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Commentary

Response to the 2009 pandemic: Effect on influenza control in wealthy and poor countries

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ABSTRACT

The declaration by the World Health Organization (WHO) that appearance of a swine-origin novel influenza virus in 2009 represented a pandemic was based on previously adopted guidelines and the new International Health Regulations. Severity of the pandemic was not part of the definition used, but it was stated to be less than severe at the time of declaration. It was necessary, when there was still uncertainty about the overall impact of the pandemic, for vaccine production to begin to have timely availability. Countries arranged to have vaccine for their populations, and WHO attempted to secure supplies for under-resourced countries.

The world had been concerned that the next pandemic might be a severe one, based on the specter of avian influenza with a case fatality of up to 80% in humans. After it was clear that the 2009 pandemic was not severe, there were accusations, especially in Europe, that countries had secured vaccine supplies mainly to benefit the manufacturers. Such charges, even when refuted, may undermine public confidence in the process which assures vaccine supply and availability of vaccine for seasonal use.

Production of pandemic vaccine is conditioned on the supply of seasonal influenza vaccine; it is unrealistic to expect vaccine to be available for pandemic use when none is used for seasonal influenza. This particularly applies to poorer counties. They have traditionally not recognized that influenza is a problem, although this attitude is changing. As we go forward, we need to keep in mind the global nature of the threat of influenza. Had the 2009 pandemic been more severe, demand would have been greater and poorer counties would have had little vaccine to meet their needs. Only by taking a broad view of influenza on an annual basis can vaccine supplies be ensured for all countries of the world.

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Beginning in 2009, the world experienced a pandemic caused by a novel H1N1 swine origin influenza virus. By June 2009, less than 2 months after the initial recognition of this virus, community level transmission of the virus had been documented in two continents which, according to previously adopted guidelines, led the World Health Organization (WHO) to declare phase 6, also termed the pandemic phase [1,2]. At that time, great uncertainty still existed about the evolution of the pandemic. Analysis of initial information from Mexico indicated that morbidity and mortality were high in identified cases [3]. It was felt that time was of the essence, since any delay in the decision to manufacture pandemic vaccine would result in delayed availability. Based on experience in past pandemics, such a delay could potentially result in millions of deaths. Accordingly, on advice from international and national organizations, influenza vaccine production was moved from seasonal trivalent vaccine to monovalent pandemic vaccine [4]. In addition, it was recognized that there was a need to make sufficient supply of vaccine not only for developed countries but also for those in the developing world [5].

Over the summer of 2009, pandemic vaccine production proceeded in several countries of the world with an attempt to have vaccine available in the Northern hemisphere prior to an anticipated large autumn wave of illness [6]. As the pandemic progressed, it became clear that morbidity and mortality were different from that expected based on previous patterns. Individuals over age 50, the ones who most frequently die from influenza had some degree of immunity to the virus and were relatively protected [7]. The rest of the population especially children and young adults experienced high morbidity. A small proportion was hospitalized; some of these individuals died but others survived following intensive care and

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antiviral therapy. Pregnant women were at particular risk, estimated to be four times higher than in other adults [8]. The fortunate fact that the pandemic turned out to be milder than anticipated has led many individuals, especially in Europe, to question the initial decision to declare the pandemic and manufacture doses of vaccine for much of the world's population. Some have even gone so far as to question the integrity of those individuals and institutions making these decisions. For example, the quasi-governmental Parliamentary Assembly of the Council of Europe conducted hearings and stated that "the seriousness of the pandemic was vastly overrated by WHO at the outset" [9]. By contrast, despite the large effort on the part of manufacturers, there was a scarcity of vaccine in the developing world which could have been catastrophic in the event of a more severe pandemic. Mexico, despite being the country where the outbreak was initially identified, had difficulty in obtaining vaccine for its population and, in January, 2010 was provided with 5 million bridging doses by Canada from that country's vaccine supplies [10].

We will explore here the rationale for the decision making process regarding vaccine production used during the initial stages of the pandemic and also the implications of the shortage of pandemic vaccine in developing countries. We feel that the time sensitive nature of the decisions which must be made when there is inherent uncertainty regarding the course of a pandemic need to be understood. These decisions, unless backed by sufficient production capacity and agreed global allocation, will inevitably result in shortages of vaccine especially in non-vaccine producing countries. All of these points must be considered in designing policy to confront any future pandemic [11].

