



PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA

One framework. Five streams. Sharing solutions.

REPORT OF THE FIRST GLOBAL CONSULTATION:

WHO PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA

**17-20 NOVEMBER 2009,
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A. EXECUTIVE SUMMARY

WHO convened the first global consultation on a *Public Health Research Agenda for Influenza* from 17 to 20 November 2009. The consultation brought together over 90 public health decision makers, academic and clinical investigators, representatives from donors/funding organizations and other key stakeholders from 35 countries. The aim of the consultation was to review the draft *Public Health Research Agenda for Influenza* proposed by WHO and to facilitate its implementation.

The first day, organized as a plenary session, set the scene and provided background information on the draft Research Agenda and the current state of knowledge for each of the research areas or 'streams':

- Stream 1. Reducing the risk of emergence of pandemic influenza
- Stream 2. Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza
- Stream 3. Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza
- Stream 4. Optimizing the treatment of patients
- Stream 5. Promoting the development and application of modern public health tools

The second and third days of the consultation were structured as five stream-specific breakout discussion groups during which participants reviewed the proposed organization, content, rationale and global public health importance of the stream; set out the key public health needs related to their stream during both pandemic and inter-pandemic periods (including both seasonal and zoonotic influenza infections) and proposed how implementation and ongoing improvement of the Research Agenda might be accomplished. The groups' findings and recommendations were presented on the final day of the consultation.

Participants were highly supportive of the need for and implementation of a *WHO Public Health Research Agenda for Influenza*. There was general agreement that the organization of the document into five 'research streams' was useful; however, it was noted that research topics relating to surveillance, diagnostics, modelling and risk communications are shared topics or tools to the different research streams as outlined in the agenda.

There was general agreement that the implementation of the *WHO Public Health Research Agenda* will require engagement with multiple partners and stakeholders such as the WHO Regional Offices, Member States, external research institutes, non-governmental organizations and donor/funding agencies. Consultation with WHO Regional Offices and individual countries can refine concepts and strategies, identify regional and local knowledge gaps and their priorities in meeting immediate needs for public health decision making. A concerted effort between the various global and regional stakeholders will minimize unnecessary duplication of efforts and lead to research outputs relevant at global, regional and national levels. However, effective and multi-pronged communication strategies to build advocacy for the agenda will be needed to promote the Research Agenda taking into account these different audiences.

All participants stressed that finalization of the agenda and its implementation should occur as rapidly as possible and utilize whatever interagency collaboration at the international level is needed. It was also recognized that implementation would be an ongoing process spanning years and based on both resource availability and scientific advances.



B. BACKGROUND

Appropriate public health measures to decrease the risk and impact of influenza can save large numbers of lives, reduce health costs and economic loss and mitigate potential societal disruption. However, insufficient knowledge in many areas has hampered efforts to more effectively plan for and address pandemic influenza as well as zoonotic and seasonal influenza epidemics. For example, national public health authorities have grappled with questions such as the need to stockpile masks for community use or to close schools in the event of a pandemic and how best to control and manage rumours and misinformation that can undermine efforts to control influenza. Answers to these and other complex questions require information about transmission of influenza, the efficacy, feasibility and cost-effectiveness of various measures as well as understanding factors that influence the beliefs and behaviours of people. Moreover, advances in knowledge regarding many fundamental aspects of influenza infection are required to improve public health responses, so that input is needed from an array of disciplines such as virology, clinical and laboratory medicine, pharmacology, immunology, epidemiology, anthropology, sociology, health economics and mathematical modelling.

A robust and multidisciplinary scientific knowledge base, therefore, is an essential foundation for modern public health practices and policy development related to influenza control. Despite these needs, the development of overarching global public health Research Agenda for influenza has not been evident in order to fill knowledge gaps and identify areas where research is needed urgently. Moreover, international coordination has been lacking to prioritize and facilitate the funding and implementation of such an agenda.

Influenza has not traditionally been recognized as a public health priority in some regions, particularly in countries with competing health needs. However, this is changing due to pandemic influenza A (H1N1) 2009 and the ongoing threat of highly pathogenic avian influenza and other animal influenza viruses. Although the development of public health Research Agenda must be underpinned by *all areas of medical science* from basic research to clinical work, applied science and operational research are areas of particular interest to public health decision-makers, especially those in less resourced countries. Research of this nature can help lead to improvements in disease surveillance, laboratory diagnosis, infection control, clinical care and management including antimicrobial drugs and vaccines. In particular, public health officials and stakeholders at decision-making and field levels must make a concerted effort to orient global Research Agenda for influenza in a direction that can lead to greater and more equitable access to effective interventions for the poor and other vulnerable populations.

The A(H1N1) 2009 pandemic and implications for research

The emergence of the pandemic influenza A (H1N1) 2009 virus and its subsequent spread highlighted many areas in which scientific information is lacking. The identification of a novel virus of swine origin prompted questions about ongoing transmission in pigs and the possible need for animal control measures as have been used to reduce the spread of highly pathogenic avian influenza A (H5N1). Questions also arose about the severity of the pandemic in affected persons, populations and countries. Some relevant parameters, such as the case-fatality ratio, require information on the number of deaths and the number of people who have been infected. However, currently available tools and operational systems do not lend themselves to an early and easy determination of these numbers. Varying epidemiological patterns were observed from country to country and among different population groups such as persons at higher risk of developing severe disease. How to best analyze and interpret such complex data has been challenging. Many countries were confronted with difficult decisions related to public health control measures like the closure of schools, businesses and cancellation of mass gatherings. The effectiveness and costs-benefits of such measures in the context of an evolving pandemic were difficult to evaluate initially and remain uncertain. In addition, the application of such measures requires effective operational and communication strategies which can be challenging under urgent situations.



At the time of the consultation – some seven months after the first cases of pandemic A(H1N1) 2009 were first detected – key clinical, epidemiological and virological features of the pandemic A(H1N1) 2009 virus infections had been established. These results represented the investigation, analysis and reporting of information by public health authorities and academic researchers, often working in close collaboration. Their findings and relevant ‘lessons learned’ were reviewed on the final day of the consultation in a series of keynote presentations (Annex 1).

C. THE PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA

C.1 Goal and objectives

The goal of the Research Agenda is to support the development of evidence needed to strengthen public health guidance and actions essential for limiting the impact of pandemic, zoonotic and seasonal influenza. Its objectives are to:

- Provide a framework reflecting public health research priorities for pandemic, zoonotic, and seasonal epidemic influenza
- Identify specific research topics, reinforce and prioritize their importance in meeting public health needs over a medium-to-long term period
- Maintain a focus on relatively less well addressed areas such as operational research and research with applications in under-resourced countries
- Facilitate discussion, coordination and interaction among researchers, donors and public health professionals
- Highlight the need and benefits of a multidisciplinary approach to address knowledge gaps in public health related to influenza and its control

C.2 Development and organization

The Research Agenda builds upon the 2002 *WHO Global Agenda on Influenza*^{1,2} and the 2006-2007 *WHO Strategic Action Plan for Pandemic Influenza*³ which included the coordination of scientific research and development as one of its five pillars.

Development of a draft *WHO Public Health Research Agenda for Influenza* began in earnest during the first half of 2008 based on discussion within WHO and with external partners including international funding organizations. In April 2008 WHO convened a technical consultation on disease control strategies and measures to respond to pandemic influenza outbreaks. This was followed by a global consultation in May 2008 to revise WHO’s pandemic preparedness guidance⁴ including recommended actions at the WHO/global and country levels before, during and after a pandemic. These consultations and other discussions with key partners brought into sharper focus the lack of scientific evidence necessary to support public health decision making and develop recommendations.

As part of the process, WHO sought input from technical and public health experts about critical knowledge gaps in pandemic, zoonotic and seasonal influenza. In addition, previous influenza-related WHO technical consultations and publications that highlighted specific knowledge gaps as well as influenza research priorities articulated by other human and animal public health agencies and organizations around the world were reviewed. An ‘influenza research topics database’ of more than 700 research questions/topics was developed based on these sources. Subsequently, the research questions were consolidated into approximately 250 questions/topics to minimize overlap and duplication. These

¹Global agenda on influenza – adopted version. Part I. Weekly Epidemiological Record, 2002; 77:179–182 (<http://www.who.int/docstore/wer/pdf/2002/wer7723.pdf>).

²Adoption of global agenda on influenza – part II. Weekly Epidemiological Record, 2002; 77:191–195. (<http://www.who.int/docstore/wer/pdf/2002/wer7722.pdf>).

³WHO strategic action plan for pandemic influenza. Geneva, World Health Organization, 2007 (http://www.who.int/csr/resources/publications/influenza/StregPlanEPR_GIP_2006_2.pdf).

⁴Pandemic influenza preparedness and response. WHO guidance document. Geneva, World Health Organization, 2009 (<http://www.who.int/csr/disease/influenza/PIPGuidance09.pdf>).



questions were used in turn to help construct and organize the draft Research Agenda around five major public health research streams as follows:

- **Stream 1.** Reducing the risk of emergence of pandemic influenza
- **Stream 2.** Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza
- **Stream 3.** Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza
- **Stream 4.** Optimizing the treatment of patients
- **Stream 5.** Promoting the development and application of modern public health tools

Within each research stream, specific areas of focus were identified and supported by a brief rationale and a list of proposed research topics of interest.

D. THE CONSULTATION

WHO convened the first global consultation on a Public Health Research Agenda for Influenza from 17 to 20 November 2009. The consultation brought together over 90 public health decision makers, academic and clinical investigators, donors/funding organizations and other key stakeholders from 35 countries. The final meeting agenda, list of participants and declarations of interests can be found in Annexes 2, 3 and 4, respectively.

D.1 Aim and objectives

The aim of the meeting was to review and finalize the *Public Health Research Agenda for Influenza* proposed by WHO and to facilitate its further implementation. The objectives of the consultation were:

- to facilitate discussion, coordination and interaction among researchers, public health professionals and funding organizations on public health research priorities for pandemic, zoonotic and seasonal influenza infection;
- to identify specific research topics and prioritize their importance in meeting public health needs for both pandemic and inter-pandemic periods, encompassing the potential threat by zoonotic viruses with pandemic potential and the impact of seasonal influenza epidemics;
- to maintain a focus on relatively less well addressed areas, such as operational research and research with applications in under-resourced countries; and
- to highlight the needs and benefits of a multidisciplinary approach to address knowledge gaps in public health related to influenza and its control.

D.2 Role of the Programme Committee

Prior to the global consultation WHO formed a Programme Committee that comprised of five Scientific Working Groups (SWG) and each SWG consisted of a Stream Lead and one or more Co-Leads, Rapporteur, other SWG Members and a WHO Point of Contact. The role of the Programme Committee was to strengthen the scientific and technical content of the Research Agenda, develop relevant background technical documents and help plan and participate in the global consultation.

Each Research Stream Rapporteur, with input and discussion from other members of the stream, developed a background document in advance of the consultation. The background documents summarized the available evidence base for each of the Research Agenda streams and served:

- to facilitate and focus discussions for each stream-specific SWG in advance of the November consultation
- to guide plenary and research stream-specific breakout group discussions at the November consultation about the content of the Research Agenda through identification of research gaps and prioritization of research topics of interest
- to provide participants with an overview of all five streams to facilitate their participation and contributions to the November consultation in areas outside of their specific expertise
- to contribute to the published literature after the consultation



D.3 The consultation process

The first day of the consultation meeting was organized as a plenary session. The WHO Secretariat presented the Agenda of the meeting and proposed Dr. Arjun Karki, Patan Academy of Health Sciences, Nepal to serve as Chairperson for the consultative meeting. The meeting participants accepted both the meeting Agenda and Dr. Karki to serve as chairperson for the meeting. A series of presentations set the scene and provided background information as follows: objectives of the consultation and the framework for discussion (S. Briand); an update on the H1N1 pandemic (A. Mounts); the global response to the H1N1 pandemic and implications for research, especially in resource-limited regions (M-M Hacen); identification of key information needed to develop control measures during the evolution of the H1N1 pandemic (N. Shindo); and an overview of the draft Research Agenda and the consultation process (J. Tam). To conclude the plenary session the five stream leads provided an overview of the current state of knowledge for each of the research streams (I. Capua, H. Oshitani, A. Monto, T. Chotpitayasunondh and S. MacKay).

