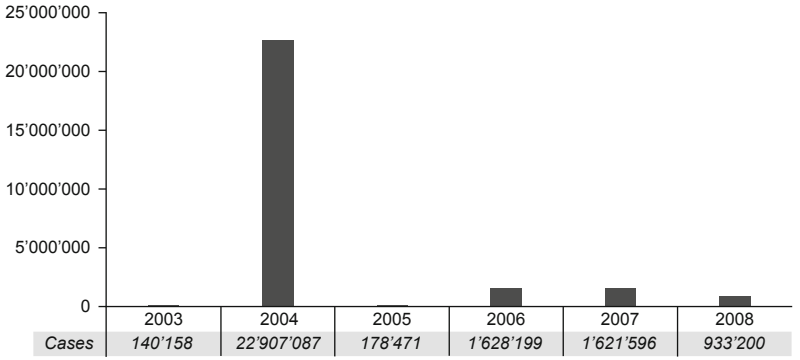

Figure 3.4 Numbers of avian influenza H5N1 cases in birds, 2003–2008

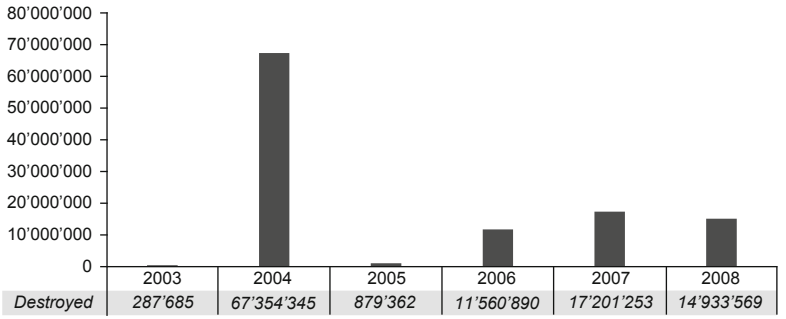

Figure 3.5 Numbers of animals destroyed, 2003–2008

remain lower than total estimated economic costs if a pandemic occurs. The international response to avian influenza was costly, in particular culling activities, vaccination campaigns, surveillance, and implementation of infection control measures. The cost was estimated at USD 10 billion in agricultural losses in 2005 alone (130 p. 4).

During the Sixth International Ministerial Conference on Avian and Pandemic Influenza held Sharm El-Sheikh, Egypt, on October 24 to 26, 2008, officials from FAO presented estimates showing that H5N1 avian influenza has cost over USD 20 billion in economic losses. (196 p. 9) According to FAO, if an influenza pandemic occurs, the cost to the global economy could be around USD 2 trillion, and investments in preventive and control strategies are likely to be highly cost effective (196 p. 9).

3.2.2 Cooperation and communication

The elaboration and the decisions of WHO officials in their recommended strategic actions and the containment protocols were based on dialogue, and were collegially decided and publicly communicated. In the avian influenza case, guidelines have been the result of a group effort after a consultation process led by the influenza pandemic task force. The Director-General was not systematically involved, as no global alert was published and no travel restrictions were issued, but proceeded to the declaration of Phase 3, according to the decision process.

Due to the relationship between animal and human disease and the global nature of the risk, cooperation among organizations was institutionalized. David Nabarro, a former WHO officer, was appointed United Nations System Influenza Coordinator in September 2005 to coordinate the action between the various bodies related to the United Nations. In addition, the OFFLU is a joint network of OIE and FAO experts on influenza that was established in 2005 to cooperate in infection control, data sharing, and biological material sharing. (197) Its primary purpose is to support international efforts to monitor and control infections of avian influenza in poultry and other bird species and to share biological material and data to support early development of human pandemic vaccines. Members of this network cooperate with WHO animal-human interface experts, in particular on the preparation of human vaccine.

Since December 2004, WHO officials have intensified the number of consultations and publications regarding this issue (e.g., "Avian Influenza: Assessing the Pandemic Threat," January 2005, followed by the "WHO Global Influenza Preparedness Plan," "The Role of WHO and Recommendations for National Measures Before and During Pandemics," the "Checklist for Influenza Pandemic Preparedness

Planning as Well as Recommendations for Strategic Actions," and in 2006, the "WHO Pandemic Influenza Draft Protocol for Rapid Response and Containment"). The avian influenza issue was discussed at the World Health Assembly in May 2005, and participants decided to continue the preparedness activities and to increase support for affected countries. In addition, WHO jointly organized with FAO and OIE a three-day conference from November 7 to 9, 2005, at its headquarters in Geneva, gathering professionals from the organization, representatives of member countries, and representatives of international organizations and civil society, as well as health experts or consultants to discuss the situation of the avian influenza, to agree upon actions to be taken, and to estimate financial needs to achieve these protection objectives.

