

Influenza vaccines

A microscopic view of several influenza viruses. The viruses are spherical with a dark, textured core and a lighter, fuzzy outer layer of spikes and proteins. They are set against a blue, slightly blurred background.

Cheryl Cohen
cherylc@nicd.ac.za

Overview

- Burden of influenza and risk groups
- Clinical presentation, diagnosis and treatment
- Influenza the virus
- Currently available influenza vaccines
- Vaccine production
- Vaccine efficacy and effectiveness
- Challenges and new approaches

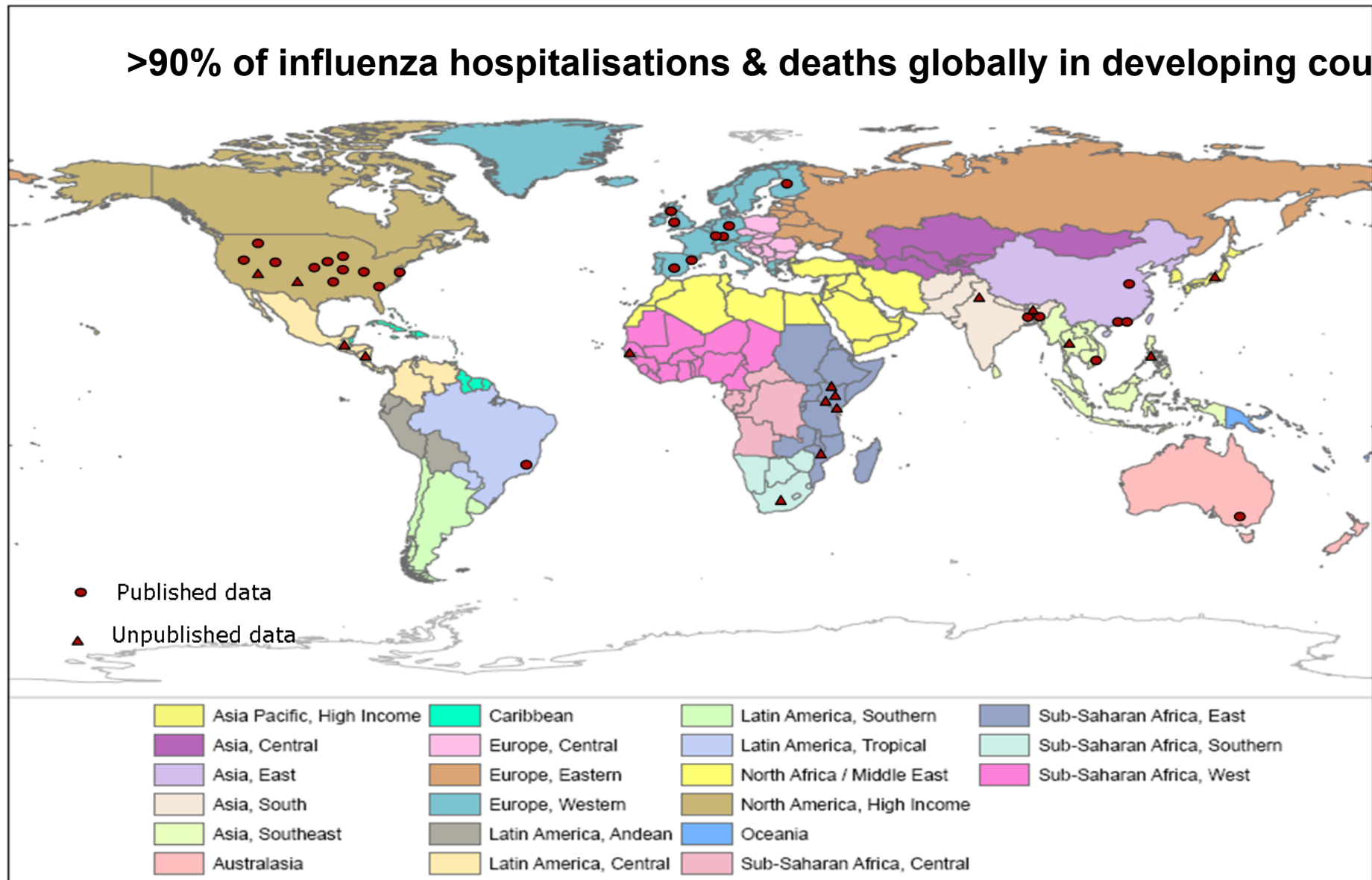
BURDEN OF INFLUENZA AND RISK GROUPS

Burden of influenza

- Annually globally seasonal influenza
 - 1 billion infections
 - 3-5 million cases of severe disease
 - 300,000-500,000 deaths
 - Large season-to-season variation
- In South Africa, annually
 - 17,000-22,000 respiratory hospitalisations
 - 2500-5700 respiratory deaths
- Pandemic burden varies
 - 1918-1919 – 50-100 million deaths
 - 2009 pandemic approximately 200,000 deaths

The global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis
Location of the 43 studies by region

