Public Health Research Agenda for Influenza

Report of a regional meeting
New Delhi, India, 18–20 August 2010

World Health Organization
Regional Office for South-East Asia

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Acronyms

ACHR	Advisory Committee on Health Research
AI	Avian influenza
APEIR	Asian Partnership on Emerging Infectious Diseases Research
ARDS	Acute respiratory distress syndrome
CDC-Atlanta	Centres for Disease Control and Prevention, Atlanta, United States of America
CDC	Coordinator, Disease Control
CDS	Department of Communicable Disease Control
COHRED	Council on Health Research for Development
FAO	Food and Agriculture Organization (UN)
GISN	Global Influenza Surveillance Network
GLEWS	Global Information and Early Warning Systems
HSADL	High Security Animal Diseases Laboratory
IEIP	International Emerging Infections Programme
ILI	Influenza-like-illness
IPC	Interpersonal communication
IVRI	Indian Veterinary Research Institute
JMG	Joint Monitoring Group
KAP	Knowledge, attitude and practice
OIE	Regional Organization for Animal Health
PPE	Personal protective equipment
SEARO	WHO Regional Office for South-East Asia
SARI	Severe Acute Respiratory Infection
STaRS	Small target reassortment screen
TUC	Thai Ministry of Public Health (MoPH) – United States (US) CDC Collaboration
WHO	World Health Organization

1. Background

The microbial world is unpredictable and pathogens emerge on a regular basis with serious implications for global health security. The Severe Acute Respiratory Syndrome (SARS) and the highly pathogenic avian influenza A (H5N1) are important regional examples.

Influenza is a global public health challenge. Whether in its zoonotic, seasonal epidemic or pandemic forms, it has led to mild and severe illness, as well as death. Every year, seasonal influenza outbreaks continue to cause significant morbidity and mortality at the global level. It is highly infectious and places the very young, the elderly and persons with chronic medical conditions at serious health risks from potential infection and its complications. Seasonal influenza epidemics can affect up to 15% of the population and extrapolation from well established evidence in temperate countries suggests that seasonal influenza epidemics can result in an estimated 250 000 to 500 000 deaths worldwide each year.

In recent years, the highly pathogenic avian influenza A (H5N1) has caused unprecedented outbreaks in poultry in Asia and devastated the poultry industry. Furthermore, the virus has managed to cross the species barrier resulting in severe illness and death in human populations as was seen Bangladesh, Indonesia, Myanmar and Thailand.

The world recently witnessed the emergence of influenza A strain: pandemic (H1N1) 2009. Since its initial detection in Mexico and the United States of America in April 2009, the pandemic virus spread quickly throughout the world. On 25 April 2009, the Director-General of WHO announced the world's first-ever "Public Health Emergency of International Concern" with the formal declaration of an influenza pandemic. The global response was swift and well coordinated, with many Member States implementing timely public health interventions. Although the impact of this virus is yet to be determined, it has caused at least 15 000 laboratory test-confirmed deaths globally in one year, mainly in young and middle-aged adults.

Research generates information for public health action, provides an evidence base for policy decisions and ensures the application of effective strategies and interventions. Research must be driven by needs and should address gaps and public health priorities of the countries concerned. At present, there is insufficient evidence available on interventions critical to reduce risk, limit spread and minimize the impact of influenza in its seasonal, zoonotic and pandemic forms. There is a need to map out what is known and identify gaps in knowledge: where gaps exist, all stakeholders must work together to address them. In November 2009, a global consultation was organized in Geneva, Switzerland, to define a public health research agenda for influenza. In addition to defining the key list of priority areas for influenza research, the meeting also requested WHO to undertake a broader consultative process through a series of regional meetings. Locally identified research priorities would then help to generate evidence to underpin appropriate public health policies to control influenza in a variety of political, socioeconomic and cultural settings.

The regional meeting held in New Delhi was organized to share experiences and develop a regional consensus on priority areas for public health research on influenza. It is therefore expected to be an important step in facilitating greater collaboration in research, and strengthening knowledge management, including the dissemination and application of research outputs.

2. Opening session

The meeting opened with Dr Jai P.Narain, Director, Department of Communicable Diseases (CDS), WHO-SEARO, delivering the message from Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia Region. In his message the Regional Director welcomed all participants to the meeting. Underscoring the need for a participatory process in defining the research agenda, the Regional Director noted that "*research must be need-driven and primarily address identified gaps and public health priorities of countries concerned*." To ensure that this was taken care of, the Regional Director underscored that "*countries must take the lead in the process including identifying and prioritizing their research needs; and undertaking and applying the research results*". He also thanked all the participants and wished them success in their deliberations (for details please refer to Annex 1). Dr Jai P. Narain expressed his appreciation for all participants and wished them a pleasant stay and a fruitful consultation.

Following this, Dr Nahoko Shindo from the Global Influenza Programme, WHO headquarters, delivered her opening remarks. A brief overview was provided of the recent pandemic, including its epidemiological and spatio-temporal features. The previous week, the pandemic had been declared over, but the unpredictable nature of influenza meant that vigilance was still required. Guidance has been developed by WHO headquarters on influenza surveillance and other key technical areas for the post-pandemic period. It was an appropriate time for review and reflection, including consideration of where gaps in knowledge existed, and how to address them. Therefore, the meeting was important and timely. It was also important to highlight that regional influenza research issues constituted a vital component of global issues, so the outputs of the meeting would be used to refine the global public health research agenda for influenza research.

Following the opening remarks, meeting participants were introduced, including national representatives, invited experts and members of the WHO Secretariat. Dr Shiv Lal was nominated Chairperson for the first day, and Dr Supamit Chunsuttiwat the overall meeting Rapporteur.

3. Objectives

Dr Chusak Prasittisuk, Coordinator, Disease Control (CDC), WHO-SEARO, briefed the participants on the aim and objectives of the meeting, which included:

3.1 General objective

- To facilitate discussion and coordination among researchers, donors/funding agencies and public health professionals.

3.2 Specific objective

- To facilitate discussion and sharing of experiences/lessons among researchers and representatives of national programmes on public health research priorities for influenza;

- To develop a document that would lay out a public health research agenda for influenza in the Region ; and
- To identify mechanisms for regional implementation of the research agenda.

4. Plenary session

4.1 Regional and global perspectives, experiences and lessons

Influenza in the South-East Asia Region and regional perspective: Dr Jai P. Narain

The burden of seasonal influenza in the WHO South-East Asia (SEA) Region is still not well understood, although information is available from India, Myanmar and Thailand. Avian influenza has a disproportionate impact in the SEA Region, with 39% of all cases and 52% of deaths occurring in Member States (namely Bangladesh, Indonesia, Myanmar and Thailand) comprising it.

All Member States of the SEA Region were affected by the pandemic influenza H1N1 2009. The clinical spectrum of pandemic influenza H1N1 2009 disease was different, with more gastrointestinal symptoms reported. Overall, the mortality rate appears to be lower than for seasonal influenza. However, it has also been noted that these may have been relatively higher in India. Deaths were mostly caused by severe viral pneumonia leading to Acute Respiratory Distress Syndrome (ARDS). Research conducted in the SEA Region indicated that improved outcome was related to earlier treatment with antiviral drugs.

At the beginning of the pandemic, the key questions were: (i) What was the transmissibility of the virus? (ii) What was the severity of the disease? (iii) Which public health interventions are needed and which are effective? (iv) Which groups should be targeted? Furthermore, as non-pharmaceutical measures remain important, better evidence is needed on their effectiveness, such as closing down of schools. It is also important to have a better understanding of how to mobilize a broad, multisectoral response, including community involvement, and how to engage effectively with the mass media.

The key activities in the post-pandemic period included a critical review of the pandemic response (including research) and assessment of measures that were found to be effective. The key questions we should be addressing to help determine the way forward for this initiative are: (i) What are the priority areas of focus in flu research? (ii) What capacity or collaboration is needed to enable implementation of the influenza research framework in Member States?; (iii) What resources need to be harnessed to enable the implementation of the framework?; (iv) What health research system issues need to be addressed to enable the implementation of the framework?; and (v) How will the framework be implemented, monitored and evaluated?

Evolving pandemic, evolving questions: key information needed for developing control measures: Dr Nahoko Shindo

Influenza pandemics occur on a regular basis. Although we know that novel influenza viruses usually originate from an animal source, the precise mechanism of emergence is not well understood. The recent pandemic presented many challenges, including considering whether to attempt containment, the need to quickly describe the epidemiology of the virus, its pathogenicity and its sensitivity to antiviral drugs. Assessment of the severity of the illness became a critical issue when questions arose about the meaning and utility of pandemic phases. All of these issues served to highlight the need to establish mechanisms for the collection and rapid analysis of key information in a timely manner. As the virus continued to spread, one of the key issues that arose was the utility and effectiveness of public health interventions. Then, as the pandemic progressed and seasons unfolded on the northern and southern hemispheres, a key issue was how the pandemic virus would interact with seasonal strains. It is still difficult to be sure if the overall impact of the pandemic strain is greater than with seasonal strains, but risk groups appear to be different and at the peak of pandemic "waves", health-care facilities and "intensive care" units did find their resources severely stretched.

