Influenza Vaccines: Pandemic, Seasonal, and Novel

23 February 2010

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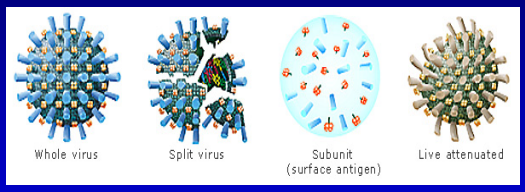
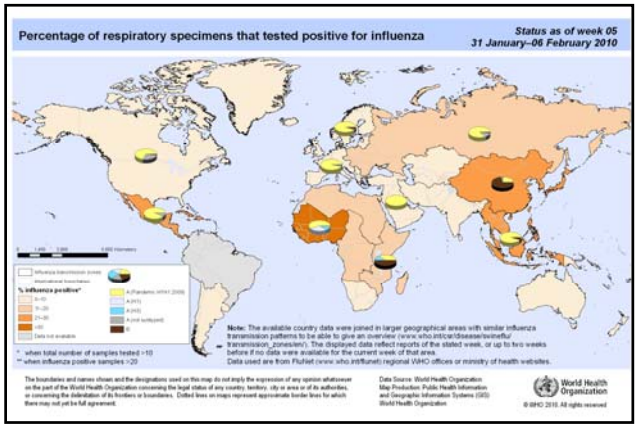
and
Wellcome Trust, London, UK

Influenza Vaccines: Outline

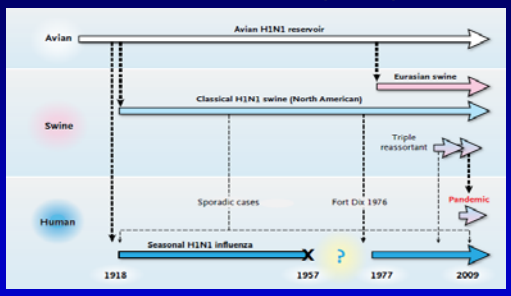
- Pandemic H1N1
  - Immunogenicity
- Seasonal Vaccines
  - Intranasal, live-attenuated
  - Pregnancy
  - Universal immunization
  - Enhancing immunogenicity in elderly
- Novel vaccines
  - New antigens/adjuvants, delivery methods, and production technologies

Approved Influenza Vaccines



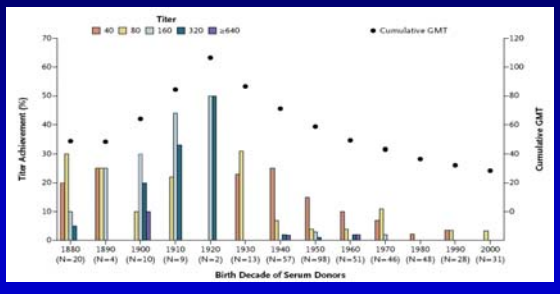


Circulation of Influenza A(H1N1) Viruses



Zimmer and Burke. NEJM 361:279, 2009

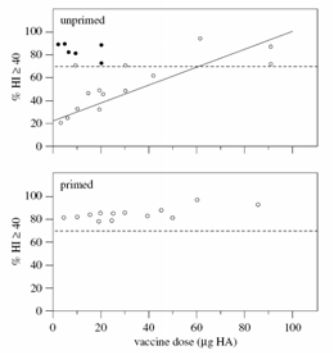
Neutralizing Antibody Titers against Pandemic H1N1 Virus according to Birth Decade



Hancock et al. NEJM 361; published 10 Sept 2009

Serologic Responses to A/New Jersey/8/79 (H1swN1) WV Vaccine

- Age (= prior exposure to H1N1 viruses) and, for unprimed, antigen dose were key variables in responding.



