

## **Influenza A (H5N1) Vaccine Stockpile and Inter-Pandemic Vaccine Use**

### **Background Document**

#### **1. Introduction**

Highly pathogenic avian influenza A (H5N1) viruses remain a pandemic threat. Since its re-emergence in 2003, highly pathogenic avian influenza (HPAI) A (H5N1) viruses have become endemic in poultry in several countries and have continued to cause severe human disease in countries where poultry are infected. Vaccines against H5N1 have been recognized as an important tool in reducing illness during a possible H5N1 pandemic and for protecting persons exposed to the virus during the interpandemic period. As a result, WHO has developed policies for the establishment and use of H5N1 vaccine stockpiles during a pandemic and guidelines for the use of H5N1 vaccines during the interpandemic period, focused on persons at high-risk of H5N1 disease because of occupational exposure. Since these policies were issued by WHO, there have been developments related to H5N1 vaccines and the epidemiology of HPAI H5N1 viruses and human disease. Notably, the Pandemic Influenza Preparedness (PIP) Framework has provided a mechanism for access to pandemic influenza vaccines during a pandemic. As a result, WHO requested that previous recommendations regarding the stockpile and use of H5N1 vaccines be re-examined.

In 2013, the WHO Strategic Advisory Group of Experts (SAGE) Working Group on Influenza Vaccines and Immunizations (WGIVI) undertook a review of evidence and discussion of two questions related to H5N1 vaccines: (1) should WHO create a H5N1 vaccine stockpile; if yes, how should the vaccine stockpile be used, what is the number of doses required, and which vaccines should be included; and (2) is there a need to change the 2009 recommendations to countries on inter-pandemic use of H5N1 vaccine?

Although each of these questions has been addressed previously by SAGE, this document reviews and summarizes evidence accumulated in the intervening years and proposes revised recommendations based on available data.

#### **2. Summary of SAGE WGIVI recommendations**

The WHO SAGE Working Group on Influenza Vaccines recommends the following based on a review of available data.

1. *WHO should not create a stockpile of H5N1 vaccines. WHO should ensure real-time access to pandemic vaccines under the “Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits” or “PIP Framework.”*

This decision is based on the following:

- a. PIP Framework “Standard Material Transfer Agreements 2” (SMTA2) are legally binding contracts that WHO will conclude with individual vaccine manufacturers and through which

WHO will secure access, on a real-time basis, to pandemic vaccine at the time of a pandemic. The availability of a well-matched pandemic vaccine in the event of pandemic reduces the value of a pre-pandemic stockpile of vaccines, acknowledging the limitations of timely supply as a result of production and distribution timelines.

- b. No significant change in the epidemiology of H5N1 viruses or disease has been observed that would change the assessment of pandemic risk. No new countries have reported cases in humans since 2009, indicating no geographic expansion of risk.
- c. Vaccines produced and stockpiled before a pandemic virus strain emerges may be poorly matched antigenically to eventual pandemic strains. The relatively poor heterotypic immune responses elicited by current vaccines mean that a stockpiled vaccine that is antigenically different than a pandemic strain may result in diminished effectiveness. The continued emergence of new clades and sub-clades of HPAI H5N1 viruses (e.g., clade 2.3.2.1) increase the likelihood that, if an HPAI H5N1 virus were to cause a pandemic in the future, the pandemic virus strain would be significantly drifted antigenically compared with past strains. Decisions on selection of vaccine candidates, therefore, would be very challenging, and potentially require a stockpile containing multiple vaccines representing various clades and subclades to ensure a well-matched vaccine is available once a pandemic strain emerges.
- d. The recent emergence of avian influenza A(H7N9) viruses in China, H3N2 variant viruses in the United States, and the 2009 H1N1 pandemic virus highlight the risk of non-H5N1 strains as pandemic threats. Stockpiling H5N1 vaccines would result in no benefit in the event that the next pandemic is caused by a virus other than H5N1.
- e. The value of stockpiled vaccine for use early in a pandemic for containment or delaying the spread of a nascent pandemic is questionable. Based on experience with the 2009 H1N1 pandemic, the rapid spread of the pandemic viruses would likely preclude targeting vaccine to populations initially affected.

2. *The 2009 recommendations for use of licensed H5N1 vaccine during inter-pandemic periods should remain unchanged.* The 2009 recommendations<sup>1</sup> can be summarized as follows:

- Vaccination is *strongly recommended* for laboratory workers involved in certain high-risk activities (e.g., large-scale production or manipulation of, or work over a long period of time with, HPAI H5N1 virus strains, work with drug-resistant HPAI H5N1 viruses or viruses that have the potential for increased transmissibility to mammals).
- Vaccination is *recommended* for first responders to human or animal HPAI H5N1 cases or outbreaks.
- Vaccination is *recommended* for health-care workers who evaluate or manage patients with suspected or confirmed HPAI H5N1 virus infection in designated referral facilities.
- Vaccine is not recommended for the following: persons who may only potentially come in contact with infected animals, for essential workers in areas where HPAI H5N1 virus is enzootic, or for the general population.
- Insufficient evidence exists to recommend use of H5N1 vaccines to immunologically prime individuals.

This decision is based on the following:

- a. As noted above, no clear change in the level of risk to exposed populations has been observed.

- b. No changes in populations at risk for HPAI H5N1 virus infection have been observed.
- c. While risk remains low, even in exposed populations, certain high risk groups may benefit from vaccination given the severity of the disease if infected.

### 3. Background

#### 3.1 Epidemiology of Human Infections with Highly Pathogenic Avian Influenza A (H5N1) Viruses

Since the previous reports by the SAGE H5N1 Vaccine Work Group,<sup>1,2</sup> the epidemiology of human infections with HPAI (H5N1) viruses is largely unchanged. The United Nations Food and Agricultural Organization (FAO) considers six countries to be endemic for HPAI H5N1 viruses circulating among poultry (Bangladesh, China, Egypt, India, Indonesia, Vietnam) with poultry outbreaks occurring frequently in nearby countries.<sup>3,4</sup> Human cases of HPAI H5N1 virus infection have declined since peaking in 2006, but sporadic cases with a high case fatality proportion continue to occur and be detected, particularly in six countries (Figure 1, Bangladesh, Cambodia, China, Egypt, Indonesia, and Vietnam).<sup>5-8</sup> The majority of cases have been comprised of children and young adults with few cases aged older than 40 years; the median case age overall is approximately 18-20 years, but has varied from year-to-year and by country. As of October 2013, 641 HPAI H5N1 cases with 380 deaths (59% case fatality proportion) had been reported to WHO from 15 countries since November 2003.<sup>9</sup>

In general, no population-level immunity to H5N1 viruses has been demonstrated. Although the number of studies is limited, persons with laboratory-confirmed infection produce antibodies and more severely ill persons mount a more robust immune response for longer duration.<sup>10</sup> However, as of October 8, 2013, the total number of persons globally reported to have been infected since November 2003 is only 641.<sup>9</sup> Recent (since 2003) limited serologic surveys to detect serum antibodies identify very low prevalence (0-3%) of antibodies to H5 viruses among persons living in HPAI H5N1 areas affected (0-3%) or in persons with an occupational exposure (0- <1%).<sup>11</sup> Together, these data suggest that few people have any anti-H5 antibodies.

