WHO PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA

Biannual Progress Review and Report 2010–2011

World Health Organization

Global Influenza Programme

Contents

Executive Summary of Two Years' Progress

In order to evaluate the impact of WHO's initiative to encourage research on better prevention and control of influenza globally, a biannual progress review was conducted. WHO Secretariat, with help from the scientific committee, identified high priority public health research topics from the five main research areas ('Streams') and commissioned literature reviews for each. Over 4000 citations of publications from 2010–2011 in more than 200 journals or other peer-reviewed publications were found through the literature reviews and database searches for this Progress Report. Defining the major achievements reflected in this large number of publications relies to a degree on subjective evaluations; however, without doubt, research related to understanding the emergence and progression of the 2009 H1N1 pandemic dominated the body of work. Publications related to specific pharmacologic interventions, influenza vaccines and antivirals, also predominated in the published work, representing more than half of the total. The work also represents a truly international effort to address influenza, with many of the publications in non-English language journals.

Major research achievements for each stream, that were felt to have a direct impact on public health, were discussed during the informal consultation and some highlights can be summarized briefly:

Stream 1: The role of mutations and re-assortment in nature of animal influenza virus genes with human virus genes to generate potential human zoonotic or pandemic strains has become clearer. This research clearly stresses the need for enhanced, molecularly based surveillance efforts at the animal-human interface, including more work in swine and those exposed to them.

Stream 2: Knowledge concerning virus survival in the environment, recognition of the importance of close contact for transmission and new evidence in support of the potential for aerosol transmission has all expanded. Further studies of the effectiveness of particular types of personal protection strategies in different settings (schools, households, healthcare) are needed.

Stream 3: Ongoing burden-of-disease and expanded epidemiological studies in the developing world are providing new information for informing seasonal influenza vaccination policy decisions. More immunogenic and in some cases more effective as well as novel broad-spectrum influenza vaccines continue to be developed and are moving closer to licensure.

Stream 4: Knowledge has increased about safety, routes of administration and dose regimens of current antivirals, including those for selected at-risk populations; in addition more is known about the effectiveness of new agents, including intravenous formulations, adjunctive therapies, and therapeutic combinations as well as about the timing and selection of antibacterial agents. Operational issues to ensure adequate health service and care require further study. The effectiveness of WHO-led

syndromic clinical approach e.g. IMAI (integrated management of adults and adolescents illnesses) and IMCI(Integrated management of childhood illness) needs evaluation.

Stream 5: Modelling was a useful tool for planning but evaluation and improvement of methodology are required. More research is warranted in the area of social and behavioural science in order to learn about people's (different audience) risk perception and behaviour.

1. Introduction

1.1 The development of the WHO Public Health Research Agenda for Influenza

From November 17 to 20 2009 the WHO Global Influenza Program held a consultation to assess the status of global research efforts to understand, prevent and treat influenza; to develop a Research Agenda that would reflect a consensus of investigators working on the disease; and to propose recommendations that would help to meet identified gaps in our understanding of the emergence, transmission, mitigation and management of influenza. This meeting was a continuation of WHO's commitment to addressing global influenza problems, as reflected by earlier documents: the 2002 *WHO Global Agenda on Influenza*[1] and the 2006–7 *WHO Strategic Action Plan for Pandemic Influenza*.[2] More than 90 investigators, research funder representatives, public- health and policy officials from 35 countries joined the WHO Secretariat in developing research agenda to ensure knowledge gained could improve public health decision-making for prevention and control of influenza. The consultation produced a consensus document, WHO's first public health influenza research agenda (**http://www.who.int/influenza/resources/research/2010_04_29_global_influenza_research_agenda_version_01_en.pdf**). This document outlined priority research recommendations in five specific areas or Streams (outlined below) covering the landscape of global research efforts. Subsequently, three WHO Regions (Africa, South-East Asia and Western Pacific) held meetings to decide regional influenza research priorities and agenda implementation strategies.[3]

