National Collaborating Centre for Infectious Diseases
Centre de collaboration nationale des maladies infectieuses

Purple Paper

Highlights of the *Options for the Control of Influenza VII* Conference Hong Kong SAR, China September 3-7, 2010

Part I

Options for the Control of Influenza began as a small scientific symposium in Keystone, Colorado in 1985. Since then, this triennial conference has become the largest international conference devoted exclusively to all facets of influenza, from basic science to health care policy. The ***Options VII*** conference was held in the Hong Kong Special Administrative Region (SAR), China from September 3 to 7, 2010, and was the first in the meeting series to be convened following an influenza pandemic. This two-part *Purple Paper* series will present some of the conference highlights, with emphasis on the 2009 pandemic response and future pandemic preparedness.

The Global Public Health Response

There were three influenza pandemics in the 20th Century: 1918 Spanish influenza (A/H1N1), 1957 Asian influenza (A/H2N2), and 1968 Hong Kong influenza (A/H3N2). Avian influenza A/H5N1 first emerged in Hong Kong in 1997. Although the highly pathogenic virus was largely stamped out by aggressive control measures implemented by Hong Kong's public health authority, the virus re-emerged in poultry and wild birds in Southeast Asian in 2003 and has since spread to other continents. As of August 31, 2010, the cumulative number of confirmed human H5N1 cases has reached 505, with 300 deaths [1]. All of these cases were reported from 15 countries, the majority of which were in Asia. As avian influenza viruses continued to infect birds and humans, and the world geared up preparedness efforts for an influenza pandemic of avian origin (H5, H7 or H9), it came as a surprise that the 2009 pandemic influenza virus was of the subtype H1N1 – a subtype that is among the

Key Points

- The 2009 influenza pandemic spread throughout the world at an unprecedented rate. However, global preparedness was also unprecedented in scale compared to previous pandemics.
- Systematic surveillance capacity remains disparate among countries. More than 100 countries have very limited or no influenza surveillance capacity. The heterogeneity of established systems and the lack of standardized indicators made global monitoring difficult.
- Current assessment methodologies have shown to be inadequate for describing the severity of the 2009 pandemic. The Centers for Disease Control and Prevention (CDC) is in the process of developing a new framework that will allow assessment of the pandemic impact based on categories of transmission and clinical severity, instead of case fatality alone. It will also include a "translation-to-action" step, whereby scientific findings can be translated into context-appropriate recommendations.
- Given the role of pigs and domestic and wild birds in the genesis of novel influenza A strains, influenza surveillance in these key animal populations should be enhanced.
- Non-pharmaceutical interventions are an integral part of the public health mitigation strategy to control the spread of influenza during an outbreak. However, the effectiveness of an individual intervention on its own is difficult to assess.
- Although border screening may not be effective in containing pH1N1, implementation of this mitigation measure in some countries might have delayed local pH1N1 transmission by an additional seven to 12 days compared to countries that did not implement border screening.
- Because school closures can have substantial economic and social costs, whether to close schools or not is a highly contextualized decision.
- Hand hygiene and the use of face masks are the chief protective measures at the individual level. However, evidence supporting the use of such measures in the community setting is, by and large, conflicting or lacking.

contemporary circulating seasonal influenza A virus strains and is included in the annual vaccine, no less. Even more surprising was that the 2009 pandemic arose in North America, while it had long been predicted that the next pandemic would spawn in Southeast Asia where cohabitation of humans with various livestock animals is ubiquitous. Dr. Sylvie Briand from the Global Influenza Programme of the World Health Organization (WHO) reviewed the global public health response undertaken by the Organization and some of the challenges it faced during the 2009 pandemic.