The public health research agenda for influenza: Dr John Tam

A robust scientific knowledge base is essential for modern public health policy development for influenza control. However, there still are knowledge gaps. Recognizing these gaps, WHO in consultation with

Member States has developed the *WHO Public Health Research Agenda* to identify relevant research topics and categories of research methodologies that provide evidence to inform public health policies. The overall goal of The Public Health Research Agenda for Influenza is to "support the development of evidence needed to strengthen public health guidance and actions essential for limiting the impact of the pandemic, zoonotic and seasonal influenza on individuals and populations". The defined objectives of the agenda are to:

(1) provide a framework reflecting public health research priorities for pandemic, zoonotic and seasonal epidemic influenza;

(2) identify specific research topics, reinforce and prioritize their importance in meeting public health needs over a medium-to-long-term period;

(3) maintain focus on the relatively less addressed areas such as operational research and research with applications in under-resourced countries;

(4) facilitate discussion, coordination and interaction among researchers, donors and public health professionals; and

(5) highlight the need and benefits of a multidisciplinary approach to address knowledge gaps in public health related to influenza and its control.

The process included a technical consultation at various levels including in 2008 and 2009, which led to drafting of *The WHO Public Health Research Agenda for Influenza*. Another technical consultation held from 17-20 November 2009 brought together public health decision-makers from Member States, academic and commercial researchers, and funding agencies to discuss, review and prioritize research topics based on public health needs. The outcomes of the meeting were as follows:

(1) An agreed global public health research agenda for influenza;

(2) Prioritization of public health research topics with short, medium or longer-term objectives for pandemic, zoonotic and seasonal influenza infection control;

(3) A guiding reference document for developing regional and country-specific public health research agenda for influenza; and

(4) A plan to build a framework for monitoring the availability of research results that can fill information gaps that are essential for public health decision-making especially in resource-limited countries.

(For details on process/output visit http://www.who.int/csr/disease/influenza)

A global platform for data sharing: Dr Nahoko Shindo

Many critical policy decisions can only be made if good quality data on influenza are collected, collated and disseminated in a timely manner. Such data come from WHO Member States and include a mixture *of* subjective assessments and quantitative information, and their sources include mandatory reporting under the International Health Regulations, the Global Influenza Surveillance Network (GISN or FluNet), which is a virologic data sharing network, four "expert networks" established during the pandemic (clinical, virorological, epidemiological and modelling), regional and global teleconferences, reviews of scientific literature, website screening (a primary source of country-level data, but extremely labour intensive and the "Friends and Acquaintances network", which is sometimes the most valuable and reliable. Collation of data presents significant challenges. Standardization is a problem because data come in a variety of formats. Timeliness is also an issue because data are frequently two weeks old. There is also a lack of standard parameters for assessing the severity and a lack of baseline to compare some data against. However, the momentum provided by the pandemic presents us with an opportunity to build a system that can serve the needs of influenza *and* other respiratory diseases by providing baseline data to put acute events in the proper context and for developing an infrastructure to support future events and meet the IHR requirements. A significant addition proposed for the "information puzzle" will be FluID. Whereas Flu Net is a web-based data reporting tool for laboratories that collects virological surveillance data, including number of specimens and types of influenza virus, FluID is a web-based epidemiological data collection tool. It collects qualitative data, including information on trends, geographical spread, intensity and impact, as well as quantitative data on ILI, ARI, SARI, pneumonia and mortality by age. Such qualitative data will help to provide information even from areas that do not have any formal surveillance system, while the quantitative epidemiological data will be important to support the interpretation of virological data and to generate accurate qualitative data. The system is

based on adaptable open-source software and it should be relatively easy to add data for other diseases. If used fully, it will provide a snapshot of individual country data; allow aggregation of local area data and help build up a global picture in near real time. Data can be entered directly online or be uploaded from an existing database. Current outputs include export of data entered into different "Excel" formats and maps of quantitative indicators. Global information products will soon include an influenza website, a weekly situation update, weekly pandemic updates, summary publications (e.g. the Weekly Epidemiological Record) and policy guidelines. It will soon have multilingual support, ability to cross-tabulate data with other global health observatory data and clickable interactive maps. A meeting was held in November 2010 to review the experience of "early adopters".

4.2 Presentations

Stream 1: Reducing the risk of emergence of pandemic influenza

The first presentation on the topic was delivered by Drs S.C. Dubey and D.D. Kulkarni. Globalization has increased the risk of trans-boundary diseases, including influenza. Influenza viruses exhibit diversity in the range of human and animal hosts they affect their pathogenicity. The last five centuries have witnessed at least 13 influenza pandemics. Influenza A/H5N1 emerged in China in 1996, followed by an epizootic in China, Hong Kong Special Administrative Region that caused 18 human cases and 6 deaths. It then reappeared in 2003 and proceeded to spread widely, causing epizootics in 60 countries across 3 continents. As of 3 August 2010, 299 human deaths out of 503 cases of H5N1 infection had been reported to WHO from 15 countries with an average case fatality rate of 60%. In many households in developing countries, backyard poultry are an important source of protein; therefore control policies must recognize the rural poor as part of the solution to reducing human health risk. Swine influenza is endemic in parts of South Asia, but does not usually cause significant mortality. However, pigs are important because of their potential role as "mixing vessels" for the influenza viruses from others species, in particular humans and birds. The present pandemic H1N1 2009 virus is believed to be a triple reassortant of human, swine and avian influenza viruses and can be transmitted from pigs to humans and *vice versa*. Local challenges to control of zoonotic diseases include highly decentralized administrations, lack of engagement with commercial poultry producers,

and inadequate human and financial support. It is possible that poor control of avian influenza might lead to high levels of virus circulation and favourable conditions for its mutation to a pandemic strain. The national avian influenza control strategy in India includes surveillance, culling and compensation and improved biosecurity along with timely diagnostics/laboratory support and development of human resources through training programmes. The HSADL, Bhopal, India, has contributed to identification of antiviral drug resistance in influenza viruses and undertakes phylogenetic analysis to facilitate tracking and evolution of viruses. Influenza research in the Region would be facilitated by improved international collaboration and information sharing, as well as improvements in laboratory infrastructure and training. Ideally, each country should have the capacity to safely isolate, identify, analyse and store isolates of all pathogens it may encounter. Additional priorities are the development of better diagnostics and improved surveillance of animals. Improved understanding on the epidemiology of influenza in Asia would also be of benefit, along with development of new treatment options and improved vaccines. All this work may be facilitated by the development and support of centres of excellence for research.

A presentation, "Reducing the Risk of Emergence of Pandemic Influenza: Research Priorities in the SEA Region" was then delivered by Dr Trihono, National Institute of Health Research and Development, Ministry of Health, Indonesia. Human cases of avian influenza A/H5N1 appeared to be decreasing, but animal disease had been reported in 16 of 33 provinces in the last six months. The broad strategic approach for control in Indonesia has been to develop complementary "road maps" for avian influenza control in animals and in humans. Areas defined for control in animals include biosecurity, selective depopulation and culling, vaccination, controlling the animal trade, surveillance, community awareness, restructuring the poultry industry and monitoring and evaluation. Research priorities for human avian influenza are determined by an expert team under a national committee for emerging and re-emerging diseases and the main areas cover sero-surveillance studies in humans and animals, surveillance for influenza-like-illness (ILI) and Severe Acute Respiratory Infection (SARI), as well as describing biological and environmental risk factors. Specific research projects include an analysis of AI preparedness at referral hospitals, spatial epidemiological analysis of human avian influenza cases, a description of the clinical course of H5N1 AI in patients at Persahabatan Hospital (2005-2008), and research for

vaccine development. Research for animal disease includes an epidemiological study on avian influenza in poultry farms in the Riau province, H5N1 surveillance in migratory birds in Java, studies on the molecular mechanisms leading to emergence of pandemic influenza viruses (via surveillance in poultry, pigs and the environment) and on the role of scavenging ducks on transmission in Java. There are also plans to undertake the following studies: (i) Spatial epidemiology analysis of human AI (H5N1) using molecular approach, remote sensing and GIS in six provinces; (ii) Molecular characterization of influenza A/H5N1 viruses isolated from 2008-2010 patients; (iii) Characterization of molecular markers in avian influenza H5N1 to predict abiltiy to infect humans; and (iv) the molecular infection mechanism of H5N1 subtype avian inluenza virus from birds to mammals. At present, significant research restraints include funding, weak infrastructure and suboptimal coordination between human health and animal sectors.