Cases in humans have been identified more frequently during cooler periods (e.g., December through March, Figure 1), suggesting seasonality associated temporally with increases in HPAI H5N1 poultry outbreaks, but sporadic cases can occur year-round in endemic countries or where HPAI H5N1 poultry outbreaks are common (e.g., Cambodia). Risk factors for human infection with HPAI H5N1 virus infection continue to be the same as reported previously for zoonotic transmission, primarily direct contact or close exposure to sick or dead poultry or environments contaminated by infected poultry (including swimming or bathing in a pond), or visiting a live poultry market.<sup>11-16</sup> Few cases have been attributed to occupational poultry exposures. For some cases, the source of HPAI H5N1 virus exposure and infection is unknown.

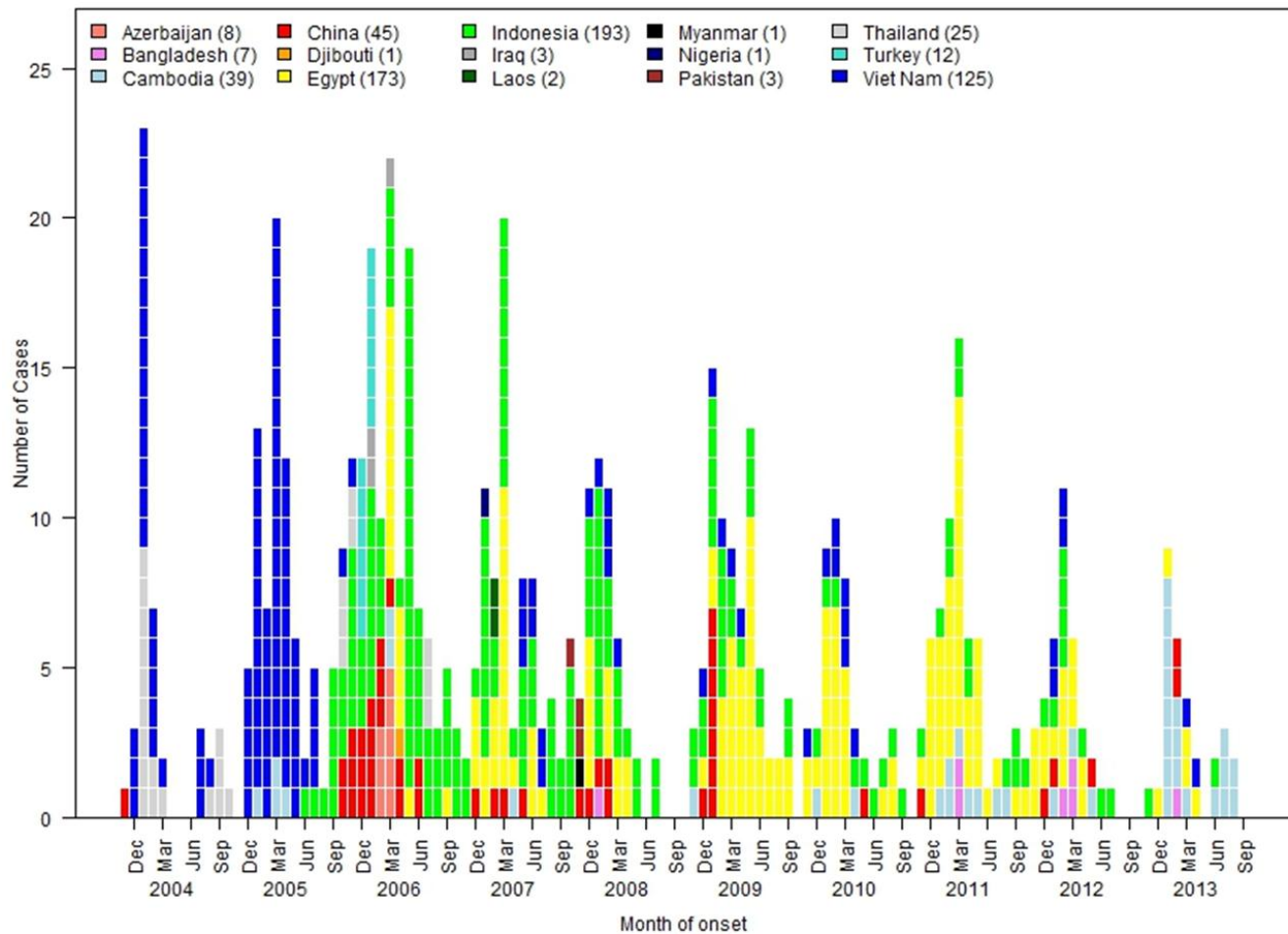
Clusters of HPAI H5N1 cases have declined, but continue to occur infrequently. The majority of such clusters are comprised of blood-related family members who shared a common exposure to poultry.<sup>17,18</sup> However, in some clusters, limited, non-sustained human-to-human HPAI H5N1 virus transmission occurred in a person without poultry exposure who had prolonged, close unprotected exposure to a symptomatic family member with confirmed HPAI H5N1 virus infection, in a household or hospital setting.<sup>19-22</sup> Only one case of limited human-to-human HPAI H5N1 virus transmission has been reported in an unrelated health care worker who had prolonged, unprotected hospital exposure to an HPAI H5N1 case-patient.<sup>23</sup> Limited seroprevalence studies have reported serological evidence of H5N1 virus antibodies in blood relatives.<sup>16,24</sup> Case clusters among blood-related family

members and not in exposed unrelated close contacts suggest the possibility of genetic susceptibility to HPAI H5N1 virus infection.<sup>25</sup>

The incubation period for HPAI H5N1 virus infection has been estimated to have a wide range (median approximately 3 days, range 2-9 days), which may be influenced by many factors, including the infectious dose of HPAI H5N1 virus, single versus multiple virus exposures, clade/subclade of virus, modality of transmission, host factors, and others.<sup>19-22,26,27</sup>

