Live attenuated influenza vaccines: potential role in an influenza pandemic

Kanta Subbarao
Director, WHO CC, VIDRL

WHO Collaborating Centre for Reference and Research on Influenza
VIDRL

Doherty Institute
A joint venture between the University of Melbourne and the Royal Melbourne Hospital

Reported HPAI Disease Events Since 1959

1. 1959: Scotland, H5N1
2. 1961: S. Africa, H5N3
3. 1963: England, H7N3
4. 1966: Canada, H5N9
5. 1975: Australia, H7N7
6. 1979: Germany, H7N7
7. 1979: England, H7N7
8. 1983-84: USA, H5N2
9. 1983: Ireland, H5N8
10. 1985: Australia, H7N7
11. 1991: England, H5N1
12. 1992: Australia, H7N3
13. 1994: Australia, H7N3
14. 1994-95: Mexico, H5N2
15. 1995 & 2004: Pakistan, H7N3
16. 1997: Australia, H7N4
17. 1997: Italy, H5N2
18. 1996-2014: Eurasia/Africa, H5N1 ("panzootic")
19. 1999-2000: Italy, H7N1
20. 2002: Chile, H7N3
21. 2003: Netherlands, H7N7
22. 2004: USA, H5N2
23. 2004: Canada, H7N3
24. 2004, 2006: S. Africa, H5N2 (ostriches)
25. 2005: N. Korea, H7N7
26. 2007: Canada, H7N3
27. 2008: England, H7N7
28. 2009: Spain, H7N7
29. 2011-3: S. Africa, H5N2 (Ostriches)
30. 2012: Chinese Taipei, H5N2
31. 2012-3: Mexico, H7N3
32. 2012: Australia, H7N7
33. 2013: Italy, H7N7
34. 2014:South Korea, Japan, Germany, Netherlands, H5N8
35. 2014-2015: Canada, USA, H5N2, H5N8
36. 2014-2016: China, Japan, H5N6