The next presentation was made by Dr Rodney Hoff, Regional Emerging Diseases Intervention Center, Singapore, to provide an overview of the outcomes of the discussion on Stream 1: "Reducing Risk of Emergence of Influenza Viruses with Pandemic Potential" at the global meeting in Geneva held in November 2009. The existence of many avian and mammalian host species and the vast variety of influenza virus subtypes contribute to the complex evolution and ecology of influenza viruses with the potential for zoonotic and pandemic spread. There is an urgent need to identify effective control measures at the animal source and human behavioural modifications to reduce virus transmission across the animal-human interface. The priority areas identified in the consultation were: (i) Factors associated with the emergence of influenza viruses with zoonotic or pandemic potential; (ii) Factors associated with human infection at the human-animal interface; (iii) Surveillance of viral transmission at the human-animal interface; and (iv) Preventive measures to reduce the risk of emergence of zoonotic and pandemic influenza viruses. Detailed outcomes of this consultation are available at: http://www.who.int/csr/disease/influenza/2010_04_29_global_influenza_research_agenda_version_01_en.pdf

A presentation was then delivered by Dr Rebecca Garten, United States Centres for Disease Control (CDC), on "Laboratory Surveillance of Pandemic H1N1 Virus: Genomic Evolution and Monitoring of Variants". Phylogenetic analyses show that pandemic influenza H1N1 2009 is derived from swine influenza. However, because good swine surveillance and virus sequence data are lacking, the possibility that other hosts are involved

before introduction to human population cannot be ruled out. In addition, it cannot be determined where or when the reassortment event(s) occurred, although it is estimated to have entered human population very recently. The strategic approach to genetic and antigenic surveillance for pandemic influenza H1N1 2009 was described. Isolates are chosen for HA, NA and M sequencing based on antigenicity, date of collection and geographic location, and a small subset undergoes full genome sequencing. If isolates are found to have reduced titers to ferret antisera raised against vaccine candidate A/California/07/2009 in HI (and which therefore may represent important variants), then the original clinical material is re-analysed and isolates sequenced. Isolates from fatal or severe infections also undergo full genome sequencing. To date, the mutation rate in HA is similar to seasonal influenza and although overall, variation is low, some genome variants are emerging. There does not appear to be any clear association between specific strain variants and increased morbidity/mortality. It is difficult to predict how this virus will behave in the future. It may effectively become another "seasonal influenza" strain and continue to circulate with or without displacement of one or more current strains. It may also become an epidemic strain in other hosts (for example, through reassortment with other non-human host strains), resulting in new epidemics in swine or human population. There is already evidence of reassortment occurring; with a virus identified in swine characterized as 2/26/10 Hong Kong Eurasian swine/H1N1pdm. Monitoring the emergence of reassortment in influenza A subtypes may be helped by the new technology known as STaRS, or Small Target Reassortment Screen. This works through the generation of small target sequences in each of the eight influenza gene segments (each around 100 base pairs in length), which are then analysed via BLAST on a small internal database to determine if a reassortment event has occurred. It requires a 96-well capillary sequencer and is currently nearing the end stage of development as an influenza sequence activity at CDC. There are plans for a future beta test site at NAMRU-3 in Egypt.

Stream 2: Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza

A presentation was delivered by Dr A C Mishra, Director, National Institute of Virology, Pune, India, entitled "*Research for limiting the spread of Influenza"*. Measures that may be applied at the "animal-human" interface to minimize the risk of infection in humans include culling, quarantining

farms, vaccination of birds and use of influenza vaccine for cullers to minimize the risk of reassortment. However, the scientific basis for these measures is not well understood. Containment may be the only strategy available in the early stages of a pandemic and can include isolation of infected persons, quarantine of exposed persons, self-exclusion, social distancing and schools/transportation closure days. However, it is questionable whether there is evidence to support these measures. Transmission of influenza is primarily through respiratory droplets or contact with contaminated objects, followed by touching of mucus membranes (e.g. mouth, nose, eyes). Transmission can be interrupted by hand hygiene: respiratory hygiene, use of PPE and cleaning/disinfection. The evidence for effectiveness of face masks is unclear. Transmission commonly occurs in community settings, such as in schools or the home, but the strategies to prevent such transmission (including utility of school closures) are also unclear. In considering these issues it is important to understand the dynamics of infection (Ro), the possible effect of environmental changes and the potential impact of different interventions (including vaccination). However, the methodology required to generate this kind of evidence is often extremely complex and results can be unreliable. Progress is most likely through a multidisciplinary approach, involving epidemiologists, statisticians and infectious disease modelling.

A presentation entitled "*Research on zoonotic influenza: the livestock sector perspective*" was then delivered by Dr Iain Wright, International Livestock Research Institute (ILRI), Regional Representative, Asia. Zoonotic influenza has human health impacts and economic and social impacts on the livestock sector. The structure of the livestock sector varies between countries and has an impact on strategies for disease control. Significant changes include increasing demand for livestock products, increasing industrialization and policy changes (e.g. zoning of livestock production in Viet Nam). Developing countries have limited resources for animal disease surveillance and control systems, so it is important to develop flexible, risk-based approaches. There is a need to build capacity to facilitate multidisciplinary research involving public health specialists, veterinary epidemiologists, environmental scientists, economists and social scientists. This philosophy is embodied by the "One Health" movement, a collaborative work involving WHO, FAO and OIE and the "Ecohealth" initiative. The "Ecohealth" initiative is a project aimed at developing better management of zoonotic EIDs in South-East Asia, currently involving six countries: Cambodia, People's Republic of China (Yunnan), Laos,

Indonesia, Viet Nam and Thailand. One of its central objectives is to build capacity in research institutions and with the researchers themselves. Priority research areas therefore include the following: understanding the evolution of structures in the livestock sector and implications for zoonotic influenzas, development of risk-based approaches to surveillance, and control and understanding incentives and policy development.

Dr Ron Waldman, USAID, then provided perspectives on limiting the spread of pandemic influenza. A whole-of-society approach to a pandemic is appropriate as many other sectors are as much involved/engaged in pandemic preparedness. Although there is a perception that the level of pandemic preparedness is better now than five or ten years ago, man probably has little evidence to support this contention. Collective efforts need to be made to undertake such evaluations, and also to advocate for multi-hazard disaster preparedness. In addition, planning should also consider the potential impact of interventions on other aspects of society, for example the impact of school closures on education, the impact of hospitalizations for influenza on provision of care for other diseases, and societal impact on the vulnerable.

Stream 3: Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza

To begin this session, a presentation entitled *"Minimizing impact of pandemic, zoonotic and seasonal epidemic influenza: Research priorities in the SEA Region: Thailand's perspective"* was delivered by Dr Supamit Chunsuttiwat. Good data on burden of influenza in Thailand are now available. Seasonal influenza accounts for approximately 900 000 pneumonia out-patient department (OPD) cases/year, 10% of hospitalized pneumonia cases and around 300 pneumonia deaths/year. Avian influenza (H5N1) caused extensive poultry outbreaks in 2004-2005 with significant economic impact and 25 human cases (including 17 deaths) from 2004-2006. Pandemic influenza reached Thailand in April in 2009 and is estimated to have infected 13% (8.4 million) of the population, with 28 036 confirmed cases and 184 deaths. Strategic responses were realigned over time from an initial attempt to detect and delay importation, followed by attempts at containment and finally to a policy of mitigation, all of which employed modalities of surveillance, public health interventions, clinical management and risk communication. Although vaccine was procured, uptake was slow partly due to its late arrival, but also because of public

concern over vaccine safety. For Thailand the questions related to the focus areas of this research "stream" are as follows:

(1) Improve immunogenicity, availability and delivery of vaccines – research issues include factors influencing immunogenicity in different target groups, seasonal and pandemic vaccine development and assessment (including clinical trials and post-marketing surveillance) and effectiveness of vaccine logistics and supply system.

(2) Determining the disease burden and social impact – better understanding is needed on the burden and impact of seasonal flu in different populations, pandemic H1N1 attack rates in various groups, influenza virus contamination and transmission in different settings, e.g. HH, schools public transport, pandemic H1N1 infection in swine, poultry and other mammals, development of appropriate mathematical models suitable for tropical country/local users.

(3) Public health policies to reduce the impact of disease – the topics include cost-effectiveness of various public health interventions, e.g. school closure, fever screening, assessment of strengths and gaps in national response to pandemic (H1N1) 2009; roles of Village Health Volunteers, community action groups and NGOs in pandemic response; development of effective, locally-oriented risk communication tools; and roles of cottage industry in production and supply of diseases prevention products e.g. face masks, PPE, hand sanitizers.

International collaboration is needed where country-level research may not give answers, for example, (i) when a large sample size is needed, e.g. to describe the epidemiology, clinical features and therapeutic options for AI; (ii) when there is a need for comparison among different settings, e.g. the impact of poultry vaccination policy on AI epidemiology and control; and (iii) when there is need for technical support, for example, a joint research team with sufficient expertise for specific research (e.g. mathematical modelling to predict the impact of pandemic influenza. Thailand is a collaborating partner in the Asian Partnership on Emerging Infectious Diseases Research (APEIR), which is supported by International Development Research Centre (IDRC), Canada and research institutes in China, Cambodia, Indonesia, Laos, and Viet Nam and Thailand. The stated objectives of APEIR are to catalyse generation of knowledge and capacity

building for multidisciplinary research on emerging infectious diseases with pandemic potential in Asia based on the eco-health concept. The current research priorities include migratory bird surveillance, backyard poultry, socioeconomic impact, control measures, risk behaviour and policy analysis.

Following this, a presentation was delivered on "*Minimizing impact of zoonotic influenza"* by Dr Yoshihiro Sakoda, OIE Reference Laboratory for HPAI and LPAI, Japan. There are 144 possible combinations of haemagglutinin (H1-H16) and neuraminidase (N1-N9). Surveillance conducted by OIE between 1991 and 2009 yielded a total of 795 isolates of avian influenza from 22 744 samples, including a huge diversity of these subtypes. Results are stored in an online database maintained at Hokkaido University, Japan. Viruses obtained through this surveillance network are used to inform understanding of the epidemiology of avian influenza, as well as development of vaccines, biologicals and diagnostic test kits. Vaccination in poultry prevents diseases and decreases the amount of virus shed, but does not confer complete immunity from infection. As long as some virus continues to be shed, this can unfortunately lead to a "silent spread" and potentially to antigenic shift of the virus. Therefore, vaccination should only be used as an adjunct to the policy of "stamping-out".