This conference was followed by the donors' pledging conference in Beijing in January 2006, sponsored by the Chinese government, the European Commission, and the World Bank in order to raise funds according to the needs and priorities defined in Geneva in November 2005. Funds amounting to USD 1.9 billion were pledged during that conference. (198) The participants also took this opportunity to set an agenda for the coming months in terms of the preparation of a protocol for rapid response and containment, as well as standard operating procedures in case of the occurrence of an influenza pandemic. Government officials' awareness had increased; from fewer than 50 countries that had a pandemic preparedness plan in spring 2005, the proportion grew to approximately 120, representing about 60% of the 194 member states of WHO (199).

Finally, the influenza pandemic risk has been a concern at the highest levels nationally and internationally and has resulted in new cooperation initiatives to address the issue globally. At WHO, pandemic issues are under the direct competence of the WHO Director-General. The international meeting of November 2005 in Geneva gathered the leading officials of OIE, FAO, WHO, and the World Bank to discuss risk assessment and produce recommendations. The avian influenza issue has also been put on the 2006 G8 agenda. Members of the G8 recognized that priority efforts should focus on the early detection and control of the H5N1 strain of avian influenza at its source, as well as on the prevention of and preparedness for a potential human influenza pandemic. Members of the G8 reaffirmed their support of the WHO-administered GOARN, of FAO and OIE, as well as of the UN System Influenza Coordination Office (UNSIC) and international financial institutions in addressing these global threats. (137) In addition, President George W. Bush announced the International Partnership on Avian and Pandemic Influenza in

September 2005 in New York. The first two objectives of this partnership consist of fostering international cooperation to protect the lives and health of people and promoting timely and sustained high-level global political leadership to combat avian and pandemic influenza (136).

In terms of communication, WHO created a specific website dedicated to avian influenza as part of the general WHO website. On its website, WHO clearly positioned itself as the coordinator of the global response to human cases of H5N1 avian influenza (200).

3.2.3 Response monitoring

WHO monitored the H5N1 avian influenza response based on national authorities' reporting of cases database. It ensured that WHO measures were put in place by following up on the completion of preparedness activities, such as elaboration of preparedness plans, antiviral stockpiling, and virus sharing for vaccine production. Finally, WHO applied an incentive-based system to obtain cooperation and enforce recommendations.

3.2.3.1 Reporting system

This WHO reporting system for avian influenza H5N1 was essentially based on voluntary notifications from states. A formal reporting mechanism was already in place in the influenza network, and state officials notify the network of outbreaks. However, as explained in Chapter 2, a challenge remains for WHO to obtain complete, timely, and accurate information. Since June 15, 2007, when the IHR came into force, state officials have been required to notify WHO of diseases that are on the list of Annex 2 or of events that qualify as PHEICs, which is the case for avian influenza H5N1. In the first two months of 2009, only China, Vietnam, and Egypt reported outbreaks, while avian influenza is known to be endemic in Indonesia. WHO will follow up on the number of cases and the number of deaths. On the one side, they are allowed to follow up on the development of an outbreak through the evolution of the increase in the number of cases and assess the risk of further spread. On the other side, they gather information about avian influenza from different sources that can be combined into useful information made available to states on the WHO website. After June 2007, while the outbreaks in poultry continued generating sporadic infections in humans, the reporting of cases stopped. (115 p. 49) WHO still obtained information about the outbreaks using nonofficial sources. The pandemic risk was considered as exaggerated, although for WHO experts, the risk still persisted, although they were not able to assess

the level of its risk without complete and accurate reporting. Reporting plays a role in both assessing and managing the risk. Without any data, WHO experts cannot accurately evaluate the risk.

WHO also administers FluNet, an Internet-based geographical information system of which time data on any country can be accessed in real time. In the avian influenza case, it could be used to learn more about circulating virus trends and epidemiological trends. The network should be able to capture a virus with pandemic potential or any outbreak of severe illness or rapid spread (115 p. 46).