The 2009 influenza pandemic spread throughout the world at an unprecedented rate. Starting in North America, the pandemic spread to all continents in less than nine weeks, and reached all corners of the world in 10 months. However, global preparedness was also unprecedented in scale compared to previous pandemics. 140 countries already had their pandemic preparedness plans in place before the 2009 pandemic. A battery of antivirals and antibiotics of a wide-ranging selection was available for the treatment of influenza illness and complications. Early detection and global sharing of information and viruses enabled rapid characterization of the virus, leading to availability of the pandemic vaccine within six months of the initial reported outbreak. More importantly, the 2009 pandemic was the first large scale response under the revised International Health Regulations[a] (IHR) framework [2]. The IHR was further supported by a resolution adopted by WHO Member States on the sharing of influenza viruses, vaccines and other benefits to advance fair and equitable access by developing nations.

The 2009 pandemic also highlighted many new and persistent challenges, with global surveillance topping the list. Systematic surveillance capacity remains disparate among countries. More than 100 countries have very limited or no influenza surveillance capacity. Among those countries with established surveillance, the heterogeneity of systems and the lack of standardized indicators have made global monitoring difficult. The WHO pandemic phases have been a useful tool for planning pandemic responses at the global and national levels, such that the phases delineate specific response activities according to the progression of the pandemic. However, when the phases were put into effect during the pandemic, confusion about the meaning of the phases was prominent in the media and among Member States.

The 2009 pandemic was the first large scale response under the revised International Health Regulations.

Communications was another challenge. During early phases of the pandemic, communications had been timely and transparent to establish rapport with the media. As the pandemic unravelled and its severity was perceived to be moderate by some, conspiracy theories began to spread in the media and on the internet. This resulted in the general public misunderstanding the public health response and might have led to low uptake of the pandemic vaccine in some countries. Furthermore, a number of technical agencies are now facing parliamentary enquiries and external reviews, questioning whether their responses had been appropriate. Naming of the pandemic had also created confusion about the nature of the virus, causing some countries to cull their swine populations – a measure that was used to control the highly pathogenic H5N1 virus in poultry but was inappropriate in this instance. Lastly, although the WHO was able to deploy antivirals and vaccines to more than 70 countries during the pandemic under the new resolution on benefit sharing, the current ad hoc mechanism is not sustainable.

Moving forward, the WHO has already begun to address some of these issues. The Organization is holding consultations with countries that have revised their pandemic plans to collect information related to operational challenges and uncertainties during their pandemic response. WHO is in discussion with national public health authorities to

[a] The IHR are an international legal instrument that is binding on 194 countries, including all the Member States of the WHO. The aim of IHR is to help the international community prevent, protect against, control and respond to acute public health risks that have the potential to cross geographic borders, and to do so without unnecessary interference with international traffic and trade. Under this revised framework, states are required to report certain disease outbreaks and public health events to the WHO, and strengthen their core surveillance and response capacities.

devise a new approach for severity assessment. It is reviewing the global surveillance plan and definitions of the pandemic phases. The Organization is also in the process of reviewing and improving its current recommendations for public health measures.

Epidemiology and Surveillance

At the Options VII Conference, Dr. Daniel Jernigan from the Influenza Division of the National Center for Immunization and Respiratory Diseases at the CDC described the U.S. experience with surveillance during the 2009 pandemic. He discussed mechanisms for situational awareness that were invaluable during early phases of the pandemic and mechanisms that could be improved. He also discussed the challenges in measuring severity in an emerging pandemic.

Surveillance of virological testing, laboratory-confirmed influenza cases, clinic visits for influenza-like illness, hospitalizations, and influenza-related deaths (usually among those aged >65 years) are the gold standards for characterizing the extent of influenza during an epidemic. However, estimation and monitoring of impact is an ongoing process. During early phases of a pandemic, such surveillance data are unlikely to be available, yet decisions need to be made rapidly. Nevertheless, situational awareness was made possible in the first days by a number of mechanisms that were already in place. Investment in preparedness prior to the pandemic has proven invaluable. Exercising its own preparedness plan allowed CDC to respond quickly. This was complemented by policy preparedness in establishing the case definitions for novel influenza viruses, which enabled rapid information collection of cases during the pandemic. As part of the overarching plan to increase diagnostic capacities, CDC had worked with industries to make sure laboratory equipment, namely devices for polymerase chain reaction (PCR), were in place or could be deployed quickly to public health laboratories that needed them, especially international laboratories that participated as National Influenza Centres. In addition, CDC had also established a repository of Influenza Reagent Resource by contracting ATCC, a not-for-profit biological resource centre and research organization, to manufacture and distribute PCR influenza reagents to qualified laboratories around the world. During initial stages of the pandemic, early communication between investigators regarding the characteristics of the virus accelerated the global response. At a national level, case-contact investigations and community surveys were critical for early characterization of local outbreaks, and they were particularly useful during the period before established surveillance systems could generate the much needed information.