Wood J. Phil Trans R Soc London 2001

A Novel Influenza A (H1N1) Vaccine in Various Age Groups

Feng-Cai Zhu, M.D., Hua Wang, M.D., Han-Hua Fang, M.D., Jian Guo Yang, M.D., Xiao Jun Lin, M.D., Xiao-Feng Liang, M.D., Xue-Feng Zhang, M.D., Hong-Xing Pan, M.D., Fan-Yue Meng, M.D., Yue Mei Hu, M.D., Wen-Dong Liu, M.D., Chang-Gui Li, M.D., Wei Li, M.D., Xiang Zhang, M.D., Jin Mei Hu, M.D., Wei Bing Peng, M.D., Bao Ping Yang, M.D., Pei Xi, M.D., Hua-Qing Wang, M.D., and Jing-Shan Zheng, M.D.*

- Single 15 µg dose of nonadjuvanted vaccine resulted in HAI titer ≥1:40 in
  - 74.5% of subjects between 3 and 11 yrs
  - 97.1% of subjects between 12 and 17 yrs
  - 97.1% of subjects between 18 and 60 yrs
  - 79.1% of subjects 61 yrs or older
- Alum adjuvant associated with poorer responses and more local reactogenicity

Zhu et al. NEJM, published 21 October 2009

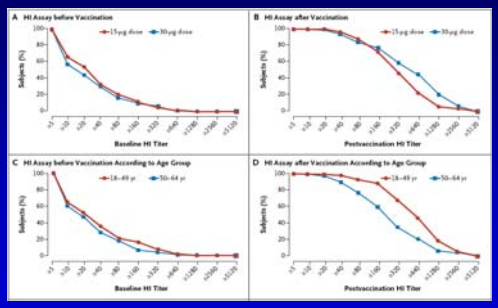
Immunogenicity of Single Doses of Non-Adjuvanted Pandemic H1N1 Vaccine

Group, age range	% with convalescent HAI ≥ 1:40	
	7.5 ug	15 ug
Adults, 18-60/64 yrs	90-95%	94-98%
Adults, ≥ 61/65 yrs	80-94%	79-93%
Children, 10/12-17 yrs	97%	97%
Children, 3-9/11 yrs*	69-77%	75-88%
Children, 6-35 mo*	45%	50-88%

*Low responses (25-36%) to single 15 ug doses in preliminary US study

Nolan et al. JAMA 303(1):E1, 2010; Liang et al. Lancet 375;56, 2010; Plennevaux et al. Lancet 375:41, 2010; Zhu et al. NEJM 361, 23 Oct 09

Immunogenicity of Non-Adjuvanted, Egg-Grown Pandemic H1N1 Vaccine in Adults



Greenberg et al. NEJM, online 10 September 2009

ACIP Guidelines – Pandemic H1N1 Vaccine

- Recommended initial target groups:
  - Pregnant women
  - Individuals who live with or care for infants aged < 6 months (parents, sibs, daycare providers)
  - Health care and emergency medical services personnel
  - Individuals aged 6 months through 24 years of age
  - Adults aged 25 through 64 with health conditions associated with an increased risk of medical complications from influenza

http://www.cdc.gov/h1n1flu/vaccination/acip.htm

TABLE 1. Estimated influenza A (H1N1) 2009 monovalent vaccination coverage among U.S. residents aged ≥6 months,* by age group and priority group status — National 2009 H1N1 Flu Survey (NHFS), December 27, 2009, through January 2, 2010

Age group/Priority group	U.S. population (millions)	H1N1 vaccination coverage: No. surveyed†	% vaccinated (95% CI§)	Estimated no. of persons vaccinated (millions) (95% CI)
Age group				
Total ≥6 mos	299	3,023	20.3 (17.2–23.4)	61 (51–70)
6 mos–4 yrs	19	500	33.0 (21.6–44.4)¶	6 (4–8)
6 mos–18 yrs	76	1,638	29.4 (23.8–35.0)	22 (18–27)
6 mos–24 yrs	101	1,716	25.9 (20.6–31.2)	26 (21–32)
6 mos–64 yrs	261	2,672	21.7 (18.3–25.1)	57 (48–66)
5–18 yrs	57	1,138	28.1 (21.7–34.5)	16 (12–20)
≥19 yrs	223	1,385	17.3 (13.8–20.8)	39 (31–46)
19–64 yrs	185	1,034	18.6 (14.5–22.7)	34 (27–42)
≥65 years	38	351	11.2 (6.5–15.9)	4 (2–6)
Priority group				
Initial target groups**	160	2,101	27.9 (23.5–32.3)	45 (38–52)
Limited vaccine subset††	62	807	37.5 (30.1–44.9)	23 (19–28)

* Coverage estimates are based on vaccinations reported as received from October 1, 2009, to the date of the interview.