3.2.3.2 Evaluating completion of measures

The evaluation of completion should be done at different levels. WHO has issued measures to help countries become prepared for a human influenza pandemic, providing them with guidance in preparedness planning. In addition, WHO and OIE have recommended containment measures that include the achievement of culling programs and the implementation of hygiene protection measures in farms and markets. Finally, in regard to human risk, information campaigns have been made to inform people about how to handle live and dead animals that are susceptible to the disease and how to protect themselves from getting the disease from these animals.

Build capacities to cope with a pandemic. WHO recommended that state officials elaborate and test an influenza preparedness plan and that they institute an antiviral stockpile. In 2006, 23 countries ordered an oseltamivir national stockpile, (130 p. 2) which continued to increase after that date. The WHO stockpile of 3 million courses of treatment was upgraded to 5 million. Countries such as the United States, Switzerland, and other countries in Europe stockpiled Tamiflu.

WHO issued a preliminary version of the preparedness plan in March 2005 and the final version in November 2005. This document is entitled *WHO Global Influenza Preparedness Plan: The Role of WHO and Recommendations for National Measures before and during Pandemics*, and aims at assisting WHO member states in responding to a pandemic influenza. This WHO guide was the result of a consultation on WHO-recommended national and international measures before and during influenza pandemics that took place at WHO headquarters in Geneva on December 13 to 15, 2004. The WHO guide on preparedness planning was applied to this situation, and is often publicly mentioned as a reference. For example, members of the European Union adopted an EU Influenza Pandemic Preparedness Plan in March 2004 based on

previous recommendations of WHO experts, following the 1999 plan, and indicated on the organization's website that they had completely reviewed their plan in order to ensure better coherence with WHO recommendations and the revised plan that was issued in 2005. The Federal Office of Public Health (FOPH) in Switzerland also based its plan on the WHO program.

This WHO preparedness plan has been one of the WHO recommendations that has been largely followed by national authorities, as evidenced by the number of plans submitted to WHO increasing regularly after some initial reluctance following the controversial announcement of a pandemic risk. Governments initially were not inclined to invest in pandemic preparedness activities, and WHO encountered difficulties in convincing countries such as the United States and certain Asian countries to elaborate their preparedness plans. Another issue was the content of the plans and the test of their operating procedures. As of November 2005, approximately 120 countries had developed a preparedness plan, compared to only 50 (201) a few months before. By August 1, 2006, over 176 countries had drafts or completed national plans, (202) although the quality was often inadequate. By 2007, the objective was that all member states would have national preparedness plans devised, implemented, and tested to provide the backbone of the response to a potential pandemic. As this objective was not met and the quality of certain plans remained poor, WHO revaluated the situation in the midterm strategic plan 2008–2013 and set further objectives. WHO reported that 90 countries have funded preparedness plans and standard operating procedures in place for major epidemic-prone diseases, such as an influenza pandemic, and that 70 countries that have the basic capacity in place for safe laboratory handling of pathogens and safe isolation of patients. (203 p. 22) The targets for 2009 are 135 countries with plans and 100 with laboratory and isolation capacities, and for 2013, 193 countries in both areas.

WHO has also communicated on a regular basis on any matter related to the human influenza pandemic risk and the status of the disease. WHO is an institution in which knowledge of the disease has been gathered, the risk analysis performed, and solutions proposed.

Coordinate research – vaccine development. One objective of WHO was to promote research to find a vaccine and increase manufacturing capacity in order to accommodate demand during a pandemic. The virus-sharing network collected, analyzed, and diffused H5N1 virus specimens in accordance with WHO's commitment to promote vaccine development

and production. Between 2003 and 2007, WHO member states shared 8,815 human and animal specimens from avian influenza A (H5N1) suspected and/or confirmed cases with WHO laboratories, where 788 viruses were isolated and maintained in WHO laboratories and 14 viruses selected for further development into A (H5N1) vaccine viruses. (204) Until January 2008, eight reverse-engineered genetics vaccine viruses, suitable for vaccine development and production, were available for distribution, and 292 institutions received one or more of these samples and developed vaccine viruses, while 47 institutions received wild-type vaccine viruses (204).