1.2 Review objectives

Although in development since 2008, the original Research Agenda and its recommendations were also made in light of the then ongoing 2009 (H1N1) pandemic. With the declared end of the H1N1 pandemic and the resulting host of 'lessons learned' documents and new scientific and public health information available, a review of the original 2009 recommendations was needed to determine whether these recommendations were still valid and, importantly, how the lessons learned from the H1N1 pandemic might change the prioritization of specific recommendations. Thus the key objectives of this current review were to (i) collate the new knowledge and progress attained since the launch of

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1 The Global Agenda on Influenza Surveillance and Control.
http://www.who.int/docstore/wer/pdf/2002/wer7722.pdf
http://www.who.int/docstore/wer/pdf/2002/wer7723.pdf
http://download.thelancet.com/flatcontentassets/H1N1-flu/surveillance/surveillance-5.pdf

2 **http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_2/en/**

3 **http://www.who.int/influenza/resources/research/en/**

the Agenda, (ii) interpret or apply this information for improved influenza prevention and control, and (iii) highlight remaining gaps and revise recommendations as appropriate.

1.3 Progress review process

The elements of the review included a 3-step process: (1) verifying consensus with the scientific committee on the priority research recommendations for the five research Streams, (2) commissioning of two to four topic-specific literature reviews per Stream and of one summary progress report, (3) convening a review committee meeting to assess these reports, evaluate the Research Agenda implementation and provide new recommendations for the WHO Secretariat.

2. Progress review

WHO's Global Influenza Program contracted for and received more than 20 literature reviews from influenza researchers around the world. A table of the reviews provided, the review topic area and their authors is attached (**Appendix 1**). The goal of these literature reviews and summaries was to provide a thorough overview of the publications since the first consultation, highlighting progress related to the original recommendations, and to identify gaps that remain. Based on these literature reviews as well as further reviews of other sub-streams not covered, lists of pertinent recent publications were developed (appendix 2–14), including citations of more than 4000 articles published in 2010 and 2011 from more than 200 journals or other peer-reviewed publications. The second component of the ongoing progress review was to bring together the original chairs and members of the five Streams to discuss progress and gaps and make recommendations for the next steps related to the WHO research Agenda.

2.1 Stream 1: Reducing the Risk of Emergence of Pandemic Influenza

Undoubtedly the most effective way to prevent emergence of a novel influenza virus in humans would be to remove the source of the virus or prevent onward transmission from the source. Since all of the human influenza A strains characterized to date have had an avian or porcine connection at some point in their evolution, the importance of knowing what influenza viruses are 'out there' in those animal populations is paramount. We also know that interactions between humans and their food animals is only going to become more frequent as both populations increase and that the likelihood of removing influenza viruses from our food animals is extremely small. Therefore, limiting the spread of zoonotic and potentially pandemic influenza viruses will directly affect our ability to reduce either the presence of the virus in the source or human contact with the source. Progress in both of these efforts has been notable since the Research Agenda was developed.

Three major areas of emphasis were identified in this Stream: 1) understanding the molecular changes/features that allow transition from an animal influenza strain into a human influenza strain, particularly one capable of pandemic transmission; 2) determining the risks associated with exposure of humans to animal viruses at the 'human animal interface', particularly behaviours that increase the probability of transmission from animals to humans; and 3) evaluating the best methods for preventing influenza in animals and/or preventing exposure to humans. Additionally, viral surveillance efforts, which are clearly of high importance in identifying and reducing risk, were reviewed and evaluated. However, since so many entities are currently carrying out influenza viral surveillance in animals and humans, and updates on these activities are regularly provided, it was concluded that a full literature

review on surveillance was not needed. As with the other Streams that follow below, several sub-areas of specific research were identified for each of the major areas of interest. These will not be covered in detail but may be referred to as needed.

Following the WHO consultation in 2009 numerous research studies have been published that are directly related to advancing our understanding of the molecular pathways that animal influenza viruses might follow to become human influenza viruses. Nearly 50 studies directly pertinent to this stream were found with 2010 and 2011 publication dates (**Appendix 2**). Most of these investigated the changes that occur in or around the virus' receptor binding site on the HA protein during adaptation from avian to mammalian epithelial cells (*5,7,15,17,28,43,46,51,53,63,73,77,85,87,88,92,96 ,98,104,109*). In particular, advances in the understanding of the types and structures of glycan preferred by human viruses were described in several papers. Additionally, work continued in full stride to understand the role of the polymerase protein PB2 in the transition from avian to mammalian viruses, as well as the role of the avian PB1-F2 peptide and the NS gene in virulence in humans (*2,3,8–10,12,24,35,38,54,55,58,67,70,74,83,97,105,113*). Another promising new research domain has been recently opened concerning the co-evolution of influenza virus and host genomes, e.g., by systematically searching for human microRNAs targeting PB1 and PB2. These microRNAs could possibly serve as markers of host resistance, depending on length and repetition of contacts between the host and pathogen RNA's (*81*).