The case fatality proportion has remained consistently high at approximately 60%, with variability by country and year. Generally, but not in all countries, case fatality is lowest in young children.<sup>28</sup> Surveillance varies by country, but most case-finding is still focused upon hospitalized patients with severe respiratory distress who had recent poultry exposures. Few countries except for Egypt have identified HPAI H5N1 cases early in the clinical course or clinically mild, non-pneumonic disease, particularly in children.<sup>29</sup> The true denominator for HPAI H5N1 virus infections is unknown. A small number of asymptomatic or clinically mild HPAI H5N1 virus infections have been identified through surveillance or through limited seroprevalence studies, predominantly among children.<sup>16,22,24,28,30-32</sup> A case of asymptomatic HPAI H5N1 virus infection in an adult was identified through investigations of contacts of a confirmed case.<sup>33</sup> However, the epidemiological evidence to date does not suggest that a large number of asymptomatic or mild illnesses have occurred. Therefore, while the case fatality proportion from cases reported to WHO may be biased upward, it is unlikely that the true HPAI H5N1 case fatality is substantially lower, especially since some severe and fatal cases are undoubtedly also being missed. Mortality from HPAI H5N1 virus infection is associated with late clinical presentation, delayed diagnosis, and late antiviral treatment.<sup>28,34-36</sup>

Figure 1. Number of confirmed human cases of laboratory-confirmed influenza A(H5N1) by month of onset. Data are current as of September 16, 2013.



### 3.2 Clinical Manifestations of Human Infections with Highly Pathogenic Avian Influenza A (H5N1) Viruses and Treatment

The clinical characteristics of human infections with HPAI H5N1 viruses remain unchanged.<sup>37,38</sup> The spectrum of HPAI H5N1 virus infection includes rare asymptomatic infection, clinically mild febrile upper respiratory illness, and severe pneumonia, respiratory failure and multi-organ disease. Clinically mild febrile upper respiratory illness has been reported in children.<sup>22,28,30</sup> In patients with severe respiratory illness, the progression from illness onset to respiratory failure is often rapid (4-6 days). Diarrhea is more common in children than adults.<sup>28,37,38</sup> At hospital admission, many patients have experienced high fever, non-productive cough, shortness of breath, dyspnea, leukopenia, lymphopenia, and moderate thrombocytopenia, with clinical and radiographic evidence of pneumonia. The most common complication is viral pneumonia, progressing to respiratory failure and acute respiratory distress syndrome (ARDS), and some patients have experienced elevation of transaminases, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH), with septic shock requiring vassopressors, disseminated intravascular coagulation (DIC), hemophagocytosis, and renal failure.<sup>37,38</sup> A few atypical presentations of HPAI H5N1 virus infection with febrile diarrheal illness without respiratory symptoms, or with fever, diarrhea, pneumonia and encephalitis, have been reported in pediatric patients.<sup>39,40</sup> Although most hospitalized patients have received treatment with broad-spectrum antibiotics, very few cases of bacterial or fungal co-infection have been reported with HPAI H5N1 virus infection.<sup>37,38</sup> One case of HPAI H5N1 virus infection was reported in a patient with HIV infection.<sup>41</sup>

While emergence of oseltamivir resistance has been reported during treatment,<sup>42,43</sup> oral oseltamivir monotherapy remains the primary treatment for HPAI H5N1 patients. Observational studies have reported that early administration of oral or enterically administered oseltamivir treatment compared to late treatment is associated with survival, and oral oseltamivir treatment versus no treatment is associated with survival.<sup>28,34,35,37,44-46</sup> Inhaled or intravenous zanamivir should be considered for documented or suspected oseltamivir-resistant HPAI H5N1 virus infection.<sup>47</sup> Since most HPAI H5N1 viruses circulating among poultry are resistant to the adamantane antivirals, WHO does not recommend use of amantadine or rimantadine except for combination treatment when treating HPAI H5N1 virus infection with known susceptibility.<sup>47</sup> However, this recommendation may need revision to support the use of adamantanes in combination with oseltamivir in countries where HPAI H5N1 viruses have shown decreased resistance to this older class of drugs. Combination antiviral treatment with drugs of different mechanisms of action as well as immunotherapy with convalescent plasma have been administered to a small number of HPAI H5N1 patients, but clinical trials or larger observational studies are needed to assess efficacy and effectiveness.<sup>38,48</sup> Importantly, clinical management for HPAI H5N1 patients involves much more than administering antiviral treatment, and includes evidence-based management of complications and appropriate supportive care.<sup>48,49</sup> An extremely important component of clinical management is to follow recommended infection control guidance to prevent nosocomial HPAI H5N1 virus transmission to healthcare personnel and family members, including guidance to prevent exposure to other influenza viruses and non-influenza respiratory viruses of public health concern.<sup>49-52</sup>