Sharing viruses is essential in order to be able to watch the evolution of the virus and to develop vaccines. However, since 2005, Indonesian authorities have shared only two virus samples with WHO (166 p. BO7), although it is the country most affected by H5N1. The Indonesian officials also stopped notifying OIE and WHO about bird flu outbreaks or human cases starting in 2007, not complying with the IHR (166 p. BO7). WHO had other sources to confirm human outbreaks, but the lack of cooperation in virus sharing was more problematic. The Indonesian Ministry of Health developed the concept of "viral sovereignty," according to which viruses should remain the property of individual states. Indonesian authorities did not see any benefit in sharing their viruses, when their country is unlikely to benefit from a vaccine in the case of a pandemic. In 2003, 62% of the world's influenza vaccines were used by nine developed countries. (123 p. 406) While 90% of the global capacity of vaccine production is located in developed countries, essentially in Europe and North America in 2009, six manufacturers in developing countries have started to acquire the technology to produce influenza vaccines and have received technical and financial support from WHO. (205) By the end of March 2007, Indonesian authorities resumed sharing vaccines after an international meeting held in Indonesia, during which new terms were issued regarding the sharing of vaccines and a commitment was received from WHO in favor of negotiating with vaccine producers to transfer technology and make vaccines available to developing countries. The Indonesia case illustrates how maintaining cooperation to reduce risk can be difficult, in particular when the burden of efforts and the sharing of benefits are not perceived as fair.

WHO also encouraged the use of vaccines for regular influenza in order to increase the demand and therefore the production capacity to satisfy this demand. Although the worldwide influenza vaccine manufacturing capacity has increased from 300 million to 420 million doses, it has remained below the demand in the case of a pandemic during

2006–2007.[20] Production of cell cultures rather than eggs or of recombinant technologies was researched, as well as ways to reduce the lead time of vaccines. In the spring of 2007, the first H5N1 vaccine was approved in the United States. Both objectives of the manufacturing capacity of a vaccine and the development of a vaccine were partially achieved in 2007.

Panzootic reduction. The panzootic has been reduced, although sporadic outbreaks still arise in certain countries, and in others, the situation is endemic, as in Indonesia or Egypt. Countries carried out massive and costly culling campaigns, but they have not succeeded in eradicating the virus so far. A compensation scheme was established, which planned for a rate of compensation compared to the market price of the animal (15% to 20%). Notifications do not occur due to economic costs to animal farmers; therefore, the compensation plan should provide an incentive to cooperate.

3.2.3.3 Incentive-based enforcement

The IHR 2005 is the only legally binding instrument that provides reporting guidelines, and it does not include enforcement mechanisms, such as sanctions for noncompliance with the rules or verification controls. As explained in Chapter 2, WHO established an incentive-based system that leverages different aspects, such as credibility, pressure from peers, and influence of the organization. The IHR 2005 added a positive incentive by linking notification to assistance and confidentiality. A country whose authorities notify WHO about an outbreak can seek assistance, and during the consultation phase, the information is not publicly disclosed. For example, this incentive was already used by Vietnamese officials in 2004. An additional benefit that can be seen from cooperating in the notification and the handling of outbreaks such as avian influenza is that information is collected from different sources by the organization and can be disseminated to state members in order to improve their response capacities. However, these guidelines do not solve the economic issue. Notification of an outbreak leads to economic losses in terms of consumption, tourism, and travel, but also can trigger trade sanctions that could remain in place for a long time. Furthermore, adequate and effective compensatory systems are not in place to promote citizens' notifying their authorities of disease, and then to WHO, OIE, or FAO. Compensation for losses incurred due to the disease itself, the massive culling of poultry, the isolation of animals, or the imposition of stricter and costly infection control measures could be

another tool to ensure adequate reporting of diseases and application of control measures.

3.3 Conclusion

Our analysis showed that WHO conducted a risk analysis that resulted in the reduction of the H5N1 avian influenza pandemic risk. Officials of WHO organized a multidisciplinary, internationally recognized, and geographically broad-based group of experts to assess risk based on the latest scientific findings and the completion of innovative steering mechanisms that relied on multistakeholders' assessments, such as the design of the protocol of containment. WHO applied risk analysis methods to determine the notification of an event, the pandemic phase, and the risk of a pandemic. The process legitimacy was first action based and then became rule based once the early and final adoptions of the IHR had taken place. WHO performed a cost analysis for internal purposes and used the World Bank estimate as a benchmark for the cost estimation of a pandemic.