>90% of influenza hospitalisations & deaths globally in developing countries

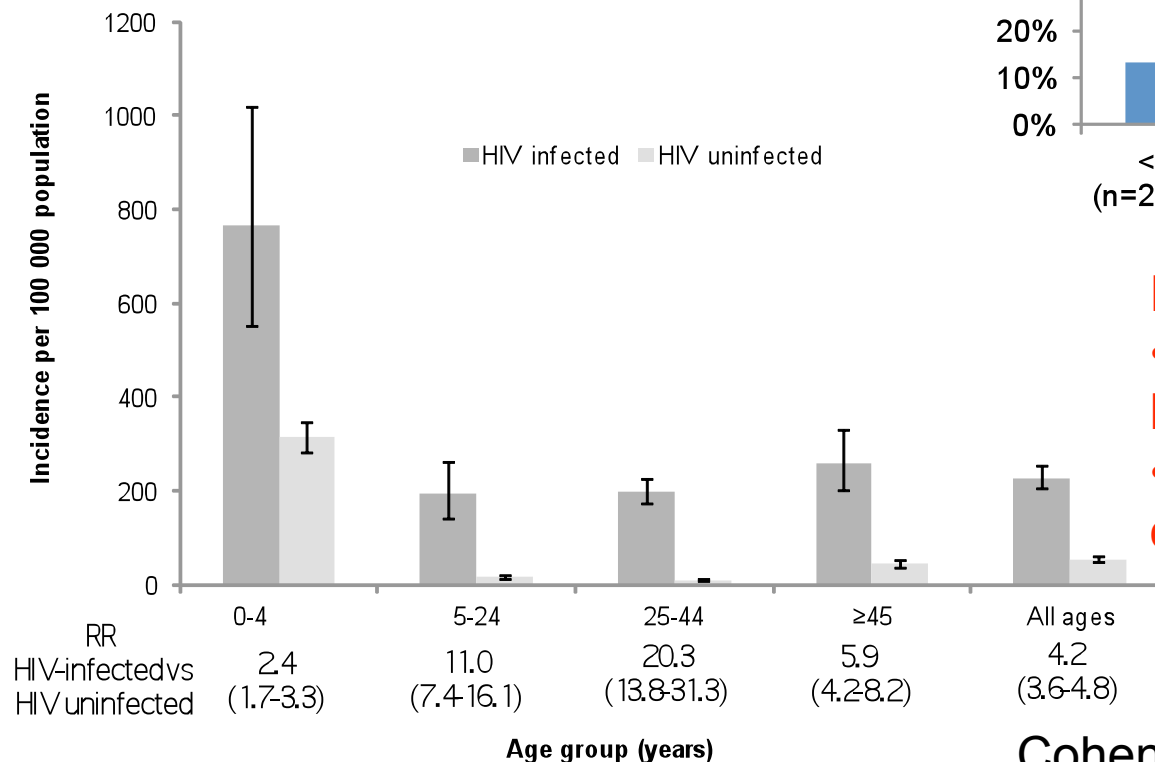


Groups at highest risk of severe influenza

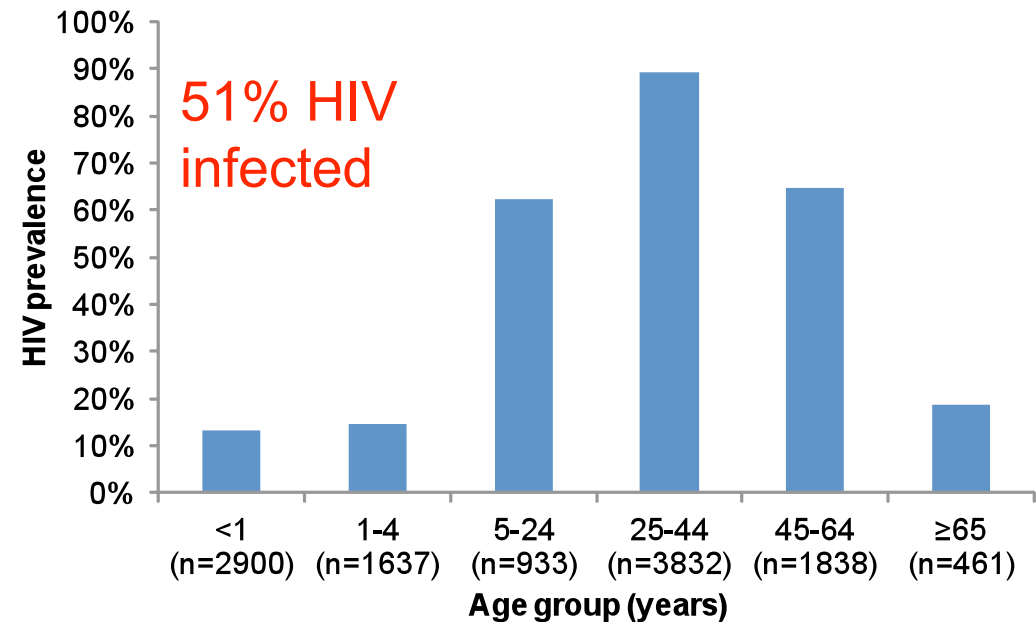
- Highest hospitalisation rates:
 - ≥ 65 years
 - Children < 5 years
- In a pandemic deaths shift to young and middle-aged adults increasing years of life lost
- Underlying conditions
 - Pulmonary, cardiac, renal, hepatic, metabolic, haematologic, neurologic, neuromuscular, immunosuppression, morbid obesity

Patients with influenza-associated acute lower respiratory-tract infection (ALRI), South Africa, 2009-2011

Incidence by HIV status and age group



HIV prevalence by age group



51% HIV infected

HIV-infected individuals have

- 3-6 times higher incidence of hospitalisation
- 6 times greater odds of death once hospitalised



World Health
Organization

Organisation mondiale de la Santé

Weekly epidemiological record Relevé épidémiologique hebdomadaire

23 NOVEMBER 2012, 87th YEAR / 23 NOVEMBRE 2012, 87^e ANNÉE

No. 47, 2012, 87, 461–476

<http://www.who.int/wer>

Contents

461 Vaccines against influenza
WHO position paper –
November 2012

Vaccines against influenza WHO position paper – November 2012

For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that pregnant women should have the highest priority. Additional risk groups to be considered for vaccination, in no particular order of priority, are children aged 6–59 months, the elderly, individuals with specific chronic medical conditions, and health-care workers. Countries with existing influenza vaccination

- **Pregnant women** (up to 2 weeks post-partum)
- Children 6-59 months
- Elderly
- Chronic medical conditions
- Health care workers

Previously healthy people can also develop severe influenza.

