

**Guideline for Rapid Response Strategies
during the Early Stages of Pandemic Influenza**

March 26, 2007

Pandemic Influenza Experts Advisory Committee

Rapid Response Strategies during the Early Stages of Pandemic Influenza

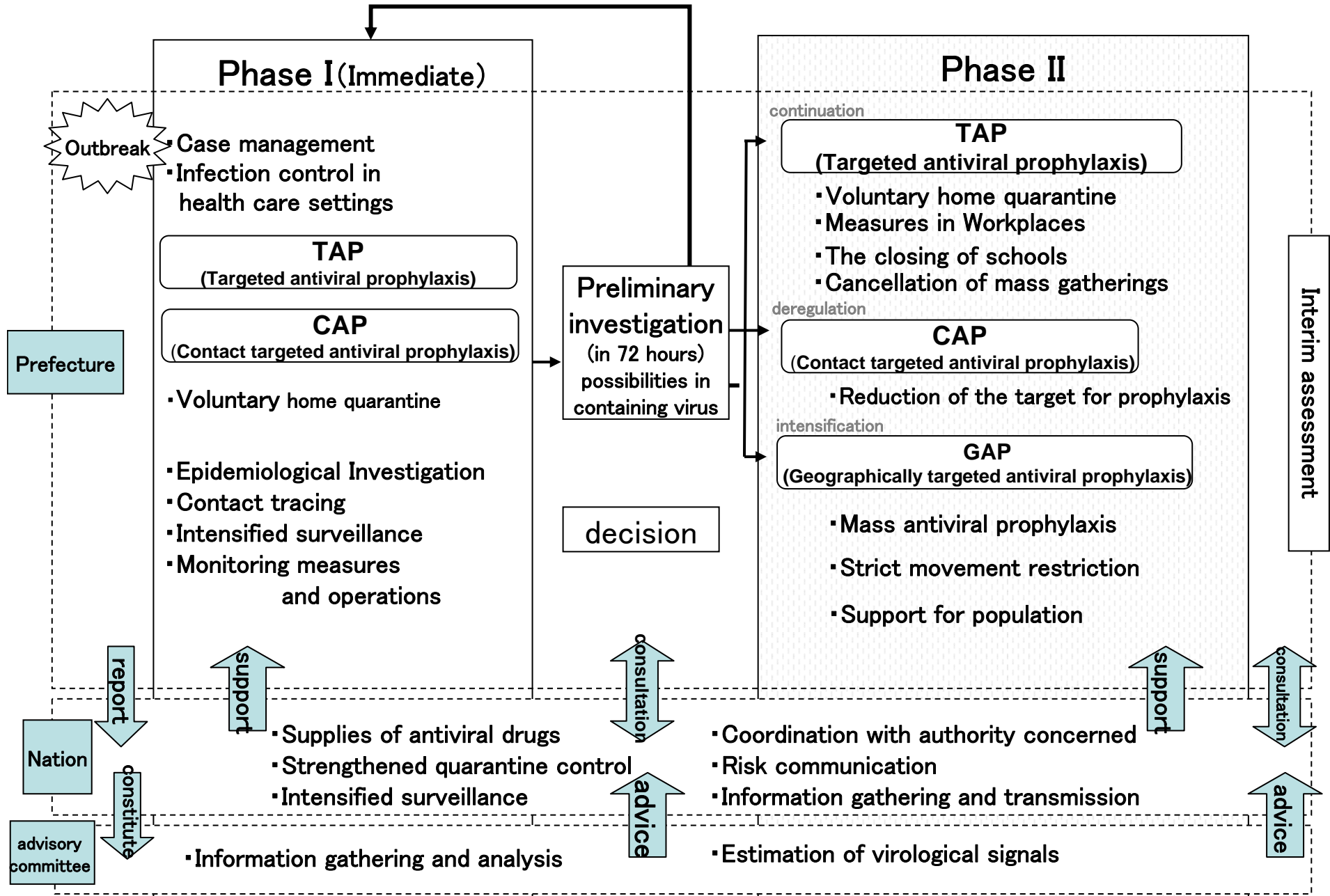
| Antiviral Prophylaxis | | Purpose | Targets of prophylaxis |
|-----------------------|---|---|---|
| ① | TAP (Targeted antiviral prophylaxis) | Prevent the spread of infection | Groups in the same households ,schools or workplaces |
| ② | CAP (Contact targeted antiviral prophylaxis) | Prevent the infection of close contacts | Close contact groups |
| ③ | GAP (Geographically targeted antiviral prophylaxis) | Contain the spread of infection | Population in the outbreak area |
| ④ | Nonpharmaceutical Interventions | Mitigate the spread of infection | Case management, Infection control in health care settings, Movement restriction, Closing of schools and workplaces, Cancellation of mass gatherings, Risk communication and so on |

② + ④ Strategy with CAP: Prevent the infection of close contact

① + ② + ④ Strategy with TAP: Prevent the spread of infection in the area

② + ③ + ④ Strategy with GAP: Contain the spread of infection in the outbreak area

Rapid Response Strategies during the Early Stages of Pandemic Influenza



Guidelines for Strategic Early Response during the Early Stages of Pandemic Influenza - Rapid Response Strategies –

Introduction

- Once pandemic influenza has occurred, neglecting to respond appropriately would lead to an explosive outbreak and enormous damage that may cause medical services and social function to collapse. The primary goal of the strategic early response is to minimize damage and maintain medical services and social functioning, control the outbreak and decelerate the spread of infection as much as possible, while accelerating the development and manufacturing of vaccines.
- Therefore, it is required to promptly identify the occurrence of domestic cases and respond quickly during the early stages of human-to-human transmission, thereby enabling effective prevention and control of the spread of infection.
- These guidelines are the first to lay out early response strategies to an influenza pandemic in Japan (rapid response strategies), and will be revised continuously in the future as examinations proceed at various levels.

1. Terms and definitions

1) Preventive measures other than drug administration

“Preventive measures other than drug administration” refers collectively to countermeasures against pandemic influenza, excluding the prevention of infection by antiviral drugs, and are the basic responses to pandemic influenza. The prevention of infection by antiviral drugs has constraints of uncertainty in efficacy and limited supplies, and cannot prevent or control infection effectively without combining the drugs with other preventive measures. Preventive measures other than drug administration include individual or local infection prevention, human transport or travel restriction, temporary closure of schools, office protocol, requests for refrainment from association or social activities, risk communication, support for local residents etc.