Singleton et al. MMWR 59, 15 January 2010

Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines

Steven Black, Juhani Eskola, Claire-Anne Siegrist, Neal Halsey, Noni MacDonald, Barbara Law, Elizabeth Miller, Nick Andrews, Julia Stowe, Daniel Salmon, Kirsten Vannice, Hector Izurieta, Aysha Akhtar, Mike Gold, Gabriel Chelko, Patrick Zuber, Dina Pfeifer, Claudia Vellozzi

	Number of coincident events since a vaccine dose			Baseline rate used for estimate
	Within 1 day	Within 7 days	Within 6 weeks	
Guillain-Barré syndrome (per 10 million vaccinated people)	0·51	3·58	21·50	1·87 per 100 000 person-years (all ages; UK Health Protection Agency data)
Optic neuritis (per 10 million female vaccinees)	2·05	14·40	86·30	7·5 per 100 000 person-years in US females (table 2)[24]
Spontaneous abortions (per 1 million vaccinated pregnant women)	397	2780	16 684	Based on data from the UK (12% of pregnancies)[24]
Sudden death within 1 h of onset of any symptoms (per 10 million vaccinated people)	0·14	0·98	5·75	Based upon UK background rate of 0·5 per 100 000 person-years (table 2)[28]

Table 6: Predicted numbers of coincident, temporally associated events after a single dose of a hypothetical vaccine, based upon background incidence rates

Black et al. Lancet, published online 31 October 2009

World Health Organization

Recommended viruses for influenza vaccines for use in the 2010-2011 northern hemisphere influenza season

February 2010

It is recommended that the following viruses be used for influenza vaccines in the 2010-2011 influenza season (northern hemisphere):

– an A/California/7/2009 (H1N1)-like virus;
– an A/Perth/16/2009 (H3N2)-like virus;#
– a B/Brisbane/60/2008-like virus.

 # A/Wisconsin/15/2009 is an A/Perth/16/2009 (H3N2)-like virus and is a 2010 southern hemisphere vaccine virus

The annual impact of seasonal influenza in the US: Measuring disease burden and costs☆

Noelle-Angelique M. Molinari[a,*], Ismael R. Ortega-Sanchez[b], Mark L. Messonnier[a], William W. Thompson[c], Pascale M. Wortley[a], Eric Weintraub[c], Carolyn B. Bridges[d]

- **Based on USA 2003 population and using probabilistic modeling, annual influenza epidemics cause an average of**
- **610,660 life-years lost**
- **3.1 million hospitalized days + 31.4 million outpatient visits**
- **Direct medical costs- $10.4 billion (95% CI, $4.1, $22.2)**
- **Projected lost earnings due to illness and loss of life- $16.3 billion (95% CI, $8.7, $31.0)**
- **Total economic burden using projected statistical life values- $87.1 billion (95% CI, $47.2, $149.5)**

Molinari et al. Vaccine 25:5086, 2007

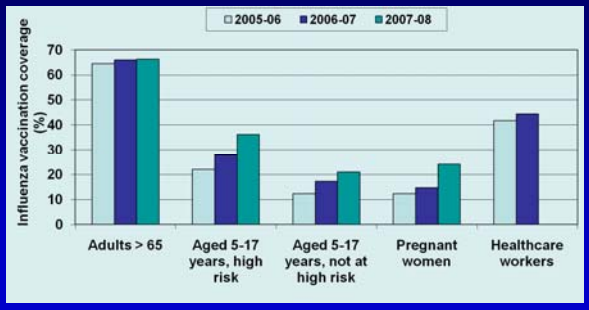
ACIP Guidelines—2009-2010 Seasonal Influenza Vaccination

- No changes in adult vaccination recommendations since last year
- Vaccinate all children aged 6 months through 18 years.
- Preference should be given to children aged 6 to 59 months and older children with underlying medical conditions at higher risk of complications.
  - 2 doses are critical for children aged 6 months to 8 years being vaccinated for the first time.

Fiore AE, et al. *MMWR Recomm Rep*. 2009;58(RR-8):1-52.
CDC. [press release]. February 27, 2008.

Vaccine Coverage Remains Low in the United States, Even in Priority Groups

CDC



Fiore AE, et al. MMWR 2009;58(RR-8):1-52.