In turn, WHO's response to the avian influenza risk resulted in a decrease in casualties, was cooperation based, and was adequately monitored. The response resulted in limitation of the international spread and reduction of the number of cases, both in humans and animals. In addition, based on World Bank experts' estimate of USD 800 billion in costs, the measures carried out were cost effective. Finally, the reporting system provided useful information at the beginning that faded once the risk decreased. Some accuracy, completeness, and reliability issues jeopardized the quality of information. WHO recommendations were largely applied, although they included no enforcement provisions. The absence of coercive enforcement means was compensated by the structure of the response, and by the incentive-based system that contributed to the reaching of an agreement on vaccines.

Although not all indicators were present at 100%, the present analysis showed that the three constitutive aspects of the risk analysis and appropriate international response to avian influenza were evidenced. The quality of expertise and the innovative ways of organizing the experts and other stakeholders gathered in a risk assessment process, including cost analysis, significantly contributed to the risk analysis, while planning encountered some legal issues until the enactment of the revised IHR. The decrease in casualties contributed to reducing the risk, but the incomplete evaluation of the cost prevented it from reaching the maximum level. Some deficiencies in reporting did not lead

to questioning about the overall presence of monitoring. The existence and the quality of the relationship between risk analysis and the formation of an internationally appropriate response to the risk of an H5N1 avian influenza pandemic under WHO is illustrated in Figure 3.6.

An influenza pandemic has the potential to significantly disrupt social and economic structures, as well as international trade and travel. WHO actions essentially focus on sanitary issues that are at stake, and WHO leaders based their analysis on expertise and the evolution of knowledge about the disease: its gravity (capacity of the health infrastructures to face a significant outbreak and even a pandemic); its morbidity and mortality (number of cases, number of deaths); and the populations concerned. A high level of uncertainty remains regarding the timing and the severity of a pandemic. Modeling studies provide a basis on which to start, but the outcomes vary significantly. Activities of WHO experts aim at reducing the pandemic risk by acting to reduce human exposure to the virus, strengthening the surveillance and early warning system, establishing containment operations (vaccine, medication, and social distancing measures), building capacity (through preparedness planning), and coordinating international research. WHO mobilized its state

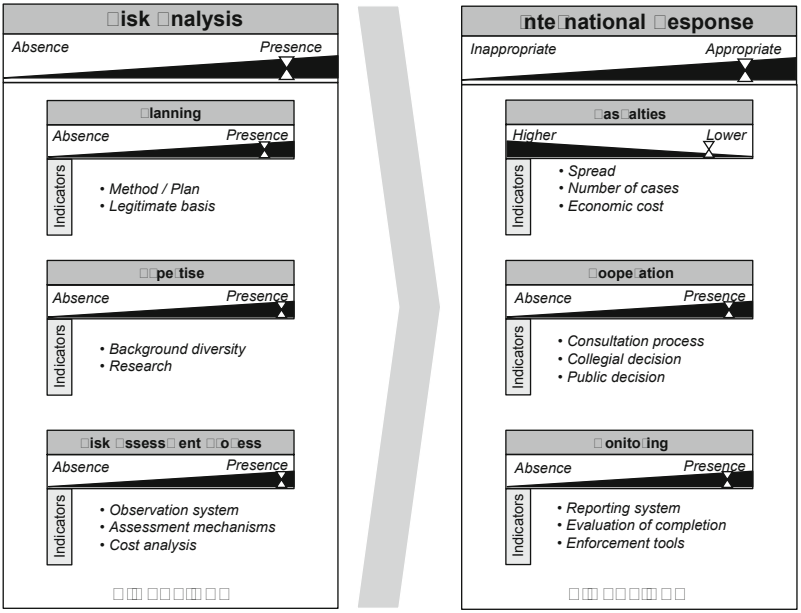

Figure 3.6 International response to avian Influenza H5N1

members, governmental agencies or organizations, NGOs, the scientific community (research centers, laboratories, and universities), the private sector, and the media. Experts at WHO have performed a pandemic risk assessment and created a pandemic preparedness plan meant to serve as a reference on a worldwide basis for government officials to develop their own plans. Officials at WHO reached an agreement with Roche managers, who decided to provide the organization with an international stockpile of Tamiflu, the only medicine proven to have some (but not systematic) efficiency in treating patients affected by the avian flu. This stockpile is aimed at treating the first zones affected, in hopes of stopping the propagation of the disease and, therefore, the development of a pandemic. In addition, the three-day international conference in November 2005 in Geneva pursued three objectives: providing a global status on the avian flu and the related human pandemic risk in the world; proposing measures to go forward; and estimating funding needs. The conference of the donors held in January 2006 was the next step in securing funding that was necessary to undertake pandemic preparedness activities.