The second and third days of the consultation were structured as research stream-specific breakout discussion groups. First, each stream-specific group reviewed and discussed the proposed organization, content, rationale and global health importance of their designated research stream. Participants were asked to consider if the proposed areas of focus and current topics of interest had global public health impact, filled a gap in knowledge necessary for public health decision making and if improved knowledge in these areas would support or change public health decision/policy making. Second, the relevant stream-specific sub-set of research questions/topics derived from the database of approximately 250 questions was distributed to each stream. The breakout groups were encouraged to propose and incorporate any additional research topics and associated questions that they considered essential but missing from the current list. Third, the groups undertook a 'road mapping' exercise to define the key public health needs related to their stream during both pandemic and inter-pandemic periods (including both seasonal and zoonotic influenza infections). All participants were asked to propose next steps for implementation of the Research Agenda at the global level, for the agenda's ongoing improvement and for its sustained progress.



E. REPORTS OF THE RESEARCH STREAM WORKING GROUPS



E.1 Stream 1: Reducing the risk of emergence of pandemic influenza

Introduction

There are many knowledge gaps in our understanding of how influenza viruses circulating in birds and other animal hosts have eventually emerged and transmitted efficiently in human leading to seasonal and pandemic influenza. In response, animal health professionals have undertaken several actions since 2004 including increasing the number of veterinary laboratories that can diagnose influenza virus infections, analyzing an unprecedented number of virus isolates containing valuable genetic information, implementing international training activities, establishing reliable contacts worldwide to provide information on local influenza activity, making funding available for surveillance in wild and domestic bird populations and expanding relevant areas of research. It is critical that animal health experts identify cross-disciplinary approaches to maximize the impact of existing or future research programmes as well as identify efficient means for sharing relevant information with their human public health counterparts.

Review of the research stream

The group proposed that the stream name be revised to 'Reducing the Risk of Emergence of Zoonotic and Pandemic Influenza' to reflect that any zoonotic influenza virus inherently has pandemic potential – through genetic change (i.e. reassortment or mutation) and associated antigenic shift. In addition, this proposed name change would highlight that the emergence of zoonotic influenza viruses can impact public health aside from their pandemic potential as has been experienced with highly pathogenic avian influenza A(H5N1).

Although the group agreed that the draft areas of focus reflected the importance of zoonotic influenza infections and their high pandemic potentials and other key areas of public health research interest, it recommended that surveillance and prevention be separated as two discrete areas of focus. Finally, the group proposed an extensive revision of the topics of interest to reflect the breadth of research questions critical to the public health issues of this stream.

1.1 Factors Associated with the Emergence of Influenza Viruses with Zoonotic or Pandemic Potential

For the first area of focus, the group proposed the following three topics of interest:

- 1.1.1 Virus-specific factors associated with zoonotic and pandemic potential (e.g. infectivity, transmissibility and pathogenicity)
- 1.1.2 Animal host-specific factors associated with zoonotic and pandemic potential (e.g. infectivity, transmissibility and pathogenicity)
- 1.1.3 Environment and management/husbandry-specific factors associated with zoonotic and pandemic potential (e.g. infectivity, transmissibility)

1.2 Factors Associated with Human Infection at the Human-Animal Interface

For the second area of focus, the group proposed the following three topics of interest:

- 1.2.1 Potential modes of transmission for human infection with animal viruses
- 1.2.2 Role of human behavioral factors associated with infection by animal viruses
- 1.2.3 Identification of genetic or other factors related to human susceptibility to infection with animal viruses



1.3 Surveillance at the Human-Animal Interface

For the third area of focus, the group proposed the following four topics of interest:

- 1.3.1 Strategy for joint animal and human health surveillance systems to monitor influenza viruses with zoonotic or pandemic potential in countries with varying capacity and resources
- 1.3.2 Diagnostic assays to support joint animal and human health surveillance systems to monitor influenza viruses with zoonotic or pandemic potential in countries with varying capacity and resources
- 1.3.3 Evaluation of joint animal and human health surveillance systems to monitor influenza viruses with zoonotic or pandemic potential in countries with varying capacity and resources
- 1.3.4 Social, political, economic and legal strategies for wider (broader) animal influenza outbreak reporting

1.4 Preventive Measures to Reduce the Risk of Emergence of Zoonotic and Pandemic Influenza Viruses

For the fourth area of focus, the group proposed the following four topics of interest:

- 1.4.1 Animal intervention strategies (e.g., culling, vaccination, bio-security) under different epidemiological and field conditions
- 1.4.2 Human intervention strategies related to the animal-human interface (e.g. behavior, legal approaches and bio-security procedures) in different social and cultural contexts
- 1.4.3 Integrated strategies for prevention
- 1.4.4 Evaluation of the public health effects of intervention strategies under different epidemiological and field conditions

Research topics and questions

Several observations were noted during the review of the previously identified research topics and questions. First, although questions referenced influenza in a limited number of animal species, a more general reference to 'animal influenza viruses' is preferable. Second, the overly broad nature of many of the questions led to overlap in several areas of focus and topics of interest. Third, references to the 'environment' in the proposed research topics should refer not only to physical factors (e.g. environmental persistence of the virus or climatic or ecologic factors associated with emergence of new strains) but also to animal husbandry and management systems. Finally, establishing criteria to identify which animal viruses pose a high risk of causing a pandemic is the single most important and overarching area of research for the human-animal interface.

The group agreed that research questions must be considered in the context of varying situations, e.g. their applicability at the international, national or local levels and for developing or 'in-transition' countries. Also, topics identified as global influenza priorities may not reflect critical research questions for an individual country's or region's experiences or situation. Finally, strategies for research programmes and projects need to consider issues of practical applicability and validity in different countries and settings.



Road mapping for a pandemic scenario

Five priority public health topics were identified for a pandemic scenario as follows:

1. Examination of host range and transmission dynamics of animal influenza viruses, through field studies and the development and use of appropriate experimental animal models to guide surveillance, control strategies and risk communication (e.g. food safety concerns)
2. Enhanced surveillance in animals and humans to monitor virus evolution
 - Early detection of novel reassortants or changes in genotype and/or phenotype related to virulence
 - Development and adaptation of epidemiological and laboratory diagnostic tools (including rapid diagnostic tools for use at local level) and capacity building to optimize case finding
 - Development of a framework for targeted surveillance in animals that address ethical, legal and social barriers to intra-pandemic surveillance and reporting
3. Deconstruction of the origins of the pandemic virus to identify factors (e.g. virological, host, ecological, epidemiological, husbandry) that permitted efficient human-to-human transmission and that may have applicability for future pandemics
4. Development of strategies to counteract economic, social and cultural disincentives of animal-based interventions at the local, national and international level (including but not limited to vaccination) to reduce intra- and inter-species transmission
5. Operational research to optimize risk communication that are linked to animal husbandry and food safety during the inter-pandemic period and in the early phases of a pandemic

Road mapping for an inter-pandemic scenario

Four priority topics were identified for an inter-pandemic scenario as follows:

1. Integration of animal and human surveillance systems
 - Development of sustainable joint surveillance programmes
 - Refinement of tests to detect animal influenza infection in humans
 - Development of improved veterinary diagnostic tools, with associated transfer of technology and capacity building
 - Evaluation of surveillance systems
 - Identification, integration and sharing of critical epidemiological and laboratory data
2. Factors associated with increased public health risk from animal influenza viruses
 - Viral determinants of host range, transmissibility, pathogenicity and antiviral resistance
 - Host factors involved in virus transmissibility and pathogenesis
 - Effect of cross protective immunity induced by infection with seasonal influenza viruses
 - Ecological and epidemiological factors involved in environmental persistence and interspecies transmission
3. Strategies to reduce the risk of emergence of zoonotic and pandemic influenza viruses
 - Reducing high risk interactions between humans and animals
 - Development of improved vaccines (e.g. broader spectrum, more efficacious, easier to administer, less costly) for targeted animal populations
 - Development and validation of strategies for the assessment of their sustainability in different contexts
4. An information, education and communication strategy to improve situational awareness
 - Identification of key messages for different stakeholders to increase awareness and facilitate behavior change
 - Advocacy for resources from governments and international donors



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

Introduction

Many of the fundamental research questions associated with limiting the spread of influenza are not new. However, these questions have proven extremely difficult to answer and it is uncertain how widely observations made in particular population groups or settings and influenza seasons can be used to develop public health policies. Much of the available information to date is from observational and human viral challenge studies that were conducted decades ago, although an increasing number of prospective, randomized trials have been undertaken recently in seasonal influenza. There is an urgent need to develop evidence-based strategies for non-pharmaceutical interventions as under-resourced countries have limited access to pharmaceutical interventions such as vaccines and antivirals. In some instances, available data from previous research may not have been formulated in a manner that is most useful for policy makers. It is critical to maintain a balance between scientific research to expand our knowledge base and operational research to inform implementation of prevention strategies, best practices and public health decision making.

The group emphasized that whenever possible, research related to limiting the spread of influenza should have the broadest possible applicability in a range of settings and resource levels. However, it was also noted that some research may have limited scopes that cannot be generalized for broader usage, such as studies of influenza transmission in health care settings.

The A(H1N1) 2009 2009 pandemic has presented new opportunities to increase our understanding of how influenza spreads and is transmitted between people which the *Public Health Research Agenda for Influenza* can build upon.

Review of the research stream

The group agreed that all the areas of focus were relevant to seasonal, pandemic and zoonotic influenza. Consequently, discussion was centered on the importance of each area of focus to public health and the research gaps that need to be addressed for all types of influenza. The group proposed that the order of the second and third areas of focus be switched to allow for a better flow from factors affecting transmission, to spread at the local and global levels, and concluding with public health measures to limit transmission of influenza. The group proposed revisions for each area of focus as well as revisions to the topics of interest within each area.

2.1 Factors Affecting Person-to-Person Transmission

For the first area of focus, the group proposed the following five topics of interest:

- 2.1.1 Importance of droplet, contact and airborne transmission
- 2.1.2 Evaluation of transmission patterns and infectivity co-factors in different settings
- 2.1.3 Transmission of influenza during different stages of infection in humans
- 2.1.4 Transmission modulated by host factors
- 2.1.5 Stability of human influenza viruses on varying environmental surfaces and conditions

2.2 Dynamics of Virus Spread at Global and Local Areas

For the second area of focus, the group proposed the following three topics of interest:

- 2.2.1 Seasonality of influenza virus infection and implications for spread of influenza viruses globally and under different climatic and geographic conditions
- 2.2.2 Assessing spread of influenza under different demographic and epidemiological settings

- 
- 2.2.3 Utility and timing of different response strategies during early spread of human cases of an animal or pandemic influenza virus

2.3 Public Health Measures to Limit Transmission

For the third area of focus, the group proposed the following three topics of interest:

- 2.3.1 Effectiveness, cost-effectiveness and feasibility of measures at the individual level
- 2.3.2 Effectiveness, cost-effectiveness and feasibility of measures at the community level
- 2.3.3 Factors to consider in the selection and timing of public health measures

Additional areas of discussion

The group discussed several over-arching issues:

- the need for input from other disciplines such as:
 - social science to evaluate the effect of social mixing on transmission and to assess social disruptions caused by interventions
 - risk communications to devise locally appropriate messages about interventions that are used and to evaluate their effectiveness

The group noted that although these issues are included in Stream 5 they cut across other streams

- the roles of decision- and policy-makers and the media in influencing public health measures should be explored.
- placement of surveillance in the Research Agenda to address research questions related to influenza surveillance methodology and strategies; the group recommended that global surveillance should be a discrete research topic and also incorporated into the relevant streams as a cross-cutting tool
- the need for serological prevalence studies to gain a more complete understanding of the clinical and asymptomatic attack rates for all types of influenza disease and the effectiveness of various interventions

Roadmap for key research priorities

The group used the criteria of 'importance to public health decision making' and 'importance for filling key knowledge gaps' to identify the key research priorities for Stream 2. The group selected the 10 topics of greatest importance to seasonal, pandemic and zoonotic influenza while emphasizing that the many other questions and topics in Stream 2 remain important. In addition the group provided specific questions for each of these priorities.