### 3.3 Virologic features of HPAI H5N1 viruses

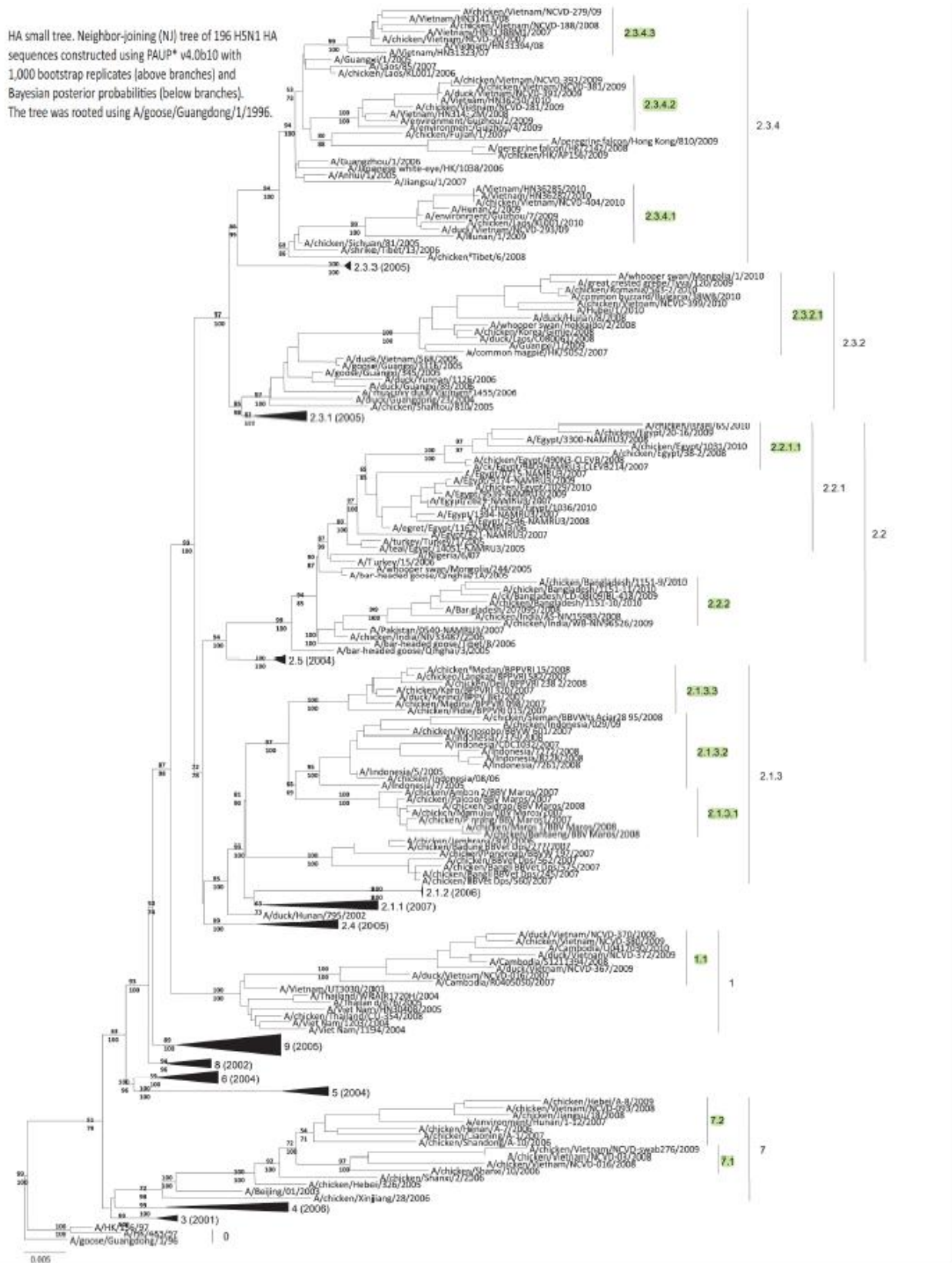
#### 3.3.1 Geographic distribution of clades

The evolution of HPAI H5N1 viruses is monitored using the sequence of the HA gene, encoding the major surface antigen. Viruses are grouped into clades based on the phylogenetic characterization and sequence homology of the HA gene. A clade is defined by three criteria: sharing of a common mode in the phylogenetic tree, monophyletic grouping with bootstrap value of  $\geq 60$  at the node, and average percentage pairwise distances between and within clades of  $>1/5\%$  and  $1.5\%$ , respectively.<sup>53</sup> There have been 25 distinct clades of HPAI H5N1 viruses identified to date (Figure 2). However, 13 of these have not been detected since 2008.

HPAI H5N1 viruses have been found in poultry and wild birds in Asia, the Middle East, Europe and Africa. Clade 1 viruses have detected in poultry populations in the Mekong River Delta since 2003 and are divided now into clades 1.1.1 and 1.1.2. Clade 2.1 viruses have circulated since 2003 in Indonesia and since 2010 have evolved as a single new clade termed 2.1.3.2a. Clade 2.2.1.1 viruses were enzootic in Egypt and detected in Israel as of 2011; these viruses have evolved into a newly designated clade 2.2.1.1a, which appears to still be maintained primarily within the commercial poultry sector. Clade 2.2.2 is enzootic in Bangladesh and neighboring countries, and they have evolved as clade 2.2.2.1. Clade 2.3.2.1 has produced three newly designated clades. Clade 2.3.2.1a (provisionally designated as A/Hubei/1/2010-like) has been dominant in Vietnam since as early as 2009, and has been detected in Bangladesh and neighboring countries in recent years. Clade 2.3.2.1b (A/barn-swallow/HK/1161/2010-like) has been identified in in China, Hong Kong SAR and Vietnam. Clade 2.3.2.1c (represented by A/Hong Kong/6841/2010) has circulated broadly in domestic and wild birds in many Asian countries, most recently in Indonesia and Vietnam.

Figure 2. Phylogenetic analysis of HA sequences.

HA small tree. Neighbor-joining (NJ) tree of 196 H5N1 HA sequences constructed using PAUP\* v4.0b10 with 1,000 bootstrap replicates (above branches) and Bayesian posterior probabilities (below branches). The tree was rooted using A/goose/Guangdong/1/1996.





### 3.3.2 Antiviral susceptibility

There are two categories of drugs available for treating human infection with HPAI H5N1 viruses: neuraminidase inhibitors (e.g. oseltamivir, zanamivir, laninamivir and peramivir) and matrix protein 2 (M2) inhibitors (amantadine and rimantadine). Current WHO clinical management and treatment guidelines recommend oral oseltamivir as the primary antiviral treatment for persons infected with HPAI H5N1 viruses.<sup>54</sup> In general, resistance to the neuraminidase inhibitors is very low across all clades and resistance to the M2 inhibitors varies over time and by clade.

At the Centers for Disease Control and Prevention (CDC), the M2 gene sequences of 213 HPAI H5N1 viruses collected between January 2011 and March 2013 were analyzed for the presence of molecular markers of resistance to M2 inhibitors, amantadine and rimantadine (Table 1). Of the 231 tested viruses, 22 were isolated from human and 191 from either birds or the environment. Viruses were collected in 6 countries, with the majority (72%) from Vietnam. The majority of viruses (90%) were isolated from poultry. Among viruses isolated from humans, eight (36%) harbored markers of M2 inhibitor resistance, including three out of five (60%) clade 1.1 viruses and all five (100%) clade 2.1.3.2 viruses. Of the remaining 191 viruses, 23 (12%) viruses were resistant to M2 inhibitors, including 18 of 20 (90%) clade 1.1 viruses and five of 167 (3%) clade 2.1.3.2 viruses. Overall, M2 inhibitor resistance declined from 18% (21/117) among viruses collected in 2011, to 12% (10/83) among those collected in 2012, to 0% (0/13) in 2013. Because the number of viruses collected and tested in 2013 is rather low, additional testing of recently collected viruses representing various circulating clades needs to be done to confirm the trend of declining resistance to M2 inhibitors.

