ANTIBODY RESPONSES AGAINST HETEROLOGOUS H5N1 STRAINS FOR AN MF59-ADJUVANTED CELL CULTURE-DERIVED H5N1 (aH5N1c) INFLUENZA VACCINE IN ADULTS AND THE ELDERLY

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BACKGROUND

The risk of influenza-associated morbidity and mortality is potentially greater with pandemic influenza than with seasonal influenza because of little or no pre-existing immunity to the virus in the human population. Unlike with seasonal influenza, healthy adults might be at similar risk of severe influenza-associated complications and death as are young children and older adults in a pandemic. Vaccines are the main prophylactic measure against pandemic influenza and have an important role in pandemic preparedness plans worldwide.

Rapid production of a vaccine specific to an emerging pandemic influenza strain is critical to the public health response. A vaccine supply system solely dependent on an egg-based manufacturing process is at risk of being easily overwhelmed by highly-pathogenic avian influenza virus that may compromise egg production or viability. To avoid egg supply dependence, Seqirus has applied a cell culture method using mammalian MDCK cells to pandemic vaccine manufacturing.

The ability of MF59-adjuvanted vaccines, such as the cell culture-derived, MF59 adjuvanted aH5N1c vaccine, to generate cross-reactive immune responses is especially relevant during the early phase of a pandemic, when stockpiled vaccines may need to be used while strain-matched vaccines are being made and in later days of a pandemic when protection against pandemic virus strains that have undergone antigenic drift may be needed.[1-3]

STUDY AIM

To measure antibody responses against heterologous influenza strain(s) by hemagglutination inhibition (HI) and microneutralization (MN) assays following two vaccinations with an MF59-adjuvanted, cell-derived H5N1 vaccine against the criteria set by the Center for Biological Evaluation and Research (CBER), and the former Committee for Medicinal Products (CHMP) criteria, in adult and elderly populations.

METHODS

- In separate but similar studies, a total of 975 subjects 18 to <65 years of age (adults), and 1388 subjects ≥65 years of age (elderly), were randomized to receive two full (7.5 µg HA of H5N1 per dose) or half (3.75 µg HA of H5N1 per dose) doses of the MF59-adjuvanted, cell-derived H5N1 vaccine, aH5N1c, on day 1 and day 22.
- In a pre-defined exploratory analysis, HI and MN antibody responses against five H5N1 heterologous influenza strains were evaluated in a subset of subjects from the full dose treatment arms in trials V89_04 and V89_13 (**Table 1**).
- Homologous antibody responses for all subjects at days 1, 22 and 43 were previously reported.[2]

TABLE 1. KEY STUDY ELEMENTS FOR POPULATIONS TESTED.

			H5N1 Strains Tested in HI, MN Assays	
Study	Phase N	Age Range (Years)	Homologous (Clade)	Heterologous (Clade)
V89_04 2013-2014 USA, AUS, TH	II N=485 Full Dose	18 – 64	*A/turkey/Turkey/1/2005 (Clade 2.2)*	*A/Anhui/1/2005 (Clade 2.3.4)* *A/Egypt/N03072/2010 (Clade 2.2.1)* *A/Hubei/2010 (Clade 2.3.2.1)* *A/Indonesia/5/2005 (Clade 2.1.3)* *A/Vietnam/1203/2004 (Clade 1)*
V89_13 2013-2014 USA, AU, NZ, TH	II N=698 Full Dose	≥65	*A/turkey/Turkey/1/2005 (Clade 2.2)*	*A/Anhui/1/2005 (Clade 2.3.4)* *A/Egypt/N03072/2010 (Clade 2.2.1)* *A/Hubei/2010 (Clade 2.3.2.1)* *A/Indonesia/5/2005 (Clade 2.1.3)* *A/Vietnam/1203/2004 (Clade 1)*

RESULTS

- For 5 heterologous strains, the geometric mean titer (GMT) on Day 43 in the adult and elderly subjects significantly increased from baseline (**Table 2**).
- Depending on the heterologous strain, HI≥1:40 was achieved by 17% to 64% of subjects on Day 43 (**Figure 1**). MN assay responses against these heterologous strains were generally higher compared with the HI assay (**Figure 2**).
- Notably, the Day 43 seroconversion (SC) rate for HI in adults 18-64 years of age for 3 heterologous strains (H5N1 Egypt, Hubei and Vietnam) had a lower bound of 95% CI at ≥40%, which exceeded the corresponding homologous strain criterion (**Figure 3**). For the elderly ≥65 years of age, 17% to 46% of subjects on Day 43 achieved SC.

FIGURE 1. PERCENT OF SUBJECTS WITH HI ≥1:40 ON DAY 1 AND DAY 43 AGAINST HOMOLOGOUS AND HETEROLOGOUS STRAINS - HI ASSAY.

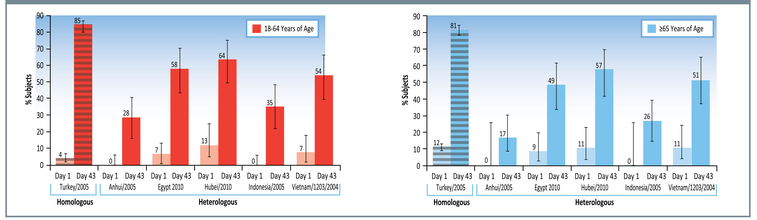


TABLE 2. GEOMETRIC MEAN TITERS (95% CI) FOR HOMOLOGOUS AND HETEROLOGOUS STRAINS — HI AND MN ASSAYS.

