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Avian Influenza

Report of a Regional Consultation
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1. INTRODUCTION

Several countries in Asia have reported avian influenza (AI) outbreaks in birds due to H5N1 subtype of influenza A virus. It is likely that H5N1 infection among birds has become endemic to the region and that human infections will continue to occur. So far, no sustained human-to-human transmission of the H5N1 virus has been identified, and no evidence of genetic reassortment between human and avian influenza virus genes has been found. However, as long as the AI outbreak among poultry persists in Asia, there is a public health threat and potential danger of a pandemic in the near future.

The extensive interaction between humans and animals and the widespread presence of H5N1 subtype of influenza A virus in poultry are likely to facilitate reassortment in viruses. This, in turn, will confer greater ability to the virus for efficient and sustained transmission between humans, leading to an influenza pandemic, with high rates of illness, death, economic loss and social disruption. Efforts to produce an effective vaccine are under way in developed countries. Vaccine prototype virus strains have already been made and provided to manufacturers to produce pilot lots for human clinical trials as well as to produce a larger quantity of H5N1 vaccine. However, mass production as well as availability of such a vaccine to developing countries within the next few years are considered doubtful.

Oseltamivir is considered effective against all the strains of influenza virus including H5N1 subtype. The drug is expensive and currently produced by only one manufacturer with limited production capacity. While some resource-rich countries have commenced stockpiling of this antiviral agent, several countries are still in the stage of planning or mobilizing resources. Sustained access to antivirals can also play a critical role in containing the infection at its source and pre-empt the pandemic.

There is thus a clear need to understand the role of avian influenza vaccine development and of possible stockpiling of antiviral drugs so that they can be used effectively in containing a potential pandemic in Member States of WHO's South-East Asia and Western Pacific Regions.

An informal consultation was convened by WHO Regional Office of South-East Asia (SEARO) to address these issues.

Eleven participants from Cambodia, Indonesia, Myanmar, Thailand and Vietnam attended the consultation (for list of participants see Annex 1). WHO staff members from Headquarters, Geneva, Regional Offices for South-East Asia and Western Pacific and country offices of Myanmar and Thailand also attended. Dr Supachai Kunaratanapruk, Deputy Permanent Secretary, Ministry of Public Health, Thailand was elected as the chairperson and Dr Sok Touch, Director, CDC Department, Ministry of Health, Cambodia, as the co-chairperson of the consultation. The programme consisted of plenary presentations and discussions (for programme, see Annex 2).

2. OBJECTIVES

The objectives of the consultation were:

(1) To review the evolving situation of pandemic avian influenza threat, with particular reference to the South-East Asia and Western Pacific Regions;

(2) To review mechanisms for ensuring stockpiling of oseltamivir at global, regional and national levels, and to discuss issues relating to use of seasonal human influenza vaccination; and

(3) To identify follow-up action for regional and national influenza preparedness and response.

3. INAUGURAL SESSION

Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia Region welcomed the participants and stated that infectious diseases continue to be a major cause of morbidity and mortality in Asia. During the last three decades alone, nearly 30 new infectious pathogens, were recorded globally. The emergence of severe acute respiratory syndrome (SARS), the first emerging disease of the 21st century, clearly reflected this growing threat.

Emerging infectious diseases posed a formidable health, social, and economic challenge, and were a cause for worldwide concern. Avian influenza is yet another example of this threat. The outbreaks of highly pathogenic avian influenza (H5N1) in poultry, which started in 2003, were

historically unprecedented in their scope and severity. The outbreaks caused a huge economic loss to those countries. Moreover, there is a growing concern on the possibility of a future influenza pandemic which may be due to avian influenza in Asia. Human casualties due to this pandemic could be in the order of millions, and the economic loss would be the worst ever.