Vaccination can reduce absenteeism and costs

CLINICAL PRESENTATION, DIAGNOSIS AND TREATMENT

Clinical presentation

- Incubation 1-3 days
- Sudden onset fever, cough, headache, sore throat, rhinorrhoea, nasal congestion, muscle aches
- Duration of symptoms – 3-5 days
- Diarrhoea and abdominal pain may occur in children
- Signs and symptoms vary with age and underlying illness
- Not be easily distinguished from other respiratory viral infections

Complications of influenza

- Exacerbation of chronic conditions eg asthma, COPD, CCF
- Viral pneumonia -> can trigger cytokine dysregulation -> acute lung injury and fulminant respiratory failure, shock and multiorgan failure
- Bacterial pneumonia
- Myocarditis
- Pericarditis
- Croup
- Bronchiolitis
- Tracheitis
- Myositis
- Rhabdomyolysis
- Encephalopathy
- Encephalitis

Influenza is highly seasonal in temperate countries

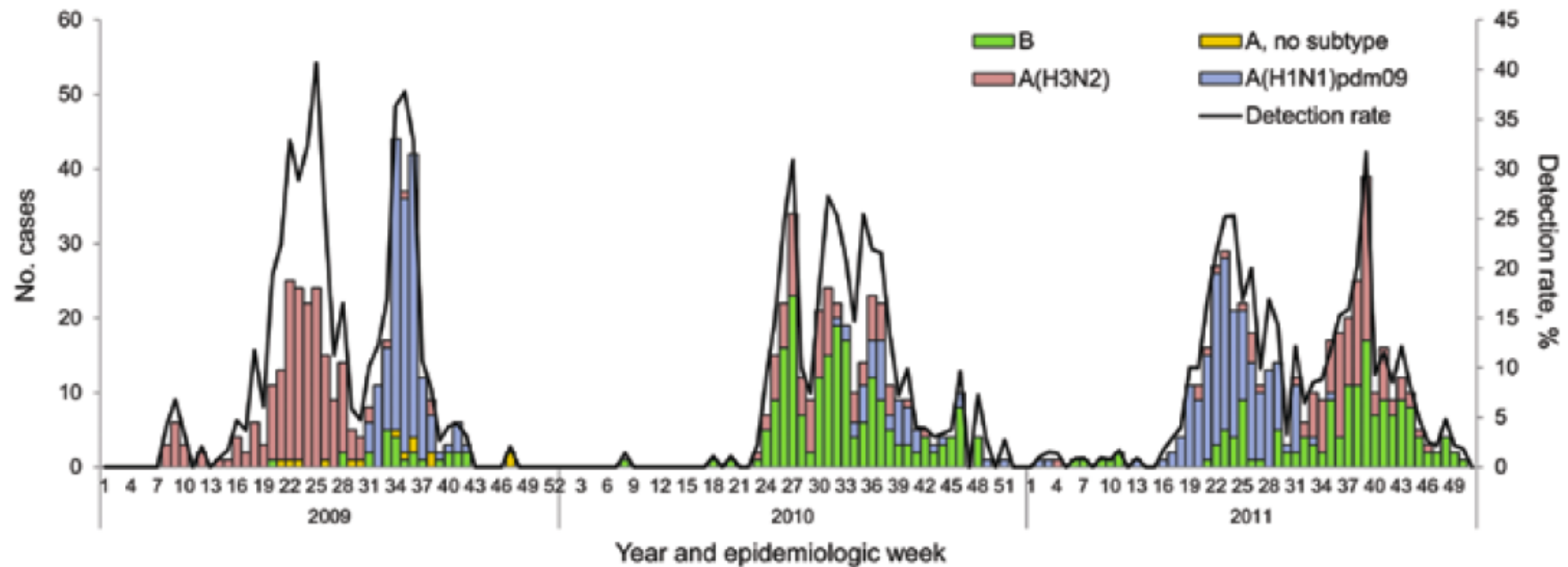


Figure 1. Number of patients testing influenza positive by subtype and influenza detection rate by epidemiologic week and year among patients with hospitalized pneumonia at 4 sentinel surveillance sites, South Africa, 2009–2011.