HPAI H5N1 viruses (n=173) collected from January 2011 through March 2013 and isolated in eggs were tested for susceptibility to the NA inhibitors oseltamivir and zanamivir (Table 2). Of these 173 viruses, 21 were collected from humans and 152 from either birds or the environment. None of the analyzed viruses contained known markers of resistance to NA inhibitors (see, H5N1 Genetic Changes Inventory, CDC). Of note, the V149A, NA substitution previously reported as having a modest effect of inhibition of NA activity by zanamivir was detected in 13 (62%) of the 21 clade 1.1. viruses.<sup>55</sup>

When compared to the respective clade median  $IC_{50}$ , a majority of viruses (170/173, 98%) exhibited normal inhibition by oseltamivir and zanamivir (<10-fold increase). The exception was two clade 1.1 viruses which demonstrated reduced inhibition by zanamivir (13- to 22-fold), and one virus from clade 2.3.2.1 with which showed a 10-fold reduced inhibition by oseltamivir. One of the clade 1.1 viruses, A/Cambodia/V04117301/2011, had the V149A and T466I changes in the NA, while the other virus, A/chicken/Vietnam/NCVD-780/2011, had the R430W substitution. The clade 2.3.2.1 virus, A/muscovy duck/Vietnam/NCVD-1220/2012, had the G147R substitution in the NA.

Table 1. M2 inhibitor susceptibility of HPAI H5N1 viruses tested by CDC (Collected from January 2011 to March 2013). (CDC, unpublished data)

Clade/host	Tested	M2 inhibitor resistant/total tested				M2 resistance markers (No.)
		2011	2012	2013	Total	
<b>Human</b>	22	4/9	4/7	0/6	8/22	L26I+S31N (3), V27A (5)
1.1	8	1/1	2/2	0/5	3/8	L26I+S31N
2.1.3.2	5	3/3	2/2	0/0	5/5	V27A
2.2.1	8	0/4	0/3	0/1	0/8	
2.3.2.1	1	0/1	0/0	0/0	0/1	
<b>Non-human</b>	191	17/108	6/76	0/7	23/191	V27A (1), A30S (1), V27A+S31N (1), L26I+S31N (18), S31N (2)
1.1	20	15/15	3/3	0/2	18/20	L26I+S31N
2.2.2	2	0/2	0/0	0/0	0/2	
2.3.2.1	167	2/89	3/73	0/5	5/167	V27A, A30S, V27A+S31N, S31N
2.3.4.2	2	0/2	0/0	0/0	0/2	
<b>All</b>	<b>213</b>	<b>21/117</b>	<b>10/83</b>	<b>0/13</b>	<b>31/213 (14.5%)</b>	<b>L26I+S31N (21), V27A (6), A30S (1), S31N (2) S31N+V27A (1)</b>

Table 2. Inhibition of Neuraminidase Activity of HPAI H5N1 Viruses Tested since January 2011 to March 2013<sup>a</sup>

Clade	Oseltamivir				Zanamivir			
	Tested (n)	Normal	Reduced	Highly Reduced	Tested (n)	Normal	Reduced	Highly Reduced
1.1	21	21	0	0	21	19	2 <sup>b</sup>	0
2.1.3.2	5	5	0	0	5	5	0	0
2.2.1	8	8	0	0	8	8	0	0
2.3.2.1	138	137	1 <sup>c</sup>	0	138	138	0	0
All	172	171	1	0	172	170	2	0

<sup>a</sup>Viruses were tested in the fluorescent NI assay using NA-Fluor kit. NA inhibition based on fold difference in IC<sub>50</sub> compared to the median IC<sub>50</sub> value of all tested viruses by clade. <sup>b</sup>A/Cambodia/V04117301/2011; NA sequence (V149A, T466I); GISAID accession pending, A/chicken/Vietnam/NCVD-780/2011 (R430W) GISAID accession no. EPI425519, <sup>c</sup>A/muscovy duck/Vietnam/NCVD-1220/2012; NA sequence (G147R), GISAID accession no. EPI425327. The WHO AVWG criteria (ref: Meetings of the WHO working group on surveillance of influenza antiviral susceptibility - Geneva, November 2011 and June 2012. Wkly.Epidemiol.Rec. 87, 369-374.) for type A viruses – Normal inhibition: <10-fold; Reduced inhibition: 10-100-fold; Highly Reduced inhibition: >100-fold.

A recent review of antiviral resistance among HPAI H5N1 virus isolates from 2002-2012, supports the findings that resistance to neuraminidase inhibitors is low and has not really changed over time.<sup>56</sup> In contrast, resistance to M2 inhibitors among isolates from humans decreased from 97% in 2002-2004, to 58% in 2005-2007, and 39% in 2008-2012.<sup>56</sup> Resistance to M2 inhibitors among isolates from birds was lower than in humans but followed the same general decrease over time.

### 3.4 Influenza A (H5N1) vaccines

#### 3.4.1 Current status of licensed vaccines

Currently, 21 H5 vaccines have achieved regulatory licensure (Table 3). Ten are inactivated whole virion vaccines, six are inactivated split virion vaccines, three are inactivated subunit vaccines, one is inactivated surface antigen vaccine, and one is a live attenuated vaccine. In addition to these 21, three additional H5 vaccines will soon be submitted for licensure: an inactivated whole virion H5N1 vaccine by VaBiotech (Vietnam), a live attenuated H5N2 vaccine by the Government Pharmaceutical Organization (Thailand), and a recombinant H5 vaccine by Protein Sciences H5 (USA).

