Making progress on the WHO Public Health Research Agenda for Influenza

Nahoko Shindo
Pandemic and Epidemic Diseases Department, World Health Organization, Geneva, Switzerland. E-mail: shindon@who.int

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In November 2009, the WHO Global Influenza Program held a consultation to assess the status of global research efforts to understand, prevent, and control influenza. This meeting was a continuation of WHO commitment to addressing global influenza problems, as reflected by earlier documents – the 2002 WHO Global Agenda on Influenza and the 2006–2007 WHO Strategic Action Plan for Pandemic Influenza. More than 90 investigators, funding representatives, public health officials, and policy-makers from 35 countries joined the WHO secretariat in developing the framework for a research agenda addressing gaps in our understanding of the emergence, transmission, mitigation, and management of influenza. The consultation produced a consensus document, the WHO Public Health Research Agenda for Influenza which was published in January 2010.

The agenda is a broad-based public health research strategy for influenza, offering high-priority research recommendations organized around a framework of five key research areas or “streams” of particular importance to public health decision-makers, especially those in less-resourced countries:

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.

In the wake of the 2009 H1N1 pandemic, an update on research activities highlighted in the research agenda was warranted. The progress review was conducted by a 3-step process: (i) verifying consensus with the scientific committee on the priority research recommendations for the five research streams, (ii) commissioning of two to four topic-specific literature reviews per stream and of one summary progress report, and (iii) convening a review committee meeting to assess these reports, evaluate the Research Agenda implementation, and provide new recommendations for the WHO Secretariat. To evaluate the impact of the agenda in the research community, WHO commissioned a series of literature reviews covering high-priority research topics across all streams during the 2-year period of 2010–2011. The intent of using literature reviews as a mechanism to monitor research progress was to (i) collate the knowledge acquired since the launch of the agenda, (ii) interpret or apply the knowledge for improved influenza prevention and control, and (iii) highlight remaining gaps in knowledge and corresponding research activities. Concluding from the process is a report of 2 year’s progress, which is available on WHO website together with the lists of references gathered under each research stream. (http://www.who.int/influenza/resources/research/en/).

At the end of 2011, the scientific committee and the secretariat met for a review consultation with the group of experts to discuss the progress being made in the research community.

Over 4000 citations of publications from 2010 to 2011 in more than 200 journals or other peer-reviewed publications were identified by more than 20 literature reviews. Although relevant publications covered a wide range of topics, research related to understanding the emergence and progression of the 2009 H1N1 pandemic dominated the body of work. Publications related to specific pharmacologic interventions such as influenza vaccines and antivirals, also figured prominently in the published work, representing more than half of the total. The body of accumulated work identified by the reviews represents a truly international effort to better understand influenza with a substantial number of the publications in non-English language journals.

This special supplement includes the key literature reviews addressing important public health questions. Also included are short updates and research summaries of several literature reviews that were published in the period between the closing of the consultation and the preparation of this supplement. Readers are encouraged to access the original, full-length reviews for more in-depth discussion of topics. In
addition, two original research articles and one editorial stemming from issues raised in the course of discussions during and after the consultation are also included.

Highlights of the articles presented in this special supplement include:

**Stream 1**

Animal influenza remains an important area of research. Our understanding of genetic processes involved in evolution of virus and resulting changes in virulence, transmissibility, and potential for zoonotic infection has improved, and epidemiological studies of H5N1 have provided us with a clearer picture of risk factors for zoonotic transmission. Animal management strategies have also been widely implemented to prevent H5N1 transmission from birds to humans; however, the effectiveness of particular interventions in preventing zoonotic infection remains unclear as it has often been difficult to establish a firm link between intervention activities and disease control. Communication and collaboration between animal and human influenza networks should be expanded and strengthened to address the continuing threat zoonotic influenza poses on health and economies.