Antiviral drugs and vaccinations against pandemic strain were important interventional tools. An important strategy was to use effective antiviral drugs early and promptly to contain the possible spread of the outbreak and to save lives. Considering the huge financial resources required and the magnitude of the logistics involved, the Member States would have limited capacity to quickly procure and mobilize such a stockpile of antiviral drugs. It was imperative, therefore, to identify suitable mechanisms for strategic stockpiling of drugs at global, regional and national levels to ensure timely access to antiviral drugs in the event of an outbreak in any Member State. It was also essential to explore possibilities of vaccine development for use in the event of early warning signals of a pandemic. Development of an efficacious vaccine and ensuring its timely delivery were critical to the effective prevention of an influenza pandemic.

Dr Samlee urged the participants to make practical recommendations which would greatly help implementing agencies in Asia-Pacific to refine the roadmap and to move forward effectively in enhancing preparedness against an influenza pandemic.

Dr Jai P Narain, Director, Communicable Diseases, WHO/SEARO, provided the background for consultation, its objectives, expected outcome and mechanism.

4. TECHNICAL SESSIONS

4.1 Overview of Global Status of Influenza

In his presentation, Dr Klaus Stohr (Coordinator, Global Influenza Programme, WHO/HQ) said that the epidemics of influenza that occurred every year were the results of the mutations in the genome of Influenza A H1 and H3 viruses which are primarily human pathogens. These epidemics killed almost 0.5 million people annually in the developed world alone. Though the figures from developing countries were not available because of inadequate surveillance and diagnostic facilities, these are believed to be substantial.

Elaborating on the possible genesis of the pandemic, Dr Stohr said that an antigenic shift in the influenza virus could create a novel subtype with virulence of H5N1 virus. Events of the past two years indicated the possibility of such a pandemic. It was estimated that should such pandemic strike, 6-28 million people will require hospitalization and 2-7 million would die. The pandemic would spread rapidly across the globe (within a few weeks) and could manifest in several ways. Apart from the mortality and morbidity, the pandemic would also disrupt essential services including health care and other critical public services. The pandemic was bound to cause tremendous economic loss because of travel and trade restrictions and other measures as indirect consequences of disease.

The world is already in a phase of "pandemic alert" in which limited or no human transmission is recorded. With the occurrence of 110 cases in the past two years in four countries and documentation of H5N1 virus in poultry in several countries, the possibility of a pandemic was growing everyday. The entrenchment of the virus in poultry and occasional transmission to human beings has occurred in Asia. In all likelihood, Asia would be the epicentre of the pandemic. The formulation of national pandemic preparedness plans and their effective implementation are essential to contain the pandemic at source and in minimizing the damage. Till date, less than 50 countries have developed respective national pandemic preparedness plans. WHO is encouraging other countries to formulate such plans using WHO Guidelines and Checklists. WHO would be willing to provide technical support to develop the national plans.

4.2 Antiviral Drugs against Avian Influenza

In his presentation, Professor Frederick G. Hayden (Professor of Internal Medicine, University of Virginia, USA) highlighted the current knowledge about the efficacy of oseltamivir in different settings. The *in-vitro* and animal studies that support effectiveness and safety of the drug against various influenza viruses were discussed. During epidemics, higher efficacy of oseltamivir was demonstrated in individuals who had pre-existing immune response due to vaccination and putative previous infections. Use of antivirals in influenza reduced the intensity of symptoms, minimized complications and was likely to reduce transmission by rapidly decreasing the viral load. Resistance to oseltamivir was found to be much less vis-a-vis amantadine in all age groups. In Japan, where there is substantial use of oseltamivir for management of influenza, only 0.4% resistance was observed.

Various applications of oseltamivir were discussed. These include mass chemoprophylaxis for pandemic threat containment, ("Ring Tamifluation"), treatment of hospitalized and ambulatory patients, post-exposure prophylaxis, outbreak control, seasonal chemoprophylaxis and protection of priority groups who are at high risk such as healthcare, and essential service workers.

The National Vaccination Advisory Committee of USA has recommended that sufficient antiviral drugs should be stockpiled to support a robust response because of the key role that antiviral drugs can play in reducing health impact. An estimated 133 million courses would treat all who are infected in the USA and support prophylaxis of health care workers and patients at highest risk whereas 40 million courses was the minimum to support critical pandemic responses.