Mandatory Influenza Vaccination of Health Care Workers: Translating Policy to Practice

Hilary M. Babcock,[1] Nancy Gemeinhart,[2] Marilyn Jones,[2] W. Claiborne Dunagan,[1,2] and Keith F. Woeltje[1]
[1]Washington University School of Medicine and [2]BJC HealthCare, St Louis, Missouri

- Introduction of mandatory immunization during 2008-09 season in large healthcare system.
- 25,561 (98.4%) of 25,980 active employees were vaccinated.
  - 0.3% received religious exemptions.
  - 1.2% received medical exemptions.
  - Eight employees (0.03%) were not vaccinated or exempted → termination.

Clinical Infectious Diseases 2010;50:459–64

Recent Seasonal Influenza Vaccine Studies

- Intranasal LAIV is superior to TIV in children (Belshe et al NEJM 356:685, 2007) but less effective than TIV in adults aged 18-49 yrs. (Monto et al. NEJM 361:13, 2009)
- Maternal immunization reduces influenza in infants + febrile ARI in mothers. (Zaman et al. NEJM 359, 2008)
- Universal vaccine program in Ontario reduced influenza-associated mortality, hospitalizations, healthcare visits, and antibiotic use by 40-60% compared to other provinces. (Kwong et al. CID 49:750, 2009)

Comparative Efficacy of Inactivated and Live Attenuated Influenza Vaccines

Arnold S. Monto, M.D., Suzanne E. Ohmit, Dr.P.H., Joshua G. Petrie, M.P.H., Emileigh Johnson, B.S., Rachel Truscon, M.P.H., Esther Teich, M.A., Judy Rotthoff, R.N., Matthew Boulton, M.D., M.P.H., and John C. Victor, Ph.D., M.P.H.

- Randomized, blinded study of LAIV vs TIV in 1952 subjects, 2007-2008 season (predominately H3N2)
  - Healthy adults aged 18-49 yrs
- Efficacies for laboratory-proven infleunza illness:
  - 68% (95% CI, 46 to 81%) for TIV
  - 36% (95% CI, 0 to 59%) for LAIV
  - Relative efficacy difference of 50% (95% CI, 20 to 69%)

Monto et al. NEJM 361:1260, 2009

Effectiveness of Maternal Influenza Immunization in Mothers and Infants

K. Zaman, M.B., B.S., Ph.D., Eliza Roy, M.B., B.S., D.C.H., Shams E. Arifeen, M.B., B.S., Dr.P.H., Mahbubur Rahman, M.B., B.S., Ph.D., Rubhana Raqib, Ph.D., Emily Wilson, M.H.S., Saad B. Omer, M.B., B.S., Ph.D., Nigar S. Shahid, M.B., B.S., M.P.H., Robert E. Breiman, M.D., and Mark C. Steinhoff, M.D.

- Study 340 pregnant women, Bangladesh, 2004-5
  - Randomized to TIV or 23-valent pneumoccocal vaccine
  - Followed to 24 weeks post delivery
- Vaccine effectiveness:
  - Laboratory-confirmed influenza in infants = 63% (95% CI, 5 to 85%).
  - Febrile respiratory illness in infants = 29% (95% CI, 7 to 46%)
  - Febrile respiratory illness in mothers = 36% (95% CI, 4 to 57%)

Zaman et al. NEJM 359, Sept 17, 2008

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The Effect of Universal Influenza Immunization on Mortality and Health Care Use

Jeffrey C. Kwong[1,2,3*], Thérèse A. Stukel[1,4], Jenny Lim[1], Allison J. McGeer[5,6], Ross E. G. Upshur[1,2,3,7], Helen Johansen[8], Christie Sambell[9], William W. Thompson[10], Deva Thiruchelvam[1], Fawziah Marra[11], Lawrence W. Svenson[12,13,14], Douglas G. Manuel[1,2]

- Universal influenza immunization program since 2000 in Ontario
- Outcomes: hospitalizations, ED and physician visits for P+I and of all-cause mortality 1997-2204
  - Comparisons of changes pre-post between Ontario and other provinces
  - Vaccine uptake from 1996 to 2005 increased in Ontario (18→ 38%) and other provinces (13→ 24%).