Several articles related to understanding the zoonotic risks and important features of the connections between humans and their food animals are listed from 2010–2011 (**Appendix 3**). A review of the importance of influenza at the human animal interface was published in 2011 (*14*) that covered the known risk factors and the 'state of the art'. Additional serological studies were published and still indicate that the incidence of subclinical or unrecognized H5N1 infections in South-East Asia appear to be relatively small to insignificant, supporting earlier findings (*4,8,10,12,* and *14*). Although prospective studies are underway, in Vietnam for example, it is still not clear whether the lack of positive serological data has major significance, and this uncertainty remains a research gap. The role of other potential environmental exposure routes and the influence of familial or other genetic factors on susceptibility to animal influenza virus infections in humans still remain unclear. Other gaps include the need for increased research collaboration between animal and human laboratories, although some good progress has been made, particularly in live animal market studies (*2,6,* and *9*), and the need for standardized case investigations for zoonotic influenza outbreaks.

Surveillance of influenza viruses in the animal world cuts across essentially all of the other Streams. Its importance cannot be overemphasized. Since surveillance now provides so much more than just identifying the presence of viruses (e.g. phylogenetic status, presence of virulence factors, re-assortment and other mutations, antiviral susceptibility), gaps persist in making this information most useful to public health authorities. Significant funding increases for influenza virus surveillance at many levels have resulted in substantial expansion of efforts globally. In particular, expansions of the use of diagnostic assays that directly identify viruses have contributed greatly to both animal and human influenza surveillance. Increases now in routine reporting of influenza viruses in swine and poultry could only help to fill gaps. There is a need to determine and establish the extent of surveillance (i.e. how much is adequate) and to what extent human adapted strains might be re-introduced into animals, particularly swine, where novel reassortants may occur. Over 150 research articles and reports

were published summarizing influenza viral surveillance data (**Appendix 4**). This body of publications clearly indicates an important and dynamic ongoing field of study.

Finally, the interventions needed to reduce the presence of virus in animal populations and the subsequent exposure to humans were reviewed in depth. More than 40 related publications and reports were found for 2010–2011 (**Appendix 5**). Progress was reported in the development and use of cost-benefit analyses and new modelling approaches to verify or predict the best ways to control avian influenza (*13,16,19,22,23,35,39*) as well as in the development of new animal influenza vaccines and approaches to vaccination (*7,20,29,31,37). Some gaps here include 1) understanding and addressing the unique differences in control measur*es and animal health agency capabilities as they exist in different countries; 2) and widely differing environments and lack of full understanding of the measurable effectiveness of various interventions and control measures. For example, are vaccination programs coupled with stamping out better than one or the other alone?

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

Most experts would agree that removing influenza viruses from our food animals is not possible in the foreseeable future, much less removing influenza viruses from nature. As such, the next two research Streams (2 and 3) form the second line of defence against a major health catastrophe should a pandemic begin. Key questions for Stream 2 are whether we can 1) determine the relative importance of different modes of influenza transmission (contact, fomites, large droplet, droplet nuclei/aerosol or other) in given situations (e.g., households, healthcare facilities, schools, tropical areas); and 2) understand and quantify the effectiveness of individual (e.g. hand hygiene, masking) and public health measures (e.g., quarantine, school closures) to limit or interrupt transmission. Answers to these key scientific questions underpin the ongoing debate and unsolved controversy over the correct Personal Protective Equipment (PPE) and related policies for influenza-related infection control measures that make sense in households, workplaces and schools. Information resulting from these lines of research should serve to mitigate all forms of influenza, zoonotic, pandemic and seasonal. Numerous recent publications address these questions (**Appendix 6**).