1. Background to the pandemic

The 2009 H1N1 pandemic was declared by WHO in June, 2009, but the approaches undertaken to control it were largely a result of two events which shocked governments and increased the urgency to plan for future health emergencies. The first event, in 2003, was the rapid spread globally of the coronavirus causing SARS [12]. Case fatality was often high and the economic and societal impact was major. SARS left behind a sensitization to the health impact of an emerging infection and the value of measures to control transmission. The SARS outbreaks were followed by the return in 2003 of the highly pathogenic avian A (H5N1) in humans, initially in South East Asia [13,14]. The case fatality, sometimes as high as 80%, jolted the biomedical world. Since all influenza pandemics of the 20th century were of avian origin, the possibility that this virus could mutate or reassort with other influenza viruses and become easily transmissible among humans raised the specter of an influenza pandemic even more serious than 1918. These events, created a supposition that the next pandemic would be of avian origin and would be severe [15].

Planning for a pandemic involved a variety of activities, including improving surveillance in humans and at the animal–human interface. In terms of prophylaxis and control of infection and disease, three pillars were identified: vaccines, antivirals and non-pharmaceutical interventions, with vaccines ideally the first line of defense [16]. Studies of the H5N1 virus vaccine demonstrated that the addition of an adjuvant allowed use of less viral antigen with improved immunogenicity which would, in turn, allow more vaccine to be made available [17,18]. In Europe regulatory filing was undertaken of "mock-up" dossiers for adjuvanted vaccines, which could apply to any pandemic virus [19]. These were implemented rapidly when the A (H1N1) pandemic occurred.

Planning at WHO also was conditioned by the specter of a potentially severe A (H5N1) pandemic. Overall, of great concern was the possibility that the world would not have vaccines or antivirals during an early period of devastating spread, resulting in social disruption. The new international health regulations (IHR) had provided guidance on handling international reporting and border closure during such a public health emergency [20]. Pandemic phases were designated to guide actions that countries should take in pandemic preparation. The first phases were designed on the assumption, based on the experience with A (H5N1) virus, that the pandemic influenza virus would gradually adapt itself to be able to transmit from human to human. Discussion of changes in the original phases had been underway for several years, in particular because of episodes of unsustained human to human transmission of H5N1, after initial transmission from poultry to humans. The new classification (Table 1), finally released in early 2009, made phase 4 the critical one as this was the phase which recognized that there was sustained human to human transmission of "an animal or human-animal influenza reassortant" [1]. It was at this point when decisions to move to pandemic vaccine production would need to be made. Because of the anticipated delay of at least 6 months from the identification of the pandemic to the availability of vaccine, it was felt that the decision as to whether or not to proceed to large scale pandemic vaccine production needed to be made early before global spread had been documented [6]. Given the short incubation period for influenza and rapid doubling time, waiting until it was absolutely certain that there was a severe global pandemic would have removed prevention by vaccination as a real option to mitigate the burden.

Barring the ability to contain a focal site of transmission, it was thought that the situation would move inevitably to phase 5 when community level transmission was documented in two countries in one WHO region, and to phase 6, or the pandemic phase, when such transmission had been documented in two WHO regions. It is

Table 1
World health organization (WHO) pandemic phases, 2009.

Phase	Description	Significance
1	No viruses circulating in animals capable of causing human disease	No threat
2	An animal influenza virus circulating among domestic or wild animals capable of causing human disease	Pandemic threat
3	An animal virus causing sporadic or small clusters of cases in humans	Increased pandemic threat
4	Verified sustained human to human transmission of an animal influenza virus	Consider shifting to pandemic vaccine production
5	Community-level transmission of the virus in two or more countries in one WHO region	Pandemic alert
6	Community-level transmission in more than one WHO region	Pandemic declared
Post-peak	Outbreaks of pandemic virus still possible	More waves possible
Post-pandemic	Return to seasonal levels	Pandemic threat ended

See Ref. [1].

important to note that assessment of the severity of the outbreak was not part of declaring a pandemic. Although there was gradual recognition of the need to assess the severity to help countries determine what measures to adopt, it was felt that it might vary globally based on local conditions so that, by spring 2009, no specific agreed formula had been developed. In retrospect, the decision not to include severity probably made communicating the rationale for the process more difficult; however, it was always felt that the assessment of severity would be independent of the phases, which would be based on extent of spread.

2. Start of the 2009 pandemic

The recognition that a novel influenza animal-human reassortment virus was transmitting in humans in Mexico and in the United States has been well described [21]. Initial reports suggested that case fatality in Mexico was relatively high; later outbreaks in the United States and Canada suggested different characteristics [3,7]. As a result of documented spread of the new virus, on 25 April 2009, an Emergency Committee of 15 members appointed by WHO as stipulated by the IHR, followed the existing procedure guidelines and advised the WHO director-general to declare that a "public health emergency of international concern" existed [22]. This involved various actions under the regulations and included intensified surveillance. WHO declared phase 4 on 27 April 2009, recognizing sustained human to human transmission of the A (H1N1) virus. By June 11, 2009, it was obvious that transmission was widespread, and phase 6 was announced [2]. By this time, many manufacturers had begun large scale vaccine production and many countries had signed contracts to obtain these vaccines for their citizens. At this point, it was realized that most illnesses were not severe, and in the communiqué accompanying the announcement, it was described as "moderate in severity". Many, remembering past pandemics still were concerned about a potential change in illness characteristics.