Effect of Universal Influenza Immunization Program (UIIP) in Ontario

- After UIIP, influenza-associated mortality decreased more in Ontario than in other provinces (relative ↓ 39%, p = 0.002).
- Similar differences between Ontario and other provinces were observed for influenza-associated
  - Hospitalizations (relative ↓ 42%, p < 0.001)
  - ED use (relative ↓ 55%, p < 0.001),
  - MD office visits (relative ↓ 59%, p < 0.001)
  - Antimicrobic use (relative ↓ 64%)

Kwong et al. PLoS Medicine 5:e211, 2008; Clin Infect Dis 49:750, 2009

Mortality benefits of influenza vaccination in elderly people: an ongoing controversy

Lone Simonsen, Robert J Taylor, Cecile Viboud, Mark A Miller, Lisa A Jackson

Lancet Infect Dis 2007;7: 658-66

- 13 influenza H3N2 seasons
- ~1 influenza death per 1,000 elderly each season
- ? Frail elderly selection bias → less often immunized

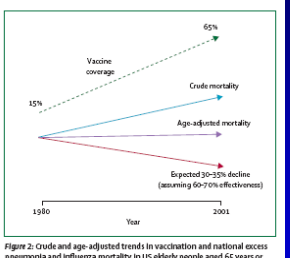


Figure 2: Crude and age-adjusted trends in vaccination and national excess pneumonia and influenza mortality in US elderly people aged 65 years or more

Effectiveness of Influenza Vaccine
in the Community-Dwelling Elderly

Kristin L. Nichol, M.D., M.P.H., M.B.A., James D. Nordin, M.D., M.P.H., David B. Nelson, Ph.D., John P. Mullooly, Ph.D., and Eelko Hak, Ph.D.

- Retrospective analysis of outcomes in community-dwelling elderly (≥ 65 yr) from 1990-2000 seasons
  - 18 pooled cohorts from three HMOs in USA
  - 713,872 person-years of observation
- Primary outcomes were P&I hospitalizations (0.6-0.7% per season) and all-cause mortality (1.0-1.6% per season)
  - Adjusted logistic regression analysis

Nichol et al. NEJM 357:1374, 2007

Vaccine Effectiveness in Community Elderly

- Vaccine effectiveness during season for
  - P & I hospitalization = 27% reduction (adjusted OR = 0.73; 95% CI, 0.68 to 0.77)
  - All-cause mortality = 48% reduction (adjusted OR = 0.52; 95% CI, 0.50 to 0.55)
- Mortality benefit varied with season and match between vaccine and circulating A/H3N2 strain
  - 37% reduction in 2 seasons of poor match
- No evidence for healthy vaccinee bias in non-influenza periods.

Nichol et al. NEJM 357:1374, 2007

Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: a population-based, nested case-control study

Michael L Jackson, Jennifer C Nelson, Noel S Weiss, Kathleen M Neuzil, William Barlow, Lisa A Jackson

- 1173 cases and 2346 controls (aged 65–94 yr) enrolled in a Seattle HMO during 2000 – 02.
  - Cases: those with outpatient or inpatient CAP episode
  - Chart review to determine "frailty" status and adjusted for "pre-influenza" period
- Outcome: reduction in hospitalizations for X-ray confirmed pneumonia = 8% (95% CI, -10%; 23%)

Jackson et al. Lancet 372:398, 2008

Age-Associated Decrease in TLR Function in Primary Human Dendritic Cells Predicts Influenza Vaccine Response

Alexander Panda,[=,1] Feng Qian,[†,1] Subhasis Mohanty,[*] David van Duin,[=,2] Frances K. Newman,[†] Lin Zhang,[†] Shu Chen,[‖] Virginia Towle,[‖] Robert B. Belshe,[†] Erol Fikrig,[=,¶] Heather G. Allore,[‖] Ruth R. Montgomery,[†,1] and Albert C. Shaw[=,1]

- By flow cytometry and intracellular cytokine staining of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs), substantial ↓ in older compared with young individuals in TNF-α, IL-6, and/or IL-12 (p40) production in mDCs and in TNF-α and IFN-α production in pDCs in response to TLR stimuli.
- Defects in cytokine production were strongly associated with poor Ab responses to influenza immunization.