Preventive measures other than drug administration includes the restriction of movement of citizens, which may vary from voluntarily refraining from unnecessary leaving the home to strict control by geographical quarantine methods depending on the severity of the pandemic (as determined by fatality rate, etc.), virulence of the influenza virus, geographical areas where the infection occurs, the number of patients, and other circumstances.

2) Preventive administration of antiviral drugs

2-i) Preventive administration for households and facilities

Preventive administration of antiviral drugs to all members of the patient’s household and the institutions to which the patient belongs (e.g. nursery, school, office, staying facility etc.); Unspecified individuals who may have come into contact with the patient at department stores, convenience stores, shops, during public transportation etc. are not included.

2-ii) Preventive administration for individuals who came into contact with the patient

Preventive administration of antiviral drugs to individuals who came into contact with the patient (See the Proactive Epidemiological Research Guidelines for Pandemic Influenza

for details) combined with a restriction on the movement of relevant individuals and a follow-up health examination of the relevant individuals at health centers.

2-iii) Preventive administration for local residents

Determine the period during which the patient was “infectious” (1 day or 24 hours prior to the manifestation of symptoms to 7 days after defervescence, where “Day 0” is considered the date of defervescence. Patients under 12 years old are considered “infectious” until Day 21, where Day 0 is the date of manifestation of symptoms) and identify geographical locations to which the patient traveled during this period. Administer preventive antiviral drugs to all citizens residing in the area where the patient resides and to all citizens residing in geographical locations determined to have been visited by the patient during the “infectious” period.

3) Operations combining preventive measures other than drug administration and preventive administration of antiviral drugs

3-i) Preventive operations for households and facilities

This operation combines “1) Preventive measures other than drug administration” and “2-i) Preventive administration for households and facilities”; this operation excludes the preventive administration of antiviral drugs to unspecified individuals who came into contact with the patient. Therefore, careful monitoring for and prompt response to new cases occurring among such individuals are essential. Although these operations are un-likely to be effective in containing the virus, they are considered effective in preventing extensive spread of infection. If contact investigations have already been done and individuals who came into contact with the patient are known, preventive administration shall be provided to such individuals as well.

3-ii) Preventive operations for individuals who came into contact with the patient

This operation combines “1) Preventive measures other than drug administration” and “2-ii) Preventive administration for individuals who came into contact with the patient”; this operation is expected to prevent the manifestation of symptoms in individuals who came into contact with the patient, but are un-likely to prevent the spread of cluster infection. Although the number of citizens targeted for antiviral administration by this operation is the smallest among the three types of operations, this operation will most-likely become difficult to implement when the number of patient cases rise because it requires the listing of individuals who came into contact with the patient through movement studies of patient cases as well as communication with each contacted individual.

3-iii) Geographical containment operations

This operation combines “1) Preventive measures other than drug administration” and “2-iii) Preventive administration for local residents”; this operation targets virus containment within the geographical area in which the infection has occurred. Because it requires strict restriction of human transport, specific conditions (indicated later) in which this operation will be implemented shall be carefully examined.

2. Methods of implementation

- The combination of preventive measures other than drug administration and preventive administration of antiviral drugs to specified clusters at risk of infection is considered to be an effective early response strategy.
- Due to our country's geographic situation and high population density, it will be extremely difficult to enforce strict restriction of human transport through geographical quarantines. Therefore, these guidelines focus on methods which combine preventive administration for households and facilities with feasible preventive measures other than drug administration.
- However, the method for community containment involving strict restriction of human transport is also described later as a possible option, because there is still a small possibility that a highly fatal and virulent pandemic influenza virus is identified at an early state in a geographical area that has a low population density, a situation where community containment may prove effective and feasible.

(1) Organization

- 1) Roles of the central government, local governments, governmental agencies and related departments

Early response to pandemic influenza aims to prevent and control the spread of infection within the relevant geographical area as well as to other parts of Japan. The Government of Japan is responsible for supporting the implementation of the early response, while the governors of prefectures are responsible for the actual implementation as well as the supervision of frontline municipalities and the provision of technical and administrative support. Related governmental agencies and departments shall collaborate to fulfill their functions under the command of the Headquarters for Pandemic Influenza Countermeasures.

- i) The role of the central government

If an influenza pandemic occurs, the Government of Japan shall put up a Headquarters for Pandemic Influenza Countermeasures ("Headquarters"). The Headquarters shall request opinion and advice from the Pandemic Influenza Experts Advisory Committee (a temporary name; "Advisory Committee"), and formulate basic principles of pandemic influenza countermeasures based on the proposals from the Advisory Committee.

In the case of preventive administration, the central government shall be responsible for the antiviral drugs, including its procurement, stockpiling and transport to individual prefectures. The central government shall also coordinate between governmental agencies, respond to prefectures where pandemic influenza has not yet occurred, and respond to the general public.

The Government of Japan shall report to the World Health Organization (WHO) and facilitate international collaboration based on the International Health Regulations 2005 ("IHR (2005)"¹). The central government shall also collaborate with its counterparts in other countries as necessary.

¹ International Health Regulations (IHR)

Refers to a convention ratified by the member states of the WHO, and comprise a set of regulations based on the WHO Charter. The IHR provides a legislative ground for international preparedness and countermeasures against infectious diseases. In addition to pest, cholera, yellow fever etc., the scope of IHR was extended substantially in 2005, in response to the recent cluster occurrence of new and

ii) The roles of prefectural governments (governors)

Prefectural governments shall be responsible for the actual implementation of early response measures and for supervising measures implemented by the twelve major cities, special districts and city's health centers within the borders of each prefecture. If patients of pandemic influenza are identified across prefectural borders, the relevant prefectural governments shall collaborate in early response.

iii) The role of municipalities

Municipalities shall provide information to local residents, refrain from unnecessary gatherings, implement preventive administration of antiviral drugs and take other administrative measures relevant to local residents.

iv) The role of governmental agencies and related departments

Agencies and related departments of the central government shall promote measures within their authority, under the command of the National Headquarters for Pandemic Influenza Countermeasures. Agencies and related departments of prefectural governments shall promote measures under the command of the local headquarters.

v) The role of prefectural public health departments

Prefectural public health departments shall disseminate and instruct infection prevention measures, coordinate appropriate medical services, provide antiviral drugs, conduct epidemiological studies and take other public health measures. In the case of preventive administration, prefectural public health departments shall transport antiviral drugs supplied by the central government within individual prefectures, administer the drugs to specified targets, and conduct the monitoring, evaluation etc. of administration.

vi) The role of the National Institute of Infectious Diseases

The National Institute of Infectious Diseases may provide technical advice as necessary.