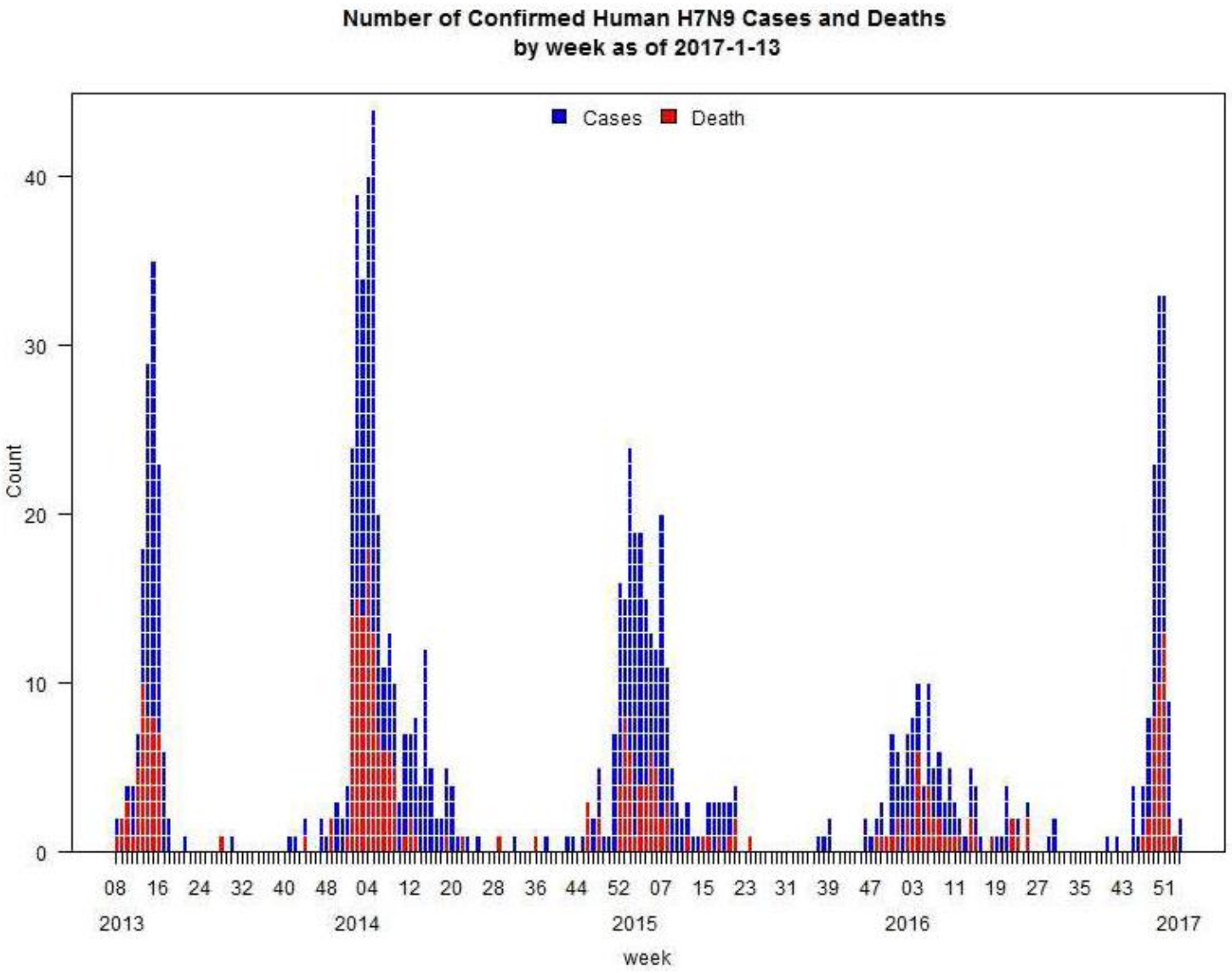
Adapted from David Suarez, SEPRL, USDA

Direct Infection of Humans with Avian Influenza Viruses

Year	Country	Subtype/pathotype	Cases	Fatalities
1959	US	H7N7 HPAI	1	0
1978-79	US	H7N7 LPAI	?	0
1996	England	H7N7 LPAI	1	0
1997	Hong Kong	H5N1 HPAI	18	6
1999	China	H9N2 LPAI	5	0
1999, 2003	Hong Kong	H9N2 LPAI	3	0
2002-03	US	H7N2 LPAI	2	0
2003	Hong Kong	H5N1 HPAI	5	2
2003	Netherlands	H7N7 HPAI	89	1
2004	Canada	H7N3 HPAI	2	0
2004	Egypt	H10N7 LPAI	2	0
2003-2017	16 countries	H5N1 HPAI	856	452
2013-2017	China	H7N9 LPAI	918	359
2014	Taiwan	H6N1 LPAI	1	0
2014	China	H10N8 LPAI	3	2
2014-2017	China	H5N6 HPAI	16	6

Sources: Perdue & Swayne (2005) Avian Dis 49:317 and EID Weekly Updates (2004) 2(18), 2, WHO

Avian influenza A (H7N9) cases in humans (2013-2017)



(https://wwwnc.cdc.gov/travel/notices/watch/avian-flu-h7n9)

Goal of a Pandemic Influenza Vaccine

To prevent severe illness and death from pandemic influenza and it's complications.

An ideal influenza vaccine will

- induce a systemic and mucosal immune response directed at the HA, NA and conserved internal proteins of the virus
- protect against a broad range of influenza viruses, within a subtype and across subtypes

Challenges in the Development of Pandemic Influenza Vaccines

- Diversity of avian influenza viruses
  - Different subtypes: H1-H16, N1-N9
  - HPAI vs LPAI
  - Eurasian vs North American lineages among many HA subtypes
  - Antigenic drift caused by natural infection or vaccine use
- Evaluation of candidate vaccines (safety and immunogenicity are evaluated but efficacy is not)
- Correlates of protection are not known
- Avian HAs appear to be poorly immunogenic; high doses or multiple doses of HA or adjuvant are needed
- Others
  - Biosafety restrictions
  - Lack of reagents for quality control
  - Use of reverse genetics

Subbarao & Joseph Nature Rev Imm 2007

Options for Vaccines for Pandemic Influenza

Principle: Induction of a protective immune response against the hemagglutinin protein.