The ten priority research topics were identified as follows:

1. Transmissibility of influenza across the progression of infection and spectrum of disease
2. Relative contributions of the different modes of transmission for influenza
3. Biological, behavioural and social host factors that influence the risk of transmission and infection
4. Patterns, drivers and mechanisms affecting the seasonality of transmission
5. Viral and population factors that influence transmission and spread of different influenza types, subtypes and strains
6. Optimal strategies to reduce the transmission of influenza in community, household and health care settings, especially in less-resourced areas of the world
7. Impact and cost effectiveness of social measures such as reducing contact with others, school closures and cancellation of public gatherings, as well as the role of surveillance in assessing when to initiate and terminate these interventions.
8. Impact, effectiveness and cost effectiveness of individual measures such as isolation and quarantine
9. Role of vaccination in limiting the spread of influenza and strategies for its use
10. Impact of antiviral treatment and prophylaxis in reducing transmission of influenza.



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

Introduction

Although influenza has been accepted as an important public health problem in developed countries, it is only gradually being recognized as such in the rest of the world. This is related in part to insufficient information on the burden of influenza disease and the attendant social, economic and health impacts on the community. Methodologies to assess burden of disease have typically used selected epidemiological parameters and assumed a distinct seasonality. However, new approaches are needed for under-resourced and non-temperate areas of the world. Such approaches include laboratory diagnostic testing and longitudinal studies to strengthen detection of influenza-related illnesses and deaths and to better define seasonal patterns.

Immunization remains a critical intervention to reduce influenza-related morbidity and mortality. However, current vaccines (inactivated and live attenuated) have well recognized deficiencies including less than optimal efficacy, especially in older and infirm populations, limited breadth of protection, especially for type B influenza virus lineages, short duration of protection with current need for annual administration, egg-based vaccine production requirements and administration by needles (apart from several intranasal live attenuated vaccines). These deficiencies limit the use of vaccine in under-resourced countries and contribute to difficulties in measuring correlates of protection and other evaluation issues.

Overarching considerations

The group noted a number of points that were viewed as key to the stream but not adequately captured in the interim draft of the Research Agenda as follows:

Measurement of disease burden and vaccine effectiveness in under-resourced countries

Information should be sought from countries such as Thailand that have undertaken influenza and pneumonia burden studies and other existing resources such as the WHO Western Pacific Regional Office's 'A Practical Guide for Designing and Conducting Influenza Disease Burden Studies' (<http://www.wpro.who.int/NR/rdonlyres/68608B77-891B-4B36-B21D-F49E526E0B28/0/GuideforDesigningandConductingInfluenzaStudies.pdf>). Possible ways to assess influenza disease burden might include development of 'sentinel surveillance zones' at country level (as was done after the introduction of rotavirus vaccines) or use of 'surveillance sentinels' at regional or sub-regional levels. Delineation of areas for surveillance should take into account different climates, altitudes, population densities and cultures. Influenza disease burden also could be estimated from vaccine 'demonstration projects' or probe studies that evaluate reductions in the occurrence and severity of disease following the implementation of vaccine programmes. Such studies should include varying age groups and populations including those with increased risk of complications and socially disadvantaged persons to best estimate disease burden and evaluate the impact of immunization programmes.

Lack of differential diagnostic tools

Part of the difficulty in establishing the burden of disease due to influenza in under-resourced countries stems from the lack of rapid diagnostic tools and adequately funded diagnostic laboratories to differentiate influenza from other acute respiratory illnesses (e.g. respiratory syncytial and other respiratory virus infections and bacterial pneumonias).



Vaccine acceptability

Joint discussion with Stream 5 focused on the importance of culturally sensitive and well-targeted communication messages about influenza vaccine to improve seasonal and pandemic vaccine uptake. There are many examples of vaccination programmes that have been undermined by myths and hostile rumours. Understanding the origin and spread of these rumours and how to effectively counter them is needed. Vaccine effectiveness trials in countries with little familiarity with influenza ideally should result in improved acceptability and governmental support for continued vaccine use.

Sustainability of influenza vaccination

Establishment of platforms that can support manufacture of multiple vaccines with production processes similar to influenza would be helpful in sustaining influenza vaccination in under-resourced countries.

New vaccine formulations

The development of vaccines that elicit broader and longer protection against influenza virus strains would facilitate use by under-resourced countries that cannot afford to revaccinate the population every year; for example, a 'universal' influenza vaccine (e.g. a vaccine comprised of conserved epitopes of the hemagglutinin [HA] protein and conserved viral proteins such as the M2 protein and/or the nucleoprotein [NP]) or an influenza vaccine for children that would induce durable, broad hetero-subtypic protection are long term goals. Vaccines that could be administered with other childhood vaccines would offer distinct advantages, especially to under-resourced countries. However, neither is likely to be realized in the near future. Other areas that could benefit from increased research and development include vaccine production technologies and substrates (i.e. use of cell-culture instead of embryonated chicken eggs); production of recombinant antigens in bio-engineered bacteria, plants or fungi; vaccine formulations incorporating adjuvants that are safe and effective, especially in persons at increased risk for complications from influenza, and dose-sparing.

Vaccine availability and accessibility

There are marked differences between countries in terms of their respective capacities, priorities and resources to establish seasonal influenza vaccination policies and to produce and distribute vaccines. These differences become even more visible during a pandemic. Vaccine availability and accessibility is limited, both for seasonal and pandemic influenza, at a global level. In turn this necessitates difficult decisions about vaccine prioritization for particular target groups (e.g. pregnant women, healthcare workers).

Review of the research stream

The group proposed that 'zoonotic' influenza be deleted from the stream title as it is not considered anywhere in the areas of focus or research topics. While the group retained the three areas of focus, they proposed revised and amplified rationales for each as well as extensive and detailed revision of the topics of interest.

3.1 Determining Disease Burden and Social Impact

For the first area of focus, the group proposed the following five topics of interest:

- 3.1.1 Operational research to determine disease burden and social impact
- 3.1.2 Evaluation of the burden of influenza disease that is preventable by vaccination and the potential impact of immunization programmes
- 3.1.3 Establishment of the economic burden of seasonal and pandemic influenza

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- 3.1.4 Determination of the best approaches for applying influenza disease burden data, coupled with cost-effectiveness analyses, to inform development or expansion of influenza control programmes in the context of competing health priorities
 - 3.1.5 Assessment of social determinants of health under different epidemiological settings and evaluation of the social impact of influenza outbreaks and pandemics based on such determinants

3.2 Improve Immunogenicity, Availability and Delivery of Influenza Vaccines

For the second area of focus, the group proposed the following 12 topics of interest:

- 3.2.1 Improvement of the vaccine strain selection process and methods to characterize optimal vaccine strains
- 3.2.2 Enhancement of properties of existing vaccines, including improvements in production, duration and breadth of protection, safety and immunogenicity profiles and dose-sparing formulations, especially for high-risk groups
- 3.2.3 Development of new vaccines and vaccine platforms, especially suitable for under-resourced country settings
- 3.2.4 Optimization and standardization of animal models for pre-clinical evaluation for new vaccines
- 3.2.5 Development of vaccine formulations and delivery systems to improve ease of storage and administration, especially in under-resourced settings
- 3.2.6 Systematic evaluation and reduction in vaccine production bottlenecks to improve rapid response and surge capacity
- 3.2.7 Development of strategies for rapid deployment and tracking
- 3.2.8 Identification of correlates of protection for different vaccines and correlates of priming, including development and standardization of methodologies
- 3.2.9 Development of innovative clinical trial methodologies for pre- and post-licensure vaccine evaluation and vaccine effectiveness
- 3.2.10 Expansion of pharmaco-vigilance for post-licensure vaccine evaluation, especially in at-risk groups that may vary geographically
- 3.2.11 Harmonization of regulatory processes, especially for rapid international monitoring and evaluation of potency and safety of vaccines
- 3.2.12 Investigation of the effectiveness and efficacy of novel vaccination strategies to reduce the burden of influenza disease in children and other high risk groups in a wide range of settings

2.3 Public Health Policies to Reduce the Impact of Disease

For the third area of focus, the group proposed three topics of interest:

- 3.3.1 Evaluation of existing and new policies and strategies to optimize vaccine uptake by, and improve vaccine acceptability to, specific population groups
- 3.3.2 Development of effective immunization policy using community-based input
- 3.3.3 Inclusion of social science research



Road mapping for a pandemic scenario

Five priority public health topics, drawn from the proposed topics of interest, were identified for a pandemic scenario as follows:

1. Identification of groups at higher risk of infection and severe disease outcome through enhanced surveillance; understanding disease severity and identification of predictors of severe outcomes
2. Investigation of vaccine effectiveness, especially in high risk groups in diverse geographic areas
3. Establishment/enhancement of pharmaco-vigilance, particularly for adverse events among at-risk groups
4. Optimization of strategies for rapid and targeted vaccine deployment
5. Rapid assessment to optimize acceptance of pandemic vaccine

Road mapping for an inter-pandemic scenario

Six priority topics were identified for an inter-pandemic scenario as follows:

1. Identification of groups at higher risk of infection and severe disease outcome through enhanced surveillance; understanding disease severity and identification of predictors of severe outcomes
2. Evaluation of the vaccination preventable disease burden and the potential impact of immunization programmes, through vaccine demonstration projects
3. Enhancement of the properties of existing vaccines, including duration and breadth of protection, safety, immunogenicity and dose-sparing
4. Development of new vaccines and vaccine platforms, especially suitable for under-resourced country settings
5. Investigation of the effectiveness and efficacy of novel vaccination strategies, including through induction of herd immunity, to reduce the burden of influenza disease in children and other high risk groups in a wide range of settings
6. Improved uptake and acceptability of vaccines for both seasonal and pandemic influenza



E.4 Stream 4: Optimizing the treatment of patients

Introduction

Knowledge about the viral and host factors leading to severe influenza illness is incomplete. Severe disease occurs mostly (60%-70%) in 'at risk' persons; other persons with severe disease are presumed to be 'healthy' or have, as yet unidentified, risk factors. Approximately one-quarter to one-half of persons with severe pandemic 2009 A(H1N1) 2009 illness have not had recognized risk factors, and like the 1918 pandemic excess mortality has been especially notable in young and middle-aged adults. Improvement of diagnostic tools could help in optimizing early initiation of antiviral therapy and other treatments. Early recognition and initiation of treatment (especially with antivirals and antimicrobials) strongly correlates with improved morbidity and mortality. However, such treatment requires timely access to good quality health services.

Review of the research stream

The group concurred with the overall organization and proposed areas of focus for Stream 4 in the draft Research Agenda. However, the group proposed an extensive revision of the topics of interest for each area of focus.