Table 3. Licensed H5 influenza vaccines

Type	Producer (country)	Commercial name	Subtype	Strain	Substrate	Adjuvant	Dose (HA content in µg)
Inactivated whole virion	Baxter (Austria)	Pandemic Influenza Vaccine H5N1 Baxter	H5N1	A/Vietnam/1203/2004	Vero cells	None	7.5
Inactivated whole virion	Baxter Innovations GmbH (Austria)	Vepacel	H5N1	A/Vietnam/1203/2004	Vero cells	None	7.5
Inactivated whole virion	Biken (Japan)	Adsorbed Influenza Vaccine (H5N1) "BIKEN"	H5N1	A/Vietnam/1194/2004	Eggs	Al(OH) <sub>3</sub>	3, 30
Inactivated whole virion	Denka Seiken (Japan)	Adsorbed Influenza Vaccine (H5N1) "Seiken"	H5N1	A/Vietnam/1194/2004	Eggs	Al(OH) <sub>3</sub>	
Inactivated whole virion	Kitasato Institute (Japan)	Adsorbed Pandemic Influenza Vaccine (H5N1) "Hokken"	H5N1	A/Viet Nam/1194/2004	Eggs	Al(OH) <sub>3</sub>	30
Inactivated whole virion	Kaketsuken (Japan)	Adsorbed Pandemic Influenza Vaccine (H5N1) "Kaketsuken"	H5N1		Eggs	Al(OH) <sub>3</sub>	
Inactivated whole virion	Valneva (France), Kaketsuken (Japan) & GSK (Belgium)		H5N1		EB66® cell line	ASO <sub>3</sub>	
Inactivated whole virion	Omninvest (Hungary)	Fluval H5N1	H5N1	A/Vietnam/1194/2004	Eggs	AlPO <sub>4</sub>	6
Inactivated whole virion	Sinovac Biotech (China)	Panflu	H5N1	A/Vietnam/1194/2003	Eggs	Al(OH) <sub>3</sub>	15
Inactivated whole virion	RIBSP (Kazakhstan)	Kazfluvac®	H5N1	A/Astana RG/6:2/2009	Eggs	Al(OH) <sub>3</sub>	
Inactivated split virion	GSK Biologicals (Belgium)	Adjupanrix / Qpan	H5N1	A/Vietnam/1194/2004	Eggs	ASO <sub>3</sub>	3.75
Inactivated split virion	GSK Biologicals (Belgium)	Prepandrix	H5N1	A/Indonesia/05/2005	Eggs	ASO <sub>3</sub>	3.75
Inactivated split virion	GSK Biologicals (Belgium)	Pumarix	H5N1	A/Indonesia/05/2005	Eggs	ASO <sub>3</sub>	3.75
Inactivated split virion	CSL Ltd (Australia)	Panvax	H5N1	A/Vietnam/1194/2004	Eggs	Al(OH) <sub>3</sub>	30
Inactivated split virion	Sanofi Pasteur (France)		H5N1		Eggs		
Inactivated split virion	Sanofi Pasteur (USA)	Sanofi pasteur Influenza Virus Vaccine, H5N1	H5N1	A/Vietnam/1203/2004	Eggs	None	90
Inactivated subunit	Microgen (Russia)	OrniFlu®	H5N1	A/Vietnam/1194/2004	Eggs	Al(OH) <sub>3</sub>	2 x 15
Inactivated subunit	Novartis V&D (Italy)	Prepandemic influenza vaccine (H5N1)	H5N1	A/Vietnam/1194/2004	Eggs	MF59C.1	7.5
Inactivated subunit	Novartis V&D (Italy)	Foclivia	H5N1	A/Vietnam/1194/2004	Eggs	MF59C.1	7.5
Inactivated surface antigen	Novartis V&D (Italy)	Aflunov	H5N1	A/turkey/Turkey/1/05		MF59C.1	7.5
Live-attenuated	Microgen (Russia), Institute of Experimental Medicine (Russia)	Ultragrivak®	H5N2	A/17/Duck/Potsdam/88/92 (H5N2) x Len 17 (H2N2)	Eggs	None	10 <sup>8.3</sup> TCID <sub>50</sub>

### 3.4.2 Current status of national H5 vaccine stockpiles

Several countries are known to have an in-country stockpile of H5 vaccines: Australia, Japan, New Zealand, Solomon Islands, Singapore, the United States, and the United Kingdom.

As an example, part of the national strategy for pandemic influenza, the United States' plan is to stockpile enough pre-pandemic influenza vaccines to cover 20 million in the critical workforce. As of 2013, the United States has stocked bulk vaccine from 4 different clades (1, 2.1.3, 2.2, and 2.3.4) of enough quantity to produce 16.61 million doses of a vaccine formulated at 90µg of HA per dose. In addition, the United States has a stockpile of bulk oil-in-water adjuvants (MF59 and ASO<sub>3</sub>). Studies are currently underway to mix and match the adjuvants and the vaccines to identify antigen-sparing regimens for use during a pandemic. The United States has spent approximately \$1 billion in these efforts to date.

### 3.4.3 Safety

The safety profile of the H5N1 vaccines currently available has been reviewed recently and comprehensively and has not changed since the previous reports.<sup>1,2,57</sup> In general, the vaccines have demonstrated a good safety profile.

Although oil-in-water adjuvanted H5N1 vaccines have shown a good safety profile in clinical trials, during the 2009 pandemic a number of studies demonstrated an increased risk of narcolepsy in persons who had received the GSK monovalent H1N1pdm09 vaccine (Pandemrix®) containing the ASO3 adjuvant, raising concerns of the possible role of the adjuvant.<sup>58-60</sup> No other immunological adverse effects have been identified with the ASO3-containing or oil-in-water adjuvanted H1N1pdm09<sup>61-63</sup> vaccines. The risk of Guillain-Barre syndrome after such adjuvanted vaccines is similar to that reported for unadjuvanted trivalent seasonal vaccine.<sup>64,65</sup> However, the association of narcolepsy with a pandemic influenza vaccine highlights the requirement for strong systems for assessments of safety in the pre- and post-licensure periods of vaccine development.

### 3.4.4 Immunogenicity

Immune correlates of protection for influenza viruses are not well understood and it is possible that the current serologic assessment criteria may not be appropriate for H5 vaccines. However, without means to assess vaccine efficacy against laboratory-confirmed infection or clinical illness, antibody-mediated immunity remains the standard. There is some work to assess the role of cell-mediated immunity; however, the data are sparse.

Most inactivated influenza vaccines are poorly immunogenic in naïve individuals, requiring 2 doses to elicit antibody responses associated with protection in a majority of vaccines. Using current assessment methods, the avian H5 hemagglutinin (HA) appears to be less immunogenic than those of human influenza viruses. For example, the standard amount of HA that is in a non-adjuvanted inactivated seasonal influenza vaccine is 15µg. Early studies of unadjuvanted inactivated H5 vaccines suggested that multiple doses of up to 90µg each would be needed to elicit antibody titers associated with protection against human influenza virus subtypes. Compared with the standard one-dose, 15µg vaccine, a two-dose 90µg vaccine translates into 12-fold fewer people that could be vaccinated with any given production, a strategy not conducive for pandemic planning.