A presentation, "Policy needs for public health research for influenza" was then delivered by Professor Richard Coker, London School of Hygiene and Tropical Medicine, London, United Kingdom. The relationship between policy and research can be defined in three ways. Firstly, there is research for policy, secondly there is research of policy and lastly, there is the issue as to how research findings are translated into policy. Research can improve knowledge; it can inform policy and practice (resulting in public health or economic gain) and it can support "capacity" building. Building capacity (including research capacity) requires tools, skills, staff and systems. Influenza research can address key issues such as prevention, containment, mitigation and recovery. Research may also help (or be helped by) the conceptualization of new paradigms for how to view subjects such as livestock production systems and the way they contribute to risk production. Influenza research can also be systematized from a disciplinary/methodological perspective and include anthropology, virology, biology, immunology, epidemiology, ecology, economics, political science, veterinary medicine, health systems analysis and infectious disease modelling. It is also important to have a very clear understanding of the strengths and weaknesses of different approaches. One key issue is whether

health systems can mitigate the impact of a pandemic. To look at this, a deterministic, compartmental model linked to availability of health service resources (antivirals, beds and ventilators, etc.) has been developed. The questions asked by the study included (i) Where are the biggest health system resource gaps, and what these resources were; (ii) What are the potential consequences of those gaps (e.g. preventable mortalities); (iii) How wide is the variation in gaps and disease burden within and across countries; and (iv) What impact could reallocation/mobilization of resources have on the disease burden? Research for policy-making on influenza should ideally address timeliness, feasibility, impact and cost of interventions, political pertinence, contextual pertinence, sectoral pertinence, disciplinary perspective, appropriate methodologies and coherence, and if possible, provide added value beyond flu.

Stream 4: Optimizing the treatment of patients

To open discussion of the third stream, Dr David Hui, Professor of Respiratory Medicine, Chinese University of Hong Kong, China, Hong Kong Special Administrative Region (SAR), delivered a presentation on "*Clinical Management of severe or progressive influenza infection: from seasonal to pandemic influenza"*. Severe influenza presents with clinical (e.g. dyspnoea, tachypnoea, hypoxia) and/or radiological signs of lower respiratory tract disease. It can also cause CNS involvement, severe dehydration, renal/multiorgan failure, progressive disease and exacerbation of underlying chronic diseases. A study in "Hong Kong SAR" demonstrated that in comparison with seasonal flu, influenza pdm patients were younger (median age 47 years versus 76 years, $p<0.001$), but more likely to be obese (5.8% vs 0%, $p=0.018$), pregnant women (7.2% vs 0.9%, $p=0.027$) or have no underlying predisposing factors (24.6% vs 5.1%, $p<0.001$). In addition, they were more likely to receive oseltamivir, but less likely to receive antibiotics. There is also increasing evidence of the efficacy of early treatment with oseltamivir in otherwise healthy and high-risk patients with severe seasonal influenza infection, including reduced oxygen requirements, reductions in length of hospital stay and decreased mortality. Outcomes for pandemic influenza H1N1 2009 also seem to be related to early treatment. Severe disease is associated with high levels of IL-6, CXCL-8(IL-8), CCL2(MCP-1) and sTNFR-1 and slow viral clearance in patients treated with antiviral drugs. There is interest in the potential efficacy of nebulised zanamavir, but evidence is currently lacking and severe adverse events have been reported, possibly related to lactose sugar in the powder

formulation used for inhalers obstructing the function of mechanical ventilator equipment. Current research initiatives include the use of double dose oral oseltamivir, use of intravenous neuraminidase inhibitors and possible roles for statins, n-acetylcysteine and convalescent blood products. Use of high-dose steroids has been associated with invasive aspergillosis in pandemic influenza H1N1 2009 patients. However, low-dose corticosteroids may be considered in the treatment of refractory septic shock. Passive immunotherapy in the form of convalescent plasma or hyper-immune globulin may be explored as rescue therapy, but IVIg should be used with caution due to its thrombogenic effects. More data are needed to explore the potential role of other drugs with immuno-modulating properties such as statins, gemfibrozil, and NAC. Non-invasive ventilation may play some role in reversing hypercapnia in patients with AECOPD.

A presentation was next delivered by Professor Suri, Safdarjang Hospital, New Delhi, India on "*Research for optimizing treatment of patients in the SEA Region*". Since May 2009, 37 000 cases and 1833 deaths from pandemic influenza H1N1 2009 have been reported in India. The time to diagnosis and delivery of care both impact the morbidity and mortality levels. Delayed diagnosis can be due to lack of access, health-seeking behaviour and patterns of presentation, including the presence of "compounding" illnesses. Coinfection of dengue and influenza has been reported. Poor sensitivity and specificity of influenza rapid diagnosis tests may also cause delay if false negative results occur. Poor assessment of severe cases at primary care level may lead to delayed referral for required treatment. Some severity assessment scoring systems for pneumonia are described and could be more widely applied. The recommended ventilatory strategies are generally based on guidelines for Acute Respiratory Distress Syndrome (ARDS). Research could be undertaken to help determine the most efficient use of resources to optimize treatment at the primary care level and ensure early and effective treatment to decrease severe morbidity and mortality. The cost-effectiveness of high dependency units at district level hospitals (or mobile intensive care units), and provision of access to expert opinion or consultation via telemedicine, telephone hot lines and the internet should also be evaluated. Studies could also better characterize the clinical profile, severity, complications and co-morbidities of influenza cases. An audit of hospitalized patients looking at clinical and biochemical markers may help define predictors of serious disease. Studies could also better describe the efficacy and toxicity of different doses,

timings and modalities of delivery of oseltamivir therapy, including combination therapy with other antiviral drugs. Better information is also needed on infection control measures, including efficacy of different types of masks. Lastly, more research on the pathophysiology and pathogenesis of disease will enhance the understanding of influenza.

Dr Hui's presentation was followed by that of Dr Piyarat Suntarattiwong, Infectious Disease Specialist, Queen Sirikit National Institute of Child Health, Thailand, on "Optimizing the treatment of influenza patients: Research priorities". Seasonal influenza is believed to cause 250 000–500 000 deaths each year, mostly from respiratory disease, including secondary bacterial pneumonia. The causes of death that are rare include myocarditis and encephalitis. Avian influenza is still endemic in the region and causes rare, but severe illness, typically with severe pneumonia and ARDS with multiple organ failure. Although evidence for effectiveness of oseltamivir exists, the high case fatality rate indicates that better case management is needed. Most patients with pandemic influenza H1N1 2009 experience mild upper respiratory infection symptoms, with fever, cough, sore throat, rhinorrhea, headache, myalgia and gastrointestinal symptoms including nausea, vomiting and diarrhoea. A minority develop rapidly progressive pneumonia and although this can affect previously healthy individuals, risk factors are identified including pregnancy, obesity and asthma. There is some overlap with risk factors for severe illness in seasonal influenza, which has been described in research undertaken in Thailand. Poor outcomes for pandemic influenza H1N1 2009 are also associated with late presentation and late treatment. A study in Argentina also described *S. Pneumoniae* to be associated with death and hospitalization in pH1N1. Early diagnosis would be facilitated by use or "bedside" rapid diagnostic tests, which currently show insufficient sensitivity and specificity and so are not recommended for pandemic influenza. There is also a need for development of new therapeutic agents, including parenteral drugs. Pharmacokinetic studies in pregnant women and children would help with rationalization of dosage regimes.

Stream 5: Promoting the use and application of modern public health tools

Thomas Abraham of the Journalism and Media Studies Centre, "Hong Kong SAR" delivered a presentation on "Risk Communication Experiences from the 2009 H1N1 Pandemic". Communication is as diverse a field as

medicine. Some commonly employed terms include risk communication, health communication, outbreak communication, advocacy, health promotion, social marketing and media relations. However, it is not always clear to everyone what these terms actually mean and how they are different. The CDC, United States, defines risk communication as communication in which, "typically the communicator wishes to provide the receiver with the expected type (good or bad) and magnitude (weak or strong) of effect from behaviour or an exposure". Typically, it is a discussion about an adverse outcome and the probability of that outcome occurring. Similarly, emergency communication has been defined as the effort by experts to provide information to help people to make the best possible decisions about their well-being within nearly impossible time constraints". Typically, it is an "information providing and sharing exercise" about events that might possibly happen, and not an exercise in persuasion. Because risks are uncertain, risk communication is a dialogue with the public and with policy-makers, it is not about experts telling the public what will happen and what they must do. Advocacy is typically aimed at influencing policy. In the inter-pandemic period, risk communication mostly involved providing information about risk assessment to public and getting feedback on public views. Advocacy was required with policy-makers for better surveillance, vaccine development and behaviour change campaigns directed at the public focused on hand hygiene. After the pandemic began, outbreak communication focused on providing rapid information to the public and policy-makers about what was known and what was unknown, as well as on directing specific advice to the public. Behaviour change and social marketing focused on promoting vaccines and protective behaviours. At a meeting recently convened by WHO to look at risk communication during the pandemic, the following observations were highlighted. Risks from emerging infectious diseases are poorly understood, making risk assessment and communication very difficult. Communication was undertaken by a variety of persons: government leaders, public health experts, journalists and members of the public, many of whom had no training. Communicating scientific uncertainty, both to the public, as well as to policy-makers is a key challenge. It was also noted that the pandemic that arrived was completely different from the pandemic that had been planned for, and that the planning process was more useful than the plans themselves. Also, in the beginning, the speed at which information was changing, and the need to change public guidance, was hard to cope with. With regard to media relations, understanding the social media and the way people accessed, used and circulated information was a priority.