WHO played a key role in the public health surveillance, risk analysis, and recommendations for action in the case of the avian flu. On one side, this role directly resulted from the competencies attributed by the member states to the organization through founding documents; in particular, its constitution and the IHR established the governance role of WHO. On the other side, WHO can rely on competency networks, capacities, and infrastructures, as well as the experience it has acquired in managing different critical public health issues around the world since its creation in 1947. Actions of WHO are limited by national sovereignty in the case of notifications and field investigations, but in the case in which officials of a country such as Indonesia discontinue their reporting of cases and refuse to share their viruses, leaders of WHO can provide a forum for addressing these concerns, as they did for Indonesia when they exposed Indonesian officials' concerns and became committed to helping them find satisfactory solutions regarding access to vaccine production for developing countries.

The response of WHO was considered appropriate for the following reasons. The WHO activities were recognized not only by its member states but also by other intergovernmental organizations, public and private research institutes, universities, pharmaceutical companies, and other actors from the private sectors as well as NGOs. In addition, WHO's new method of organizing expertise guaranteed a more diverse background of participants to assess the risk and make recommendations.

The fact that this expertise can be mobilized rapidly to intervene in countries is also a factor of success. Moreover, officials of WHO positioned the organization as a worldwide coordinator of efforts to prepare for a pandemic. While WHO was leading the governance process at early stages, OIE and FAO claimed their legitimacy for action to control the disease at its animal source. (206 p. 217) OIE competed with WHO to have the avian influenza put on top of the animal health and respectively human health agenda, to be recognized as the leading organization in global risk governance, widen their scope of action and obtain more funding resources. (207) Despite tensions and disagreement due to their own logic, interests, and practices, these organizations cooperated. WHO had to collaborate with leaders of other UN bodies such as OIE and FAO, funding institutions, governments, the private sector, research institutes, laboratories, and universities to keep the pandemic preparedness activities in process. Also, the worldwide institutional structure and involvement of WHO officers who were committed at all levels of the organization allowed them to carry out the response.

Finally, the adoption of the IHR provided WHO with an adequate instrument for addressing global risk. By December 2008, authorities in 193 countries designated focal points, in 152 countries accessed the event information management site, and in 56 countries nominated national experts for the roster of experts. (158) By June 2009, the capacities have been upgraded based on WHO assistance. Although it was not yet approved when the H5N1 outbreak started, the IHR revision draft was applied until its anticipatory entry into force in 2006 or its regular entry into force in 2007. The functioning of a task force acting as an emergency committee, as planned under the IHR, ensured direct communication between subject matter experts and top management of WHO in addressing the risk.

The international response was impacted primarily by cooperation issues with countries' authorities who refused to report or reported unreliable information. This action was not only the source of incorrect or nonavailable data, but it also prevented WHO experts from further carrying out the risk assessment in good conditions and, therefore, making the best targeted recommendations. Sovereignty arguments were used by Indonesian authorities to obtain some guarantees about the availability of vaccines to developing countries. Indonesian officials balanced their country's sovereignty rights and shared commitments, and finally decided to cooperate in virus sharing. The IHR does not include sanctions in such cases of noncompliance with the rules. The potential consequences of noncompliance are considered as a

compliance tool, as well as pressure from other states' leaders, WHO officials, and public outcry.

Another issue was the duration of the outbreaks. After the initial measures generated a decrease in the number of outbreaks in animals and humans cases, some governments began to believe that the risk was exaggerated. The question of the effectiveness of measures taken to reduce the probability of occurrence of the pandemic risk remained open. Finally, the cost of these measures played a role, as well. Costly measures were requested over a long period of time, stretching the resources of certain countries, while international compensatory mechanisms and national mechanisms operated slowly – for a pandemic that has not come.

Despite these weaknesses in monitoring and cooperation, empirical evidence showed that WHO's risk analysis process integrated more actors, included cost analysis and funding needs evaluation, and contributed to improving pandemic preparedness worldwide and reducing the risk of an avian influenza pandemic. The H5N1 avian influenza remains an example of an appropriate international response, reinforcing the leading role of WHO in dealing with infectious diseases at the global level.