Because of the poor immunogenicity of the H5 HA, adjuvants have been used in an effort to enhance the quantity, breadth and durability of the immunologic response. Further, the use of adjuvants allows for a dose-sparing approach which is appealing for pandemic preparedness (i.e., more people can be vaccinated with less

antigen). The three main adjuvants used in the currently licensed H5 pandemic vaccines are  $\text{Al}(\text{OH})_3$ , ASO<sub>3</sub> and MF59.  $\text{Al}(\text{OH})_3$ , or alum, is an aluminum salt and is the only adjuvant licensed for use in humans in the United States. In general, studies using  $\text{Al}(\text{OH})_3$  in H5 inactivated vaccines have produced variable results that are less than impressive.<sup>57</sup> In contrast, the two oil-in-water adjuvants, ASO3 and MF59, have demonstrated substantial improvements in the immunogenicity inactivated H5 vaccines. Although antibody response to two-dose vaccine regimens generally were reduced after 6 months and low or absent 12-17 months after primary vaccinations.<sup>57</sup>

In an effort to improve the durability and cross-reactivity of the antibody response to H5N1 vaccines, several studies have investigated the safety and immunogenicity of booster doses administered at different intervals after primary H5N1 vaccination. Using homologous H5N1 vaccine for the priming and boosting inoculations, both unadjuvanted and adjuvanted vaccines primed for more robust boosted responses, even when antibody responses to primary vaccination were modest.<sup>66-68</sup> Using adjuvanted vaccines for both priming and boosting generally elicits the most robust and cross-reactive antibody responses. H5N1 vaccination can also prime for boosting with a heterologous vaccine. Priming is associated with more rapid, more robust and more durable responses following heterologous H5N1 vaccine boosting with improved breadth of cross-clade antibody responses.<sup>66,68-71</sup> These findings suggest that priming with an available H5N1 pre-pandemic vaccine and boosting with a heterologous H5N1 vaccine antigenically matched to an emerging pandemic strain may be an effective and dose sparing approach to protecting populations during a pandemic.

#### 3.4.5 Heterotypic (hetero-clade) immune responses

H5N1 viruses continue to evolve and produce new, distinct clades. This viral evolution highlights the need for a vaccine that confers cross-reactive immunity and cross-clade protection. A few clinical trials of H5N1 vaccines have assessed cross clade immunogenicity or the presence of anti-H5 antibodies after seasonal influenza vaccination. H5N1 vaccination strategies that include the use of oil-in-water adjuvants (MF-59 or AS03) and/or heterologous prime and boost vaccination provide the best cross-clade H5 antibody responses seen to date.<sup>66,72,73</sup> Priming with clade 0 adjuvanted vaccine induced memory B cell responses that are expanded following boosting with a clade 1 vaccine and resulted in high titers of neutralizing antibody against antigenically diverse clade 0, 1 and 2 viruses.<sup>74</sup> Similarly, clade 1 vaccine prime and clade 2 vaccine boost strategies have achieved antibody responses to both clades that were substantially higher than those achieved by primary vaccination alone.<sup>73</sup>

## 4. Should WHO create a stockpile of H5N1 vaccines for pandemic use?

### 4.1 Review of WHO stockpile recommendations and status of current stockpile/situation

In May 2007, the World Health Assembly adopted Resolution WHA60.28 that requested that WHO “establish, in close consultation with Member States, an international stockpile of vaccines for H5N1 or other influenza viruses of pandemic potential as appropriate, for use in countries in need in a timely manner and according to sound public-health principles...”<sup>75</sup> In October 2007, a WHO scientific consultation reviewed options for the use of a WHO H5N1 influenza vaccine stockpile.<sup>2</sup> Based on the data available at that time, SAGE recommended that WHO establish a stockpile of approximately 150 million doses, including 50 million doses for use in aborting or delaying nascent pandemics and 100 million doses for distribution to low and middle-income member countries to help maintain essential services during a pandemic.<sup>76</sup> WHO received two manufacturer pledges totaling 110 million doses towards this goal, but did not establish a physical stockpile. In 2009, these two pledges were

partially converted into donations of H1N1 pandemic vaccines. Following the end of the H1N1 pandemic, given that many doses of H1N1 pandemic vaccine donated by both GSK and Sanofi Pasteur had not been used by WHO, both companies renewed their pledges of H5N1 vaccines towards the international stockpile.

The SAGE recommendation to create an international stockpile of H5N1 vaccines became an integral part of the PIP Framework, adopted by the 194 countries of WHO in May 2011. Among its objectives, the PIP Framework aims to ensure real-time access by developing countries to pandemic vaccines. Section 6.9 of the Framework requests the WHO Director-General to establish and maintain a stockpile of vaccines for H5N1 and other influenza viruses with human pandemic potential and specifies that the WHO stockpile will initially include 150 million doses of H5N1 vaccine for use in accordance with expert guidance.”<sup>77</sup>

The PIP Framework also requires WHO to conclude contracts (called “Standard Material Transfer Agreement 2” or “SMTA2”) with vaccine manufacturers to secure access, on a real-time basis, to pandemic vaccines. An SMTA2 was signed in December 2012 with GSK. Under its SMTA2, GSK has committed to provide to WHO access to 10% of its real-time production of pandemic vaccine. The agreement specifies that the GSK commitment to provide pandemic vaccine replaces GSK’s previous pledge of H5N1 vaccine doses to the WHO stockpile. It is expected that Sanofi Pasteur will also replace its pledge towards a H5N1 stockpile, with a commitment to provide real-time access to pandemic vaccine. As a result, it is anticipated that as of 2013, there will no longer be any pledges to the WHO stockpile of H5N1 vaccine.

#### 4.2 Review of options for creating a WHO H5N1 vaccine stockpile

Subsequent to the original SAGE recommendations in 2007,<sup>2</sup> two options were considered by SAGE WGIV: 1) no stockpile, with reliance on donated vaccine during a pandemic; and 2) a physical stockpile of vaccines produced and stored before a pandemic. A third possible option briefly discussed included a “virtual stockpile” in which vaccine producers maintain a perennial rotating stock of H5N1 vaccines that are designated for donation to WHO in the event of a pandemic. A virtual stockpile would require that manufacturers have ongoing production of H5N1 vaccine.<sup>78</sup> Given that no such ongoing production exists or is planned, this option was not considered a sufficiently viable option and is not discussed further.

Option 1. *A physical stockpile of H5N1 vaccines produced and stored before a pandemic to be distributed in the event of a pandemic.* This option reflects the existing WHO recommendations and previous SAGE guidance. While the creation of a stockpile would require decisions on formulations, number of doses, location of storage, and plans of its use, the SAGE WGIV focused its discussion on the advantages and disadvantages of creating the stockpile, rather than these details.

##### Advantages.

1. Timely availability of vaccine to target populations following the emergence of a pandemic. Because of the timeline of influenza vaccine production and distribution, having vaccine already produced and ready to ship (or be filled and finished if stored in bulk) would maximize the opportunity to protect target populations. Because stockpiled vaccine could arrive in the first few weeks

following pandemic emergence, persons might be vaccinated before exposure. This option produces the possibility of using a vaccine for early mitigation or slowing spread of a pandemic in its early phases. This option also could be used in a containment strategy during the very beginning of a pandemic.<sup>2</sup>

2. Early vaccination of target populations could be used to prime high-risk persons for more rapid and robust immunity when pandemic vaccine is available.