Panda et al. J Immunol 184:, 25 January 2010

Strategies for Increasing Protection by Influenza Vaccines in Elderly

- Repeat same-season immunization - ineffective
- Increase immunogenicity of HA-based vaccines
  - Increase dose of HA antigen
  - Combination TIV + intranasal LAIV
  - Intradermal delivery
  - Adjuvants
    - Oil-in-water adjuvants
    - Sublingual interferon – ineffective
- Conserved antigen vaccines (M2e, NP)
- Reduce risk of influenza exposure
  - Immunization of household and other contacts

Randomized, Double-Blind Controlled Phase 3 Trial Comparing the Immunogenicity of High-Dose and Standard-Dose Influenza Vaccine in Adults 65 Years of Age and Older

Ann R. Falsey,[1,2] John J. Treanor,[2] Nadia Tornieporth,[3] Jose Capellan,[3] and Geoffrey J. Gorse[3]

- Randomized comparison of 15 vs 60 ug HA doses in ambulatory adults ≥65 yrs old
- Seroprotection (serum HAI ≥ 1:40) for all [≥ 75 yrs]
  - A(H1N1): 77 vs 90% [22 vs 48%]
  - A(H3N2): 97% vs 99% [53 vs 68%]
  - B: 68% vs 79% [25 vs48%]
- More frequent local pain with high dose

Falsey et al. J Infect Dis 200:172, 2009

Comparative Immunogenicity of Standard and High Dose TIV in Ambulatory Elderly

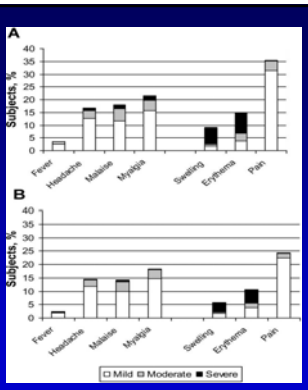
HAI antibody responses (day 28)	High dose (60 ug HA) recipients (N = 2,576)	Standard dose (15 ug HA) recipients (N = 1,275)
GMT		
A/H1N1	115.8	67.3
A/H3N2	608.9	332.5
B	69.1	52.3
% with HAI $\geq$ 1:40		
A/H1N1	89.9%	76.8%
A/H3N2	99.3%	96.5%
B	79.3%	67.6%

- Superiority in seroconversion rates for all 3 antigens (42-69% vs 23-51%) and in GMTs for 2 of 3 antigens

Falsey et al. JID 200:174, 2009

Reactogenicity of Standard and High Dose TIV in Elderly

- No overall differences in systemic symptoms
  - Fever >38°C in 1.1% vs 0.3%
- Higher frequency of local pain with increased HA dose.

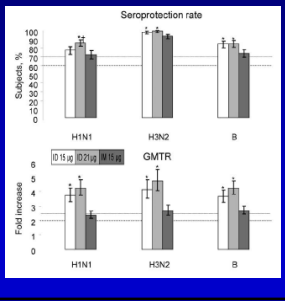


Falsey et al. JID 200:174, 2009

Intradermal Influenza Vaccine Administered Using a New Microinjection System Produces Superior Immunogenicity in Elderly Adults: A Randomized Controlled Trial

David Holland,[1] Robert Booy,[2] Ferdinandus De Looze,[3] Peter Eizenberg,[4] James McDonald,[4] Jeff Karavasch,[4] Maureen McKeirnan,[1] Hatem Salem,[4] Graham Mills,[1] Jim Reid,[1] Françoise Weber,[4] and Melanie Saville[4]

- 1107 volunteers aged > 60 yrs randomized to intradermal TIV (15 or 21 ug HA per strain) or IM (15 ug) vaccine
- Seroprotection rates, seroconversion rates, and mean titer increases were superior for intradermally administered vaccine.