2) National Pandemic Influenza Experts Advisory Committee (a temporary name)

Early response comprises Stage 1, which refers to actions implemented immediately after the identification of occurrence, and Stage 2, which include actions implemented based on the initial evaluation of circumstances (Details will be described later). Because the initial evaluation requires views of experts as the basis of decision making, the central government shall put up the National Pandemic Influenza Experts Advisory Committee (a temporary name; "Advisory Committee"), as an organization to provide views of scientific experts. The Advisory Committee shall comprise about ten experts in the areas of medicine, public health, epidemiology, virology etc. The member of Advisory Committee shall examine scientific findings, situations of outbreak in Japan and overseas, virological information etc., and provide inputs on measures taken by the central government.

reemerging infectious diseases, as well as to prepare for pandemics. The reporting of pandemic influenza to the WHO is required since June 2007.

3) Collaboration and information sharing

i) Domestic collaboration

In early response, both “vertical collaboration” and “horizontal collaboration” must be ensured promptly and effectively. “Vertical collaboration” refers to collaboration through chain of command, while “horizontal collaboration” signifies collaboration between different sectors and departments. The national and prefectural headquarters shall establish effective data management systems to ensure adequate monitoring of important information. Typical important information includes information on the occurrence of pandemic influenza (cases designated for observation, suspected cases, confirmed cases, cases in serious conditions and deaths), epidemiological research data, data of follow-up studies on contacting individuals, virological information, occurrence of hospital infection, implementation status of related measures (such as the restriction of human transport, coverage of preventive administration, support to local residents and needs evaluation), evaluation of the effects of related measures (e.g. continuous evaluation by surveillance, horizontal evaluation) , and information of goods assistance.

Networks shall be established to connect experts and representatives in clinical, virological and epidemiological sectors operating in and between geographical areas, thereby promoting regular opinion exchange and information sharing.

For effective information management, it would be useful to establish databases and teleconferencing systems (through telephone, TV etc.).

ii) International collaboration

International collaboration is critical in pandemic influenza countermeasures. The Government of Japan and the WHO shall exchange information on the occurrence of pandemic influenza, and consult and collaborate with each other in related measures, as required by the IHR (2005) and the general assembly resolution on pandemic influenza. Close information sharing and collaboration shall be ensured through the Health Science Division, the Secretariat of the Minister of Health, Labour and Welfare, which is identified as the “focal point²” of Japan under the IHR (2005). The Government of Japan shall also share information and collaborate with its counterparts in other countries.

In addition to the official information sharing and collaboration, it is important to make use of unofficial information. The Government of Japan shall collect official and unofficial information through the National Institute of Infectious Diseases, and facilitate appropriate information exchange.

(2) Procedures for early response

1) Stage 1 (immediate response)

Measures to be taken immediately following the identification of a pandemic influenza case include the following items. Required items shall be selected as necessary, in accordance with the actual situations.

² Focal point

Refers to the window of the central government of each country, which shall be responsible for continuous communication with the WHO as specified by the IHR (2005).

- i) Case control (isolation and treatment)
- ii) Infection prevention at medical facilities
- iii) Preventive administration for households and facilities

In the early stages of pandemic influenza, preventive administration for households and facilities shall be implemented to minimize the scale of infection spread. Antiviral drugs shall be administered to all members of the patient's household and the institutions to which the patient belongs (e.g. nursery, school, office etc.), while that patient is considered infectious. Unspecified individuals who contact the patient at department stores, convenience stores, shops, public transportation etc. are not included. Regardless of the days of contact, oseltamivir phosphate shall be administered at a dose of 75 mg per day to adults, and at a dose of 2 mg per kg of bodyweight per day (not exceeding 75 mg), over ten days as one course. In combination with the preventive administration, studies shall be conducted on the compliance rates, health status of individuals, and adverse effects of administration. It is desirable to obtain the cooperation of the heads of the relevant households and facilities, and the range of cooperation shall be determined by the prefectural governments that implement the preventive administration. It is necessary to achieve the compliance rates of 80% or higher.

- iv) Preventive administration for contacting individuals

The necessity for preventive administration for individuals who contacted the patient but are excluded from iii) shall be determined based on the status of occurrence. If the number of patients is relatively small and local health centers are able to list individuals contacted the patients and track each of such individuals, preventive administration shall be provided to such individuals. If the number of patients is so large that it is practically impossible to implement preventive administration for such individuals, this option shall be abandoned.

- v) Restriction of movements of individuals receiving preventive administration (Refrainment from outings)

Individuals receiving preventive administration shall be requested to refrain from going out of their homes or their neighborhoods.

- vi) Infection prevention by individuals, households and offices

See the Guidelines for Infection Prevention by Individuals, General Households, Local Communities and Municipalities, and the Guidelines for Pandemic Influenza Preparedness at Business Entities and Establishments.

- vii) Port actions

The inflow of additional cases shall be prevented through bolstered quarantine measures.

- viii) Report to the central government

The governors of prefectures shall report any identified cases of pandemic influenza immediately to the central government (Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare).

- ix) Information provision to other prefectures and the implementation of bolstered surveillance programs

The Ministry of Health, Labour and Welfare shall notify the occurrence of pandemic influenza to the governors of other prefectures, using the health hazard control and information support system etc., and instruct the governors to bolster the pandemic influenza surveillance programs.

2) Epidemiological research and information collection for the initial evaluation

i) Epidemiological research of identified cases

Includes proactive epidemiological research aiming to identify the general picture of the occurrence, studies on infection sources and routes of the identified cases, studies on the movements of the identified cases (geographical areas visited by them) while they were infectious, and investigation into epidemiological relationship between cases. (See the Proactive Epidemiological Research Guidelines for Pandemic Influenza for details.)

ii) Tracking of contacting individuals

For individuals who contacted the patients of pandemic influenza, studies shall be conducted on their compliance rates, health statuses and adverse effects of drug administration, over the ten days following the final contact. The tracking survey shall be conducted by local health centers for the members of the patients' households. Local health centers shall also identify contact information at nurseries, schools, offices etc., obtaining the cooperation of the heads of such facilities as necessary. The necessity for preventive administration for individuals who contacted the patient but are not the members of the same households or facilities shall be determined based on the status of occurrence. If the number of patients is relatively small and local health centers are able to list individuals contacted the patients and track each of such individuals, preventive administration shall be provided to such individuals. If the number of patients is so large that it is practically impossible to implement preventive administration for such individuals, both the preventive administration to contacting individuals and the tracking of such individuals shall be abandoned.

iii) Bolstered surveillance programs

If pandemic influenza occurs, specified surveillance programs shall be bolstered in each prefecture. Cluster surveillance, syndrome surveillance and other types of surveillance shall be combined to promote the identification of cases and clusters of cases.

iv) Geographical information

Information shall also be collected on geographical areas where infection occurs, areas visited by the patients, the municipal geography, available medical resources and social infrastructure in the municipality etc.

v) Effective and efficient data management (Use of databases)

To manage and make use of diverse information collected during early response in an adequate and timely manner, it is necessary to establish effective databases in advance.