Several countries have started stockpiling antivirals. Till date, around 25 countries, mostly in the industrialized world, have invested substantially in maintaining stocks of oseltamivir. Of these, 10 have adequate stocks to treat 20-25% of their populations. At present, there is only one manufacturer of this drug in the world. The production capacity of the manufacturer has been quadrupuled in the last two years and is likely to double in next 12 months. Yet, the countries who wished to place orders now may not get any supplies till the end of 2006. It is imperative that the countries must consider other options to meet the short-term challenge of a pandemic.

The other issues which were discussed included criteria for use of antivirals as prophylactic and therapeutic tools, constraints in availability, high cost and mechanism for rapid shipment to affected areas and their role in containing the pandemic at its source.

Need for having a stockpile of oseltamivir was clearly felt. While WHO is planning establishment of an international stockpile for global use, it was realized that having additional stock-piles by regional associations such as ASEAN and SAARC shall provide extra benefit and rapid access to the drug in the Member Countries of the respective regional associations. Dr Supachai emphasized that mechanism and management of such stockpiles require political agreement at the highest level and informed that Thailand may take lead in discussing this issue with ASEAN Health Ministers in forthcoming meetings.

4.3 Vaccines in Prevention and Treatment of Avian Influenza

In his presentation, Dr Klaus Stohr said that, almost 95-99% of seasonal influenza vaccine was produced in nine countries. Though the requirement for this vaccine in non-producer countries was increasing, yet, a very small population had access to it. Historically, it was seen that the vaccine became available only after a few months of the onset of a pandemic and hence was of limited utility. Currently, seven candidate vaccines against H5N1 were in various stages of development. A limited stockpile of H5N1 vaccine was available for USA.

Although seasonal influenza epidemics were known to occur in countries of the Asia-Pacific Region, vaccination was not a national policy in most countries. Consequently, despite significant vaccine manufacturing capacity in the Region, no influenza vaccine was produced.

Clearly, the current influenza vaccine production capacity was primarily in western countries and may be used to meet the needs of those countries only. Therefore, in the event of a pandemic, there was no way that the current vaccine manufacturing capacity could be scaled up suddenly to meet the increased global demands. Unfortunately, due to the unpredictable nature of future epidemics and the lack of a coherent and firm immunization policy in most countries of the world, manufacturers have no incentive to make huge investments for influenza vaccine production without some degree of certainty of demand.

WHO has clearly stated in all its technical guidelines on the preparation and response to a potential pandemic of avian influenza that vaccination was one of the key components of a comprehensive response. Further, WHO was actively encouraging institutions, countries and manufacturers to conduct research on development of vaccines as well as small-scale experimental production of a vaccine against avian influenza by providing technical support and genetically characterized prototype vaccine viruses.

WHO could also provide technical support to potential manufacturers in such areas as production feasibility studies, ensuring good manufacturing practices, quality assurance and quality control and strengthening national regulatory authorities. WHO has a role in fostering private/public partnership and donor interest to support such activities.

In view of the grave concerns regarding the potential outbreak of an influenza pandemic and in view of the absence of influenza vaccine manufacturing capacity in the Region, all efforts must be made to encourage Member States, development partners, private/public partnerships and manufacturers to work together to enhance capacity for influenza vaccine production in the Asia-Pacific Region, Dr Stohr added

4.4 Plans for Enhancing Preparedness against Influenza in South-East Asia and Western Pacific Countries

In their presentations, Dr Richard Brown (Epidemiologist, Manila) and Dr Jai P. Narain (Director, Communicable Diseases, WHO/SEARO) said that several countries of the South-East Asia and Western Pacific Regions have started formulating their national pandemic preparedness plans. The Regional Offices were providing technical support using WHO guidelines. In addition to the activities being planned by the Regional Offices, the importance of adopting a multisectoral approach and generating evidence-based activities were highlighted. The importance of Asia as the potential epicentre of a pandemic and the need for scaling-up the preparation and international collaboration and partnerships was crucial.