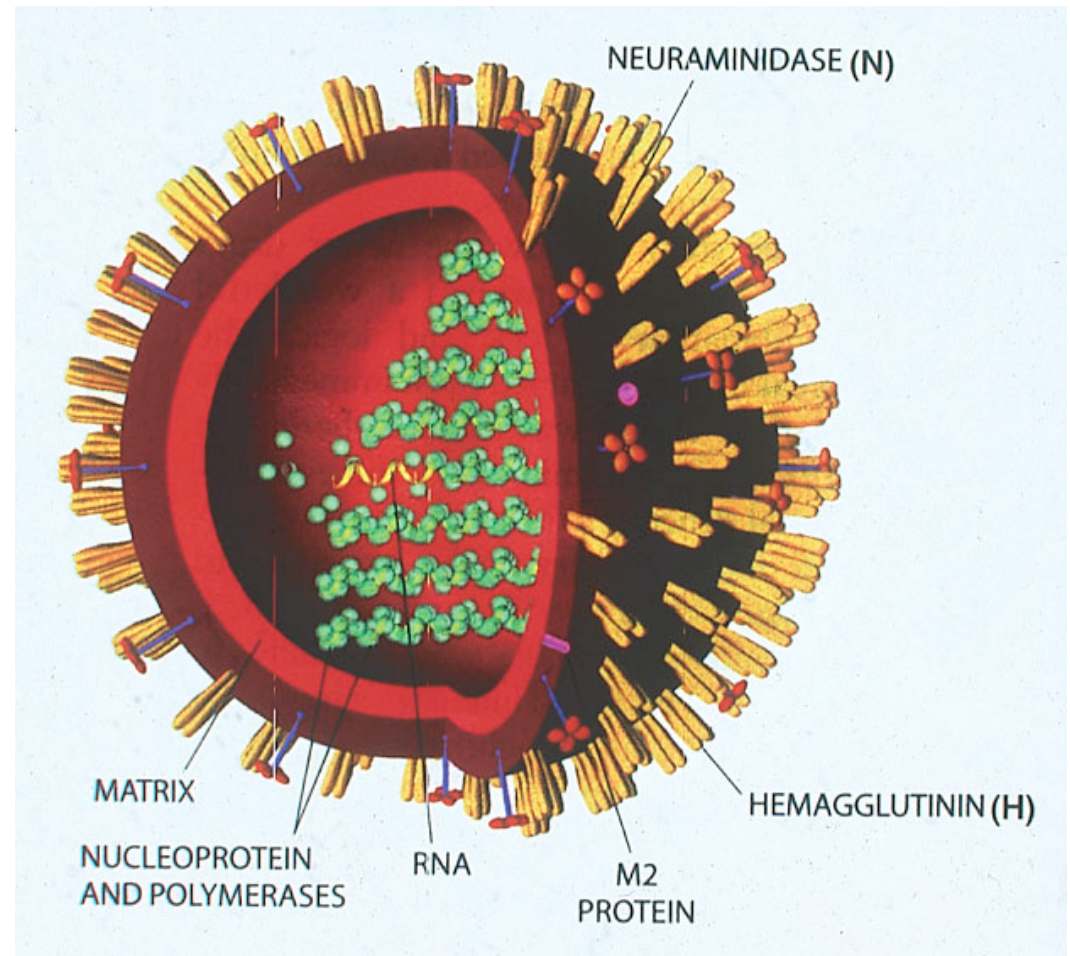
Diagnosis and treatment

- Diagnosis
 - Polymerase chain reaction of respiratory specimens (culture, antigen testing, serology – less useful)
 - Rapid tests lack sensitivity
- Treatment
 - Influenza-specific antiviral agents
 - Oseltamivir (& Zanamivir)
 - Must start in 1st 48 hours based in clinical suspicion
 - Indicated for severe illness or underlying risk conditions
 - Seldom utilised in Africa

INFLUENZA THE VIRUS

The influenza virus

- First isolated from humans in 1933
- 8 single stranded RNA segments encoding 11 proteins
- 3 types: A, B & C
- A and B cause annual epidemics
- Error-prone polymerase -> mutations in antigenic hemagglutinin and neuraminidase
- Antigenic shift and drift
- Annual updates to vaccine



Species Infected by Influenza A, HA and NA Subtypes

H1		N1
H2		N2
H3		N3
H4		N4
H5		N5
H6		N6
H7		N7
H8		N8
H9		N9
H10		
H11		
H12		
H13		
H14		
H15,16		

Emergence of pandemic strains

- Direct interspecies transmission OR
- Molecular exchange between influenza viruses infecting humans
- Segmented genome -> coinfection of single cell with 2 viruses -> reassortment (antigenic shift)
- Can cause pandemic if resulting virus has HA to which no pre-existing immunity and capable of human-human spread
- 2009 pandemic relatively mild
- Strains like H5N1 highly virulent and potential for future outbreaks

Timeline of major events in influenza vaccine development



1918	Spanish Flu caused by H1N1
1933	Isolation of influenza virus ³⁶
1935-1941	Early vaccination studies identified the importance of dose and matching strains ³⁶
1942-45	Trials with concentrated and inactivated vaccines ³⁶
1945	First commercial influenza vaccine available in the US ³⁶
1947	Global surveillance initiated by WHO
1957	"Asian flu" caused by H2N2
1960s	Attempts to generate attenuated viruses
1968	Pandemic caused by H3N2
1976-1977	Subunit influenza vaccine was developed and found to be less reactogenic than inactivated whole virus vaccines ⁴⁷⁻⁴⁹
1976-1977	Swine flu (H1N1) outbreak in Fort Dix, US, prompting a short-lived mass vaccination campaign
1977-1978	"Russian flu" outbreak (H1N1)
1980s	Russians developed cold-adapted attenuated vaccine strains ^{64,65}
1997	Outbreak of highly pathogenic H5N1 in Hong Kong
1990s	Reverse-genetics system developed, leading to attenuated H5 vaccine strains ^{78,79}
2003	FluMist, intranasal LAIV licensed by FDA for adults*
2003-2004	Outbreak of highly pathogenic H5N1 in Asia
2007	H5 vaccine from Sanofi-Pastuer approved by FDA*
2007	Optaflu, MDCK-cell derived vaccine approved for use in Europe^
2009	Swine Flu pandemic (swine origin H1N1)
2009	FluZone High Dose licensed and recommended by ACIP for elderly*
2009	Adjuvanted vaccines against 2009 swine flu strain approved under exceptional circumstance for use in Europe^
2010	ACIP recommends National Influenza vaccination for all ages 6 months and older*
2011	FluZone Intradermal licensed by FDA*
2012	Vepacel, Vero-cell derived influenza vaccine by GSK, licensed in Europe^, Flucelvax, MDCK-cell derived vaccine, Fluarix (quadrivalent TIV) and FluMist Quadrivalent, approved by FDA*
2013	FluBlok (baculovirus-derived) approved by FDA*

CURRENTLY AVAILABLE INFLUENZA VACCINES

Trivalent inactivated influenza vaccine (TIV)

- Trivalent
 - A H3N2
 - A H1N1
 - B – 2 lineages Yamagata and Victoria
- 3 Major formulations
 1. Inactivated whole virus - reactogenic
 2. Split product – detergent dissociate envelope
 3. Subunit – HA further enriched
- Antibodies against haemagglutinin (HA)
- Contain 15µg HA per strain (45µg total)
- Delivered IM
- 2 doses 4 weeks apart in children (6m-8y)
- 1 dose >9y

Limitations of TIV

- Need for annual updates
- Available vaccines only modest protection
 - Lower effectiveness in young children
 - Elderly
 - Risk groups
- No RCT of TIV efficacy in age 2-17 years
OR elderly

Live inactivated influenza vaccines

- Create vaccine which mimics natural infection
- Induce cellular and humoral immunity
- Temperature sensitive phenotype
 - Grow at 25°C (nasal passage) and not at 35°C (respiratory tract)
- Stable, immunogenic, non-transmissible
- New HA and NA genes inserted through reverse genetics each year
- Delivery intranasal
- Longer lasting Abs than TIV
- Effective in children 2-7 years