Adults 18-64 Years of Age (V89_04)							
		Homologous N=478	Heterologous Strain N=69				
STRAIN		Turkey/2005	Anhui/2005	Egypt/2010	Hubei/2010	Indonesia/2005	Vietnam/1203/2004
HI	Day 1	6.11 (5.78-6.46)	5.02 (4.87-5.18)	5.87 (4.51-7.63)	7.12 (5.01-10)	5.02 (4.87-5.18)	5.97 (4.41-8.06)
	Day 43	250 (208-302)	11 (6.64-17)	39 (22-71)	56 (31-102)	16 (9.17-28)	44 (24-81)
	Day 43/Day 1	41 (34-49)	2.09 (1.29-3.37)	6.52 (3.62-12)	7.3 (4.01-13)	3.12 (1.81-5.39)	6.99 (3.84-13)
		Homologous N=69	Heterologous Strain N=69				
MN	Day 1	6.7 (5.62-7.98)	16 (12-21)	15 (11-22)	7.2 (6-8.63)	8.79 (7-11)	5.59 (4.98-6.27)
	Day 43	250 (208-302)	156 (131-186)	522 (398-685)	51 (41-63)	114 (89-146)	27 (21-34)
	Day 43/Day 1	61 (44-86)	9.93 (7.47-13)	34 (23-49)	7.07 (5.56-8.98)	13 (9.42-18)	4.76 (3.74-6.06)
Older Adults ≥65 Years of Age (V89_13)							
		Homologous N=693	Heterologous Strain N=35				
STRAIN		Turkey/2005	Anhui/2005	Egypt/2010	Hubei/2010	Indonesia/2005	Vietnam/1203/2004
HI	Day 1	8.29 (7.57-9.08)	5 (5-5)	6.86 (4.94-9.53)	7.43 (5.28-10)	5 (5-5)	7.81 (5.24-12)
	Day 43	129 (110-152)	8.53 (5.92-12)	27 (15-47)	36 (20-64)	12 (8.02-18)	34 (19-63)
	Day 43/Day 1	16 (13-19)	1.71 (1.18-2.46)	3.88 (2.27-6.64)	4.83 (2.8-8.32)	2.39 (1.6-3.56)	4.41 (2.57-7.57)
		Homologous N=35	Heterologous Strain N=35				
MN	Day 1	7.49 (5.87-9.56)	28 (20-41)	25 (15-41)	11 (7.98-16)	18 (13-27)	7.32 (5.39-9.95)
	Day 43	169 (107-268)	128 (99-165)	303 (206-447)	42 (31-58)	87 (63-120)	27 (19-39)
	Day 43/Day 1	23 (13-39)	4.52 (2.93-6.97)	12 (6.69-22)	3.75 (2.6-5.4)	4.77 (3.1-7.34)	3.68 (2.62.5.17)

RESULTS (CONT'D)

FIGURE 2. PERCENT OF SUBJECTS WITH MN ≥1:40 ON DAY 1 AND DAY 43 AGAINST HOMOLOGOUS AND HETEROLOGOUS STRAINS - MN ASSAY.

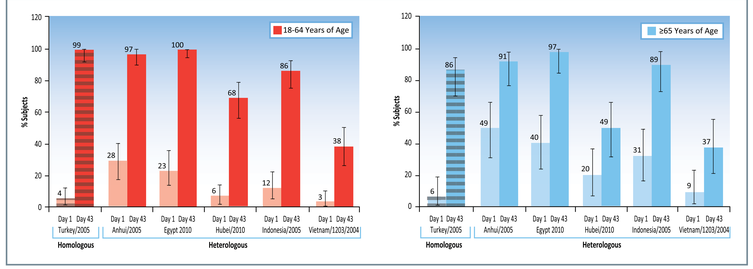
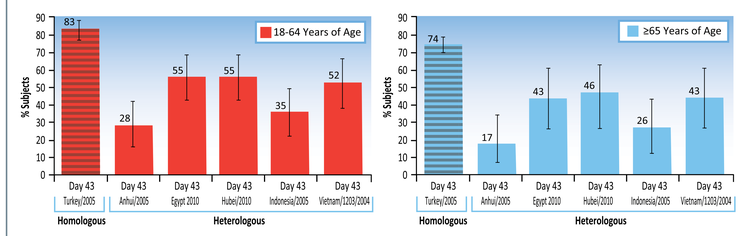


FIGURE 3. PERCENT OF SUBJECTS WITH SEROCONVERSION AGAINST HOMOLOGOUS AND HETEROLOGOUS STRAINS AT DAY 43 - HI ASSAY.



CONCLUSION

In adults and the elderly, two 7.5 µg doses of an MF59-adjuvanted H5N1 cell cultured vaccine (aH5N1c), administered three weeks apart, demonstrated increased immunogenicity from baseline against multiple heterologous H5N1 strains, of five separate genetic clades. These findings illustrate the potential for the aH5N1c vaccine to provide cross-protection against other H5N1 strains.

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