Building relationships of trust between the media, public health communicators, and scientists during "peace time" was also important to facilitate a dialogue between scientists and the media on scientific uncertainty. It was also evident that journalists needed access to experts and that some journalists and news organizations would always sensationalize and pre-judge stories. The best strategy to limit this is perhaps relationship building. On observing how the pandemic was handled politically, it was apparent that governments were judged by how they handled events like a pandemic, but that many persisted in seeing the pandemic as an "imported problem" that could be prevented through border controls. Important subjects for research on risk communications include studies on communicating scientific uncertainty to the public and studies on how public accesses, uses, interprets and contributes to social media. There is a need to conduct joint workshops with the media, health communicators and scientists to build understanding and trust.

A presentation, "Risk communication**:** research needs in light of experiences and challenges – India" was made by Dr Reuben Samuels. India demonstrated advance planning by establishing a command and coordination structure for risk communication. Communications were also incorporated into training for rapid response teams. A Joint Monitoring Group (JMG) comprising line ministries and partners was established to approve communication strategies and messages prepared by its media subgroup. Even before the pandemic was declared, a risk communication strategy and products had been prepared for avian influenza H5N1, which provided a "jumpstart". Proactive communication was initiated by the Union Ministry of Health and Family Welfare, including travel advisories, "dos" and "don'ts" and information on H1N1 symptoms, screening centres, and home isolation. Daily media briefings started immediately and media campaigns in print and electronic media were subsequently undertaken. Transparency was promoted through daily press conferences and by issuing regular press releases. Situation updates and guidelines were posted on the websites of the Ministries of Health and Family Welfare, Animal Husbandry and Information and Broadcasting. A national media workshop was also held to share information on pandemic influenza and to connect the media to key information sources. In order to build trust, messages and responses were reviewed and revised periodically, and guidelines were prepared to address public concerns. To allay fears, key officials and experts issued periodic statements and a "24x7" helpline was established. However, despite best efforts, there was panic in some cities and an initial media

frenzy that was not immediately addressed due to a delay in rolling out the mass media campaign. In addition, although this campaign created awareness, it did not appear to impact on care-seeking behaviour. There was also confusion over policies for school closure. Research could usefully include an in-depth analysis of national, state and local media reports, for their tone, accuracy and sourcing – especially in cities where panic was evident. Studies would also help to map out availability and accessibility of information, describe the clarity and adequacy of information given to the media and document levels of understanding of media persons. The outcomes would then help to tailor need-based media strategies and enable more effective media engagement. Knowledge, attitude and practice (KAP) studies involving cities with many cases as compared with those with few cases would improve understanding on precautionary measures, respiratory etiquette, symptoms and care-seeking behaviour. The outcomes of these studies will help in assessing the impact of the media and mass media campaigns, and the reach and credibility of the channels of communication. It appeared that inter-personal communication (IPC) worked well in parts of Maharashtra state, although overall, IPC remained weak. Studies should also examine the existing community mobilization networks to identify best practices and consider how to strengthen and utilize them for pandemic risk communication.

A presentation entitled "The development and application of modern public health tools: Thailand experience" was then delivered by Thitipong Yingyong, Bureau of Epidemiology, Ministry of Public Health, Thailand. Influenza surveillance in Thailand has five components: (i) National disease surveillance (R506); (ii) Severe pneumonia/pneumonia deaths; (iii) Sentinel surveillance; (iv) Event surveillance (outbreak notification); and (v) ILI surveillance. The National Disease Surveillance System has operated nationwide since 1973 and collects data based on syndromic case definitions (utilizing ICD10) and some confirmed cases. Epidemiological and clinical data are collected for each case, initially on paper, but submitted via the Internet. Data are collated by time, place and person and presented as graphs, tables and maps. If abnormal patterns of data are detected, a detailed epidemiological study may be undertaken, including collection of additional clinical and laboratory data. Although the system is well established and is geographically representative, there is some delay in reporting because of inconsistency of case definitions used by providers. Pneumonia surveillance was established during the outbreak of avian influenza and has been operating since 2003. Detailed epidemiological and clinical data are collected on each case and submitted within 24 hours

through either a web-based application or facsimile or electronic-mail. Although reporting is timely and data can be integrated into the GIS, the system is more labour intensive. The sentinel system was primarily established to facilitate virological surveillance. Data are collected from 24 geographically representative areas across the country by two departments (the National Institute of Health since 2004 and the Bureau of Epidemiology since 2009). The system is relatively costly and labour-intensive; therefore sustainability is an issue. The system of surveillance and rapid response teams extends from central to regional, provincial and district levels, including even some municipalities and subdistricts. Teams have surveillance, notification, investigation and control responsibilities and are required to notify any outbreaks occurring in their catchment area by email, telephone, mobile, or facsimile. The ILI surveillance was established in July 2009 after the onset of the pandemic. Aggregate data are collected by more than 900 hospitals nationwide every day, allowing trends of ILI and any admitted pneumonia to be followed. The system is used to collect the number of visits to OPD and in-patient department (IPD) each day, and the corresponding numbers of ILI cases and pneumonia cases admitted each day. The cases were defined as patients running a temperature $\geq 38^0$ C or having a history of fever in the five days preceeding their visits to a clinic with symptoms of cough or sore throat. Alternatively, health-care facilities collected data on cases by using ICD10 code J00, 029, 069, 09, 10 and 11. Pneumonia cases were those of patients diagnosed by a doctor and admitted to IPD, or cases coded similarly by using ICD10. These four categories of aggregated data were reported through a web-based application and through an SMS notification. The system allowed real time reporting and feedback, and data were considered generally useful for local planning. However, there was some duplication of efforts with routine surveillance and with the requirement for daily as well as weekly reporting. Greater efforts were also needed for programme development, maintenance and monitoring, and data interpretation was sometimes problematic. During the pandemic, data from all these five streams was fed to a central "influenza" group that reported to the director of the bureau and to policy-makers; this resulted in recommendations for action and regular public announcements on the evolving situation. The ideal model for a national or regional influenza surveillance system would be one that is able to characterize influenza seasonality and activity, estimate the disease burden and allow early detection or signals of an influenza outbreak. It should be simple, adaptable and user-friendly, and it should not require complicated analysis and interpretation. Also, it should be inexpensive to develop and maintain.

5. Group work and discussions

A presentation on *"Update, implementation process and aims of stream-specific discussion"* was made by Dr John Tam who underscored the need for developing a global influenza research framework around five major public health research streams. The implementation plan determined after the initial global meeting in November 2009 consists of the following components: (i) Development of regional-level research agenda(s) for influenza; (ii) An annual "update" meeting for the agenda; (iii) Provision of information and research resources; and (iv) Establishment of a mechanism to monitor gaps in research. There are a number of important cross-cutting issues, including surveillance, diagnostics, modelling and risk communication. For example surveillance features in Stream 1 (surveillance in animals for circulating viruses); Stream 2 (surveillance for transmission during outbreaks); Stream 3 (disease burden estimations and vaccine strain selection); Stream 4 (surveillance to identify risk groups); and Stream 5 (analysis of surveillance data for modelling and communication of surveillance results). Developing common platforms and technology would help to integrate methodology, facilitate data analysis, and similar datasets that could be utilized for different areas from fieldwork to modelling. Similarly, diagnostics would benefit from an integrated approach. This would facilitate collection and analysis of specimen under different field conditions, which would also help characterization of antiviral resistance, and novel influenza subtypes. Advocacy for the research agenda, including establishing a dialogue with research institutes and funding agencies is required. It has been proposed that a research monitoring group should be established together with a number of research monitoring centres on specific identified research topics.

An introduction was then given on the specific arrangements for the breakout sessions (group work) for the five different research streams. The aim of the session was to define a comprehensive list of influenza research topics and priority activities for the SEA Region. Expected outputs were therefore a list of priority influenza research topics for the SEA Region and agreement on a clear way to take this work forward. Each working group was to consider as a starting point the list(s) agreed for each stream at the global consultation held in November 2009. If the group agreed with this list, then no changes would be required, but if any important issue or topic were to be identified, then it was to be added. The mechanism to be employed for prioritization was the one developed by the Council on

Health Research for Development (COHRED). The advantages of employing an explicit methodology for prioritization are that it provides some structure to the decision-making process, ensures that the most relevant and important factors are taken into account and that by using an established method transparency, acceptability and accountability are achieved. The COHRED method assumes that there is a list of research topics that require prioritization and then asks a group of experts to give each subject a score based on four categories, namely appropriateness: (*Should we do it?*); relevance: (*Why we should do it?*); the chance of success: (*Can we do it?*); and the impact of the research outcome: (*What do stakeholders get out of it?*). In addition, all groups would be asked to brainstorm on ways in which a regional public health research agenda could be advanced and implemented.