**Stream 2**

Genetic susceptibility to influenza in humans is clearly an under-developed area of research. Some pioneer studies have recently been published, although the majority of our molecular understanding continues to come from animals. IFITM3 in particular appears to play a role in susceptibility to severe influenza in mice, and some evidence suggests that it may also be important in human infection with the pandemic strain of 2009. Studies of influenza transmission are difficult with so many confounding variables and relatively few have been conducted with investigation of transmission modes as a primary objective. Nevertheless, all routes of transmission (droplet, aerosol, and contact) have a role to play and their relative significance will depend on the set of circumstances. However, of all the routes, evidence in support of the importance of aerosol transmission is increasing.

**Stream 3**

Minimizing the impact of influenza spans several related topics. Research suggests that pandemics like that of 2009 may disproportionately affect disadvantaged populations, although the degree of disparity may vary. For example, although available studies suggest that certain populations such as ethnic minorities in North America (relative to non-ethnic minorities) may have been more adversely effected by the H1N1 pandemic of 2009, by and large the burden was high and not significantly different across low-, middle-, or high-income countries. Similarly, a macroeconomic analysis of the impact of influenza on lower and middle income countries indicates that while lower income countries may likely be more affected by pandemic influenza, the overall costs appear to be relatively small for milder pandemics such as the H1N1 pandemic of 2009. In order to make sense of economic modeling and evaluation data, a critical assessment of key parameters used in economic modeling is also presented, not unexpectedly tying lower quality evidence to increased variability in values used in economic evaluations. Vaccines are an important tool in minimizing the impact of influenza, and progress is being made in the development of effective vaccines, with the WHO Global Influenza Surveillance and Response System (GISRS) continually improving the process by which virus strains are selected for vaccines.

**Stream 4**

Treatment of patients should improve with a better understanding of disease and antimicrobial therapies. Observational studies suggest that commonly prescribed antivirals such as oseltamivir and zanamivir may reduce mortality, hospitalization and duration of symptoms, and earlier treatment with such agents is generally associated with better outcomes than later treatment. Taking a broader perspective, results from an ecological study using country-level data on mortality and supply of antivirals demonstrates a positive association between aggregate antiviral supply and decreased mortality during the H1N1 pandemic of 2009. In addition to antivirals, vaccination provides benefit to clinical outcome of patients. For example, studies suggest that vaccination of immunocompromised patients provides clinical benefit in terms of direct protection. Similarly, vaccination of healthcare workers appears to provide some level of indirect protection to patients in certain settings. A complementary review of the social science literature provides a qualitative assessment of the factors influencing HCW decisions on whether or not to receive vaccination. The importance of coinfection on severity of illness and implications for treatment antibiotics and antivirals is also discussed along with the clinical management of patients with severe influenza. Under the circumstances where vaccines and antivirals are not available, quality clinical management of critically ill patients is an essential element in mitigating the burden. Several new international initiatives have begun to develop syndromic management strategies for resource-limited settings including the WHO’s Integrated Management of Childhood Illness (IMCI) and Integrated Management of Adult and Adolescent Illness (IMAI) programs. A sustainable, global impact on outcomes due to severe
influenza and other severe illness will require an ongoing and concerted international effort to implement, evaluate, and refine.

Stream 5

The 2009 H1N1 pandemic appears to have had a substantial impact on a number of areas related to influenza preparedness including the communicating of risk. The supplement wraps up with a social science perspective on topics in risk communication including popular perceptions, misconceptions, and rumors.

Not included in the supplement, but important areas for continued research were summaries of two reviews; one covering the clinical spectrum and natural history of human influenza and the other the role of outbreak analysis and mathematic modeling in developing public health responses to infectious disease outbreaks.

Although encouraging progress has been made in all areas, further research is needed across the board – more coordinated and focused research. Many of the reviews commissioned for this progress could only come up with moderately strong or qualified recommendations and general trends in reporting. Increased coordination might make the results of many future studies more comparable, providing greater weight in identifying effective interventions and associations. It is hoped that the next progress report will see the closing of many of the gaps identified in this first update of the research agenda.

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Conflicts of interest

The author has no potential conflicts to declare.

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