The key current research efforts to address transmission are related to the physical aspects of human-to-human spread, although the molecular markers within viral genes that promote transmissibility are under intense study in several laboratories (*16,69*). Research evidence is drawn from several areas: knowledge concerning virus survival, i.e., retention of infectivity, in the environment, recognition of the importance of close contact for transmission, and data supporting the potential for aerosol transmission. Available evidence indicates that all routes of transmission are possible; circumstances will determine their relative importance. A workshop on influenza transmission held in 2010 at the US Centers for Disease Control and Prevention,[1] outlined the state of the science for many of these areas, as does the literature review linked to this progress report. Remaining areas of needed research include further defining close contact (e.g., how close is close?), understanding the role of fomites and hand contamination-self-inoculation, evaluating heterogeneity of infectiousness among individuals, characterizing the impact of aerosol generation in health-care settings, as well as

[1] http://www.cdc.gov/influenzatransmissionworkshop2010

the relative contributions of contact, aerosol, and droplet transmission on the dynamics of epidemics/pandemics. Further important questions include the contribution of asymptomatic, pre-symptomatic and subclinical infection phases to transmission of virus and the impact of masks/respirators for those exposed and of masks for source control, increased hygiene, case isolation, contact quarantine, antiviral treatment, and combinations of these modalities.

The dynamics of the spread of influenza at global and local levels are still poorly understood. Broader questions regarding intercontinental spread unrelated to human travel/movement have also been raised. Data that quantify the impact of particular non-pharmaceutical interventions (NPIs), like prohibiting mass gatherings, school closures, border control and quarantine policies or combinations of NPIs and, in particular, optimizing the timing of such interventions (stopping as well as starting) would represent a considerable research advance for public health officials and health policy makers. Several studies and publications have shown NPI effects (**Appendix 7**), though many were instituted well into the H1N1 pandemic, and quantitative assessments of impact are difficult without matched controls. Assessing the magnitude of their effectiveness and the costs and consequences of their implementation are essential to public health decision-making,

New public health policies for preventing viral transmission could also take into account considerations coming from the at-risk social networks favouring dissemination. Recent literature on the role of social (familial, professional, educational) networks in the spread of contagious diseases shows that it is now possible to get data and build efficient models in this field. The social networks' growth occurring in a demographic and geo-climatic context, in which populations are not constant in size and location, are contrary to the hypotheses made in the large majority of models of influenza propagation. The use of demographic and geo-climatic data bases from the national census offices could improve the predictive power of the models, the challenge being to acquire progressively the same accuracy as meteorological forecasts. Validation of the various models with high-quality surveillance data remains an unmet need.

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

Stream 3 research efforts focus on better understanding of the true burden and social impact of influenza on a global scale and on evaluating various methods used to minimize the impact of influenza, both the disease and its transmission. Vaccination of course has always been the cornerstone of efforts to control and minimize the impact of influenza, but vaccination programs can be expensive compared to other potential control methods that might reduce the impact of the disease, particularly in its mild forms and in the context of competing public health needs. In particular, early recognition of the disease and its transmission characteristics has direct impact on public health policies including the use of vaccines, antivirals and NPIs. Further, policy development and implementation for influenza control vary widely among countries and considerable gaps exist in knowledge of how to effectively deliver vaccines, antivirals and other control measures. If immunization is to remain the cornerstone of mitigation efforts, then we know, for pandemics at least, that we need much faster vaccine production and preferably approaches that yield broader and longer-lasting protection. A considerable amount of research in these areas has been published since the Report of the First Global Consulta-

tion,[1] and research progress on novel broad-spectrum and long-duration influenza vaccines has been regularly reviewed at WHO meetings, the fifth of which was held on 16–17 November 2011.[2]