The first wave of the pandemic hit North America and some other countries, such as the United Kingdom and Japan, in spring/early summer 2009. These countries had stockpiled antivirals for just this eventuality: pandemic spread with no vaccine availability. Approaches varied, the most aggressive being in the UK with use of antivirals drug initially for prophylaxis, especially to control school outbreaks, and then for treatment; antivirals were dispensed to those with appropriate symptoms following a call to a toll-free number [23]. The value of the antivirals, particularly in treatment, is still being evaluated. In Canada, the lower impact of infections in Northern populations in the second wave compared to the first may be related to the more widespread use of antivirals during the latter period in that country [24].

3. Pandemic vaccine availability

A variety of different H1N1 vaccines were produced in the world. A live attenuated vaccine was used in the United States and Russia. However, the bulk of vaccines available globally can be broadly divided into adjuvanted or non-adjuvanted inactivated preparations; the viral antigen might be split or subunit. As discussed above, due to the poor immunogenicity of the A (H5N1) virus, had this pandemic been caused by that virus, all vaccines would have had to be adjuvanted. However, since the swine origin—A (H1N1) virus was distantly related to viruses that had circulated previously in humans, it was decided in the US and some other countries to take a calculated risk and rely on unadjuvanted vaccines. In the United States, this had an advantage from the regulatory standpoint as the vaccines would represent only a strain change, so that approval could be facilitated. However, the decision in the US to use unadjuvanted vaccines which required much higher antigen content inherently reduced the amount of vaccine antigen which would be available for non-manufacturing and developing countries [6]. Because of prior experience with adjuvanted influenza vaccines and because of the mock-up regulatory dossiers, adjuvanted H1N1 vaccines were produced for much of the world. With the adjuvant MF-59, 7.5 mcg of antigen was sufficient and with adjuvant AS-03, only 3.8 mcg per dose was needed to produce a satisfactory immunologic response; in contrast, 15 mcg per dose was required in the US vaccine. The use of adjuvanted vaccine was supported by WHO because this would result in a larger number of vaccine doses being available for the rest of the world [25].

Governments purchased vaccine throughout the developed world in spring 2009. Contracts were negotiated either by the national authorities with immediate effect or with certain triggers, such as the declaration of phase 6 by the WHO. These agreements were typically made before it was clear whether two doses would be required or how the pandemic would evolve. In fact, there was considerable media attention at that time on the occasional deaths in H1N1 infected individuals. There were also predictions that the pandemic virus would become further adapted to human to human transmission, and associated disease might become more severe, as has hypothesized to have occurred in the 1918 pandemic. In any event, only a small proportion of initial vaccine production was left for use by the developing countries.

4. Disease impact and timing

The H1N1 virus spread from Mexico to the United States and Canada in March 2009. Unlike seasonal influenza or the more recent pandemics of 1957 and 1968, there was relative protection of older individuals. Attack rates were high in the young and in pregnant women and in some of these individuals there were complications leading to hospitalizations and deaths. In many cases, underlying conditions existed to explain the severe outcomes, but in a significant proportion, varying with age, there were none. Pregnancy was a major risk factor, as seen in past pandemics, but morbid obesity was a new predictor of severe outcome. The outbreaks moved through communities rapidly. Even the relatively small number of severe cases occurring over a short period of time resulted in pressure on hospitals and in particular on intensive care units [24,26].

Overall estimates of the number affected globally has been made difficult by the requirement, in some jurisdictions, for laboratory confirmation before attributing cases to the pandemic virus, resulting in major undercounts of cases. The CDC has estimated the number of cases by extrapolating from laboratory confirmed ones. The total number of cases in younger people was close to the 30% attack rates seen in past pandemics. Hospitalization numbers were similar to those seen in a major seasonal outbreak, but the age distribution was different, with children and younger adults experiencing most of these events. In contrast, mortality was lower than seen in seasonal outbreaks, mainly because of the relative sparing of older individuals, who typically experience 90% of the deaths [27,28]. However, because the deaths were mainly in younger individuals, the impact on life expectancy was particularly high; the estimate, for the US during the period May–December, 2009, was that there were between 334,000 and 1,973,000 years of life lost [29]. This range encompasses the number of life-years lost in the typical seasonal H3N2 pandemic and the estimated life-years lost during the 1968-69 A/Hong Kong pandemic.