3) Initial evaluation (Evaluation of diagnoses and identification of infection circumstances)

i) Lead time for initial evaluation

The government of a prefecture where a case of pandemic influenza is identified shall complete the information collection for initial evaluation and commence official consultation with the central government within 72 hours of the identification of the case. The central government shall immediately consult the Advisory Committee (a temporary name) for views and proposals. The Advisory Committee (a temporary name) shall provide the central government with proposals on the principles of Stage 2 etc., including a proposal to continue Stage 1 and observe the development. In this case, the central government shall consult the Advisory Committee within 48 hours of such proposal.

ii) Information required for initial evaluation

Information to be identified by prefectural governments

○ Information to be compiled in advance

- Geographical information of municipalities

Population, age distribution, transportation, social infrastructure, key transportation routes for geographical quarantine, political and economical situations, and information on medical institutions (e.g. the overall number of beds, the number and scale of facilities, designated medical institutions for infectious diseases, available hospitalization facilities)

○ Information to be collected following the occurrence

- Information on cases

Epidemiological information of cases (e.g. dates of manifesting symptoms, dates of hospitalization; addresses, sexes, dates of birth of patients; epidemiological relationship between cases), infection sources and routes, locations of infection (both domestic and overseas), the occurrence and situations of hospital infection (infection status of patients and hospital personnel), the occurrence and situations of facility infection

- Epidemiological information of geographical areas where infection occurs

The numbers of cases designated for observation, suspected cases and confirmed cases; the numbers of patients in serious conditions (the number of endotracheal intubations and the number of patients under intensive care); the number of deaths; the numbers of individuals contacting patients or cases designated for observation; the number of individuals under preventive administration for households and facilities

- Virological information

Data of virological tests and traits of cases

- Information on measures taken by prefectural governments

Measures related to medical institutions:

Statuses of treatment, management and isolation of cases (including reactions and adverse effects to antiviral drugs, status of hospital response and isolation); transfer and hospitalization of cases designated for observation, suspected and confirmed cases

Measures related to preventive administration of antiviral drugs:

Identification of individuals targeted by preventive administration for households and facilities (including the level of identification of such individuals), compliance rates, incidence rates among individuals under preventive administration, adverse effects to antiviral drugs, procurement

and logistic support of goods and supplies (including drug supplies and distribution, as well as compliance instructions)

Refrainment from outings:

Health centers shall identify the compliance status (rates) among individuals under preventive administration for households and facilities, obtaining the cooperation of the heads households and facilities as necessary. Municipal governments shall identify the status of local implementation in municipalities where infection occurs, and in surrounding areas of such municipalities, as well as the status of voluntary measures in other municipalities in the same prefecture.

Status of bolstered surveillance programs:

Tracking of contacting individuals;

Status of local residents (including inquiries, complaints, confusions, panics and acceptance), and residents moving out of the area where infection occurs (evaluative movements);

Status of response at prefectural headquarters and related departments

Information to be identified by the central government

- Virological information

Analysis of virological traits of isolated virus (such as mutation)

- Nationwide situations

In the early stages of pandemic influenza, infection may have occurred in multiple prefectures. While the first prefecture identifying infection is likely to collect information required for initial evaluation ahead of other prefectures, the central government shall collect the latest information from nationwide before conducting initial evaluation.

- Infection status overseas

The central government is also responsible for the collection of official information from and the sharing of such information with the WHO, through the Health Science Division, the Secretariat of the Minister of Health, Labour and Welfare, which is identified as the focal point of Japan under the IHR (2005). The central government shall also collect information from other countries through the Ministry of Foreign Affairs, the National Institute of Infectious Diseases etc.

iii) Assessment and decision making on principles

The Advisory Committee (a temporary name), prefectural governments and the central government shall assess and make decision on the feasibility of geographical containment.

- Prefectural governments shall evaluate the status of cases and actions in Stage 1, and identify municipalities with infection risks based on the geographical areas visited by the patients. Subsequently, prefectural governments shall evaluate the status of transportation (demographic movements) between the high-risk municipalities and other areas. According to the study by Ferguson et al., Nature 437: pp. 209-214, 2005, a mathematical model indicates the necessity for geographical containment (quarantine) of an area within 15-km radius, and for preventive administration of antiviral drugs to the entire population of 50,000 in that area, with the possibility of success calculated at 90%, assuming the occurrence of pandemic influenza with the basic reproduction number (R_0) of

about 1.6 in a rural area of Thailand³, followed by the commencement of preventive administration when about twenty cases have been identified. Because approximately one-third of all municipalities in Japan have the population of 10,000 or smaller, geographical containment may require the quarantine of municipalities surrounding the high-risk municipality as well, even though no infection has been identified in such surrounding municipalities.

○ The Advisory Committee (a temporary name) shall assess the possibility of successful containment of pandemic influenza by geographical quarantine, based on the epidemiological information of pandemic influenza in the relevant prefecture; geographical, political and economical traits of the relevant municipalities; international epidemiological and virological findings; and other related information.

○ The central and prefectural governments shall determine the principles for Stage 2, combining the assessment by the Advisory Committee (a temporary name) with feasibility data including available medical resources, inventory of required medical agents, quantity and quality of available human resources, understanding of local residents and other operational issues.

iv) Establishment of a continuous monitoring system

A continuous monitoring system for Stage 2 shall be established, based on the bolstered surveillance scheme established during Stage 1. Bolstered surveillance may be also required in Stage 2.

4) Stage 2

i) Preventive operations for households and facilities

In principle, preventive operations for households and facilities shall be based on the relevant operations in Stage 1. The principles for preventive administration of antiviral drugs shall not be changed from Stage 1. In these operations, preventive administration of antiviral drugs is only provided to specified individuals, excluding unspecified individuals contacting with the patients. Therefore, it is critical to identify and respond to additional cases promptly, to enable containment and effective prevention of infection spread. Just as in Stage 1, it is desirable that diverse measures for general citizens other than the patients' families and specified contacting individuals are undertaken at the same time throughout a municipality.