A number of studies (**Appendix 8**) evaluated the economic and other burden/impact of the 2009 H1N1 pandemic in several regions, concluding not surprisingly that the waves of this relatively mild pandemic still had significant impact on several levels, such as health-care systems, households and overall economies. Other studies looked at various interventions and assessed cost effectiveness (*5,15,17,18,20,34,41,42*). A review of the studies listed in appendix 8 indicate that the burden of the 2009 H1N1 pandemic was similar across countries, although many ongoing studies directly comparing impacts in low resource settings are yet to be published. At least one burden study published following the first consultation has described the impact of seasonal influenza in low resource settings (*54*). Gaps in this area include insufficient data from low income countries where financial assessments of influenza burden are very sparse, questions on how to extrapolate data from a mild pandemic to a severe form and the need for standardized reporting of interventions in socially disadvantaged groups. Additionally. standardized approaches to define severity measures and develop burden of influenza studies that will have the most meaningful results to WHO and other public health agencies are needed. For example, should viral surveillance efforts be preferentially targeted among paediatric rather than adult patients, among hospitalized patients compared to community-dwelling ones, or in the context of populations rather than vaccine 'probe' studies?

An extraordinary number of studies on the development of new influenza vaccines, vaccination approaches and policies have been published since the last review. More than 1800 publications, reviews, commentaries and case reports were found (**Appendix 9**). Progress has been significant in several areas, including development of such novel approaches to influenza vaccination as so-called 'universal" or conserved epitope vaccines (*72,162,194,259,310,397,423,438,632,778,930,1122,1183,1284,1313,1362,1479,1496,1587,1801*), use of adjuvants for dose-sparing and enhanced protection (*62,63,74,93–95,106,130–132,138,173,174,180,189,208,219,231,237,238,252,256,269,296,311,312,325,341,361,372,379,413,415,439,441,455,461–463,467,508,511,540,561,634,635,641,682,691,729,739,782,783,806,897,920,823,949,994,996,1024,1028,1084,1099,1108,1125,1162,1202,1283,1350,1390,1381,1407,1411,1437,1459,1521,1522,1525,1574,1596,1631,1651,1664,1769,1779,1782,1788,1794*), advanced development and efficacies of cell-based (*57,82,139,140,479,517,557,574,601,616,656,716,786,900,950,957,1195,1239,1245,1410,1531,1599,1639,1790*) and recombinant influenza vaccines (*112,147,200,405,612,698,801,843,919–920,940,1025,1281,1296,1317,1445,1451,1475,1544,1556,1562,1574,1589,1590,1664,1706,1737,1775,1794,1787*), and technology transfer of existing and new technologies to low resource countries (*327,1238*), just to highlight some.

Based on lessons learned from the pandemic, new research initiatives have been funded to shorten the time to availability of pandemic vaccines by improving potency and sterility assays to yield faster regulatory release of vaccines and by improving strain selection and vaccine candidate development methods. These initiatives have also focused on making better use of bioinformatics approaches to

[1] http://www.who.int/influenza/resources/research/2010_11_report_of_the_first_global_consultation_november_2009.pdf

[2] http://www.who.int/vaccine_research/diseases/influenza/meeting_16_17_Nov_2011/en/index.html

predict optimal vaccine design. Areas that need more attention are (1) understanding and addressing the real and perceived (e.g., rumours) issues of safety of different vaccines, (2) overcoming the challenges of vaccine distribution in developing countries, (3) meeting the information needs of policy-makers and the public to increase influenza vaccine uptake at community levels, and (4) addressing the unique needs of specific target risk groups. The role of live-attenuated intranasal influenza vaccines (LAIV) also needs to be further explored, particularly for the very young (<2 yo), for risk groups, and for rapid production and deployment in pandemic situations. Further studies on identifying correlates of protection for these LAIV's as well as other non-traditional (non-HA-based) influenza vaccines are needed, as are improved understanding of such correlates (e.g., hemagglutination-inhibition and neutralizing antibody levels) of current vaccines.

2.4 **Stream 4:** Optimizing the treatment of patients

Scores of reports from many countries on the clinical spectrum resulting from infections with the H1N1pdm09 virus were published in 2010 and 2011 (**Appendix 10**). These characterized viral and host factors affecting pathogenesis, clinical features, laboratory findings, prognostic risk factors and groups, mortality rates and problems with distinguishing pandemic influenza from other ILI's. While previously known groups had higher risk for severe influenza-associated complications (e.g., pregnant women, immunocompromised individuals and disadvantaged populations), morbid obesity emerged as a new risk factor for severe illness.