4.1 Dynamics of Virus Spread at Global and Local Areas

For the first area of focus, the group observed some overlap in the area of burden of disease with Streams 2 and 3; however, it was agreed that some elements of disease burden were critical to Stream 4, and that the role of novel host genetic factors in susceptibility to infection and severe illness was important and not covered by other streams.

The group proposed the following six topics of interest in this area of focus:

- 4.1.1. Roles of virus factors (including replication sites, duration and levels) and innate and adaptive immunity and other host responses in the severity of disease and associated complications
 - This change broadened the emphasis from viral replication to a wider range of virus factors and allowed for inclusion of host responses and their effect on severity such as innate and adaptive immunity and immunomodulators.
- 4.1.2. Defining the clinical spectrum and natural history of human disease, including risk factors and prognostic markers for severe disease and complications
 - This change placed the emphasis on severe progressive disease and not on asymptomatic disease which is not relevant for treatment and considered in other streams
- 4.1.3. The incidence, site, etiology and pathogenesis of secondary bacterial infections associated with influenza, as well as optimal treatment modalities and prophylactic and/or preventive measures
- 4.1.4. The role of pre-existing infections (e.g. tuberculosis, human immunodeficiency virus) and viral co-infections (e.g. dengue and other respiratory viruses) on the severity of disease
 - This new topic of interest highlighted the importance of concurrent medical conditions/infections in optimizing patient treatment as well as the body system location of these co-infections (e.g. respiratory versus gastrointestinal pathogens) which may also be important
- 4.1.5. The role of host genetic factors on susceptibility and severity of infection and/or person-to-person transmission
- 4.1.6. The identification and mechanisms of risk factors (such as co-morbidities and demographic factors) for the susceptibility to, and severity of, infection with influenza



2.2 Improve Clinical Management of Patients

For the second area of focus, the group observed some overlap with Stream 2 on diagnostic tools and on surveillance. In addition to the development of antivirals that could be useful and cost effective for under-resourced countries, the group noted that other pharmacological interventions are also important and need to be better defined in the Research Agenda (e.g. immunomodulators, immunoglobulin therapies and natural products). Accordingly, the group proposed that alternative treatment modalities be added as a new topic of interest. Research to determine best practices in intensive care should be applicable across a range of resource settings, but the group noted that the standard of care for influenza spans a broad range of treatment practices, including folk medicine and other alternative treatments, so that identifying a basic common standard at the global level will be challenging.

The group proposed the following five topics of interest in this focus area:

- 4.2.1. Rapid, reliable, affordable point-of-care diagnostic tests for the influenza virus
- 4.2.2. Identification of clinical markers and development of new tools for diagnosis, prognosis or management that are applicable at point-of-care
- 4.2.3. Optimizing the effectiveness of current and novel antiviral treatments through expansion of relevant evidence, development of new formulations, delivery routes or systems, and combinations of treatments
- 4.2.4. Development of novel and effective treatment strategies including assessment of adjunctive treatments (e.g. immunomodulators, immunoglobulin, natural products) that are applicable in low resource settings and easy to administer in paediatric and intensive care settings
- 4.2.5. Optimizing management of persons at higher risk of, or presenting with, severe disease and/or disease complications, including intensive care practices that are applicable across a range of resource settings

2.2 Health Care Capacity and Response

For the third area of focus, the group observed some overlap with Stream 2 on non-medical means to limit transmission (i.e. personal protective equipment and hand hygiene) and with Stream 3 on prevention measures (e.g. antiviral chemoprophylaxis and effects of treatment on transmission). However, it was agreed that these areas be retained in Stream 4. The group emphasized the importance of assessing how prevention measures from higher resource settings can also be applied in under-resourced settings.

Two new topics of interest were added to this area of focus: rapid assessment and introduction of new interventions during health emergencies, especially in countries that lack drug registration policies; and assessment of the effectiveness of pandemic plans to explore why gaps in pandemic planning were not identified and rectified prior to the 2009 pandemic. These two new topics require development of new assessment tools which could be linked with Stream 5.

The group proposed the following six topics of interest:

- 4.3.1 Evaluation of the effectiveness of global, national and local responses to pandemic, epidemic and zoonotic influenza, and development of new assessment tools
- 4.3.2 Evaluation of surge capacity needs, including development of triage schemes in different health care and resource settings, and surge planning to maintain adequate staffing
- 4.3.3 Development of alternative health delivery systems for care of patients including home care, community facilities other than hospitals and other venues
- 4.3.4 Development of best practices that provide protection to health care workers and other care-givers in different health care and resource settings
- 4.3.5 Identification of evidence-driven clinical care pathways and principles which optimize health care delivery in a range of resource settings

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- 4.3.6 Development of principles and practices for rapid assessment and introduction of new interventions during health emergencies, including systems for collation, sharing and assessment of clinical data in real time

Road mapping for a pandemic scenario

The group considered that the greatest treatment-related impacts achievable during the 2009 pandemic depended upon identification of best practices for identification and management of severely ill persons and those at risk for severe illness (e.g. pregnant women) in different resource settings. The group thought that WHO should coordinate and facilitate information-gathering and sharing on clinical management issues. Access to rapid diagnostic tools is an essential component, but further research is needed as current rapid tests are of limited value. Improved understanding of the pharmacokinetics of available antivirals, particularly oseltamivir, and their efficacy in different patient groups is important. Development of evidence to guide effective dose selection and duration of therapy was discussed also in the context of under-resourced areas or limited drug availability. It was noted that simple solutions for under-resourced settings may also apply to high resource areas, particularly when there is a need for the mitigation of high levels of surge capacity.

Six priority public health topics were identified for a pandemic scenario as follows:

1. Collaboration and coordinated sharing of data, protocols, regulatory and other implementation strategies and databases from different countries on all aspects of patient management and outcome to accelerate improvements in patient care
2. Development of best practices on patient management in different settings, including checklists and algorithms for clinical care and treatment, prognostic parameters and tests to predict potential for the development of severe disease
3. Rapid, reliable, simple, low-cost point-of-care diagnostic tools for influenza
4. Best use of current antiviral drugs and optimal formulations in different target populations, such as parenteral and other routes of administration for severe infections
5. Studies of combination therapies, including use of adjunctive therapies (e.g. use of convalescent plasma and immunomodulators)
6. Role of ongoing viral replication, host responses and the effect of co-infections in the pathogenesis of severe disease

Road mapping for an inter-pandemic scenario (seasonal influenza)

Among the priority areas for further research during inter-pandemic periods, clinical evaluation of currently available antivirals among persons at increased risk (particularly in children <1 year of age and pregnant women) was considered important. Clinical trials to assess treatment of severe disease would occur over several years, and should generate more efficacy, safety and pharmacokinetic information. Evaluation of the cost-effectiveness of antivirals in different countries for both mild and severe disease would also be useful. Inter-pandemic periods should offer more time to develop pre-pandemic protocols for antiviral agents and to submit them to regulatory authorities.

Seven priority public health topics were identified for an inter-pandemic seasonal influenza scenario as follows:

1. Research on the burden of severe disease (in developing countries, with a focus on regional-specific factors, such as the relationship of influenza to the burden of malaria, TB and HIV) and optimization of pandemic preparedness and management
2. Development of new antiviral strategies and validation of virological endpoints which may aid in advancing understanding of disease progression
3. Further clinical evaluation of current antiviral drugs particularly in populations at higher risk
4. Integration of seasonal influenza with pandemic preparedness; strengthening of health care systems, capacity research and preparedness planning; improvement in surveillance

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5. Improving diagnostics assays (e.g. multiplex assays for viruses and bacteria), including antiviral resistance testing at point-of-care
 6. Lessons learned, dissemination of best practices, situation analysis, preparation for next epidemic (e.g. establish protocols for rotating stockpiles of antiviral drugs)
 7. Increased attention to basic science research such as studying immunomodulatory drugs

Road mapping for an inter-pandemic scenario (zoonotic influenza)

The group concurred that WHO should continue to promote research on further characterization of infection with avian influenza A viruses (H5N1 and others) and their treatment including parenteral administration of neuraminidase inhibitors, antibody preparations, and possibly nebulised drugs for paediatric populations. Studies on the potential for the development of antiviral resistance due to reassortment between influenza virus sub-types and subsequent spread were considered important. Vigilance and advance preparation (e.g. development of clinical treatment and study protocols) for the possible emergence of a new zoonotic virus must be ongoing.

Five priority public health topics were identified for an inter-pandemic zoonotic influenza scenario as follows:

1. Antiviral susceptibility of circulating zoonotic viruses (e.g. H5, H9, H7 influenza viruses)
2. Reassortment between zoonotic and human influenza viruses and the potential for inter sub-type spread of antiviral resistance and virulence markers
3. Development and sharing of clinical treatment protocols in anticipation of the emergence of a new zoonotic virus
4. Further characterization of human infections with avian H5N1 and other animal influenza viruses including geographic variability in morbidity and mortality, genetic susceptibility factors and sites of infection and viral replication
5. Monitoring for the development of antiviral resistance during treatment of A(H5N1) virus infection



E.5 Stream 5: Promoting the Development and Application of Modern Public Health Tools

Introduction

In recent years, rapid developments in technology and communications have brought an almost bewildering array of possibilities to develop new tools to detect, monitor, model and control influenza outbreaks. One challenge is how best to evaluate which tools have the most potential in terms of effectiveness, cost-effectiveness and applicability to a range of different settings and local contexts.

New tools present new opportunities, but there are also questions relating to how the development and application of existing tools can be scaled up for use in low and/or high resource settings. Stream 5 focused on the development and application of tools in three areas of interest, namely early detection and monitoring of disease (also referred to as surveillance), modelling and risk communications. Their application is closely related to the other four streams and so it is logical that their development and application should be linked to providing answers to the highest priority questions arising in each of the other streams, as well as providing the most appropriate solutions.

The group considered a number of unique research questions arising in each of the three distinct areas of interest. However, the group also identified a number of interesting questions relating to the interaction of one or more of these three areas with each other. For example, what implications does the communication of surveillance data and/or the results of modelling have for communicating risk to the public; or how can new tools for surveillance inform modelling in real-time situations?

There was insufficient time in this initial consultation to explore many of these new, cross-cutting questions in sufficient detail. Therefore, it was recommended that a future, more in-depth consultation be undertaken to consider innovations in Stream 5 and the interaction between them.

Review of the research stream

Stream 5 proved to be challenging, given the breadth of its focus, and the interconnection with each of the other streams. The group did, however, agree on the need for a unique stream dealing with innovation, not least to avoid such critical areas as surveillance, modelling and risk communication being overlooked. In order to maximize linkages with the key research questions arising from the other four streams, group members joined other stream discussions during the consultation.

Initial stream plenary discussions centered on how best to shape Stream 5; it was agreed from the outset the development of modern public health tools must be considered in terms of the needs of the end-user. Such needs will vary from region to region, and from country to country, particularly in relation to their suitability for application in high or low resource settings.

While there was general enthusiasm for embracing advances in information and communication technologies (ICT), they should not be embraced for their own sake. The group stressed the need to identify ‘the right tool for the right user at the right time in the right place.’ To be useful, tools must be available and in use before a pandemic strikes, speaking to the importance of investing in emergency preparedness. Valuable experience can be gained in applying tools to zoonotic and seasonal influenza as well as other diseases, as a rehearsal for a future pandemic influenza event.

One major cross-cutting issue was the question of how to deal with uncertainty. For example, when modelling exercises make projections of pandemic impact, how best can the uncertainty be communicated to both decision makers and the public; how do risk communicators best convey to the public that there are still gaps in scientific knowledge; and more broadly, how should the scientific/technical community claim credibility in the face of uncertainty and disagreement?