○ Preventive administration of antiviral drugs

Health centers etc. shall provide compliance instructions and obtain consent to the administration, by the unit of households, nurseries, schools, offices (business establishments and enterprises), staying facilities etc. Administration to the members of a facility shall be implemented with the cooperation of its head. The heads of facilities shall cooperate in preventive administration from the viewpoint of labor health, consulting industrial doctors.

Replenishment of antiviral drugs due to loss etc. shall not be admitted, because it may lead to personal stockpiling, illegitimate resale etc.

○ Monitoring compliance rates and health hazards

³ Basic reproduction number (R_0)

An indicator of the virulence of pathogens, representing the number of individuals who are expected to be infected by a single patient entering a demographic group without immunity to the relevant pathogen; The larger the R_0 is, the higher level of infection prevention is required.

In collaboration with municipalities, prefectural governments shall evaluate continuously the compliance rates of individuals targeted by preventive administration, based on surveillance programs, interviews by phone and other regular studies and investigations. Prefectural governments shall also survey and evaluate health hazard incidents related to preventive administration. The central government shall provide technical assistance in such evaluation activities as necessary.

○ Refrain from going outside

Individuals who contacted patients or were administered preventive antiviral drugs shall be requested to stay home for ten days. Health centers shall observe the development of such individuals. If epidemiological relationship has been confirmed between all of the identified cases, it is unnecessary to require other individuals to stay home. However, if any of the identified cases has no epidemiological relationship, individuals living in the same municipality as the relevant patient shall refrain from going out and stay home as far as possible.

○ Restriction from moving into geographical areas where infection has occurred

Schools shall be closed temporarily and as necessary, in the municipality where infection occurs. If infection spreads extensively, all the schools in the same prefecture may be closed down. The period of temporary closure may stretch over several months, if extended response is required or if infection spreads throughout the region or the country. The Ministry of Education, Culture, Sports, Science and Technology, boards of education and individual schools shall examine in advance how to provide appropriate education in such cases.

In the municipality where infection occurs, unnecessary association, events and festivals shall be refrained. Movie or performance theaters and other public facilities may be requested to suspend operations. The scope of such refrainment and suspension may be expanded to the entire prefecture if situations require.

○ Restriction from moving between geographical areas where infection has occurred and other areas

If epidemiological relationship has been confirmed between all of the identified cases, only individuals who contacted the patients or are taking preventive administration shall be recommended to refrain from unnecessary outings. It is unnecessary to restrict movements of other individuals.

However, if any of the identified cases has no epidemiological relationship, or if the number of cases exceeds a specified level, individuals living in the same geographical area as the relevant patient shall refrain from unnecessary outings.

○ Restriction from moving into geographical areas where infection has occurred

If epidemiological relationship has been confirmed between all of the identified cases, it is unnecessary to restrict movements from other areas to the geographical area where infection occurs. However, visits to individuals who contacted the patients or are taking preventive administration shall be refrained from.

If any of the identified cases has no epidemiological relationship, the Government of Japan shall request its people to refrain from unnecessary visits to the relevant geographical areas.

○ Countermeasures at business establishments and enterprises

Business establishments and enterprises shall have appropriate measures in place to prevent infection, ensure their business continuity, and fulfill their social responsibilities. It is desirable that business entities formulate pandemic influenza preparedness plans in advance and take appropriate response in line with such plans, consulting industrial doctors as necessary. See the Guidelines for Pandemic Influenza Preparedness at Business Entities and Establishments for details of infection prevention at offices. Business establishments and enterprises in the municipality (or the entire prefecture if situations require) where infection occurs shall commence their protocol.

○ Support for local residents

Support for local residents include direct support on basic issues such as the provision of appropriate medical treatment, food, clothes and accommodations; support in the retention of social functions such as electricity, gas, water and communications; and support for institutional, corporate and social activities such as information provision to telecommuters.

In addition, appropriate information based on needs evaluation and adequate risk communication shall be provided as a primary support.

By providing occasions for remote participation in social activities, the operations against pandemic influenza can be further promoted through enhanced participation of local residents. Similarly, the provision of remote entertainment service is beneficial in the viewpoint of retaining mental health of local residents.

Another key item of support for local residents is the maximum provision of medical treatment to patients.

○ Mental health care and risk communication

It is important to provide mental support to cases, contacting individuals and other related persons under great mental stress. In particular, individuals in direct contact with patients (such as individuals who heavily contacted with patients, ambulance paramedics, epidemiological researchers interviewing patients in person, health care workers etc.) have great concerns. Prefectural governments shall provide consultation service to such individuals as appropriate.

It is critical to ensure appropriate information provision and risk communication to individuals targeted by diverse early response measures. Combining these with remote communication support to the relevant geographical area (such as telecommunications and the Internet), the isolated feeling of targeted individuals will be substantially relieved.

○ Bolstered surveillance programs

Surveillance programs required in this stage include the support system to research suspected cases, outpatient syndrome surveillance, hospitalized pneumonic syndrome surveillance, cluster surveillance etc. See the Surveillance Guidelines for details.

○ Proactive epidemiological research

Health centers shall undertake proactive epidemiological studies on the health status of individuals who heavily contacted with patients, aiming at the prompt identification of additional cases. These studies shall continue until the end of the tenth day after the date of the heavy contact. Remote research and teleconference systems using videophones and the Internet are highly effective to identify the manifesting of symptoms promptly, and to protect researchers from infection.

○ Collecting information and monitoring the effects of countermeasures

The following issues pertaining to the implementation of countermeasures require continuous monitoring: trends of (suspected) patients and cases designated for observation, tracking of contacting individuals, efficacy and adverse effects of antiviral drugs and other treatments at medical facilities, compliance rates in the administration of antiviral drugs, evaluation of supports to local residents etc.

ii) Preventive operations for contacting individuals

In these operations, required measures shall be selected from the components of preventive operations for households and facilities, excluding the scope of preventive administration of antiviral drugs. Individuals targeted by preventive administration in these operations agree with the targets of proactive epidemiological research. Therefore, health centers shall provide compliance instructions and confirm the targets' consent to administration, in combination with proactive epidemiological research.

iii) Geographical containment operations

If all the following conditions are satisfied, geographical containment shall be included in the possible options of response, and be examined together with the two abovementioned operation patterns. If any of the following conditions are not met, either preventive operations for contacting individuals, or preventive operations for households and facilities, shall be continued.

a) Conditions for successful geographical containment

○ Lead time for successful geographical containment

Geographical containment is unable to prevent the spread of infection effectively, unless the relevant geographical area is quarantined swiftly following the occurrence of pandemic influenza virus and the start of infection or transmission. A simulated analysis based on mathematical modeling suggests that, for geographical containment operations to be successful, the relevant geographical area must be quarantined, and antiviral drugs should be administered to the entire population of that area, within 21 days of the occurrence of the index case of human-to-human transmission.