Because of incomplete surveillance and sampling, questions still remain regarding the variation in mortality rates observed, the percentages of asymptomatic infections, and the causes of severe illness and death during the 2009 H1N1 pandemic. Some progress was made on assessing the role(s) of virus and host factors in the clinical progression of disease (*69,72,77,87,92,99,113,114,136,153, 158*). It is still not known, however what factors are important in the severe disease caused by the H5N1 avian viruses. Studies are underway to elucidate potential genetic factors for susceptibility as many cases have strong blood relative linkages. Further work is needed to determine prognostic factors that might be used at initial clinical presentation to guide therapeutic decisions.

Currently commercially available point-of -care rapid diagnostic tests perform generally with acceptable specificity, but with highly variable sensitivity, especially in adults, and are inadequate to guiding management (**Appendix 11**). Progress has been made in developing sensitive viral nucleic acid amplification assays for same-day diagnosis, but these tests remain technically complex and costly.

A very large number of studies related to antiviral treatment of influenza infections, development of new antivirals and treatment approaches, antiviral resistance and pharmacokinetics have been published since the last consultation (see **Appendix 12**). More evidence has become available showing that early oseltamivir use reduced hospitalization/mortality, although some patients developed severe disease despite early initiation of antiviral therapy (*535,975*). Prophylaxis with the standard prophylactic dose showed few failures in most retrospective studies (*58*). Whether full therapeutic dosing should be used for prophylaxis in general against a new virus for which the population is immunologically naïve requires further study. Immonocompromised individuals have a higher chance of giving a rise to resistant viruses.

Knowledge gaps have been filled in terms of pharmacokinetics of oral oseltamivir in the groups with increased risk for severe disease: children < 1 year of age, pregnant women and obese persons. No new safety signals were identified with the neuraminidase inhibitors, and the available data also supported the safety of oseltamivir in the very young and during pregnancy (*1419*). Absorption of extemporaneous oseltamivir delivered through naso-gastric tubes was adequate in treating severely ill patients in the absence of parenteral therapy (*70,1335*). However, nebulized delivery of zanamivir in its lactose-containing commercial formulation was found to be dangerous in mechanically ventilated patients. A considerable number of publications described use of the investigational intravenous neuraminidase inhibitors (NAIs), particularly zanamivir, in individual cases or case series of severely ill patients with suspected or proven oseltamivir resistance. Further studies of intravenous NAIs in hospitalized patients are in progress and future work should examine both antiviral combinations and combinations of antivirals and host biologic response modifiers. Resistance to treatment with antivirals continues to pose significant challenges and antivirals with novel (non-neuraminidase targeted) modes of action and antiviral combinations are needed.

Co-bacterial infection was identified in one third to one half of fatal cases resulting from (H1N1) pdm09 virus infections. Common community-acquired pneumonia pathogens such as *S. pneumoniae*, *S. Aureus*, including methicillin resistant strains, *S. pyogenes*, and *H. influenzae* were most frequently identified in these patients. The relative effectiveness of different antimicrobials for difficult-to-treat mixed viral-bacterial or secondary pneumonia like methicillin-resistant S. aureus requires further study. Only a few studies have been done on non-antiviral therapies for the severely ill, and best practices for case management of the severely ill in resource-limited settings. The possible value of immunomodulatory interventions are clearly knowledge gaps.

The clinical research response to the 2009 H1N1 pandemic was inadequate (*552*) and key pathogenesis and treatment information emerged slowly. The mechanisms by which influenza infection led to severe viral pneumonia, lung injury, and acute respiratory distress syndrome (ARDS) remain incompletely understood. In the absence of quality data, many clinicians used systemic corticosteroids for treating influenza-related ARDS, but subsequent reports showed that this approach was associated with increased complications and mortality (*1419*). In the future, establishing and strengthening outbreak-ready, multi-centre clinical research networks in geographically diverse regions would facilitate the rapid detection of cases and assessment of disease manifestations, as well as enable sequential collection of key clinical data and samples for analysis by specialized laboratories. This information will form the basis of policies related to the clinical management and healthcare system response. Such clinical research consortia can undertake prospective studies of treatment modalities, as well as contribute to collecting and distributing information. Clinical studies to address outstanding questions and protocols for prospective data collection should ideally be tested during inter-pandemic periods. Development and sharing of simple research protocols that can be applied in lower resource settings should be facilitated by the international research community.