Day 3 commenced with feedback from the five working groups. For each group (and corresponding research stream), the five specific research topics that were given the highest priority are listed in Annex 3. The complete list of research topics defined at global level (from which these lists of five SEARO priorities are selected) is available at: http://www.who.int/csr/disease/influenza/2010_04_29_global_influenza_research_agenda_version_01_en

Deliberations of the working groups were based on participants' understanding of published research, country experiences and presentations made at the plenary sessions. There was consensus across all working groups that the global public health research agenda for influenza should cover all aspects of regional research needs, with some minor additions. In general, these additions could be made by redrafting the text of the existing "global" list of research topics rather than adding completely new subjects. However, country-specific research needs may vary from country to country. Therefore, it will be necessary to consider development of different research agendas at national level. Coordination and establishment of partnerships between stakeholders is a high priority (for example, partnership between public health and animal health is vital for research at the human-animal interface). Capacity building to establish and/or strengthen research infrastructure is an urgent requirement. It will also be desirable to consider the feasibility of undertaking some specific research topics in different settings before funding regional research activities or holding training programmes. Advocacy for influenza research at country level is important. Resource mobilization for implementation of identified research priorities is also critical.

The current low capacity in countries to undertake some specific types of research (for example infectious disease modelling) was noted. This perhaps suggests a need to use research to assess how techniques like modelling can help us. It also appears that improved advocacy is needed to inform public health decision-makers on the potential utility of some specific types of research.

A proposal was also put forth that research be undertaken, and tools developed for other diseases (e.g. TB, HIV/AIDS) should be harnessed rather than new tools developed for flu. One example might be research undertaken on the most effective modalities for risk communication in a particular socio-cultural context.

In terms of the general approach of research, it was suggested that there should be a focus on research for programmatic purposes rather than for pure science. Similarly, operational research should be a priority.

Support should also be provided for publication of existing research.

It was also suggested that it may be more pragmatic to consider a research agenda that distinguishes between development of research capacities for seasonal, pandemic and avian influenza – reflecting the different degrees in which countries of the SEA Region are affected.

6. Public health research agenda for influenza: perspectives of partners

A presentation, "*Food and Agriculture Organization of the United Nations (FAO) perspective: Activities and input to influenza research meeting"* was delivered by Dr David Castellan, FAO Regional Veterinary Epidemiologist. The core activities of FAO include agriculture, economic and social development, fisheries and aquaculture, forestry and technical cooperation. Its work is also contained within key programmes, including an initiative on soaring food prices, development of emergency prevention systems and Global Information and Early Warning Systems (GLEWS), and support to emergency response, food security, agricultural development and capacity building. Its strategy for infectious disease control includes elements for prevention to deal with root causes and drivers, enhancing emergency response to facilitate containment, promotion of multisectoral and

multidisciplinary collaboration and research to identify drivers, transmission routes and identify trends. The expected outputs of regional coordination include improved knowledge of the epidemiology of animal influenza, and its significance with regard to the human-animal health interface, improved policy to improve disease control and prevention, functional laboratory and epidemiology networks and strengthened capacities for animal and public health emergencies. Collaboration on research at the wildlife interface includes HPAI wildbird studies conducted in Bangladesh, China, India, Mongolia, Thailand, research on bats in Thailand and the Philippines, environmental and ecological research in Thailand, China and Bangladesh, cross-border studies for disease prevention and control and studies on market chain analysis. Support has also been provided for capacity building in veterinary field epidemiology and for village animal health workers. Integration of influenza research should involve integration of knowledge on all influenzas in wildlife, domestic animals and the environment. It should also aim to facilitate sharing of information regionally and sub-regionally (in the Indo-Gangetic Plain and the Greater Mekong Sub-basin). The building and linking of research should build on disciplinary and sector strengths.

Dr Renu Lal, CDC Influenza Coordinator, India, then delivered a presentation on the *"Indo-US CDC Collaborative Influenza Programme"*. Confronting emerging infectious disease threats requires an integrated and holistic approach, including preparedness and communication, surveillance and detection, response and containment. All these activities should be underpinned by research. The work undertaken by the influenza division of the CDC, Atlanta, United States of America, includes studies on disease burden, vaccine effectiveness, antiviral drugs, non-pharmaceutical interventions and the animal-human interface. At present, collaborative work in India includes cooperative agreements for influenza surveillance (with ICMR in 2004), for disease burden estimation (with National Institute of Virology, in 2008) and on influenza vaccine effectiveness (with UAB/AIIMS in 2008). Work on the estimation of influenza disease burden in India consists of a prospective population-based observational study in rural India to determine incidence, assess the clinical spectrum of those hospitalized with influenza, undertake indirect estimation of influenza-related mortality and evaluate risk factors for severe outcomes. It is evident that influenza accounts for >10% of severe medically-attended cases and there is a need to assess the role of other respiratory pathogens. A prospective, household randomized, controlled, observer-blinded influenza

vaccine study has begun in rural villages in India that aims to estimate the effectiveness of influenza vaccination in children, as well as the herd immunity effects. Enrolment and immunization rates appear to be high, reflecting a high community acceptance.

A presentation was then delivered by Itsuo Shimohira, OIE Regional Representative for Asia and the Pacific on "HPAI, the *OIE control project in Asia"*. Activities of OIE include improvement of animal health information systems and communication, standardization of registration for veterinary medicinal products, prevention and control of HPAI, prevention and control of emerging/trans-boundary animal diseases, prevention and control of aquatic animal diseases, prevention and control of BSE and other transmissible spongioform encephalopathies and support for WTO-SPS Agreement, including risk analysis. The OIE has supported a number of HPAI control and prevention projects in Asia. The HPAI has been continuously reported since 2003 with negative economic impacts and risks to animal and human health. An OIE project for HPAI control in South-East Asia conducted in 2006-2007 was followed by a second phase in 2008-2009 and supplemented by a parallel five-year project from 2008-2012. Support is also provided for capacity building in HPAI diagnosis and surveillance, including national workshops for RT PCR diagnosis and regional training courses for genetic analysis of HPAI. Support is also provided for renovation of laboratories and procurement of laboratory equipment and materials in Bangladesh, Bhutan, India, Mongolia, Nepal, Pakistan and Sri Lanka.

A presentation was then delivered by Dr Sonja Olsen from the International Emerging Infections Programme (IEIP) of the Thai MoPH – United States CDC Collaboration (TUC). The presentation focused on four areas: where did the emergence occurs; understanding seasonality in the tropics; rapid assessment of the severity; and prevention of childhood pneumonia through influenza vaccination. The threat of avian influenza A (H5N1) influenced expectations in that authorities concerned planned for the pandemic virus to emerge in birds, not swine. They also planned for the pandemic virus to emerge in South-East Asia, and not in North America. Importantly, they planned for the worst case scenario, keeping in mind the level of severity of the 1918 pandemic and not the 1968 pandemic. The emergence of the "swine flu" virus illustrates the need for good surveillance in both humans and animals. The previously accepted dogma about the seasonality of influenza in tropical countries was that it occurred at low levels, year-round. However, good knowledge of seasonality is important

because it has implications for timing of prevention efforts (e.g. vaccine) and it helps to put the emergence of new influenza into the proper context. Understanding the severity of illness in the recent pandemic was challenging for a number of reasons. One possible approach to deriving this information more quickly is the so-called "Sentinel City Approach". This involves taking a medium-sized city (500-750 000 people) and undertaking surveillance in all health-care establishments to determine the frequency of various outcomes in a period of time and determine the proportion of ILI and SARI deaths. Although data would not be strictly "representative", they would be valid. Additional problems with estimation of severity include the fact that access to health care varies widely, that deaths often at home are not recorded and that verbal autopsy data can be inaccurate and are often available in only relatively small areas. In addition, it may not be possible to generalize the sentinel approach, the selected site may not be representative of other areas in the country, the proportion of underlying diseases in a community may also vary and as influenza illness outbreaks are focal, communities may be affected differently.

Influenza has been shown to be an important cause of childhood pneumonia in Thailand, and there is an increasing case to be made for expanded paediatric influenza in developing countries. Firstly, children are at increased risk for pneumonia and other serious complications, which play an important role in propagating epidemics. Secondly, influenza is associated with at least 10% of those hospitalized with pneumonia as also with secondary complications such as bacterial pneumonia, otitis media and, fever admissions. In addition, there is a potential to establish "herd immunity" if vaccine coverage is sufficient; adoption of systematic vaccination may decrease health-care costs and indirect costs (lost work, school). Lastly, increased, constant vaccine demand could lower per-dose costs and help to stabilize global vaccine supply. Some key constraints are that global supply is currently limited and is mainly driven by demand from wealthy countries, there are technical limits to vaccine production (e.g. egg-based vaccines) and they currently have a relatively high cost as compared with EPI vaccines. There is also the requirement for annual vaccination and for two vaccinations in the first year for young children.