○ Virulence of pandemic influenza virus

The two papers published respectively on Nature and Science, which provided theoretical grounds for the WHO's geographical containment protocol, assume the basic reproduction number (R_0) below 1.8 as an indicator for the virulence of pandemic influenza virus.

The WHO and the governments of many countries in Europe, North America and elsewhere formulate pandemic influenza plans for the varying values of R_0 . The value of R_0 increases as virus becomes more virulent. The larger the R_0 becomes, the shorter the lead time for geographical containment must be, and the more thorough quarantine of the relevant area would be required for successful containment.

○ Situations of infection

• The number of cases and epidemiology

If the occurrence of pandemic influenza is identified, it is highly likely that multiple individuals have been already infected. If epidemiological relationship is not confirmed between identified cases, it is rational to consider a local outbreak has already started. In such cases, geographical containment operations are unlikely to succeed. Even though the number of cases is still small, geographical containment becomes difficult if a patient contacted a large number of individuals in an extensive range while he or she was infectious. If patients are identified in an extremely restricted geographical area, and if epidemiological relationship is suspected between such patients, geographical containment of the relevant area could be an option.

• Locations of infection

Geographical containment is unlikely to succeed if infection occurs in an urban area, with high population density and heavy traffic. If infection occurs in a rural area or remote island with low population density and light traffic, containment of the relevant area could be an option.

• Social conditions

The containment of Nagatacho, the center of politics in Japan, or Kasumigaseki, the center of national administration, or other areas at the center of economic activities, could interfere seriously with pandemic influenza countermeasures in general, and/or cause enormous damage to the economy. Also in other parts of this country, geographical containment may reduce human movements, resulting in possible serious problems such as the infringement of human rights and the stagnation of social activities. If the disadvantage of geographical containment seems to exceed the advantage as suggested above, this option shall be dropped. If the advantage is likely to exceed the disadvantage, geographical containment could be an option.

• Prevention of the inflow of additional cases

To obtain the goal of geographical containment in Japan, it must be combined with bolstered port quarantine measures etc. to prevent the intrusion of additional cases from outside Japan.

• Thoroughness of geographical containment operations

Geographical containment is unlikely to succeed if it is difficult to restrict the human movements within the relevant area or between the relevant area and other areas (e.g. there are geographical conditions that enable easy exit of the area) , or if systems are not in place to monitor

the compliance rate of antiviral drug administration and the situations of infection inside and outside the relevant area. It is considered that the compliance rate must be 90% or higher for geographical containment to succeed.

Note that it is a critical factor for the success of geographical containment operations that there is no inflow of additional cases.

b) Components of geographical containment operations

- Components of geographical containment operations include the chain of command and roles and responsibilities; risk communication; monitoring and evaluation systems; entry control of additional cases from overseas (port measures); treatment and management of patients; infection prevention at medical facilities; requests for the restriction of movements within the relevant area and between the relevant area and other areas (i.e. quarantining the area); procurement, distribution, simultaneous administration of antiviral drugs; infection prevention of individuals; restriction of social activities in the relevant area (e.g. requests for refrainment from outings and cancellation of association and events); infection prevention at offices; temporary closure of schools; bolstered surveillance programs; epidemiological research; tracking of contacting individuals; virological test systems; support to local residents; etc.
- For the details of treatment and management of patients; infection prevention at medical facilities; infection prevention of individuals; infection prevention at offices; epidemiological research; tracking of contacting individuals; and virological test systems; see the respective guidelines.

c) Procedures for geographical containment operations

- Items continued from Stage 1

In principle, items implemented in Stage 1 shall be continued. preventive administration of antiviral drugs shall be continued until all the targeted individuals complete administration. The subsequent principles of preventive administration are indicated later.

- Bolstered port control

For effective geographical containment, it is necessary to minimize the intrusion of additional cases. Quarantine measures implemented in Stage 1 shall be continued and bolstered as necessary (See Quarantine Guidelines).

- Restriction of movements within the relevant area and between the relevant area and other areas

The scope of geographical containment shall include all the municipalities that were visited by patients while they were infectious. In principle, human movements shall be restricted within the relevant area and between the relevant area and other areas, by cordoning off the relevant area, requesting local residents strongly to stay home, etc.

○ Quarantine of individuals

If individuals need to move from the contained area to other areas for unavoidable reasons, they shall be isolated at accommodations controlled by prefectural governments and considered as free from infection risks, and put under health observation for ten days. If the relevant individuals have special reasons pertaining to their health etc., they shall be put under health observation at appropriate medical institutions outside the contained area, receiving appropriate medical treatment under required infection prevention measures. Quarantine measures as above shall be lifted if the quarantined individuals manifest no symptoms over the ten days.

○ Period of geographical containment

Geographical containment shall be lifted if no additional cases occur in the relevant area over the twenty days following the date of secure isolation of the final case in that area (ten days of preventive administration followed by ten days of health observation), or if the geographical containment operations are canceled.

If additional cases occur during the period of geographical containment, preventive administration of antiviral drugs shall be continued over the ten consecutive days following the date of secure isolation of the final case in that area, without no intermittence.

○ Simultaneous preventive administration of antiviral drugs

The central government shall distribute the required quantity of antiviral drugs to the relevant prefecture from the national stockpiles. The government shall be responsible for the safety of the abovementioned transportation.

Prefectural headquarters shall transport the drugs to health centers governing the contained area. Prefectural governments shall provide information on the administration of antiviral drugs to the targeted individuals through diverse local media (e.g. area broadcast, PR vehicles, TV, radio, Internet etc.), and distribute one course of antiviral drugs (75 mg per day for ten days for an adult) to each of the targeted individuals through municipal agencies. The drugs shall be distributed without fail to the targeted individuals. Replenishment of drugs due to loss etc. shall not be admitted. Dosage to children shall vary by their bodyweight, and therefore requires much time of preparation. Therefore, simple measures must be examined for distribution to children.