- Inactivated vaccine: a reassortant virus containing HA and NA from an animal influenza virus (or an antigenically similar "Surrogate" virus) and internal genes from A/PR/8/34
- Live attenuated cold-adapted (ca) vaccine: a reassortant prepared with master ca strain A/Ann Arbor/6/60 used in 'FluMist' or A/Leningrad/47/57 in the Russian LAIV
- Purified expressed HA protein
- HA expressed in a vectored vaccine e.g. vesicular stomatitis virus or Newcastle Disease virus
- DNA vaccine encoding the HA and ?other genes from the avian virus

Lessons from H5N1 vaccine development

- H5-containing vaccines are only modestly immunogenic.
- Options for inducing an antibody response
  - Large dose of split virion vaccine
  - Split virion vaccine combined with an oil-in-water adjuvant
  - Whole virion vaccine
- Magnitude and quality including cross reactivity of Ab can be influenced by adjuvant
- Titers decrease over ~6-12 months but are boosted with additional doses of vaccine

Baz et al. *Virus Research* 178: 78-98, 2013

Potential advantages of live attenuated influenza virus vaccines (LAIV)

- A single dose of vaccine may be sufficient to elicit an immune response
- Seasonal LAIV induces serum and mucosal antibody responses and T cell responses
- Seasonal LAIV induces broader cross-protection against antigenic drift variants than inactivated virus vaccines do in naïve populations
- If the yield of LAIV in embryonated eggs is 10^9 $TCID_{50}$/ml and the dose of vaccine is 10^7 $TCID_{50}$ in 0.2 ml, 5000 doses of vaccine can be produced from 1 egg

The LID/NIH Pandemic Influenza Vaccine Program

Program: CRADA with MedImmune

Clinical Trials:

- Center for Immunization Research, JHSPH
- University of Rochester

Approach: Live attenuated cold-adapted vaccines

Evaluation: Inpatient setting

Replication of H5 and H7 pLAIV in healthy adults

Vaccine	Dose ($log_{10}TCID_{50}$)	First dose		
		N	% culture +	% RT-PCR +
H5N1 VN 04 ca	6.7	21	0	10
H5N1 VN 04 ca	7.5	21	0	14
H5N1 HK 03 ca	7.5	17	6	47*
H7N3 BC 04 ca	7.5	21	24	81*
H7N3 BC 04 ca	7.5	20	5	65*
H7N7 NL 03 ca	7.5	16	19	56

Karron et al. JID (2009) 199:711; Talaat et al. Vaccine (2009) 27:3744; Babu et al. *Vaccine* 2014; 32(50):6798-804

Antibody responses to H5 and H7 pLAIV

Vaccine	Dose (log_{10} $TCID_{50}$)	# doses	% vaccinees with ≥ 4-fold rise in serum antibody response indicated by				
			HI	NtAb	IgG ELISA	IgA ELISA	Any assay
H5N1 VN 04 ca	6.7	2	10	0	0	10	14
H5N1 VN 04 ca	7.5	2	10	5	38	52	62
H5N1 HK 03 ca	7.5	2	0	0	6	18	24
H7N3 BC 04 ca	7.5	2	62	48	48	71	81
H7N3 BC 04 ca	7.5	1	0	0	0	0	0
H7N7 NL 03 ca	7.5	2	0	0	33	0	0

Karron et al. JID (2009) 199:711; Talaat et al. Vaccine (2009) 27:3744; Babu et al. *Vaccine* 2014; 32(50):6798-804

Hypothesis

Prior receipt of pLAIV will prime for a higher Ab titer and greater frequency of seroconversion to an inactivated pandemic influenza vaccine

- Recall subjects who were previously vaccinated with H5 or H7 pLAIV
- Boosted with suboptimal dose of inactivated subvirion H5N1 VN04 or H7N7 vaccines (sanofi)

Rationale for prime-boost studies

- Recombinant expressed HA, DNA encoding HA and inactivated vaccine prime for a robust HAI and neutralizing response to an inactivated subunit H5N1 vaccine
- Robust serum H5 antibody responses were observed following the booster vaccination even in individuals who had no detectable antibody response following the initial vaccination.

Treanor et al Vaccine 2001; Goji et al JID 2008, Ledgerwood et al Lancet ID 2011, Nicholson et al Lancet 2001; Stephenson et al Vaccine 2003