Generation of live influenza vaccines

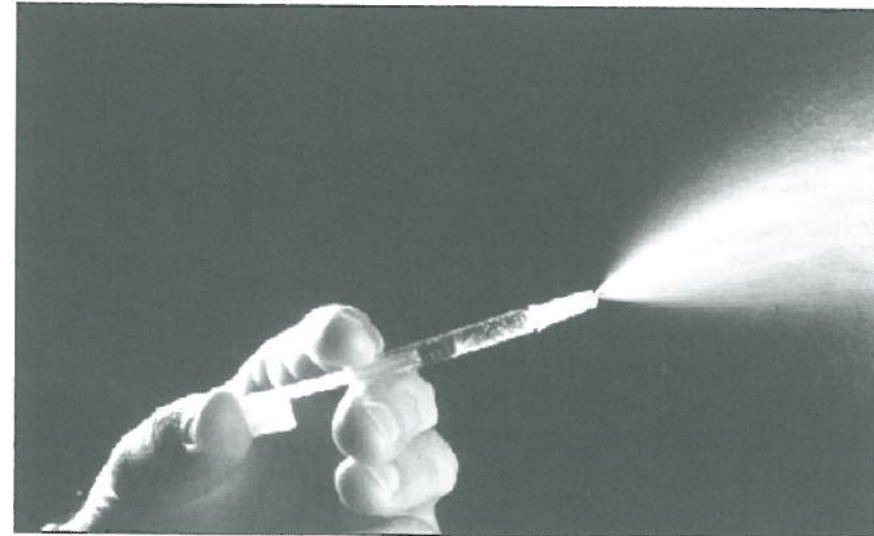
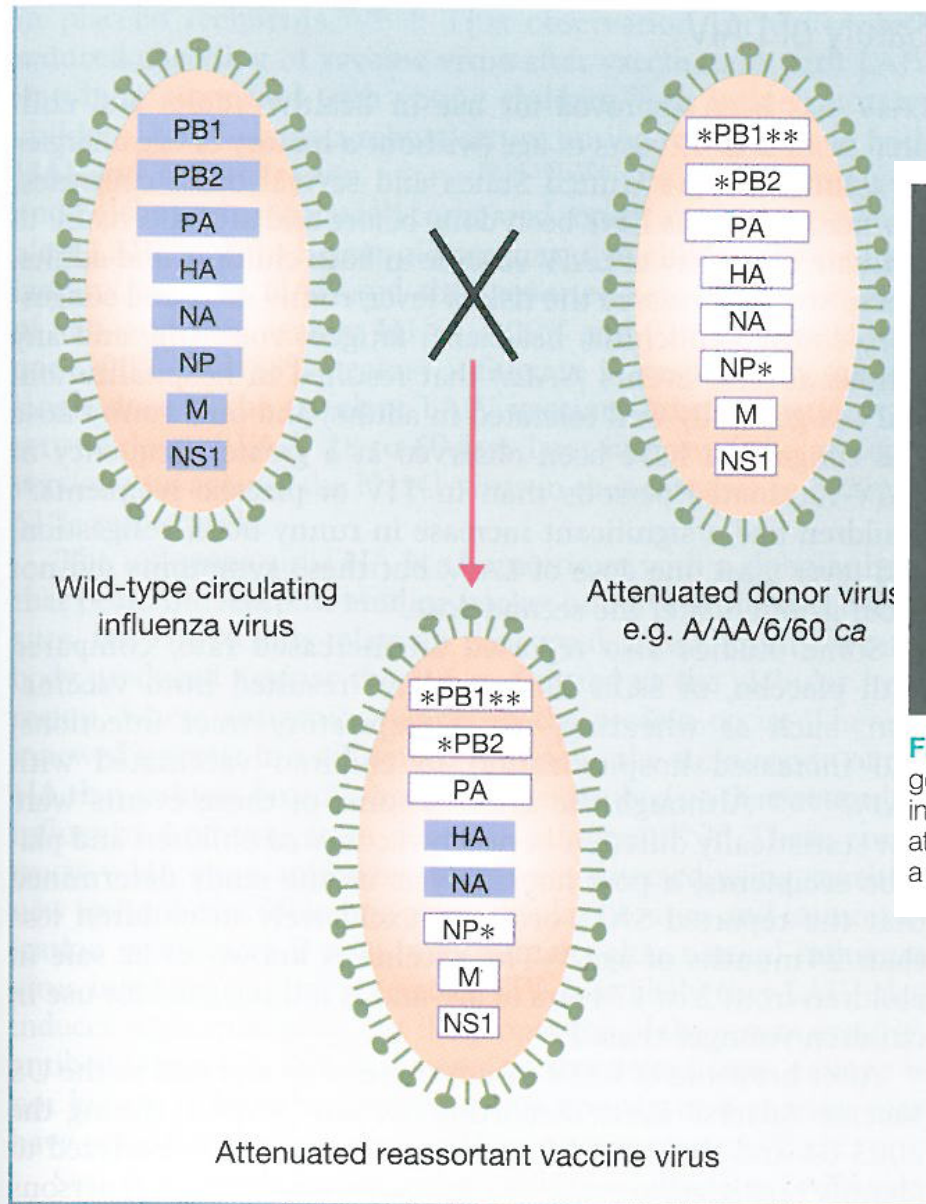
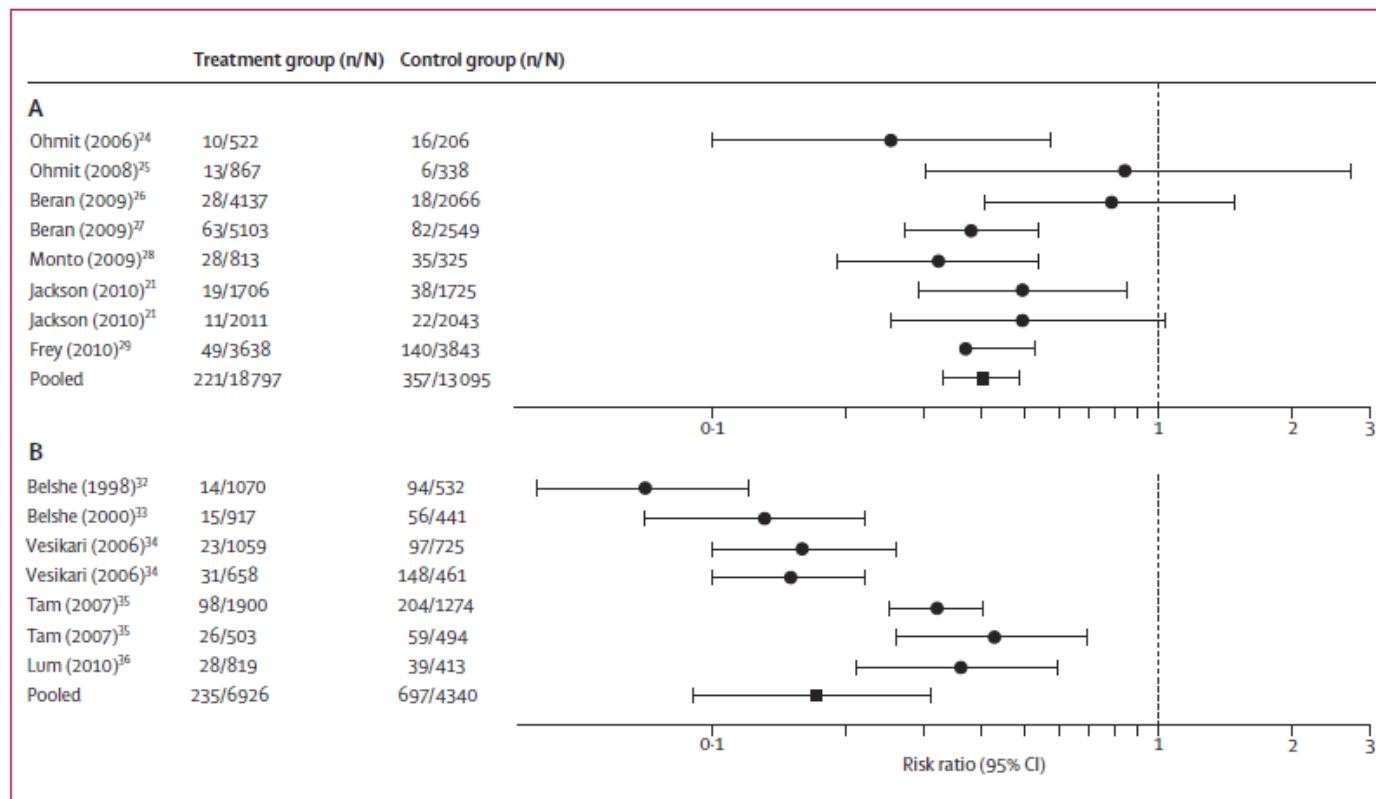