7. The way forward: options for implementation

A presentation was made by Ms Gina Samaan, on "A framework for public health research agenda for influenza in South-East Asia: the way forward". Implementation of the research framework will be contingent on further consultation within individual countries and identification of required technical, financial and support structures. For the SEA Region, the research framework should consider general system challenges. It was noted that the WHO Advisory Committee on Health Research (ACHR) and the WHO-SEARO meeting on research priorities in communicable diseases had identified the following issues: (i) Strengthening national health research systems; (ii) Allocating appropriate research funding; (iii) Establishing mechanisms to develop an interface between researchers and policy-makers to facilitate translation of research into policy; and (iv) Building institutional capacity for the conduct of research in communicable diseases.

A possible way forward could be the formation of a small number of working groups based on research streams and priorities. These working groups would use their institutional networks and collaboration to build momentum for researchers to undertake various research opportunities in influenza, maximize collaboration and sharing of research findings, and assist in coordinating and monitoring the progress in respect of research priorities.

In order to identify and harness the resources required for the conduct of various types of research, a possible approach would be to establish a dialogue between WHO, donors and Member States to identify resources, map existing technical resources such as laboratory support, skills in research design or data analysis available in the Region, and then to formulate mechanisms for collaboration that ensure equitable outcomes. This would require a solid understanding of the roles and responsibilities of different parties.

Furthermore, assessing and addressing institutional strengthening to enable implementation of the research framework could include: enhancing skills in research design or conduct and communication of research outputs. Member States should consider conducting an assessment of existing capacities to determine where gaps exist. Framework implementation will need strong knowledge management. This would help to ensure that research activities are not duplicated, that research is

designed in accordance with international standards and ethical practice, that research outputs actually influence policy and that research addresses the needs of specific target groups (e.g. the poor or the vulnerable). Knowledge management could be facilitated by WHO, together with the different working groups. The progress in implementing the framework should be evaluated and adjusted at a follow-up meeting to be conducted within two years after endorsement of the SEA Region Research Framework.

8. Conclusions and recommendations

Influenza, in its pandemic, zoonotic and seasonal epidemic forms, is a formidable public health threat. Seasonal influenza causes an estimated 250 000 to 500 000 deaths worldwide each year. Zoonotic infection by avian influenza remains a threat to human and animal species. The pandemic (H1N1) 2009 virus emerged, spread quickly and caused more than 18000 deaths by the time it was over.

Lessons from seasonal, highly pathogenic avian (H5N1) and pandemic (H1N1) 2009 influenza indicate that there are gaps in knowledge and evidence for decision-making on appropriate and timely interventions critical to reduce risk, limit spread, and minimize the impact of influenza.

Recognizing the public health challenge influenza poses, and the critical role of research in generating evidence, the participants of the meeting appreciated the initiative taken by WHO to develop a public health research agenda for influenza that would provide an evidence-based platform for policy decisions and public health practices.

Recommendations

In view of the experiences, lessons and best practices, as well as the challenges and gaps in combating influenza, the following recommendations were made:

(A) For Member States

- Assess the existing research capacity and needs in order to identify areas that require strengthening.

- Consider building research capacity as an integral part of planning and development of national health programmes/ systems.
- Develop a mechanism to ensure that research outcomes are translated into policy and practice.
- Establish a public health research agenda for influenza appropriate to the regional and national contexts, and identify priority areas of work for the short, medium and long term, as well as mechanisms to ensure dissemination of research findings.
- Where relevant, consider partnerships within and outside countries, and with institutions of excellence (including academia) that support influenza research activities.

(B) For WHO

- Finalize the Regional Framework for Public Health Research on Influenza.
- Support Member States to develop a national influenza research agenda.
- Support Member States in mapping the research capacity for influenza and other infectious diseases.
- Advocate and facilitate networking and partnerships among stakeholders, including government, academia and research institutions within the Region and beyond, in implementation of the public health research for influenza.
- Facilitate coordination of intercountry support for conducting research in the Region, including development of generic protocols/tools, and resource mobilization, as necessary.
- Consider organizing a regional conference on public health research.

(C) For partner organizations

- Support bilateral and multilateral activities to strengthen national and regional capacity for influenza research, including for advocacy and resource mobilization.
- Promote technical cooperation between national, regional and international institutions to strengthen capacity for influenza research.
- Support research networks and strengthen collaboration to enhance public health research for influenza.
- Support and enhance efforts for dissemination and application of research findings in public health.

9. Closing session

In his keynote concluding remarks, Dr V.M. Katoch, Secretary, Department of Health Research and Director-General, Indian Council of Medical Research, New Delhi, India, underscored the critical role of research in generating evidence for public health policy decision-making. He noted that it was imperative to promote sharing of experiences and networking of researchers and research institutions. In this perspective, he highlighted, that the forum provided an opportunity for further collaboration and networking within the Region and beyond. Dr Katoch expressed his appreciation to the organizers and participants for according due importance to this need.

Dr J.P. Narain, Director, Department of Communicable Disease Control, WHO-SEARO provided the closing remarks. He noted that the meeting had been very successful and had provided a useful forum for discussion. He pointed out that the recommendations would be further revised based on the discussions of the meeting and will be followed up for implementation. A meeting report will also be produced along with the regional framework. He emphasized that a similar framework may need to be developed by every country in the SEA Region, and that countries may therefore wish to consider holding similar national-level meetings. The meeting was then declared closed.

Annex 1

Message from Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia Region

Delivered by Dr Jai P. Narain,
Director, Department of Communicable Diseases

Ladies and gentlemen,

I am pleased to welcome you all to the Regional Consultation on Public Health Research Agenda for Influenza. I would also like to take this opportunity to convey greetings and best wishes from the World Health Organization to all at this important gathering.

I also express my appreciation and sincere thanks to all of you for sparing time to participate at this consultative meeting.

Ladies and gentlemen,

Experiences and lessons learned to date demonstrate that the microbial world is dynamic, unpredictable and fast changing. Pathogens emerge on a regular basis and are capable of starting a pandemic, with serious implications for global health security.

The emergence and rapid spread of Severe Acute Respiratory Syndrome (SARS), the first pandemic of the Twenty-first century, is a clear example of this phenomenon.

Frequent and massive outbreaks of highly pathogenic avian influenza A (H5N1) have also occurred in poultry since 2003 and caused tremendous economic loss in Asia and beyond. The threat of high morbidity and mortality from a human pandemic caused by highly pathogenic avian influenza A (H5N1) or a closely-related strain therefore remains a source of serious concern.

Every year, seasonal influenza continues to cause millions of infections in humans and claims many thousands of lives around the world.

Respected participants, ladies and gentlemen,

In 2009, an outbreak of influenza started in the western hemisphere and spread internationally in a short period of time. The outbreak was subsequently confirmed as having been caused by a new strain of influenza A (H1N1). This fact once again demonstrated the capacity of infectious pathogens to emerge, adapt and spread fast.

On 25 April 2009, the Director-General of WHO declared the world's first-ever Public Health Emergency of International Concern as detailed in the provisions in the International Health Regulations 2005, resulting in the formal declaration of an influenza pandemic.

WHO provided timely guidance and support to strengthen the efforts of Member States in responding to this public health emergency.

The global response to the pandemic was swift, well coordinated and highly transparent, and it adapted to the evolving nature of the threat. As a result public health interventions were implemented by many Member States.

I am particularly happy to note that the response of Member States of the WHO South-East Asia Region have been proactive, transparent and well coordinated.

Our Member States have done a commendable job. Their work also provides important lessons for further strengthening our collaboration in combating public health threats irrespective of their source or origin.

Ladies and gentlemen,

Research generates critical information for public health action. It provides evidence-based knowledge for policy decisions and ensures application of effective strategies and interventions. Research must be need-driven and primarily address identified gaps and public health priorities of countries concerned. Countries must take the lead in the process including identifying and prioritizing their research needs; and undertaking and applying the research results. For research to be effective, it must result in a high-quality product.

Recognizing the important role of research in ensuring public health security, we have undertaken several initiatives to support research capacity in the Region. In March 2009, WHO organized a consultative meeting on research priorities in

communicable diseases. Likewise, in March 2010, WHO organized a regional conference on epidemiology, which among others, recommended strengthening of research in the Region, including establishing regional networks to enable sharing of expertise and information. Furthermore, WHO encourages national research through grants for operational research in tropical diseases or neglected diseases of poverty. It also supports capacity building including strengthening of epidemiological and research skills.

Respected participants, ladies and gentlemen,

It is true that evidence-based interventions applied in a timely fashion play a critical role in reducing the risk and impact of influenza, thereby saving lives, reducing health-care costs and mitigating societal disruption. However, we also know that there is insufficient knowledge and evidence available to decision-makers and health authorities on all the interventions that are critical to reduce risk, limit spread and minimize the impact of influenza in its seasonal, zoonotic and pandemic forms.

Therefore, there is a clear need to systematically map out what is known in these areas and to identify gaps in knowledge. Where gaps exist, it is imperative that all of us, including scientists, public health managers, policy decision-makers and technical and funding partners work together to address these gaps.

WHO acknowledges the current gaps, but has already begun to take important steps to address these issues by undertaking a consultation with technical experts, public health decision-makers and international research institutions, as it is important to define the Public Health Research Agenda for Influenza.