High dependency medical services such as intensive care units (ICU) were most affected during the 2009 H1N1 pandemic because of surges of patients with primary viral pneumonia requiring ventilation. Basic health care capacity and response vary dramatically among the various developing countries, and understanding how to increase the effectiveness of the global response to a pandemic, given these constraints is an important area for study.

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

Finally, it is universally recognized that the expanded use of modern public health tools and the development of new fit-for-purpose ones could have an impact on controlling influenza. Three of these – advanced surveillance/monitoring and reporting approaches, disease impact and transmission modelling for public health decision making, and novel strategic communications approaches – were identified as the major themes of research efforts recommended in the original Research Agenda.

Disease transmission and other types of modelling efforts directly related to the 2009 H1N1 pandemic were increased quite substantially during and after the pandemic. The establishment of several coalitions of modellers by WHO and other agencies provided a strong quantitative framework to apply the huge amount of surveillance data available from pandemic H1N1 spread. Numerous studies were published in 2010 and 2011 evaluating impact or effects of vaccination, antivirals, diagnostics, facemasks, increased hygiene, school closures and other measures on the progression of the pandemic; economic and social impacts were evaluated as well. While modelling is still a powerful tool to help public health officials make decisions or assess different scenarios (**Appendix 13**), gaps still exist in model validation (some assumptions were inadequate), in communication with both policy-makers and the public about what modelling can do, and in the time required to linking modellers to epidemiological data and results of control and intervention.

Risk communication and risk communications research are both complex and difficult. Communication of course is a key strategy in responding to any epidemic or pandemic disease. Accurate communication is complicated by the rapid evolution of public perception shaped by easy access to alternative, and sometimes erroneous or conflicting sources of information on the internet and in social media. Communications effectiveness during a public health crisis is dependent in large part on the trust the public has in general in the public health or government officials doing the communicating. There are different levels of trust across countries: very briefly, it appears that the least trusted are governments, media and pharmaceutical industries while the most trusted are health professionals and sometimes national health authorities.

We know from recent published studies (**Appendix 14**) that the effectiveness of communication varies from country to country and by the strategies employed, so that making broad generalizations about the best ways to communicate risk is difficult if not impossible. Still, a considerable body of information has become recently available on risk and pandemic perceptions, vaccination perceptions and practices, rumours and their propagation, and risk and health communication practices. However, there is still a limited interaction between the social sciences producing this knowledge and the decision- makers. Social sciences are often seen as a tool to be used when the response strategy does not work. while they should be embedded in the response process from the beginning.

Health-care workers (HCWs) have been targeted as a priority group for receiving seasonal and pandemic vaccinations in many countries because of the risk of their both contracting and spreading influenza (*1,5–7*) However, when questioned, HCWs rarely identify themselves as being particularly vulnerable to the disease. On the contrary, they perceive that their immune systems are ‘strong’ and that they can mount an appropriate response to influenza infection (*8–11,13–15*).

Immunization of HCW's against both seasonal and pandemic influenza is thought to protect patients from nosocomial infection, reduce health care-related costs, and protect the health-care infrastructure during outbreaks (*7*). Despite these strong and practical arguments in favor of vaccination, HCWs often choose to receive the vaccine based on a personal motivation to protect themselves (*8, 16,18,19*). While patient protection is often cited as a reason to receive the seasonal flu shot, this is often secondary to self-protection as a motivator for vaccination (*7–8,16,19*).

Social science studies often last long and the results are not available on a real- time basis. More effort is needed to ensure that social sciences can contribute effectively to the response process by developing 'quick and dirty' operational research during a crisis and by accelerating the publishing process; for example, a greater initiative towards the study of compliance with vaccination, as well as other mitigation efforts, can be of crucial importance as the pandemic unfolds.