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Although these prefatory investigative tools could shed some light on the still-unfolding pandemic, Dr. Jernigan warned that public health authorities must manage the expectations of stakeholders and decision-makers. While public health authorities need to interpret and provide the limited data to decision-makers, it is equally important for public health authorities to ensure decision-makers understand the uncertainties related to the estimates. Another issue that should also be conveyed is that an upsurge in laboratory-testing to confirm cases is difficult to maintain over time, thus obligating migration from PCR-confirmed case counting to estimates of cases, hospitalization and deaths. Public health authorities should prepare the media and decision-makers so that they understand the approach taken in anticipation of a surge in laboratory testing in the second wave.

As the U.S. moved through the second wave, cumulated national surveillance data painted a more complete picture of the extent of the pandemic, and it was becoming clear that mortality figures alone did not reflect the full impact of the pandemic. Although the cumulative number of reported deaths during the pandemic did not appear significantly higher than that of a regular influenza season, the difference in age groups in which most deaths occurred was telling. During a "normal" influenza season, 90% of deaths generally occur among adults aged >65 years. However, for the 2009 pandemic, 90% of deaths were among people aged <65 years. Because testing guidelines changed during the second wave and laboratory-confirmed cases were underreported, the number of laboratory-confirmed deaths were also likely underestimated. Moreover, potential life lost in the U.S. was estimated to be between 334,000 and 1,973,000 years [3]. That said, efforts to develop a more robust severity assessment framework are underway. As Dr. Briand mentioned in her presentation, the WHO is in consultation with experts from around the world to identify a new approach to severity assessment that takes into consideration various factors, including the vulnerability of the population.

Instead of assigning influenza A viruses to discreet species-specific categories, all influenza A viruses should be viewed as "One Flu".

At CDC, experts are gathering input on a new framework which allows collection of information from early virological and field investigations and community surveys, as well as collection of information from established surveillance systems that are generated after the emergence of a pandemic strain. The new framework will allow assessment of the pandemic impact based on categories of transmission and clinical severity, instead of case fatality alone. Perhaps the most intriguing aspect of this new framework is that it will also include a "translation-into-action" step, whereby scientific findings can be translated into context-appropriate recommendations. As Dr. Jernigan pointed out, this "translation-into-action" step requires more than scientific information. It takes into account other factors such as vulnerability, risk factors, resource limitations, acceptability and effectiveness of the interventions in the community, and capability of local authorities to carry out these interventions. In essence, scientific assessment needs to be decoupled from the "translation-into-action" step in some respects so that local authorities can take the information on transmission and clinical severity and apply the needed interventions based on their own interpretation of that scientific information in their own local context.

On a separate topic related to surveillance, Dr. Robert Webster from the Department of Infectious Diseases at St. Jude Children's Research Hospital in Memphis, Tennessee, argued that systematic influenza surveillance should be enhanced for pigs, and domestic and wild birds to complement surveillance systems that are already established for humans.

Migratory aquatic birds are the reservoirs of all influenza A viruses, harbouring all 16 HA and 9 NA subtypes known to date. Influenza A viruses can spread within and between species, but such mixing is limited by the birds' migratory patterns. Hence, Influenza A viruses in the wild bird reservoir are divided globally into two major clades: Eurasian and American. It is widely believed that zoonotic transfer of influenza viruses from the avian host to human obligates a transitory phase via the pig. Inside this intermediate host, avian influenza viruses must acquire the necessary characteristics through reassortment with mammalian influenza viruses to cross the species barrier for human infection. This is theoretically conceivable, at least in agricultural settings where multiple livestock species are kept in close proximity – a farming practice that is prevalent in Southeast Asia. However, what has been unclear is how pigs acquire influenza viruses from the wild bird reservoir. As it turns out, domestic ducks act as a shuttle and mediate interaction of viruses between the natural and terrestrial poultry gene pools, thereby facilitating the generation of novel influenza virus variants circulating in poultry [4]. The hypothesis that pigs are "mixing vessels" for the genesis of novel influenza A viruses is reinforced by the observation that the pH1N1 virus contains genes from both avian and swine viruses.