Another critical issue is the importance of addressing complex new ethical, legal and policy questions that arise from the use and sharing of health data using such new tools. The fragile interface between science and politics gives rise to many difficult questions relating to the use of data in surveillance, modelling and risk communication. Indeed, as was discussed extensively, the challenges of communicating risk in a highly charged political situation cannot be understated.

Finally, there was some discussion about how best to address research questions relating to capacity building and training in general as well as their relationship specifically to the application and use of modern tools. However, the group failed to reach consensus on whether this should become a new area of interest within Stream 5, or whether relevant research questions can be sufficiently addressed across the five streams. Even without consensus it must be stressed that how best to build capacity for zoonotic, seasonal and pandemic influenza control is an important research question in itself.

5.1 Modern tools for early detection and monitoring of disease

This break out group focused on a range of new ICT tools for surveillance, as well as other tools for detection, such as influenza diagnostic kits and self-triage. Discussion focused on how such tools can be applied at local, national and international levels, for influenza as well as for different public health events. Wherever possible, new tools should integrate with existing health information systems, and not attempt to assimilate or duplicate them.

There are many different types of tools to be considered, for example for data collection, analysis, consolidation, exchange, reporting, decision making and capacity building; their appropriateness can vary according to the level where they are to be used. New opportunities are opening up for data collection and exchange, for example through mobile phones, or in terms of audio and video through real data transports. Wherever possible, generic solutions should be adopted for use across all disease control efforts, using multiple data sources.

Innovative thinking and partnerships will be required to make solutions available as freely and widely as possible. From the outset, attention needs to be paid to the issue of sustainability, and the amount of investment and incentives that need to be offered to those who will introduce and use the new systems. New tools should not make onerous demands on individual users, and as soon as possible need to provide tangible benefits to institutions in terms of improved decision making at local, national and international levels.

Interoperability is also vitally important, to ensure that as far as possible IT systems can ‘speak’ to each other in terms of language, logic and syntax. Finally, establishing efficient feedback mechanisms to capture field experience will be critical if the potential of new tools is to be reached.

The group modified the rationale for the area of focus and proposed a revision of the topics of interest as follows:

- 5.1.1 Identification, appraisal, exploitation and adaptation of modern technologies for early detection of epidemic and pandemic influenza
- 5.1.2 Development, integration and continuous evaluation of innovative approaches and channels for influenza surveillance and monitoring with other existing disease monitoring systems
- 5.1.3 Development of efficient mechanisms to address the global challenges for sharing information, data, clinical specimens and viruses with consideration for local, ethical, legal and research perspectives
- 5.1.4 Identification of the data needs, timeliness and quality required from local to district, regional, national and global levels for the respective stakeholders

For each topic of interest the group revised the previously drafted research questions and in some instances proposed new ones.



5.2 Role of modelling in public health decision making

The group modified the rationale included in the draft interim agenda, and edited the topics of interest. The list of research questions formed the basis of subsequent discussion. The group felt it would be useful to distinguish questions largely concerned with modelling; those in which modelling feeds into other streams; and those relating to modelling with an emphasis on policy and communications issues. The latter would not necessarily address scientific research priorities, but constituted important public health needs nonetheless.

The group also discussed that modelling extends beyond transmission dynamics and includes, for example, the analysis of antigenic, genetic, serological and structural data. Sequence analysis and phylogenetic methods are powerful approaches for reconstructing the evolutionary history of influenza viruses; antigenic cartography is useful for vaccine strain selection and evolution studies; and modeled structural data could be critical in the future for receptor-binding studies.

The group proposed a revision of the topics of interest as follows:

- 5.2.1 Application of modelling to understand epidemiological and evolutionary processes and to estimate key parameters for pandemic and seasonal influenza
- 5.2.2 Application of modelling to predict the public health impact of influenza and the effectiveness of interventions
- 5.2.3 Application of modelling to assist public health policy planning and strategic decision making
- 5.2.4 Improvements in model accuracy and realism, and incorporation of emergent interdisciplinary advances

5.3 Modern tools for risk communication

Given the scope of this area, the group acknowledged the need to bring in expertise from a wider range of relevant fields including anthropology, marketing, communication, broadcasting, media research and behavioural and social sciences.

The group also recommended broadening out the term 'risk communication' to 'strategic communication'. This change would acknowledge the many different types of communication involved in achieving effective influenza control, not all of which are related to communicating an individual's own risk; for example, advocacy to engage decision makers, communication for crisis management, or communication to engage and mobilize health care providers around an issue such as support for a vaccination strategy.

One major topic for discussion was the lack of peer reviewed, statistically validated studies specifically relating to communication during influenza outbreaks, or disease outbreaks more generally. A more thorough literature search, drawing on experience across a wide range of relevant disciplines was, therefore, identified as a high priority. This will be an essential activity to help identify gaps in knowledge, and to better direct future research efforts.

The group was unanimous on the urgent need to increase investment in identifying effective approaches and in developing and evaluating new tools on strategic communication. During the pandemic of A(H1N1) 2009, many countries requested technical assistance to develop evidence-based communication strategies and approaches.

One of the most pressing questions is how to provide clear, credible and appropriate communication that meets the needs of diverse communities and at the same time retains public trust during a dynamic process characterized by great uncertainty and political complexity.



The group modified the topics of interest as follows:

- 5.3.1 Review international evidence and experience on health and health crisis communication from relevant disciplines, such as behavioural and social sciences, media studies and marketing and gather and organize knowledge, as well as stimulate new studies in areas where gaps have been identified to support evidence-based practice in strategic communication
- 5.3.2 Identify, develop and evaluate communication tools and methods to more rapidly and accurately assess and monitor knowledge, attitudes, beliefs and practices in different population groups over time to guide communication efforts
- 5.3.3 Identify, develop and evaluate communication tools and approaches for communicating in different cultural settings, which engage and empower individuals and communities to practice and promote appropriate risk reduction measures
- 5.3.4 Understand the dynamics of inaccurate and contradictory information, rumours, myths and narratives through tracking, monitoring and analyzing different communication sources and channels and to develop effective ways to respond
- 5.3.5 Understand the potential ethical, social, economic and political dimensions of communicating in national and international crisis situations and develop strategies for working within constraints and maximizing opportunities.

Road mapping

5.1 Modern tools for early detection and monitoring of disease

The group focusing on surveillance tools concluded that the agreed topics of interest were equally applicable during a pandemic or during an inter-pandemic period.

5.2 Role of modelling in public health decision making

Road mapping for a pandemic scenario

The group identified key research topics/questions from a discussion of fundamental gaps in our knowledge, rather than selecting them from a proposed list of questions. Topics specific to the pandemic period included the use of modelling to answer important questions about the immediate situation (e.g. transmission characteristics, severity and extent of spread), as well as the origin of the virus and its characterization. Longer-term questions concern the ability to forecast the potential time course and impact of the pandemic, as well as the feasibility and potential efficacy of interventions. The ability to forecast in this way is contingent on several cross-cutting issues. The effects of seasonality, the characterization of relevant human travel patterns and the quantification of transmission in different settings are examples of important factors, which were also discussed in other streams, that require more research.

Five priority public health topics were identified for a pandemic scenario as follows:

1. Identification and quantification of the environmental and behavioral determinants of seasonal variation in influenza transmissibility in tropical and temperate regions
2. Estimation of the relative transmission risk associated with different types and duration of contacts in various settings by comparing measured contact patterns with detailed outbreak data
3. Incorporation of validated models of behavioral responses to risk and control measures into transmission models of pandemic influenza
4. Development and implementation of novel technology for real-time sero-surveillance during a pandemic
5. Development of an integrated experimental and theoretical framework for assessment of the level of host adaptation to forecast evolution of receptor specificity, antigenicity and virulence



Road mapping for an inter-pandemic scenario (seasonal influenza)

Public health priorities in this period relate to seasonal influenza, as well as zoonotic infections. Questions of situational awareness and forecasting, as described above, apply equally to both. Virological surveillance and genetic analysis has already yielded novel insights into the evolutionary dynamics of seasonal influenza. Nonetheless this work also highlights the need for improved tracking of currently circulating viruses, with more frequent updating, greater global coverage and better quality of data. Second, a better understanding of the underlying processes driving influenza evolution would allow more refined approaches for forecasting seasonal strain dynamics. This would have obvious public health implications, for example in vaccine strain selection.

Monitoring zoonotic infections during the inter-pandemic period is an important part of preparedness for the next pandemic. To this end a better understanding of transmission and evolutionary dynamics in animal reservoirs, including wild birds and domesticated animals is needed. Such developed understanding of the current situation could allow us to forecast potential geographical hotspots and focal transmission species on which surveillance may be concentrated.

Five priority public health topics were identified for an inter-pandemic scenario as follows:

1. Integration of genetic, antigenic and epidemiological analyses to refine understanding of the spatiotemporal spread of circulating strains, to improve forecasts of virus evolution for vaccine strain selection and to anticipate likely burden of disease
2. Quantifying the relative contributions of different modes of transmission of human influenza and developing mechanistic modelling of transmission processes
3. Cross-disciplinary research using novel data-capture technologies to better characterize human contact and mobility patterns at local, regional and global scales, and to understand how they correlate with transmission risk
4. Integration of genetic, antigenic and epidemiological analyses to optimize surveillance for newly emerging pathogens at the animal-human interface
5. Identifying and quantifying human and environmental ecological, behavioral and demographic determinants of the risk of cross-species transmission and pandemic emergence

5.3 Modern tools for risk communication

Road mapping for a pandemic scenario

During a pandemic scenario, the group prioritized topics and questions relating to rapid action and response. In particular they considered questions relating to communicating risk to the population as a whole, recognizing the need to identify the particular needs of groups at higher risk.

Three priority public health topics were identified for a pandemic scenario as follows:

1. Identification, development and evaluation of tools and methods to more rapidly, accurately and over time assess and monitor knowledge, attitudes, beliefs and practices in different population groups, and thereby guide future communication efforts
2. Evaluation of communication tools and approaches for communicating in different cultural settings, which engage and empower individuals and communities to practice and promote appropriate risk reduction measures
3. Increased understanding of the dynamics of inaccurate and contradictory information, rumours, myths, and narratives through tracking, monitoring and analyzing different communication sources and channels and to develop effective ways to respond



Road mapping for an inter-pandemic scenario (seasonal influenza)

During an inter-pandemic phase, a more comprehensive approach should be applied to research, prioritizing a range of questions that will build a more solid foundation to guide strategic communication for influenza control. Recommended priorities included the undertaking of a thorough and wide-ranging global literature review, upstream development of better ways to measure population perceptions in both crisis and routine situations and development of ‘state of the art’ communication approaches and strategies. A reflective review to better understand the political, social and economic dynamics of past crisis situations would also be possible here.

Four priority public health topics were identified for an inter-pandemic scenario as follows:

1. Review of international evidence and experience related to health and health crisis communication from relevant fields, such as behavioural and social sciences, media studies and (social) marketing to gather and organize knowledge, stimulate further research to fill the gaps and support evidence-based practice in strategic communication
2. Identification and development of tools and methods to more rapidly, accurately and over time assess and monitor knowledge, attitudes, beliefs and practices in different population groups, and thereby guide future communication efforts
3. Identification and development of communication tools and approaches for communicating in different cultural settings, which engage and empower individuals and communities to practice and promote appropriate risk reduction measures
4. Increased understanding of the potential ethical, social, economic and political dimensions of communicating in national and international crisis situations and develop strategies for working within constraints while maximizing opportunities



F. IMPLEMENTATION OF THE RESEARCH AGENDA: NEXT STEPS

Participants in each of the research streams proposed how implementation and ongoing improvement of the Research Agenda might be accomplished. There was general agreement that advancement of the WHO *Public Health Research Agenda for Influenza* will require engagement with multiple partners and stakeholders such as the WHO regions, individual countries, research institutes, non-governmental organizations and funding agencies. Consultation with WHO regions and individual countries can refine concepts and strategies, identify regional and local priorities and minimize duplication of efforts. These discussions can yield a Research Agenda that is relevant at global, regional and national levels.