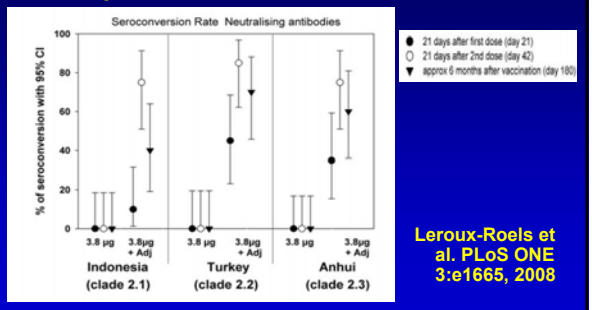
Holland et al. JID 198:650, 2008

Immunogenicity of Candidate H5N1 Vaccines

Vaccine type	Adju-vant	HA dose (ug) X 2*	Reference
rHA (baculovirus)	0	90	Treanor, 2001
Subvirion (eggs)	0	90	Treanor, 2006
Subvirion (eggs)	Alum	≥30	Bresson, 2006 Bernstein, 2008
Subvirion (eggs)	ASO3	3.8	Leroux-Roels, 2007
Whole virus (eggs)	Alum	10	Lim, 2006
Whole virus (Vero)	0	7.5	Ehrlich, 2008

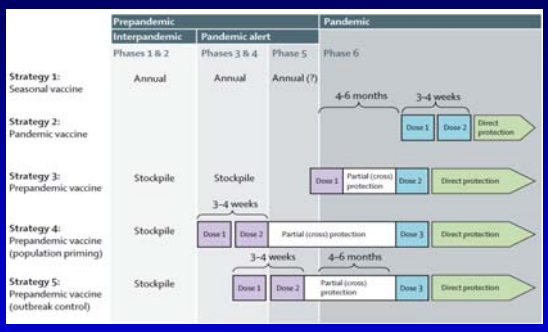
*Dose required to reach serologic endpoint. Endpoint varied by study.

Duration of Cross-Clade Antibody to ASO3-Adjuvanted Clade 1 H5N1 Vaccine



Leroux-Roels et al. PLoS ONE 3:e1665, 2008

Potential Uses of H5N1 Vaccines



Jennings et al. Lancet Infect Dis 8:650, 2008

- Prototype pandemic vaccine
- True pandemic vaccine

Examples of Investigational Influenza Vaccines

- Baculovirus-derived HA*
- Baculovirus* and lentivirus-derived virus-like particles*
- NS1-protein deleted (ΔNS1)* and M2 tail deleted LAIV
- Vectored vaccines
  - DNA plasmids (gold particles, liposomes)*
  - Recombinant adenovirus (oral, intranasal)*
  - Vaccinia
- M2e vaccines (flagellin* and NP+ISS conjugates)
- Transdermal heat-labile enterotoxin (LT) patch*
- Nanoemulsion-adjuvanted inactivated nasal vaccines
- Production substrates- mammalian cells*, plants, fungi

*Clinical studies in progress

DNA vaccination protects against an influenza challenge in a double-blind randomised placebo-controlled phase 1b clinical trial

Suzanne Jones[a], Kirsten Evans[a], Hilary McElwaine-Johnn[a], Michaela Sharpe[b], John Oxford[c], Rob Lambkin-Williams[c], Tim Mant[d], Andrew Nolan[d], Maria Zambon[e], Joanna Ellis[e], John Beadle[f], Peter T. Loudon[b,*]

- 3 plasmids for HAs ± plasmid for A + B subunits of *E. coli* heat labile enterotoxin as DNA adjuvant
  - Dose of 2 ug + adjuvant or 4 ug delivered by PMED™ (particle mediated epidermal delivery)
  - HAI antibody responses to 2 of 3 influenza HAs
- Laboratory confirmed influenza illness in 61.5% of placebo, 50% of 2ug, and 33.3% of 4ug subjects.
  - 4 ug dose with efficacy of 44% (P = 0.06) and 75% ↓ in nasal virus AUC compared to placebo

Vaccine 27 (2009) 2506–2512

4th Meeting on Influenza Vaccines that Induce Broad Spectrum and Long-lasting Immune Responses

Contributors: Wellcome Trust and World Health Organization

Wellcome Trust, Euston Road, London, UK, 9-10 Nov (Monday-Tuesday)

http://www.who.int/vaccine_research/diseases/influenza/meeting_09_10Nov09/en/index.html

Influenza Vaccines: *Comments*

- Diversification of seasonal influenza vaccines by target population:
  - Intranasal LAIV for children
  - Standard TIV for adults
  - High-dose TIV for elderly
- Policy issues
  - Mandatory immunization of HCWs
  - Universal immunization
  - Interpandemic use of H5N1 vaccines
  - Healthcare reform and vaccine coverage