5. Recommendations

What can we learn from the recent pandemic response? Many countries and international agencies are involved in "lessons

learned" exercises. These will likely result in attempts to fine tune future actions when a pandemic occurs. Most recently, a WHO review committee has submitted a report to the World Health Assembly with specific recommendations [30].

Of particular importance in refining the response plan for future pandemics will be the issue of how severity can be assessed early and how this information can be used to modulate the pandemic response plan. However, there are broader issues that need to be addressed, which may not be considered in more technical reviews. One concern is that had the pandemic been more severe, the use of unadjuvanted vaccine by the US and consequence antigen "overuse" could have resulted in needless deaths due to lack of vaccine availability in the developing world. The lack of a pre-approval dossier system for pandemic vaccines in the US perhaps fostered this situation. Another concern is the perception in some quarters that the response to the 2009 pandemic was an overreaction that cost governments money for vaccines and antivirals at a point when, because of the global recession, resources were particularly limited. It is important that there be recognition that there was a high level of uncertainty regarding the severity and potential time course of a pandemic at the point when decisions on vaccine purchases had to be made. If the pandemic had not been as mild as the 2009 pandemic, millions of lives could have been at risk if a "wait and see" approach had been taken. This seems to have been understood in countries where communication between the government, the press and the public were good. In these countries the focus of discussion has been on ways to increase speed and timing of vaccine availability, real issues which can be addressed. This shows what can and must be accomplished even in a situation fraught with inherent difficulties and uncertainties.

As we go forward, we need to be sure that the furor over the "faked pandemic" is addressed where it exists and does not spread to other parts of the world where it does not. The committee, commissioned by WHO to review their response to the pandemic, has submitted its report, which confirms the difficulty in making recommendations at a time of uncertainty and states that there was "no evidence of malfeasance". Pandemics occur at irregular intervals and are not all created equal. The next one might be very severe and delays in decision making due to misperceptions regarding the 2009 pandemic could have tragic results.

While pandemics are usually limited to several times in a century, seasonal influenza occurs each year, producing preventable morbidity and mortality. The new improvements in vaccine technology spurred by pandemic planning will help in seasonal control as well. In the United States, there is now a universal recommendation for influenza vaccine use [31]. Everyone 6 months of age or older is recommended to receive vaccine annually, according to current policy. From a practical standpoint, seasonal production is tightly linked to availability of vaccine for pandemics. It is currently impossible to have facilities ready to produce pandemic vaccine when they have not been producing a similar seasonal vaccine. This has been recognized in some countries but not in others.

Most of the world's population lives outside of the Americas and Europe. An even moderate pandemic could have an enormous impact on the under-resourced areas and could result in social disruption. Yet pandemic vaccines for those areas will not be available without annual production of vaccines for seasonal control. It is impossible to produce a preparation only for events occurring several times a century, whatever the improvements in technology. Efforts at regional production of vaccine have begun, led by the WHO and other organizations which could ameliorate the unethical disparity between rich and poor countries [32]. However, sustaining these programs will only be possible if it is demonstrated that there is a significant burden of seasonal influenza in less developed regions requiring vaccine use, at least for some segments of the population. We are beginning to see evidence of this in burden studies in Bangladesh and other heavily populated, under-resourced regions [33]. The demonstrated impact to date is in young children, and not yet in the elderly, the traditional risk group in the developed world.

Globally, we now have an unbalanced situation, with some developed regions moving toward widespread implementation of vaccine programs for seasonal influenza while others are suspicious of current programs and not willing to use technologies that they can easily afford. The rest of the world, where most people live, is only gradually gaining awareness that a problem exists. This is an unsustainable situation. We should try to move to a more uniform global recognition of the importance of seasonal and pandemic influenza, and help improve public confidence in the current control approaches which do work, with understanding that even better technologies are on the way.

In summary, at the outset of the 2009 pandemic, it was impossible to say how it would evolve. It was at this point in 2009 that many were working hard to ensure supplies of vaccine for their own countries and for countries in the developing world. We have tried to address the hard choices that must be made early in a pandemic and explore the context in which these decisions were recently made. It is often easy in retrospect to criticize decisions made during the course of an event. However, such criticism must take into account the potential harm that delay of vaccine availability in a severe pandemic can cause. In addition, it must be recognized that the only way to assure adequate global supply of influenza vaccine in a pandemic is to develop sufficient seasonal influenza vaccine manufacturing and distribution for the developing world. Thus, obtaining more information on the burden of influenza in the developing world to assess whether annual vaccination with seasonal vaccines is warranted should be a high priority to facilitate planning for the mitigation of future pandemics.

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