Efforts are being made in Thailand to develop a vaccine against a pandemic strain which include characterization of virus, designing clinical studies and establishment of a production plant. International support to strengthen Thailand's effort was needed.

A pandemic, either due to H5N1 or some other novel subtype, was imminent. No one can predict the time-frame within which it will hit the world, but it is bound to bring about considerable devastation. While efforts were being made by Member Countries and international communities, a lot more needed to be done to combat the pandemic, especially its containment at source.

5. CONCLUSIONS

(1) Realizing the imminent threat of the influenza pandemic, Member States should proactively formulate comprehensive National Pandemic Preparedness Action Plans as soon as possible and implement them with a high priority.

(2) WHO should provide technical support to Member States in developing and implementing their National Preparedness Plans.

(3) There is a real opportunity in Asia to pre-empt the pandemic at the source through early detection of cases followed by aggressive containment measures including the timely and early use of antivirals. This will require stockpiling of antivirals which could strategically be used to prevent the amplification of focal outbreaks into a pandemic.

(4) In addition to many other public health interventions which are part of a National Pandemic Preparedness Plan, the stockpiling of antivirals should also be considered.

(5) WHO should continue to work towards establishing a sufficient international stockpile of antivirals to enable an initial response to an impending pandemic. In addition, the added value of a sub-regional stockpile of oseltamivir, created through regional associations such as ASEAN and SAARC, with technical support from WHO, should be considered.

(6) Member States should identify approaches to close the gap between the demand for pandemic influenza vaccine and the current availability. As an option, increased use of seasonal vaccine should be explored as an intermediate and long term objective.

(7) WHO should assess the existing production capacity for seasonal influenza vaccine in the Asia-Pacific region and explore the potential for expanding production through public-private partnership as well as international collaboration including technology transfer.

(8) WHO should develop concept papers articulating the urgency of responding to the potential threat of an avian influenza pandemic and use these as advocacy tools.

6. CONCLUDING SESSION

Dr Supachai Kunaratanapruk (Deputy Permanent Secretary, Ministry of Public Health, Thailand) concluded the consultation by highlighting that the threat of a pandemic was real and that it required concerted and coordinated efforts by everyone. The tools available to combat the pandemic were limited but their judicious use could be critical in mitigating the impact. Dr Jai Narain, on behalf of WHO, thanked all the participants for their useful contributions and for attending the consultation at short notice.

Annex 1

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Annex 2

PROGRAMME

Day 1, 01 August 2005

0830 hrs	Registration	
0900 hrs	• Address by Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia Region • Objectives • Introduction of participants • Election of chair and rapporteur • Adoption of Agenda • Administrative announcements	
0930 hrs	Overview of Global Status of Influenza	*Dr Klaus Stohr*
1015 hrs	Group Photograph	
1045-1230 hrs	**Technical Session 1**	
	Antiviral drugs against avian influenza	
	• Technical issues • Financial requirements • Stockpiling • Management and logistics implications	
	Introduction and an overview	*Dr Klaus Stohr and Dr F Hayden*
1330 hrs	Technical Session 1 continued	
	• Discussions • Formulation of Recommendations and steps forward	
1545 hrs	**Technical Session 2**	
	Development of vaccine for influenza and avian influenza	*Dr Klaus Stohr*
	• Technical issues on seasonal influenza vaccine and human influenza vaccine • Current status of production and research on avian influenza vaccine • Availability in developing countries	
	Introduction and an overview	

Day 2, 02 August 2005

0830 hrs	Technical session 2 contd	
	Formulation of Recommendations and steps forward	
1100 hrs	Overview of plans for enhancing preparedness against influenza in WPR Countries	*Dr R Brown*
1145 hrs	Overview of plans for enhancing preparedness against influenza in SEAR countries	*Dr Jai Narain*
1330 hrs	Wrap up on Recommendations	
	Issues for consideration and follow-up	
	Technical Support from WHO for Preparedness	
1600 hrs	Closure	