Figure 18-2 Transilluminated illustration of large-particle aerosol generated for intranasal administration. The tip of the applicator is inserted into the anterior nares, and the plunger is depressed to administer the live attenuated vaccine to a nostril. Removing the flange on the plunger allows a second spray to be administered into the other nostril.

TIV vs LAIV

LAIV consistently higher protection in 2-7 years compared to TIV Stensho, Lancet infectious diseases, 2012



TIV

LAIV

Figure 2: Vaccine efficacy compared with placebo (Mantel-Haenszel random-effects model)

(A) Trivalent inactivated influenza vaccine in adults aged 18–64 years. (B) Live attenuated influenza vaccine in children aged 6 months to 7 years. Studies were prospective (risk ratio) which are equivalent to case-control (odds ratio). n=cases of influenza. N=group size.

Limitations of live attenuated influenza vaccine

- Need approval for all ages (only indicated healthy persons 2-49 years)
- Formulations which can be administered without special nasal spray device eg. drops
- Not recommended for immunocompromised or those in contact with
- May not work for zoonotic strains (don't replicate in human upper respiratory tract)

Quadrivalent influenza vaccine

- Contains additional B lineage
- Available since 2014
 - Europe and USA
 - Not available in South Africa
- Immunogenicity and safety similar to TIV
- Available as inactivated and live formulations
- More costly than trivalent formulations

INFLUENZA VACCINE PRODUCTION

The WHO Global Influenza Surveillance Network (GISN)



- ▲ National Influenza Centres
- H5 Reference Laboratories
- WHO Collaborating Centre for Studies on the Ecology of Influenza in Animals
- WHO Collaborating Centre for Surveillance, Epidemiology and Control of Influenza
- WHO Collaborating Centre for Reference and Research on Influenza



GISN: Vaccine formulation



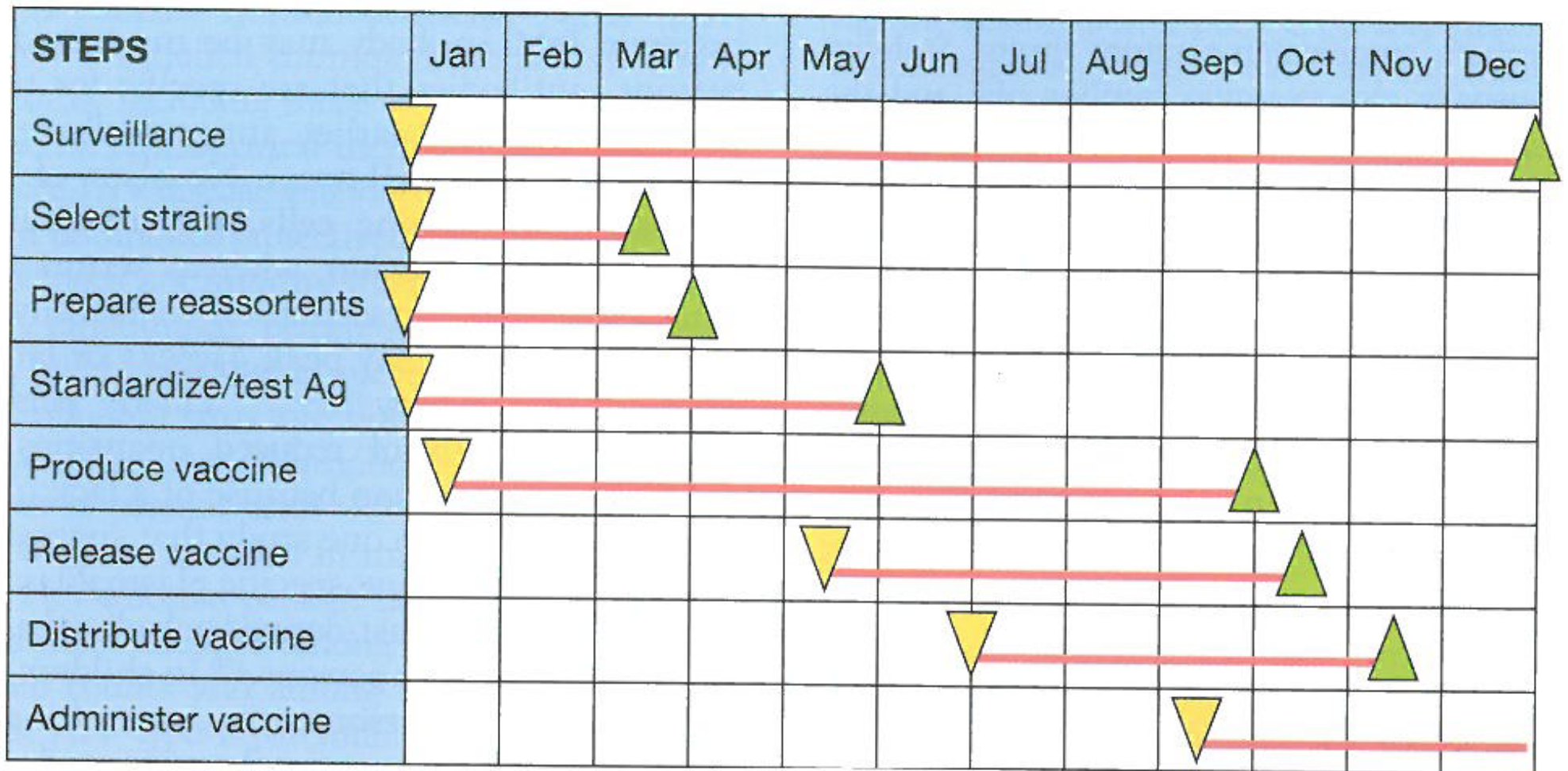
- **Meetings:** 2 Formal Annual meetings per year in Geneva:
 - **February:** formulation of the Northern hemisphere vaccine
 - **September:** formulation of the Southern hemisphere vaccine
- new recommendations for vaccines formulations for northern and southern hemisphere annual vaccination to vaccine manufacturers,
- **Two informal Consultation for Improving Influenza Vaccine Virus Selection, (July and December 2011)**
 - exploration and potential application of new approaches and technologies