WHO Regional Offices can advocate for the global goals with their respective countries, at the same time stressing the benefits of the Research Agenda as they relate to each country. Consultations with countries can help to determine how they can best participate in, contribute to and benefit from the proposed research. Regional Offices may also provide a venue for a forum on research of particular regional interest and for wider information sharing.

At country level there should be a national process to scope the research needs, current research capacities and potential for augmentation of those capacities through involvement in designated research activities. Local scientists and investigators should be encouraged to participate through cross-sectoral and international collaboration. Countries should also encourage and ensure a robust and timely process for ethical review of proposals.

There is a critical need to advocate with major international partners, foundations, non-governmental organizations, funders and governmental funding agencies, to stress the requirement for research capacity building, both in terms of infrastructure and human resources. WHO may be well placed to promote the organization of regional consortia. In addition, WHO may wish to consider developing 'WHO Collaborating Centres for Clinical Science' and/or coordinating clinical networks. International alliances that involve investigators and scientists from developing countries should be fostered so that they can help improve the applied, public health oriented research sector at national level. In addition, advocates, such as individual 'champions,' scientific boards of major donor agencies and members of affected communities, can play a critical role in moving the WHO *Public Health Research Agenda for Influenza* forward and facilitating funding for priority research.

Effective and multi-pronged communication strategies are needed to promote the Research Agenda taking into account different target audiences. WHO should consider how to work best with the media in this regard. Information about the Research Agenda should be disseminated from the outset, establishing an effective process to capture and share new knowledge as it is created during implementation. Technical experts and scientists working in the field of influenza should be encouraged to reference the WHO *Public Health Research Agenda for Influenza* when addressing unmet needs and knowledge gaps.

A common set of indicators would be helpful so that research done in different settings and different countries can be compared and adapted for use in a variety of settings. Development of a research database that can be accessed by relevant stakeholders would be a valuable tool to organize information about research underway (e.g. investigators, key objectives, results) and to help avoid unwanted duplication. Inventories of current research and research capability and capacity at the regional/country level may be helpful. However, development of such databases would be resource-intensive and frequent updating would have to be sustained. Finally, ongoing horizon scanning can help ensure that the global agenda remains a living, relevant document.

Given that modern public health tools are still a new technical area, the Stream 5 Working Group recommended a follow-up consultation or workshop specifically focused on Stream 5, particularly in the areas of surveillance and risk communication. Given the linkages with the other streams it was recommended that key experts from other streams be involved in such a meeting.



All participants stressed that finalization of the agenda and its promotion should occur as rapidly as possible and utilize whatever interagency collaboration at the international level is needed.

G. CONCLUDING REMARKS

The Chairperson thanked all the speakers and participants for their contribution to an informative meeting. John Tam, project lead of the Public Health Research Agenda for Influenza, also thanked everyone for their participation and concluded with the following points as a way forward:

- The WHO will value and consider the suggestions outlined in this consultation and to finalize the Research Agenda as rapidly as possible
- Plans will be developed to implement the Research Agenda as recommended in the consultative meeting
- Activities related to the four cross cutting research topics that are applicable to the five research streams, namely surveillance, laboratory diagnosis, mathematical modelling and risk communication, will be developed.



ANNEX 1. SUMMARY OF KEYNOTE PRESENTATIONS

Editorial note: The consultation included a series of presentations summarizing current information about virological, epidemiological and clinical features of pandemic influenza A (H1N1) 2009, the development of relevant guidance for antiviral drugs and pandemic vaccines, the roles of risk communications, mathematical modelling and ethics and the generation of viruses with pandemic potential at the animal-human interface.

Each of the presentations is briefly summarized below; accompanying slide sets can be viewed from the following web site:

http://www.who.int/csr/disease/influenza/research_agenda/en/index.html.

Early warning signs of the H1N1 pandemic: importance of laboratory surveillance

Nancy Cox, Centers for Disease Control and Prevention, Atlanta, GA USA

Lessons learned for laboratory preparedness

- Surveillance for influenza in domesticated animals is an essential component of pandemic preparedness
- The swine, avian and human origins of pandemic A(H1N1) 2009 influenza is a potent reminder of the ongoing exchange of influenza viruses between humans and domestic and companion animals
- Improved dialogue between human and veterinary health officials and researchers is critical for pandemic preparedness and response
- Rapid information and virus sharing is essential for an effective pandemic response
- Global preparedness for a possible H5N1 pandemic made response to the A(H1N1) 2009 pandemic easier
- Well developed global networks (e.g. the WHO Global Influenza Surveillance Network), relationships and partnerships allowed for a more coordinated and measured global response
- Ongoing dialogue with public health partners, regulatory agencies, laboratories and industry facilitated a more rapid response
- Rapid publication of genetic sequences facilitated development and assessment of molecular tests
- Accessible viruses, reagents, and proficiency panels facilitated more rapid diagnostic test development
- More sensitive and inexpensive point-of-care tests are necessary for field deployment, patient management, detection of antiviral resistance and rapid, accurate testing for immunity to the pandemic virus
- The availability of diagnostic tests that can detect different influenza virus subtypes in clinical settings may detect new viruses and assist with patient management

The more than decade long experience with avian influenza A (H5N1) and careful study of previous pandemics and epidemics shaped global expectations and preparedness planning for the first pandemic of the 21st century. However, contrary to expectations, the new pandemic virus emerged in North America, not Asia; originated in swine, not birds; and did not approach the severity of a 1918-like pandemic, the scenario most often envisioned by pandemic planners.

Preparing diagnostic capability for a pandemic is challenging because of the ever evolving nature of influenza viruses and varying diagnostic needs for different settings and users. Clinicians in ambulatory care need rapid and accurate point-of-care tests to assist with patient management and supportive care; clinicians in hospitals and intensive care units need to detect and control nosocomial spread of influenza and manage patients with severe respiratory disease; and public health officials need these same tools as well as more complex laboratory tests to monitor severity and spread of epidemics/pandemics of influenza, select vaccine viruses, determine vaccine match and antiviral susceptibility and identify newly emerging influenza viruses.



Diagnostic preparedness for influenza epidemics and pandemics requires a multi-pronged approach that includes the development of new laboratory tests to improve diagnostic capabilities; enhancement of laboratory surge capacity; establishment of proficiency testing programmes; consideration of policy and regulatory issues; improved access to viruses and reagents; and enhanced virological surveillance. The timely detection and characterization of the first isolates of pandemic AH1N1) 2009 influenza in the United States were facilitated by such broad based laboratory preparedness.

Risk communication: the Mexico experience

Ljubica Latinovic, Mexico Ministry of Health, Mexico City, Mexico

Lessons learned for risk communication

- Follow a precautionary, transparent and evidenced-based approach as much as possible
- Plan for frequent updating of guidance and information documents in a rapidly evolving situation
- Utilize modern tools such as the internet and electronic social networks
- Target information to specific audiences
- Seek feedback from your audiences to assess the effectiveness of communication messages

The pandemic response in Mexico was guided by two principles: first, the protection of health and preservation of life and second, continuity of the social, cultural, economic and political dynamics of the nation.

Risk communications were based on a precautionary, transparent and evidenced-based approach. 'Intervention Packages' were created that included 'criteria documents' incorporating information about the pandemic virus from both domestic and international sources. Frequent updating of these documents was necessary as new information became available and experience grew. A portfolio of guidelines were developed for numerous settings (e.g. home, workplace, public transport, hotels, schools, day care facilities, shelters, migrant stations and cruise ships) and activities (e.g. public events, electoral process and community workshops). Included in the guidelines were recommendations about personal and environmental hygiene and various preventive measures (e.g. maintenance of a healthy distance between people in theaters, restaurants and other crowded settings).

Health officials used the internet and social networking tools such as Twitter to disseminate information. Information about the pandemic was 'branded' with a popular cartoon character to increase engagement and recognition. Several mechanisms were used to help health authorities gauge the risk communication needs including monitoring radio and television 'talk' programmes with open phone/internet lines for listener/viewer questions; tabulating the most frequently asked questions received by Call Centers; tracking and analysis of risk perception studies and surveys done by different marketing companies and media; daily analysis of messages in the press with national coverage; and monitoring of the ministry's influenza blog.

Audiences that were targeted included children, pregnant women, decision makers at different levels, migrants and other high risk populations, employers and medical practitioners. Adolescents were one of the groups that we did not reach with our risk communication strategy, different approach was needed. Various surveys have helped officials assess the effectiveness of their risk communications programme. In May 2009 a survey on public knowledge, attitudes and acceptability of different mitigation measures was conducted in Mexico City and the State of Mexico. This was coupled with direct observation of the re-opening of schools to assess implementation of triage procedures and hygiene measures. In October 2009 another survey assessed people's perception, knowledge and intention to receive the pandemic vaccine. Finally, a survey will be undertaken in December 2009/January 2010 in all Mexican states to assess knowledge, attitudes and practices about various control measures that were implemented and promoted by the health authorities.



Clinical experience on care of severely ill patients with influenza infection

Kevin Rooney, Royal Alexandra Hospital, Greater Glasgow and Clyde Health Board, Scotland, UK

Lessons learned for clinical management

- Analysis and interpretation of 'severe' cases of pandemic A(H1N1) 2009 infection have been hampered by a lack of standardized definitions for severity and underlying or co-morbid conditions
- Approximately 1%-10% of persons with clinical illness required hospitalization and 10%-25% of these required intensive care
- On average, about 50% of hospitalized patients have had one or more underlying medical conditions; about one third of patients with very severe illness admitted to an intensive care unit were previously healthy persons
- Patients with severe illness generally deteriorated 3-5 days after the onset of symptoms and in some instances rapidly progressed to respiratory failure in 24 hours
- Intubation and, in some instances, advanced ventilatory techniques or extracorporeal membrane oxygenation have been used to manage respiratory failure
- Successful treatment depends on a high index of suspicion, early diagnosis and early treatment with oseltamivir, prompt invasive ventilation, a conservative fluid strategy and awareness of the risk for secondary bacterial infections

The clinical spectrum of pandemic A(H1N1) 2009 influenza has ranged from a non-febrile, mild upper respiratory tract infection to severe illness, including rapidly progressive pneumonia; most persons have experienced a typical febrile influenza-like illness. Overall, approximately 1%-10% of persons with clinical A(H1N1) illness have required hospitalization. It is reasonable to assume that a minimum of 10% of hospitalized cases will require intensive care unit treatment; however, sensible planning assumptions may be as high as 25% depending on the background prevalence of co-morbidities.

The highest hospitalization rates have been observed among infants, young children and young adults. While people >65 years have been much less likely to become ill with pandemic H1N1 infection, once ill, their risk of hospitalization is increased. On average, about one third of severely ill persons have had one or more severe co-morbid conditions; a third of patients have had risk factors like asthma and pregnancy; and the remaining third have been previously healthy. Indigenous populations or socially deprived persons may be at increased risk of severe disease.

Initial treatment decisions should be based on a patient's clinical presentation and available epidemiological data. Treatment should not be delayed while waiting for laboratory confirmatory testing. Real time-polymerase chain reaction testing provides the most timely and sensitive evidence of pandemic A(H1N1) 2009 infection; however, false negatives and false positives occur. Sequential sampling of respiratory secretions, particularly those from the lower respiratory tract in severely ill patients, may help to confirm the diagnosis, to understand viral load/clearance during illness and to detect the development of antiviral resistance.