As part of this process, in November 2009, a global consultation was organized in Geneva, Switzerland. The meeting reiterated the importance of developing a global influenza research framework. It also requested WHO to organize a broader consultative process, to identify knowledge gaps and research needs for different regions around the world. Research findings from locally-identified priority research areas could provide evidence to support more regionally appropriate public health decision-making to control influenza in a variety of political, socioeconomic and cultural settings.

Underscoring the critical role of research for public health action, the South-East Asia Advisory Committee on Health Research (ACHR) in July 2009 recommended strengthening of national research capacities including developing the required infrastructure and expertise, and promoting collaboration and

networking among research institutions and centres of excellence. The ACHR also called for promoting a multisectoral approach, including engagement of experts in animal and public health, economists, sociology and behavioural sciences. Furthermore, it requested WHO to support countries to identify research priorities and strengthen research management. Accordingly, WHO organized a regional consultation to identify research priorities in communicable diseases; convened a regional conference on epidemiology; and established a Regional Task Force on Avian Influenza Research that identified the need for research on epidemiological, clinical, virological, vaccines and diagnostic tools, as well as on the social, behavioural and economic aspects of influenza.

Distinguished participants,

This consultation has been organized to share experiences and lessons among stakeholders; and to develop a regional consensus on priority areas for public health research on influenza. I have no doubt that it will be an important step in facilitating greater collaboration on research, and in strengthening knowledge management, including dissemination and application of research outputs.

Once again, I thank all participants from countries, and from UN and partner agencies for sparing their valuable time to attend this important consultation.

Ladies and gentlemen, I wish the meeting all success in its deliberations.

Thank you.

Annex 2

Agenda

Day 1, 18 August 2010

08:30–10.30	Opening Session
	RD's message by Dr Jai P. Narain, Director, CDS
	Opening remarks by Dr Nahoko Shindo, Global Influenza Programme, WHO/HQ
	Objectives and Introduction of Participants; Dr Chusak Prasittisuk, CDC/SEARO
	Nomination of Chairperson and Rapporteur
	Announcements by Dr Madhu Ghimire, DSE
	Group Photograph
10:30–12:30	Plenary Session Chair: Dr Shiv Lal
	Influenza in South East Asia Region and Research Perspectives; Dr Jai P. Narain
	Public health knowledge gaps and needs in influenza pandemics: the A (H1N1) 2009 experience; Dr Nikki Shindo
	Development of the WHO Research Agenda for Influenza; Dr John S. Tam
	Global pandemic (H1N1) 2009 surveillance: what worked and what didn't; Dr Nikki Shindo
	Discussion

3:30–15.30	Panel Discussion Moderator: Dr Pratap Singhasivanon
	Reducing the risk of emergence of pandemic influenza (Stream 1) Dr Rodney Hoff, Dr Trihono & Dr S.C Dubey
	Limiting the spread of pandemic, zoonotic and seasonal epidemic influenz (Stream 2)
	Lab surveillance of pandemic H1N1 virus: genomic evolution and monitoring of variants.
	Speaker: Dr Rebecca Garten
	Research priorities for limiting the spread of influenza Speakers: Dr A.C Mishra, Dr Iain A Wright & Dr Ron Waldman
16:30–17:00	Minimizing impact of pandemic, zoonotic and seasonal epidemic influenza (Stream 3) Dr Supamit Chunsuttiwat & Dr Yoshihiro Sakoda
	Open Discussion

Day 2, 19 August 2010

09:00–11:00	Panel Discussion Moderator: Prof N.K. Ganguly
	Optimizing the treatment of patients (Stream 4)
	Clinical management of severe or progressive influenza form seasonal to pandemic influenza; Dr David Hui
	Research priorities for optimizing treatment if patients; Dr J C Suri & Dr Piyarat Suntarattiwong
	Promoting the use and application of modern public health tools (Stream 5)
	Risk communication: experiences gained from the current H1N1 pandemic; Mr Thomas Abraham
	Research for promoting use and application of tools; Dr Thitipong Yingyong & Ms Shamila Sharma

11:30–12:30	Plenary Chair: Dr Arjun Karki
	Implementation of WHO Public Health Research Agenda for Influenza; Dr John S. Tam
	Introduction of Research Streams for break-out sessions; Dr Richard Brown & Gina Samaan
13:30–17.30	Break-out session: research priorities
	Group work by research streams (Stream leaders)

Day 3, 20 August 2010

09:00–12:30	Plenary: Research priorities and way forward Moderator: Dr Agus Purwadianto
	Way Forward – Ms Gina Samaan
	Feedback from the group work
	Global pandemic (H1N1) 2009: impact on directions on influenza research; Dr Sonja Olsen
	Discussion
13:30–15:30	Plenary Chair: Dr Shiv Lal
	Partnerships for Influenza research; Dr Renu Lal
	Public Health Research Agenda for Influenza: perspectives of partners; Dr Itsuo Shimohira; Dr David Castellan; and Dr Sonja Olsen
	Conclusions and Recommendations
	Closing remarks –
	Dr V.M. Katoch, Secretary (Dept. of Health Research) and DG-ICMR
	Dr Jai P. Narain

Annex 3

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Annex 4

Top five research priorities identified through group work for each 'stream'

Reducing the risk of emergence of pandemic influenza (Stream 1)

(1) Develop diagnostic tests to support joint animal and human health surveillance systems.

(2) Study the environmental and animal management / husbandry-specific factors associated with zoonotic and pandemic potential.

(3) Investigate and develop animal intervention strategies (e.g. culling, vaccination, biosecurity) under different epidemiological and field conditions that can reduce risk of zoonotic infection.

(4) Investigate potential modes of transmission in human infection with animal viruses

(5) Conduct operational research to integrate animal and human health strategies for prevention

Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza (Stream 2)

(1) Study the transmission dynamics of influenza and the factors that influence infectivity in different settings and associated activities

(2) Examine the usage of surveillance data in assessing the needs and effectiveness of public health interventions in different situations such as the identification of emerging of novel viruses; determining the time for initiation of public health interventions; selection of appropriate public health interventions; evaluate effectiveness of interventions and guiding decision-making regarding cessation of public health interventions

(3) Conduct studies to understand the seasonality of influenza virus infection in different regions and its implication in global spread of epidemic and pandemic influenza

(4) Examine the role of host factors such as age, pre-existing immunity, antiviral treatment and prophylaxis, and vaccination in modulating influenza transmission

(5) Investigate the relative importance of droplet, contact and airborne transmission in seasonal and pandemic influenza

Minimizing the impact of pandemic, zoonotic and seasonal influenza (Stream 3)

(1) Study the role of social science research such as its involvement in establishing social, ethical and legal standards in public health policy application; the public perception of influenza and its impact on societies particularly in under-resourced populations.

(2) Determine best approaches for applying influenza disease burden data, coupled with cost-effectiveness analyses, to inform development or expansion of influenza control programs in the context of competing priorities.

(3) Assess social determinants of health under different epidemiological settings (such as socially disadvantaged, indigenous populations etc.) and evaluation of the social impact (such as disruptions in commerce, health care systems, public safety, social and political fabrics etc.) of influenza outbreaks and pandemics based on such determinants.

(4) Evaluate the influenza vaccine preventable disease burden and the potential impact of immunization programs (e.g. vaccine demonstration projects).

(5) Establish the economic burden of seasonal and pandemic influenza in conjunction with epidemiological studies.

Optimizing the treatment of patients (Stream 4)

(1) Define the clinical spectrum and natural history of human disease, including risk factors (such as comorbidities and demographic factors) and prognostic markers for severe disease and its complications.

(2) Identify clinical markers and develop point-of-care tools for the prognosis and management of influenza disease.

(3) Conduct studies to develop best practices that provide protection of health care workers and other care-givers in different health care and resource settings.

(4) Develop rapid, reliable, affordable point-of-care diagnostic tests for influenza virus

Promoting the use and application of modern public health tools (Stream 5)

(1) Examine the timeliness and quality of data needs required for early detection of disease from local to district, regional, national and global levels for the respective stakeholders.

(2) Conduct studies to identify, appraise, exploit and adapt modern technologies for early detection of epidemic and pandemic influenza as well as their application in surveillance at the human-animal interface.

(3) Conduct studies to improve model accuracy and realism, and incorporation of emergent interdisciplinary advances.

(4) Conduct studies to review international evidence and experience on health and health crisis communication from relevant disciplines, such as behavioural and social sciences, media studies, marketing etc. to gather and organize knowledge, as well as to stimulate new studies in areas where gaps have been identified to support evidence-based practice in strategic communication.

(5) Identify, develop and evaluate communication tools and methods that can rapidly, accurately and over time for the assessment and monitoring of knowledge, attitudes, beliefs and practices in different population groups, to guide communication efforts.

A Regional Meeting on Public Health Research Agenda for Influenza was organized in SEARO, New Delhi from 18-20 August 2010 as a follow-up to the Global Consultation held in Geneva from 17-20 November 2009. The objectives of the meeting were to share experiences and lessons, identify research priorities and define mechanisms for implementation of the research agenda. The overall goal was to promote research and generate evidence needed to strengthen public health guidance and bolster actions essential for limiting the impact of pandemic, zoonotic and seasonal influenza on individuals and populations. The report outlines experiences and lessons learnt from seasonal, highly pathogenic avian (H5N1) and pandemic (H1N1) 2009 influenza, and lists the research priorities and recommendations for strengthening the public health research agenda for influenza.

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