Process of vaccine production

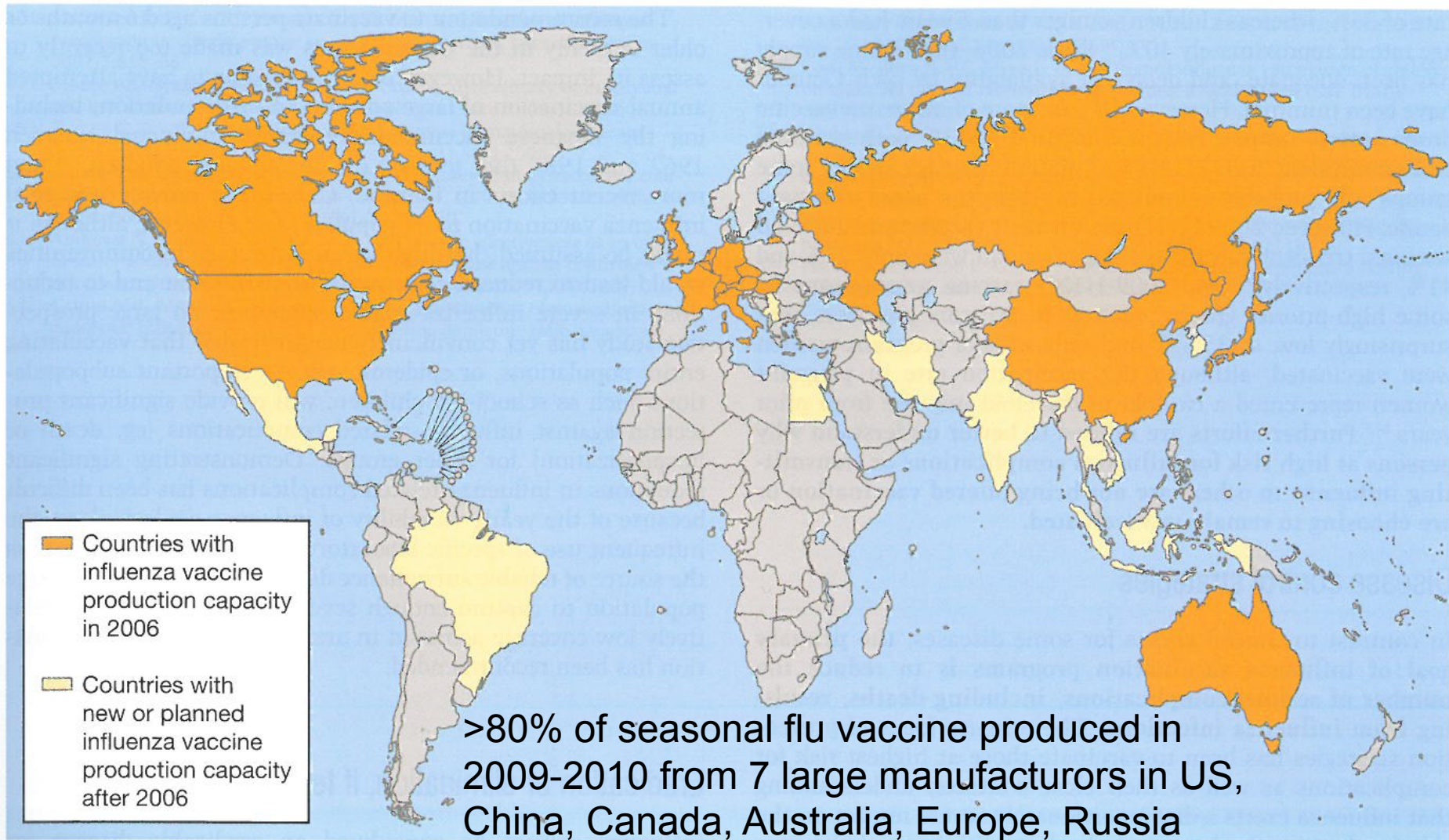
- Strains selected
- Vaccine reference strains developed (hybrid viruses with egg-growing lab strain) – weeks
- If low yield then further egg adaption needed (serial passage)
- Amplify virus in hundreds of millions of embryonated chicken eggs (each individually inoculated with each virus type)
- Inactivate and purify
- Formulate package and distribute