Rapidly progressive respiratory failure is relatively common preceding admission to an intensive care unit and underscores the importance of monitoring respiratory rates and oxygen saturation. Most patients with severe respiratory disease have required invasive ventilation and in some instances more advanced respiratory ventilatory techniques or extracorporeal membrane oxygenation. Early treatment with oseltamivir is recommended and critically ill patients may benefit from higher dosing schedules and a longer duration of therapy to help limit the duration of viral shedding and ensure therapeutic levels. Increased availability of parenteral-administered antiviral agents is needed to rapidly and reliably deliver high levels of drug.



Evidence-based development of guidelines: the WHO antiviral guideline

Charles Penn, Global Influenza Programme, World Health Organization, Geneva, Switzerland

Lessons learned for antiviral guidance development:

- It is possible to make strong recommendations based on low quality evidence
- Independent assessment of relevant data is important
- Guidance may need to go beyond regulatory-approved usages
- Consensus may be hard to achieve especially when high quality data are lacking
- Guidelines need to be adaptable to local needs and clinical judgment
- Guideline recommendations need to be implementable across a spectrum of available resources and capacities; drugs need to be in easy-to-use formulations
- Monitoring the impact and effectiveness of the recommendations can assist in future revisions
- Guidance must be kept under ongoing review and updated in evolving circumstances
- Multifaceted communications planning and information dissemination that takes into account multiple audiences helps to reinforce the message

Early in the response to pandemic A(H1N1) 2009 influenza it became clear that global guidance was needed on the use of antivirals, especially to limit morbidity and mortality associated with severe illness and viral pneumonitis. WHO convened an expert panel in June 2009, two months after the start of the A(H1N1) 2009 pandemic, and published 'emergency' antiviral guidelines in August 2009. These recommendations were based on available evidence with the intention to review and revise the guidance in early 2010 as new information became available.

Despite the paucity of available evidence it was possible to make strong recommendations regarding antiviral treatment, albeit with the clear caveat that the advice was based on low quality information. Early clinical experience in treating severely ill patients suggested that WHO guidance needed to address issues for which clinical trial data were lacking, such as new patient groups (e.g. infants, pregnant women), higher dosing and longer-than-usual treatment courses. In some instances, such as the safety and potential efficacy of immunomodulators like corticosteroids, it was difficult to achieve consensus due to the lack of high-quality data.

To be useful on a global level, it was important that recommendations by WHO could be adapted to local needs and settings and leave room for clinical judgment. However, some challenges to implementation rested with the drugs themselves; e.g. need for easy-to-use pediatric formulations and parenteral formulations suitable for treatment of critically ill patients.

Monitoring the impact and effectiveness of WHO's 'emergency' antiviral treatment guidelines is ongoing. This information, together with new developments (e.g. emergence of a small number of resistant pandemic A(H1N1) virus isolates) and improved understanding of the clinical and epidemiological features of the pandemic virus will be incorporated in updated guidance planned for early 2010.

From wild birds to humans: the H5N1 experience

Malik Peiris, University of Hong Kong, Hong Kong SAR, China

Presented by: *Richard Webby, St. Jude Children's Research Hospital, Memphis, TN USA*

Lessons learned for the animal-human interface:

- Poultry can act as an intermediate host for direct transmission of avian influenza viruses to humans
- Live bird markets are high risk areas for the generation of novel influenza strains
- Live poultry markets maintain and amplify avian influenza viruses
- The development and evaluation of intervention strategies in live markets based on scientific data can be successful
- Highly pathogenic avian influenza can spread on a global level
- Highly pathogenic avian influenza can infect, cause disease and be spread in wild birds



- Highly pathogenic avian influenza can infect a surprising number of mammalian hosts
- The distribution and types of molecular receptors can only partially explain host range barriers
- Reassortment of avian haemagglutinin with human strains is not sufficient for development of a human pandemic virus
- Scientific evidence for understanding pandemic risk is primarily observational data

The initial detection of avian influenza A (H5N1) in 1997 in Hong Kong – initially in chicken farms followed by subsequent spread to humans – demonstrated with striking clarity that avian viruses can be transmitted to humans, cause illness and in some instances result in death. This small, but explosive and surprising outbreak reinforced the importance of understanding the animal-human interface for the generation and spread of influenza viruses.

Live bird markets are now well recognized high risk areas for the generation, maintenance and amplification of novel influenza viruses. Multiple studies have demonstrated that virus concentration is generally low at the farm or household level, increases at wholesale markets, and is further amplified and sustained at live animal markets, where virus may be disseminated back to farms and households. Targeted surveillance coupled with evidenced-based intervention strategies (e.g. institution of ‘rest days’ in retail poultry markets, removal of certain species such as Japanese quail and removal of all birds from the market at night) have resulted in decreased rates of influenza virus isolation in market poultry.

Highly pathogenic avian influenza H5N1 has been noteworthy for its subsequent geographic spread, ability to cause disease in wild birds (unlike other viruses which result in asymptomatic carriage) and its ability to infect a surprisingly diverse number of mammalian species. This later finding has underscored our fledgling understanding of how host receptors affect viral infectivity and pathogenicity and the pandemic potential of avian influenza viruses.

Vaccine development: experience from H5N1 to pandemic (H1N1) 2009 influenza

Marie-Paule Kieny, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Lessons learned for vaccine development

- Adjuvants have been shown to have a dose-sparing effect for H5N1 and A(H1N1) 2009 vaccines and could have applicability for seasonal influenza vaccines
- Although the development and initial availability of a vaccine for pandemic A(H1N1) 2009 influenza took just 6 months, more modern vaccine production technologies and substrates are urgently needed to shorten production times
- Development of vaccine production facilities in low- and middle-income countries and provision of technology transfer and expertise can help increase global vaccine production and improve access to seasonal, zoonotic and pandemic influenza vaccines
- Ongoing monitoring and evaluation suggest that pandemic vaccines are as safe as seasonal influenza vaccines with side effects similar to those observed for seasonal influenza vaccines
- Although WHO has secured donations of pandemic vaccine for use in low- and middle-income countries, countries need to have plans in place (e.g. logistics, identification of priority groups) before vaccine can be released

Studies on the antigenic properties of influenza A(H5N1) vaccine viruses and their relation to emerging H5N1 viruses are ongoing. All H5N1 influenza vaccines tested have demonstrated a good safety profile; antigen dose sparing has improved with the new generation of oil-in-water adjuvants.

Both adjuvanted and non-adjuvanted pandemic A(H1N1) 2009 vaccines have induced high level immune responses in healthy adults in clinical trials. Preliminary safety data for pandemic A(H1N1) 2009 vaccines indicate a relatively low frequency of local and systemic reactions; a small number of severe events -- mainly due to allergic reactions—have been reported.

WHO has estimated that the global manufacturing capacity for pandemic influenza vaccines is about 3 billion doses per year if all available capacity is devoted to pandemic vaccine production. This falls far



short of the total global need necessitating prioritization of a scarce resource. WHO has recommended that health workers be given first priority for vaccination to protect themselves and their patients, and help keep health systems functioning over the course of the pandemic. Other groups at higher risk for severe illness, based on clinical studies, should also be considered including pregnant women; those aged above 6 months with chronic medical conditions; healthy young adults of 15 to 49 years of age; healthy children; healthy adults of 50 to 64 years of age; and healthy adults of 65 years of age and above. National authorities must develop and implement vaccination plans based on circumstances within the country.

WHO has helped secure significant donations of vaccines from countries and partners for 95 low- and middle-income countries. The goal of WHO is to provide each of these 95 countries with enough vaccine to immunize at least 10% of its population. National health authorities, however, must be ready to implement national vaccination campaigns (i.e. have plans, logistics, priority groups, legal requirements in place).

Application of modelling in public health decision-making

Neil Ferguson, Imperial College London, London, UK

Lessons learned for modelling in public health decision-making

- Advanced analysis and modelling are useful to assist public health policy making at strategic and tactical levels
- Analysis and modelling have helped to assess some of the key epidemiological and clinical characteristics of pandemic A(H1N1) 2009 influenza
- Fundamental data gaps remain in some areas and would benefit from improved capacity building within public health organizations and sharing of detailed data
- Real-time modelling during the A(H1N1) 2009 pandemic has been proven exceptionally challenging

The public health roles of modern outbreak analysis and modelling include quantification of risk, analysis and interpretation of data, extrapolation to the future and assessment of the impact of prevention and control measures. During the A(H1N1) 2009 pandemic, modelling has been used to help quantify transmission and spread of the pandemic virus to underpin decisions about pandemic phase changes; assess severity, interpret case trends, predict the trajectory of pandemic; assess the impact of interventions and inform study design. For example, modelling suggested that while school closure may offer some potential benefits (e.g. an approximate 40% reduction of peak incidence), it has very high costs. In addition, communities have little tolerance for long periods of school closure. More recent modelling has examined how to maximise benefits, while minimizing cost.

It was hoped that real-time modelling of the A(H1N1) 2009 pandemic might be possible. However, this has proven exceptionally challenging due in large part to the unavailability of key supporting data. Fundamental data such as the infection attack rate over time, the proportion of the population who sought care from a health provider, the impact of seasonal variation in transmissibility and the effectiveness of many non-pharmaceutical interventions were not available.

In addition to the unavailability of key data, the A(H1N1) 2009 pandemic highlighted a number of communication challenges including the difficulty in communicating uncertainty (e.g. the likelihood that modelling estimates may change over time as new information becomes available) and in explaining inconsistencies between countries and researchers.

Despite these challenges, the interaction between modellers and the public health community improved preparedness planning at global and national levels, enhanced overall situational awareness during the pandemic response and forged an enduring partnership that will continue beyond the current pandemic.



Ethics in public health policy development for influenza: experiences from developed and developing regions

Marc Guerrier, Espace éthique / Assistance Publique–Hôpitaux de Paris, University Paris XI, Centre Collaborateur OMS pour l'éthique CHU Saint Louis, Paris France

Lessons learned for ethical public health policy development

- Research in the context of a global pandemic will be strengthened by explicit ethical underpinnings
- More research is needed on key ethical topics for planning and response related to the A(H1N1) 2009 pandemic and global infectious disease crises
- The interactions between researches in ethics, medical sciences, public health policies and social science are of the utmost importance

Setting research priorities in the context of a global infectious disease outbreak is challenging. The ethical underpinnings of a Research Agenda must include the principles of equity/fairness, transparency, efficiency, empowerment and responsiveness.

A number of issues related to research activities and public health ethics have emerged in the context of a global pandemic and were discussed as part of WHO Technical Consultation in June 2009. First, ethical review is a time-consuming process; typically, research ethics committees take several weeks/months to assess projects. In the context of a global pandemic or other global crisis 'it is crucial to streamline the ethics review process. Appropriate yet flexible mechanisms and procedures for ethical oversight need to be established that are not limited to traditional research ethics committee systems.' Second, although urgent, challenging ethical questions have arisen in this infectious disease emergency, 'the principles and values embodied in international and national ethics guidelines must be upheld.' Third, 'defining the boundary between public health-oriented research and practice remains a critical challenge in public health ethics. The purpose in distinguishing the two activities goes beyond semantic concerns because of the different ways in which public health research and practice are regulated in many countries.' A classic example of this tension relates to public health surveillance and instances in which it might be considered epidemiological research.

The sharing of knowledge, information and samples has been critical to advance our understanding of the new pandemic virus and develop appropriate prevention and control measures. However, rapid information sharing may raise specific ethical issues, such as confidentiality. Key research information such as raw data and results often have not been disseminated but rather kept confidential. Ideally, a specific overarching 'set of rules' governing raw research data, peer-review and publication during global public health emergencies need to be developed. As part of this process, consideration must be given as to how the principles of reciprocity and responsibility (among others) can be fairly applied in such settings.