In preventive administration as above, complete administration by all the targeted individuals shall be pursued, but it is not the ultimate goal of these operations. It is the most important to achieve 90% or higher compliance rates throughout the contained area. It is necessary to minimize the number of individuals refusing the administration or losing distributed drugs, but administration cannot be forced if there are uncontrollable reasons. Consent to administration must be obtained from the targeted individuals, or their parents, adult caretakers etc. (collectively referred to as “targeted individuals etc.”). It is desirable that consent is obtained in writing as far as possible. The form and process of written consent shall be simplified as far as possible to ensure speedy implementation.

- Measures for individuals who live outside the contained area but work at facilities inside the area

Individuals who live outside the contained area but work at facilities inside the area shall be put under preventive administration of antiviral drugs and stay at home for ten days. Health centers governing their addresses shall undertake the health observation of such individuals during the abovementioned period.

- Monitoring compliance rates and health hazards

Same as the section of preventive administration operations for households and facilities

- Restriction of movements inside the relevant area

All the schools within the contained area shall be closed down temporarily. The period of temporary closure may stretch over several months, if extended containment is required or if infection spreads throughout the region or the country. The Ministry of Education, Culture, Sports, Science and Technology, boards of education and individual schools shall examine in advance how to provide appropriate education in such cases.

Unnecessary association, events and festivals shall be suspended. Movie or performance theaters and other public facilities shall be requested to suspend operations.

- Refrainment from outings

The targeted individuals shall refrain from going out and stay home as far as possible. To enable this, it is recommended to stock in advance food, water, daily supplies and other necessary goods at home, so that the relevant individuals need not go out for a specified period. Should they go out, they shall remain in the vicinity of their homes, and refrain from visiting distant places as far as possible. (For infection prevention of the relevant individuals, see the Guidelines for Infection Protection for Individuals, General Households, Local Communities and Municipalities.)

- Measures at business establishments and enterprises

Same as the section of preventive administration operations for households and facilities

- Support for local residents

Same as the section of preventive administration operations for households and facilities

- Mental health care and risk communication

Same as the section of preventive administration operations for households and facilities

- Bolstered surveillance programs

Same as the section of preventive administration operations for households and facilities

- Proactive epidemiological research

Same as the section of preventive administration operations for households and facilities

- Collecting information on and monitoring the effects of countermeasures
Same as the section of preventive administration operations for households and facilities

3. Measures outside the geographical area where infection occurs

Regardless of the option selected for Stage 2, proactive response by preventive measures other than drug administration shall focus on the municipality where infection occurs (the scope may be expanded to the entire prefecture if situations require). At the same time, the following measures shall be implemented in other municipalities in the same prefecture and in other prefectures, where infection has not occurred.

(1) Risk communication

Provide adequate information to the general public, and disseminate methods for official information provision (such as various mass media, websites, telephone numbers of automatic answering lines and fax services).

Identify the needs of the general public using interactive media such as telephone inquiries, fax services, websites, data communications by digital broadcast etc.

(2) Infection prevention by individuals and households

Infection prevention measures shall be recommended, such as frequent hand washing and stocking necessary supplies in the case of stay at home.

(3) Restriction of movements

Restriction of domestic or international travels shall be recommended as appropriate, based on epidemiological analysis data.

(4) Implementation of bolstered surveillance and information sharing

Bolster surveillance programs nationwide, assuming that the identified cases only represent a tip of the iceberg. (See the Surveillance Guidelines for details.)

4. Interim evaluation and the review of principles

(1) Timing and objective of interim evaluation

- When pandemic influenza occurs, scientific findings have not been established in any of the related fields, such as virulence of virus, infection spread, rate of patients in serious conditions, effects of antiviral drugs and other measures, adverse effects of drugs and agents, etc. As scientific findings are obtained and accumulate, countermeasures against pandemic influenza shall be modified for increased effects and efficiency through interim evaluation. A wide range of studies and investigations must be also promoted, in case pandemic reaches Phase 6, the second and third waves of infection emerge, and/or another pandemic is likely.
- The national and prefectural headquarters for pandemic influenza countermeasures shall compile and assort epidemiological and virological findings and information on implementation status etc. as appropriate, and conduct interim evaluation on the situations of infection and effects of measures in progress. At the same time, the central government shall organize the Advisory Committee (a temporary name).
- During the abovementioned process, efficiency of discussion shall be increased through teleconference systems (using videophones etc.).

(2) Review of principles

- Measures in progress in Stage 2 shall be reviewed, whether they shall be continued, modified, completed etc., considering the consistency and collaboration with subsequent procedures.

(3) Examination of cancellation or termination of geographical containment

- The central and prefectural governments shall consult with each other immediately if the continuation of geographical containment is considered difficult. This includes, for example, the cases where infection continues to spread within the contained area, the required compliance rates are not achieved among local residents and related individuals, additional cases continue to occur in surrounding areas and the expansion of contained area is not likely to control the situations, pandemic occurs on a worldwide scale, and/or the disadvantage of continued geographical containment seems to exceed the advantage. After requesting views and proposals from the Advisory Committee (a temporary name), the governments shall determine the discontinuation of operations. Geographical containment shall also be discontinued or terminated if it succeeds to provide desired effects.

(4) Important issues in preparation for Phase 6

- The central and prefectural governments shall promote proactive studies and investigations in preparation for Phase 6, focused on important issues such as the valuation of basic reproduction number (R_0) of pandemic influenza virus, effects of medical treatment, effects of preventive administration, evaluation of asymptomatic infection during preventive administration and the status of immunity development, virological analysis (of mutation etc.), evaluation of virus tolerant to drugs, evaluation of effectiveness of masks and other personal protective equipment (PPE), occurrence of unmanifest infection, immunity development among individuals contacting cases in person (such as health care workers and public health personnel), status of hospital infection etc. Field studies and investigations are related closely to prefectural measures, and therefore must be implemented under the command of prefectural headquarters. The central government shall support field studies and investigations with the agreement of prefectural governments, dispatching experts in required fields such as medicine, infection prevention, microbiology, epidemiology, statistics etc. The central government

shall establish research groups to lead research on issues that do not require field studies and investigations.