Priming with pLAIV followed by IAV boost elicits a robust antibody response

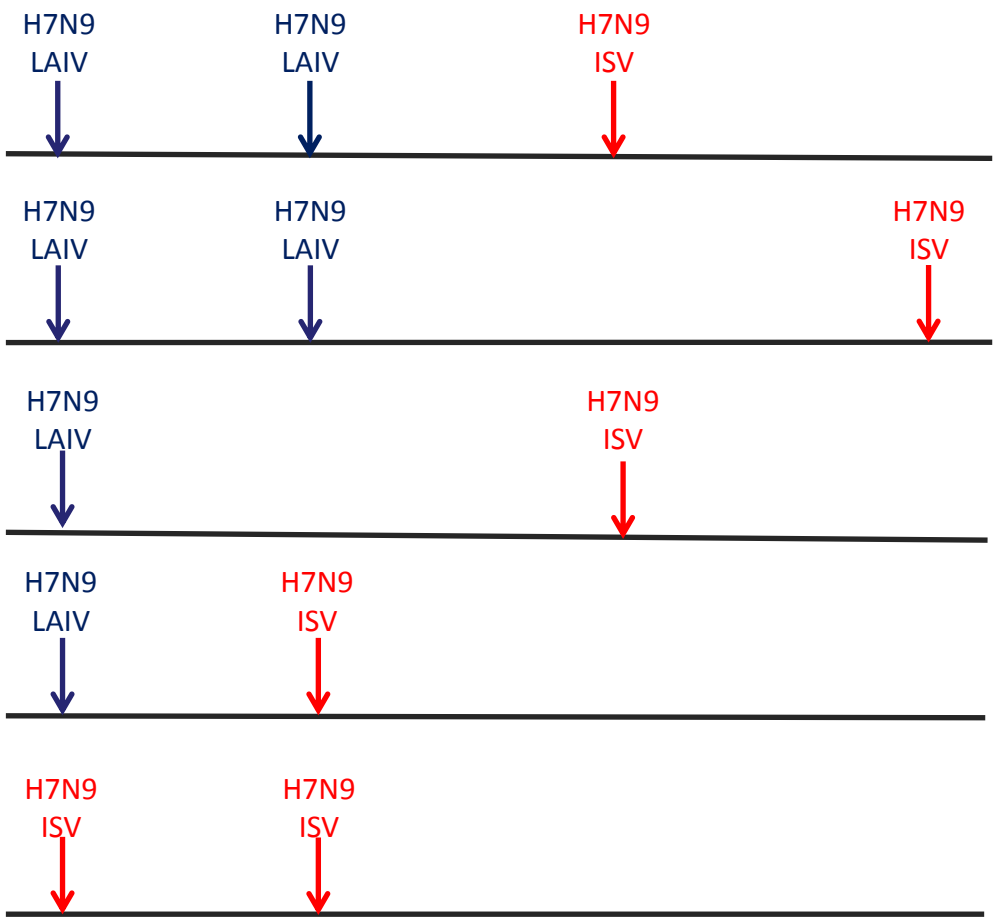
pLAIV		IAV/ dose	Interval (months)	HAI titer 14 days following IAV			
Vaccine	# doses			n	GMT (range)	Responders %	Responders GMT
H5N1 VN04	2	H5N1 VN04 45µg	56	11	48 (5-1280)	64	165
H7N7	2	H7N7 45µg	19-24	13	34 (2-1024)	69	119

Talaat et al. *J Infect Dis* 2014; 209(12): 1860-9; Babu et al. *Vaccine* 2014; 32(50):6798-804

Summary

- Prior receipt of pLAIV primes for
  - Higher titer response to a suboptimal dose of inactivated subunit vaccine
  - Increased frequency of response and enhanced affinity (SPR)
  - Rapid response – as early as day 7
  - Greater breadth of reactivity against different clades of H5 viruses, and H7 viruses from North American and Eurasian lineages.

Number of Priming Doses and Intervals Human H7N9 LAIV-ISV vaccines



Implications

- Clear evidence of a long lasting B cell memory response to pLAIV.
- Priming with pLAIV allows the use of a lower dose of unadjuvanted ISV: dose sparing.
- The rapid response to injected inactivated antigen suggests that pLAIV recipients may be protected from severe illness in the event of natural exposure.
- Ongoing investigations:
  - Should the pLAIV and ISV be matched or mismatched?
  - Will 1 dose of pLAIV priming be sufficient if booster is with adjuvanted-ISV?
  - Can the order be rearranged i.e. ISV followed by pLAIV?

Acknowledgements

NIAID, NIH:
Catherine Luke
Yumiko Matsuoka
Office of Clinical Research Policy and Regulatory Operations

Center for Immunization Research, JHU, Baltimore, MD
Kawsar Talaat
Ruth Karron

University of Rochester Medical Center
John Treanor
Diane O'Brien

MedImmune/Astra Zeneca
Hong Jin
George Kemble
Kathy Coelingh
Matthew Downham
Helen Bright

PATH Vaccine Solutions
Kathy Neuzil
Kristen Lewis

BARDA
Bob Huebner
Armen Donabedian

CBER
Hana Golding
Surender Khurana
Galina Vodeiko

Southern Research (SRI)
Diana Noah

The Volunteers

The Melbourne WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health.