Surveillance is the underpinning of all aspects of control options for influenza. Recognizing the role of pigs and domestic and wild birds in some of the most devastating influenza outbreaks in recent history necessitates the urgent rethinking of current national and global surveillance systems and calls for a more comprehensive strategy to enhance influenza surveillance in these animal populations.

The local and global burden of influenza in swine should be estimated and should be based on virological and serological surveillance in apparently healthy pigs – a model that is already in use in Hong Kong. Keeping in mind that influenza A viruses do not cause disease in their natural reservoirs, it is important to regularly survey influenza genomes from wild birds and track their evolutionary movement to predict which viruses have pandemic potential.

Dr. Ilaria Capua from the World Organisation for Animal Health (OIE) Collaborating Centre for Diseases at the Human-Animal Interface at Istituto Zooprofilattico Sperimentale delle Venezie in Legnaro, Padova, Italy, further corroborated Dr. Webster's urge for enhanced influenza surveillance in key animal populations by introducing the "One World, One Health, One Flu" concept.

In the past few years, the "One World, One Health" concept has gained traction and has begun to mobilize public health and veterinary communities to work together to address human health and infectious disease risks at the human-animal interface. Adopting a truly integrated "One World, One Health" approach for the control of influenza has become more urgent than ever given recent events. Faithful migration of wild birds, and increased movement of people, animals and animal products across continents as a result of globalization mean there will be more opportunities for influenza A viruses to reassort.

Influenza surveillance capacity needs to be established worldwide where surveillance in humans and animals will have equal weight.

As the possibility of future pandemics continues to be a global threat, preparedness remains critical. Before we can improve our prediction capacity on pandemic potential and viral characteristics, we need to understand how influenza genes migrate across species and continents as a single gene pool. Instead of assigning influenza A viruses to discreet species-specific categories, all influenza A viruses should be viewed as "One Flu". As such, influenza surveillance capacity needs to be established worldwide where surveillance in humans and animals will have equal weight.

Underlying the seamless cross-sectoral collaboration between human and animal health is the open sharing of and equal access to all essential information. In a Tripartite Concept Note released jointly by the Food and Agriculture Organization of the United Nations (FAO), OIE and WHO in April 2010, the three international organizations outline their current and future collaborative efforts to fulfill the "One World, One Health" vision for the prevention, detection and control of all emerging diseases that present a risk to human and animal health [5].

Public Health Measures

Public health mitigation strategies of large-scale infectious disease outbreaks usually consist of both pharmaceutical and non-pharmaceutical interventions. Individual interventions are imperfect but they are imperfect in different ways. By layering pharmaceutical and non-pharmaceutical interventions serially to form a comprehensive mitigation plan, the likelihood that infection events will penetrate all intervention levels and propagate can be reduced. This, in effect, would drive the outbreak below self-sustaining levels, which is the implicit goal of all public health mitigation strategies.

Dr. Gabriel Leung, the Under Secretary for the Food and Health Bureau of the Government of the Hong Kong SAR, presented an overview of some of non-pharmaceutical public health mitigation interventions implemented in Hong Kong during the 2009 pandemic. His discussion began with perhaps one of the most controversial non-pharmaceutical interventions targeted at the population-level – border screening. According to Dr. Leung, border screening must be implicitly coupled with quarantine in order to be effective. However, border screening and quarantine were generally not recommended by the WHO because asymptomatic travellers would likely be able to cross borders undetected even with screening mechanisms and technologies in place. Furthermore, modeling studies suggest that border screening would unlikely bring about containment of an influenza pandemic.