#### Disadvantages.

1. Because of the continuing evolution of HPAI H5N1 viruses, a stockpiled vaccine may be a less effective vaccine should a pandemic virus be antigenically dissimilar to stockpiled vaccine virus strains.
2. Should a non-H5N1 influenza A virus cause the next pandemic, an H5N1 vaccine stockpile would be ineffective.
3. Due to the presence of circulating viruses representing multiple antigenic clades, a stockpile of H5N1 vaccines may require multiple H5N1 vaccines to best ensure an antigenically well-matched vaccine is available at the time of a pandemic.
4. Because H5N1 vaccines are currently not in production, supply of vaccines for a stockpile may not be available.
5. The costs of a stockpile are likely to be substantial. Creation of a stockpile requires purchase, maintenance and scheduled rotation of stocks. It is estimated that a “pay-as-you-go” physical stockpile of 150 million donated doses would cost around \$85 million but would need replenishing every 3-5 years.<sup>78</sup> If donations are not available, the cost of purchasing the vaccine was estimated at \$450 million. The cost to have a “committed replenishment” of a physical stockpile was estimated to range from \$360 to \$880 million depending upon the replenishment cycle.<sup>78</sup>
6. The high cost of creating and maintaining a physical stockpile would produce opportunity costs. For instance, efforts to continue to enhance routine preparedness efforts (e.g., surveillance, rapid response capabilities) might be compromised if investing in vaccine stockpiles was prioritized.

The WGIWI did discuss a variant of Option 1 – the creation of a small stockpile (fewer than 100,000 doses) for rapid deployment to populations initially affected. The advantages and disadvantages were qualitatively the same as those of the large stockpile initially recommended by SAGE, while costs concerns would be relatively reduced (even so, the absence of donated vaccine, would result in substantial costs for this option). The group determined that one additional, important disadvantage to this option was the lack of data to support early intervention with vaccine as a tool to contain or slow the spread of an early pandemic. Additionally, the small supply would likely be only enough for one country, so if multiple outbreaks were identified simultaneously, decisions on allocations would be challenging. The



experience with the rapid early spread of 2009 H1N1 virus highlighted the challenges in early detection and rapid deployment for the purpose of containment.

Option 2. No stockpile, with reliance on negotiated agreements regarding access to vaccine during a pandemic (PIP Framework SMTA2s).

#### Advantages

1. Best ensures antigenically well-matched vaccines to the pandemic virus strain, thereby maximizing vaccine effectiveness.
2. Supply is assured under the PIP Framework. Agreements for real-time access to pandemic vaccine can be negotiated in advance of a pandemic.
3. Costs are lower to WHO and are mainly related to transport of vaccine at the time of a pandemic. No costs are incurred for maintenance and replenishment of vaccine stockpiles.
4. Logistically simpler if vaccine distribution is managed by vaccine manufacturers, rather than requiring agreements to ship from vaccine stockpile locations.
5. Is not reliant on interpandemic vaccine production schedules of manufacturers.

#### Disadvantages

1. Vaccine availability in the event of an H5N1 pandemic would be delayed compared with Option 1, assuming that the stockpiled vaccine is determined to be appropriate for prevention of infection with the pandemic strain (that is, they are reasonably matched antigenically). Because of the time required for vaccine production, reliance on development of pandemic vaccines that are produced using the pandemic virus H5N1 strain would mean that vaccine would likely not be widely available during the initial waves of a pandemic. In addition, use of vaccine in attempts to slow the early spread of a pandemic would have to rely on other methods of control (e.g., antiviral use or nonpharmaceutical methods such as social distancing).
2. Communication challenges should the lack of a stockpile be interpreted as poor planning by WHO.

The SAGE WGIVI recommended Option 2 as the preferred option.

## **5. Should the 2009 recommendations for the use of licensed H5N1 vaccines during the interpandemic period be changed?**

### **5.1 Review of 2009 recommendations and rationale for the recommendations**

In April 2009, the SAGE H5N1 Working Group reported on the use of licensed H5N1 influenza vaccines in the interpandemic period.<sup>1</sup> Based on available data from five licensed vaccines and several others in the licensure process, the following vaccine recommendations were made:

Vaccination was *strongly recommended* for laboratory workers involved in certain high-risk activities (e.g., large-scale production or manipulation of, or work over a long period of time with, HPAI H5N1 virus strains, work with drug-resistant HPAI H5N1 viruses or viruses that have the potential for increased transmissibility to mammals). Vaccination was *recommended* for first responders to human or animal HPAI H5N1 cases or outbreaks, and for health-care workers who evaluate or manage patients with suspected or confirmed HPAI H5N1 virus infection in designated referral facilities. However, vaccination was not recommended for persons who may only potentially come in contact with infected animals, for essential workers in areas where HPAI H5N1 virus is enzootic, or for the general population. The group noted in several cases that the risks and benefits to specific populations should be weighed carefully and that the persons themselves be involved in the decisions regarding vaccinations. While discussion about the use of H5N1 vaccines to immunize against future pandemic virus exposure was undertaken, the group determined that too few data were available to recommend H5N1 vaccines for this purpose. Finally, the group highlighted the need to gather more data on several issues and stressed that vaccines currently stockpiled could be used to fill gaps in knowledge.

The full text of the discussion and the data reviewed are available.<sup>2</sup>

## 5.2 Rationale for maintaining current WHO recommendations

- a. No significant change in the epidemiology of HPAI H5N1 viruses or disease has been observed that would change the assessment of risk to the general population, nor to persons potentially exposed in affected countries. Between 2010 and 2013, relatively few cases of HPAI H5N1 virus infection in humans were reported [mean of 42 cases and 24 (57%) deaths in humans each year<sup>79</sup>]. Furthermore, no new countries reported cases in humans since 2009, indicating no geographic expansion of risk.
- b. No changes in populations at risk for HPAI H5N1 virus infection have been observed. That is, the group could not identify additional risk groups for which vaccine might be recommended, nor has additional data been developed to identify a change in risk among persons in previously known risk groups.
- c. While risk remains low, even in exposed populations, certain high risk groups may benefit from vaccination given the severity of the disease if infected.
- d. In persons exposed during laboratory work, it is possible to immunize them using an antigenically well-matched vaccine.

The WG acknowledged that, lacking ongoing production of new H5N1 vaccines, the recommendations for the use of H5N1 vaccine during the interpandemic period might be relevant only to populations that have access to existing stockpiled vaccines. Countries without existing stockpiles, but who wish to vaccinate the risk groups above would be encouraged to discuss methods to obtain vaccine with manufacturers or countries where stockpiles currently exist.

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