Public health decision making usually rests on evidence-based information. However, many of the critical decisions about guidance related to prevention and control measures such as the use of antivirals, vaccination and masks have been made with incomplete and evolving information. Decision-makers have had to prioritize access to scarce interventions such as vaccines, antivirals and healthcare facilities such as intensive care units thus raising complex ethical issues such as global justice and equity, resource allocation among countries and public health goals. Other interventions such as social distancing measures (e.g. border management, quarantine, school closures) may involve ethical considerations that relate to individual liberties or confidentiality.

Finally, the duties and rights of healthcare workers and certain other professionals have arisen during the A(H1N1) 2009 pandemic, specifically regarding the issue of vaccination and if health care workers should be obliged to receive vaccine. Clear policies are lacking in many countries.



ANNEX 2: MEETING AGENDA



WORLD HEALTH ORGANIZATION

Consultation on Public Health Research Agenda for Influenza
(17 - 20 November 2009 - Geneva, Switzerland)

FINAL AGENDA

Day 1, 17 November 2009: Plenary session, CIGG

- 08:15 - 09:00 *Registration*
- 09:00 - 09:15** Welcome and opening remarks (*Special Adviser to the Director-General for Pandemic Influenza, Keiji Fukuda, WHO*)
- 09:15 - 09:20** **DESIGNATION OF CHAIRPERSON AND ADOPTION OF AGENDA**
- (**CHAIRPERSON: ARJUN KARKI, PATAN ACADEMY OF HEALTH SCIENCES, NEPAL**)
- 09:20 - 09:30 Objectives of the consultation and framework of discussion
(*Sylvie Briand, Global Influenza Programme, WHO*)
- 09:30 - 10:00 Presentation of participants
- 10:00 - 10:30 Global update of the current H1N1 pandemic
(*Anthony Mounts, Global Influenza Programme, WHO*)
- 10:30 - 11:00 *Refreshment Break*
- 11:00 - 11:30 The global response to the current H1N1 pandemic and implications for research especially for resource limited regions
(*Mohamed-Mahmoud Hacem, Health Security and the Environment, WHO*)
- 11:30 - 12:00 Identification of key information needed for the development of control measures during the evolution of the current H1N1 pandemic
(*Nahoko Shindo, Global Influenza Programme, WHO*)
- 12:00 - 12:30 Presentation of draft Research Agenda and the consultation process
(*John Tam, Global Influenza Programme, WHO*)
- 12:30 - 14:00 **GROUP PICTURE (in front of Podium)**
Lunch Break
- 14:00 - 14:30 Introduction of research streams (Chair and Moderator *John Tam GIP/WHO*)
Presentation - Stream 1: Reducing the risk of emergence of pandemic influenza
(*Ilaria Capua, Istituto Zooprofilattico Sperimentale delle Venezie, Italy*)
- 14:30 - 15:00 Presentation - Stream 2: Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza
(*Hitoshi Oshitani, Tohoku University, Japan*)
- 15:00 - 15:30 Presentation - Stream 3: Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza
(*Arnold Monto, University of Michigan, USA*)
- 15:30 - 16:00 *Refreshment Break*



- 16:00 - 16:30 Presentation - Stream 4: Optimizing the treatment of patients (*Tawee Chotpitayasunondh, Queen Sirikit National Institute of Child Health, Thailand*)
- 16:30 - 17:00 Presentation - Stream 5: Promoting the use and application of modern public health tools (*Stream Lead: Susan MacKay, Kasetsart University, Thailand*)
- 17:00 - 17:15 Closure of the day and housekeeping announcements
- 17:30 - 19:00 *Reception*

Day 2, 18 November 2009: Break-out session I, WHO HQ

- 08:15 - 09:00 *Registration*
- 09:00 - 09:15 Introduction of the Working Group and agenda for the next 2 days (*Stream leaders, Co-Leads and WHO Point-of-Contact*)
- 09:15 - 09:45 Feedback on the development process of the Research Agenda (*All participants*)
- 09:45 - 10:30 Presentation of the draft interim Research Agenda (*WHO Point of Contact*)
- 10:30 - 11:00 *Refreshment Break*
- 11:00 - 11:45 Presentation of the background information document (*Stream Rapporteur*)
- 11:45 - 13:00 Open discussion on stream specific research gaps
- 13:00 - 14:00 *Lunch Break*
- 14:00 - 16:00 Open discussion on stream specific research gaps (continuation)
- 16:00 - 16:30 *Refreshment Break*
- 16:30 - 17:00 Consolidation of Research Agenda
- 17:00 - 17:10 Closure of the day

Day 3, 19 November 2009: Break-out session II, WHO HQ

- 09:00 - 09:30 Main results and summary of day 2
- 09:30 - 11:00 Roadmap: Defining the knowledge gaps in current H1N1 pandemic phase
- 11:00 - 11:30 *Refreshment Break*
- 11:30 - 13:00 Roadmap: Defining the knowledge gaps in non-pandemic phase (Phase 3 situation)
- 12:30 - 14:00 *Lunch Break*
- 14:00 - 15:30 Highlighting next steps for implementation of Research Agenda at global level
- 15:30 - 16:00 *Refreshment Break*
- 16:00 - 16:30 Preparation of stream presentation to Plenary next day
- 16:30 - 17:00 Discussion and closure of break-out session



Day 4, 20 November 2009: Plenary session, EB room (HQ)

Lessons Learned Series Keynote Presentations

Moderators: *Abdulsalam Nasidi, Federal Ministry of Health, Nigeria*

- 08:30 - 09:00 Early warning signs of the H1N1 pandemic: importance of laboratory surveillance system.
Speaker: Nancy Cox, Centers for Disease Control and Prevention, USA
- 09:00 - 09:30 Risk communication: the Mexico experience.
Speaker: Ljubica Latinovic, Ministry of Health, Mexico
- 09:30 - 10:00 Clinical experience on care of severely ill patients with influenza infection.
Speaker: Kevin Rooney, Royal Alexandra Hospital, UK
- 10:00 - 10:30 Evidence-based development of guidelines: the WHO antiviral guideline.
Speaker: Charles Penn, Global Influenza Programme, WHO
- 10:30 - 11:00 *Refreshment Break*
- 11:00 - 11:30 From wild birds to human: the H5N1 experience.
Speaker: Malik Peiris, University of Hong Kong, Hong Kong SAR
- 11:30 - 12:00 Vaccine development: experience from H5N1 to pandemic H1N1 2009.
Speaker: Marie-Paule Kieny, Initiative for Vaccine Research, WHO
- 12:00 - 12:30** Application of modeling in public health decision making.
Speaker: Neil Ferguson, Imperial College London, UK
- 12:30 - 13:00** Ethics in public health policy development for influenza: experiences from developed and developing regions.
Speaker: Marc Guerrier, Espace Ethique AP-HP, University Paris XI, France
- 13:00 - 14:00** **LUNCH BREAK**
- 14:00 - 14:30 Moderator: *John Tam, GIP/WHO*
Feed-back from the working group 1 and discussion (*Stream 1 presenter*)
- 14:30 - 15:00 Feed-back from the working group 2 and discussion (*Stream 2 presenter*)
- 15:00 - 15:30 Feed-back from the working group 3 and discussion (*Stream 3 presenter*)
- 15:30 - 16:00 *Refreshment Break*
- 16:00 - 16:30 Feed-back from the working group 4 and discussion (*Stream 4 presenter*)
- 16:30 - 17:00 Feed-back from the working group 5 and discussion (*Stream 5 presenter*)
- 17:00 - 17:30 Next steps and closure of the meeting
(*John Tam, Global Influenza Programme, WHO*)



ANNEX 3. LIST OF PARTICIPANTS



WORLD HEALTH ORGANIZATION

Global Consultation on Public Health Research Agenda for Influenza
17 to 20 November 2009, Geneva, Switzerland

LIST OF PARTICIPANTS

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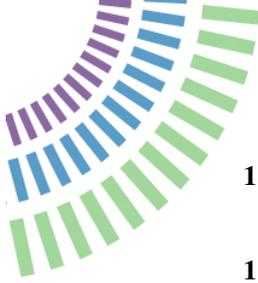
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ANNEX 4. DECLARATION OF INTEREST

The Research Stream participants completed the WHO standard form for declaration of interests prior to the meeting. At the start of the meeting, all participants were asked to confirm their interests, and to provide any additional information relevant to the subject matter of the meeting.

The following participants declared current or recent (<1 year) personal financial interests related to commercial organizations as listed below (separated by Research Stream and their areas of interest for the Stream):

Stream 1. Reducing the risk of emergence of pandemic influenza

Area of interest: human-animal interface

Peiris	Consultancy, research and service agreements and sponsorship from vaccine manufacturers including GSK, Baxter and Sanofi-Pasteur for his institution
Perez	Declared interest with patent pending (Company UMD) with no commercial interest

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

Area of interest: virus transmission, surveillance and public health policies

Jennings	Consultancy as chairperson of an interest group APACHI which is supported by a number of commercial vaccine and antiviral manufacturers, not related to the area of interest of Research Stream 2
Van der Werf	Consultancy and research support from vaccine and antiviral manufacturers including GSK, Roche and Danone, institutional and not related to the area of interest of Research Stream 2
Watkins	Consultancy from vaccine and antiviral manufacturers including MSD, Sanofi-Pasteur and Roche, institutional and not related to the area of interest of Research Stream 2.

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

Area of interest: Burden of illness and vaccine research

Bright	Declared past employment and current stock holding >\$10,000 of vaccine research company Novavax, but currently employed by NGO (PATH)
Monto	Consultancy and research support from vaccine and antiviral manufacturers including GSK, Sanofi-Pasteur, Novartis, Biosyst, Baxter and Roche, <\$10,000, institutional
Nicholson	Consultancy and research support from vaccine and antiviral manufacturers including GSK, Novartis and Baxter, <\$10,000, institutional

Stream 4: Optimizing the treatment of patients

Area of interest: Antiviral drugs and associated treatment for influenza research

Chotpitayasunondh	Research support from vaccine manufacturer Sanofi-Pasteur, \$50,000, institutional and not related to the area of interest of Research Stream 4
Hay	Technical adviser to GSK <\$1000, personal
Hien Nguyen	Research funding declared, not specified, work in public institution
Kiselev	Declared employment, consultancy and research support from commercial entity in Russia, not specified



Osterhaus	Declared employment by Viroclinics B.V., \$56,015; research support from public institution and other interests. He only attended day 1 plenary session without discussion on Stream-specific topics.
Tisdale	Declared employment, consultancy (GSK, Biota and Biocryst) and stock (GSK) >£1,000, served as Rapporteur for the Stream 4 discussion with no input
Hayden:	Unpaid adviser (sometimes with access to confidential information) for Alios, Adamas, Kirin, Abbott, Crucell, Nexbio, Biocryst, GSK, Roche, Toyama, Respirivert, 3V biosciences, Inhibikase, Vaxinnate.

Stream 5: Promoting the Development and Application of Modern Public Health Tools

Area of interest: Modern tools for surveillance, mathematical modeling and risk communication

Ferguson	Declared consultancy with vaccine and antiviral manufacturers GSK and Roche, \$2,000, personal and not related to the area of interest of Research Stream 5
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The following participants declared non-commercial academic interests in the subject of the meeting, and have (co-)authored publications that include reports on commercially funded clinical trials or opinions or recommendations on specific antiviral treatment of influenza virus infection:

Peiris, Hay, Hayden, Nicholson, Chotpitayasunondh, Monto

Many participants described academic interest in the subject matter of the meeting, including participation in non-commercially funded clinical studies. These were not regarded as conflicts of interest since they formed the basis of the expertise of the panel. In addition, in consideration of the breadth of the subject matter of the consultation, and the overall number of participants, WHO determined that the above declared interests of a small minority of participants would not affect their participation in the meeting.