5. Stockpiling antiviral drugs for preventive administration

It is difficult to estimate the quantity of antiviral drugs required for preventive administration in Japan, because no simulated studies have been conducted on this issue. Referring to the abovementioned study assuming outbreak in a rural village in Thailand and other studies conducted by American researchers, it will be necessary to stockpile antiviral drugs for several millions of individuals. Assuming the case where four geographical areas need be contained, each of those areas have the population of 100,000, and the containment is continued over sixty days, the quantity of required antiviral drugs reaches 4 areas x 100,000 x 6 courses x 75 mg per capsule, which equals 2,400,000 clinical doses (This calculation is not adjusted to variation in dosage for children).

Combining the above calculation with the requirement for additional preventive administration of antiviral drugs to health care workers, who may be exposed directly to infected individuals without sufficient protection, particularly until pre-pandemic vaccines are manufactured and administered, it will be necessary to stockpile antiviral drugs for at least three millions of individuals.

6. Continuity with post-“early stage” measures in pandemic phases

Strategic early response has a clear goal to contain pandemic influenza virus within limited geographical areas. Once this goal is achieved or determined as difficult to achieve, strategic early response shall be terminated without delay. If this case, preventive measures other than drug administration shall be continued without intermission, regardless of pandemic phases announced by the WHO. Such preventive measures shall switch swiftly to measures in pandemic phases. During this process, if the quantity of stockpiles enable preventive administration of antiviral drugs, either preventive administration for households and facilities or for contacting individuals shall be conducted.

7. Risk communication

(1) Advance risk communication

Effective early response requires swift implementation as well as sufficient understanding among related individuals and the achievement of required compliance rates in administration. Therefore, it is essential that shared understanding shall be formed between the central government, prefectural governments, municipalities and other administrative entities, public health personnel, health care workers, members of related agencies and departments, the general public and other stakeholders, on the threats of pandemic influenza and the necessity for early response and subsequent measures in pandemic phases (in preparation for Phase 6). In addition to this, it is important that respective individuals and organizations make necessary preparations, establish systems for information communication and sharing, and construct and enhance systems and networks for collaborative actions. The central and prefectural governments shall ensure day-to-day risk communication as the basis of abovementioned measures and actions.

(2) Risk communication before and during early response

Before implementing early response measures including geographical containment operations, it is important to build sufficient understanding among the targeted individuals and related personnel. It is also critical to provide adequate information satisfying the needs of the targeted individuals while the measures and operations are in progress. Appropriate information shall also be provided to the residents of surrounding areas and the relevant prefecture, as well as to the general public, who are not targeted by the early response.

8. Developing and securing required human resources

(1) Classification of required operations

If pandemic influenza occurs, a large number of human resources will be required to conduct necessary studies and investigations. Therefore, regular operations and other required operations shall be classified in advance into those that may not be outsourced to external agencies, those that may be outsourced to external human resources including temporary and voluntary workers after providing specified training, and those that may be outsourced to external agencies.

(2) Training of related personnel

To prepare for the occurrence of pandemic influenza, required seminars and training shall be provided to related personnel, especially to the workers in charge of operations that may not be outsourced to external agencies.

(3) Surge capacity⁴ (Training of temporary staff etc.)

In a geographical area where pandemic influenza occurs, various needs will grow while help from other areas will become less available. Therefore, a system must be established in advance to secure necessary human resources inside each area. For example, in the case of preventive administration of antiviral drugs as part of geographical containment operations, the number of individuals targeted by preventive administration may reach several tens of thousands. Human resources will be required for the transportation and distribution of drugs, compliance instructions, monitoring of compliance rates and other operations. Continuous follow-up studies are also required on the health status of individuals contacting cases of pandemic influenza. Although health centers, municipal hygienists and other public welfare personnel are primarily responsible for these operations, they will not be able to cover all the required workload by themselves. To fill this gap, it may be required to mobilize retirees, medical and nursing students, and other potential human resources inside the area as temporary staff and voluntary workers for low-risk operations without direct contact with patients (such as telephone surveys and routine telephone services). Such temporary staffing requires various arrangements in advance, on positions, authorities, necessary training and qualification, coordination between related parties etc. Therefore, the central government shall establish a surge capacity scheme in advance, combined with local planning by prefectural governments.

⁴ Surge capacity
Refers to the capacity that can be mobilized swiftly in response to an emergency.

Reference 1

WHO pandemic influenza draft protocol for rapid response and containment (updated draft 30 May 2006) URL: <http://www.who.int>
Longini, IM, et.al. Science 309: 1083-1087, 2005
Ferguson, NM, et.al. Nature 437: 209-214, 2005
Germann TC, et.al. PNAS 103 : 5935-5940, 2006

Reference 2

The study by Ferguson et al., Nature 437: 209-214, 2005, assumes a rural area in Thailand, and the range of geographical containment within 10-km radius with the population of 10,000 to 50,000. The WHO's draft protocol for rapid response and containment adopts the same assumption. However, calculations for Japan shall assume a larger population, considering its generally high population density and heavy human traffic.

As of October 2006, there are approximately 1,800 municipalities in Japan, of which about 90% have the population of 150,000 or smaller, and 80% of 100,000 or smaller. About one-third of all municipalities have up to 10,000 residents.

Assuming the case where four geographical areas need be contained, each of those areas have the population of 100,000, and the containment is continued over sixty days, the quantity of required antiviral drugs reaches 4 areas x 100,000 x 6 courses x 75 mg per capsule, which equals 2,400,000 clinical doses (This calculation is not adjusted to variation in dosage for children). There will be additional requirements for antiviral drugs due to preventive administration during Stage 1, as well as preventive administration for contacting individuals following the completion of geographical containment operations.

The above indicated study by Longini, IM, et.al., Science 309: 1083-1087, 2005, states that geographical containment will require the stockpile of antiviral drugs for 100,000 to 1,000,000 individuals, and the study by Ferguson, NM, et.al., Nature 437: 209-214, 2005, suggests that it will be necessary to stockpile antiviral drugs for three millions of individuals.

The study by Germann TC, et.al., PNAS 103 : 5935-5940, 2006, performs a mathematical model analysis assuming the occurrence of pandemic influenza with the virulence of $R_0 = 1.9$ and 2.1 in the United States, and the nationwide simultaneous commencement of response measures when the number of cases reaches 10,000 (approximately twenty to thirty days after the index case occurs). This analysis estimates that antiviral drugs will be required for 1,600,000 individuals in the case of $R_0 = 1.9$, and for 3,300,000 individuals in the case of $R_0 = 2.1$, considering that TAP (equal to "preventive administration for households and facilities" in these guidelines), temporary closure of schools, and social distancing⁵ are conducted in combination.

⁵ Social distancing
Refers to measures to take social distance between individuals, such as avoiding crowds and refraining from association.