Nonetheless, a number of countries, including Hong Kong, did implement some form of border screening during the 2009 pandemic. Dr. Leung argued that although modeling studies do not support the use of border screening as a mitigation measure, the same literature does suggest that border screening, together with quarantine, can delay the onset of local transmission by two to three weeks. For this reason, the objective for implementing border screening was not to isolate communities, but rather to increase the time available for ramping up mitigation measures in advance of the first case of community spread. Indeed, implementation of entry screening during the 2009 pandemic was associated with delays in local transmission by an average of an additional seven to 12 days compared to nations that did not implement entry screening [6]. Moreover, from a political point of view, implementing border screening was also a way of managing heightened public anxiety at the very early stages of the pandemic when the general public expected the government to be proactive in its mitigation efforts. Dr. Leung added that being idle during initial stages of the pandemic was simply not tenable given Hong Kong's past experiences with the 1997 H5N1 and 2003 SARS outbreaks.

Effective isolation and quarantine are difficult to implement and may only be feasible at the very beginning of a pandemic when there is still a limited number of cases. As the pandemic progresses, the number of infected persons can become overwhelming very quickly. Effective implementation of isolation and quarantine are further complicated by the fact that disease can be transmitted by those who have not yet developed symptoms and by those with sub-clinical or asymptomatic presentation. Nevertheless, on May 1, 2009, following laboratory-confirmation that a Mexican hotel guest had contracted pH1N1, Hong Kong's government ordered a full quarantine for a period of seven days on nearly 300 guests and staff of a hotel in the territory. This controversial move to contain the pH1N1 virus made headline news around the world and continues to be hotly debated; its outcome and effectiveness have yet to be determined.

School closure is a social distancing measure that was frequently proposed for the mitigation of the 2009 pandemic. Mathematical modeling studies suggest that even though sustained proactive closures may reduce peak attack rates, school closures in general would likely have a limited effect in reducing the transmission of pH1N1 and the final size of the outbreak. In addition, because school closures can have substantial economic and social costs, whether to close schools or not is a highly contextualized decision. This decision should also be based on whether resources and back-up systems are available to deal with the flux of out-of-school children. In this respect, school closures should be coupled with other social distancing measures, such as liberal leave policies and cancellation of mass gatherings, to allow parents to take care of their children at home.

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After the first reported case of community spread of pH1N1 on June 10, 2009, Hong Kong's government announced immediate proactive closure of all primary schools, kindergartens, childcare centres and special schools, initially for 14 days. This closure was then extended until the start of summer vacation on July 10, 2009. Secondary schools generally remained open, while those schools with at least 1 confirmed case were closed for 14 days. As a result of such measures, the pandemic peak was delayed at the population-level and transmissibility was reduced by 12% to 25% over the duration of school closures and the entire summer period [7]. At this point, most school aged children (five to 19 years) remained largely unaffected as revealed by seroprevalence studies. Yet, once school reopened in September 2009, 40% to 50% of school-aged children were infected within approximately one month's time [8].

Hand hygiene and use of face masks are the chief protective measures at the individual level. However, evidence supporting the use of such measures in the community setting is, by and large, conflicting or lacking. Other factors that also influence the effectiveness of these personal protective interventions are the frequency and correctness with which they were practised. In a survey study examining the personal protective behaviours of Hong Kong residents between April and November 2009, it was found that hand hygiene and the use of face masks in the community did not increase with the growth of the epidemic [9].

The effectiveness of many non-pharmaceutical public health interventions in mitigating the impact of influenza outbreaks remains unclear. Before we can begin to delve into the issue, we must first answer fundamental questions related to the transmission route of influenza in different settings, and the seasonality of influenza and how it interacts with, or is confounded by, population behavioural and social determinants, including the timing of school closure. We must also improve our understanding of population psycho-behavioural traits to help us better tailor messages for communicating risk.

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See the next edition of the *Purple Paper* for highlights on *antivirals*, *vaccine*, and the *public health vision*.