An example of the need to invest in operational research on HCWs during a pandemic was seen in that, prior to the 2009 (H1N1) pandemic, much of the literature focused on the factors influencing compliance of HCWs with seasonal influenza vaccination (*4,20*). Although much of the research has now shown that the previous uptake of the seasonal influenza vaccine should predict uptake of a pandemic vaccine (*9,13,30,32,33,24,25*), the reality was that in many countries adherence to vaccination against H1N1 during the 2009/2010 campaign was still very low (*19,24,39,40*). Efforts in the initial stages of the pandemic were made to collect data on factors associated with the *intentions* of HCWs to comply with vaccine efforts (*9,13,26,27,30,33,35*). While the publication of these studies filled a gap in our knowledge about willingness among this group to be vaccinated with a novel vaccine, relatively fewer articles actually focused on the factors and motivators for *receipt* of the vaccine. While research on intentions to be vaccinated is informative, studies on actual vaccination behaviours is necessary as there are numerous factors that can modulate the intention-behavior relationship (*41*). Studies on perceptions and factors associated with pandemic vaccine receipt in HCWs were published mostly in 2010 and 2011 (*10,19,21,24,25,32,36,42,48*). These shed some light on the factors that have influenced behavior and will help inform vaccination efforts from now on.

Risk communication often focuses on targeting different audiences. However, little is known about the 'audience' and there needs to be greater understanding of the concerns and fears of different sub-groups in order to design effective messages that will persuade them to comply with mitigation measures.

The findings from the social sciences literature have shown that HCWs, despite their role as the caretakers of society, are often found to have very low participation in voluntary immunization with the influenza vaccine (*7*). Within this group failure to comply with vaccination is often greater in nurses than among physicians (*11,13,21,23–26*). There could be many reasons for this gap in compliance, although the most important finding here is that there is a need to tailor messages and persuasive efforts differently for physicians and nurses in order to ensure that the specific barriers that relate to each sub-group are addressed and that compliance is achieved across all categories of HCWs (*7*).

Rumors are not the result of failures of communication. They are often viewed as obstacles to official prevention programs; they emerge in a context of asymmetries of power and lack of responses to doubts and questions; they provide parallel information when official communication is limited to a

top-down approach. Denying rumors is not sufficient: work needs to be done on alternative hypotheses and narratives, evidence must be provided and questions and doubts have to be answered.

Identified research needs include accurate assessments of public health crisis narratives, longitudinal assessments of risk perceptions among the general population, determining role and impact of journalists' professional practices in a context of public health crises and identifying role and impact of public health authorities' risk communication practices.

2.6 Work of the Secretariat

i. RA has gone regional to solicit research needs and implementation in resource-low settings (AFRO, SEARO, WPRO)

ii. WHO Secretariat has worked with key technical and financial support agencies to align WHO RA with institutional research priorities

iii. IHR review committee recommendation 15 to pursue a comprehensive influenza research and evaluation programme.

3. Conclusion

The Report of the First Global Consultation on the Research Agenda identified several objectives:

- 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

These objectives remain central to facilitating progress in influenza research but will require a sustained effort to assure that they are ultimately met. Clearly, the amount of ongoing research on influenza has mushroomed in recent years and billions of dollars of funding have been provided for influenza research by funding agencies since the spread of H5N1 began nearly 10 years ago. It is important to perform expert evaluation of such outlays of money, and the WHO Research Agenda initiative provides at least an independent qualitative evaluation, albeit without comparative costs or performance criteria. Additionally. the initiative directly supports the multidisciplinary approach specified in the objectives by assuring that all aspects of research into solving influenza problems are addressed, including research by animal health professionals, clinicians, basic researchers, economists and modellers. The second Consultation held in Geneva in November of 2011 and the extraordinary amount of information published since the first Consultation two years earlier unquestionably confirmed the considerable progress that has been made towards addressing the research gaps identified in the first.

3.1 Next steps

The WHO Public Health Research Agenda should be updated and continue to be analysed and modified through expert consultations. The present progress report illustrates both the dramatic increase in influenza research since the pandemic and the need for periodic assessments to determine if the agenda remains valid.

The coordination with various stakeholders on the Research Agenda should continue and be enhanced by incorporating regional input and obtaining support from funding agencies, policy-makers, and scientists.

Global evaluation of current funding levels for each of the Streams would provide very useful information, particularly if some determination of the proportion of research in low-income countries were available. However, much of this information is proprietary or confidential, especially as related to diagnostics, vaccines, and therapeutics, and consequently an accurate assessment will be difficult in some topic areas.