Production timetable for influenza vaccine manufacture (Northern Hemisphere)



Southern Hemisphere starts October each year

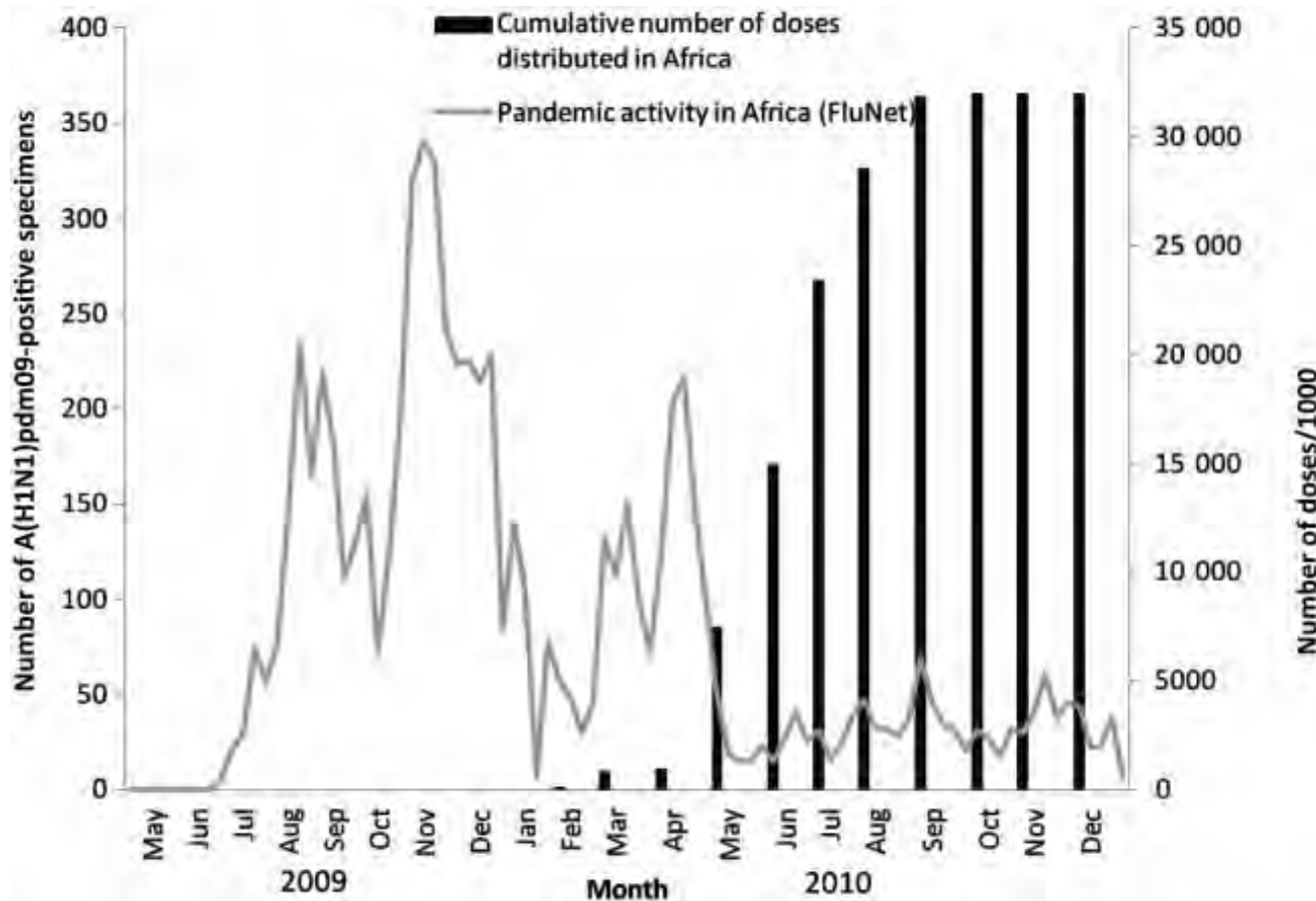
Global distribution of influenza vaccine manufacturing capacity



Experiences in 2009 H1N1 pandemic

- Successes
 - Safe, immunogenic vaccine produced and distributed in 8 months
- Challenges
 - Seasonal production already started when virus identified
 - Uncertainty initially so continued seasonal flu vaccine production & begin separate pandemic production
 - Compressed production timeline due to virus evolution
 - Lower yields of HA protein
 - Low public acceptance of vaccination
 - Most doses available after peak
- Immune response challenges with pandemic vaccine (avian)

2009 pandemic influenza A vaccine distribution in Africa



- WHO-USAID
- 32.2 million donated doses
- 34 countries
- 64% administered
- Coverage 4% (0.4-11%)
- Most distributed after the peak
- Average delay 261 days - letter of intent to implementation

VACCINE EFFICACY AND EFFECTIVENESS

Influenza vaccine effectiveness

- Influenza vaccines 15-89% effective in healthy adults
- Factors affecting vaccine effectiveness:
 - Recipient
 - Age
 - Immune response
 - Match between circulating and vaccine virus strains

How effective are influenza vaccines in the elderly?

- Only one RCT – 58% VE, serologic endpoint -> overestimate VE
 - No RCT with PCR-confirmed endpoint
 - Mortality impact of large-scale vaccine programmes in the elderly limited ($\pm 5\%$)
-

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

See The Lancet Online/ Comment
Published September 24, 2007
DOI:10.1016/S0140-
6736(07)61389-0

National Institute of Allergy
and Infectious Diseases
(L. Simonsen PhD) and Fogarty

Influenza vaccination policy in most high-income countries attempts to reduce the mortality burden of influenza by targeting people aged at least 65 years for vaccination. However, the effectiveness of this strategy is under debate. Although placebo-controlled randomised trials show influenza vaccine is effective in younger adults, few trials have included elderly people, and especially those aged at least 70 years, the age-group that accounts for three-quarters of all influenza-related deaths. Recent excess mortality studies were unable to confirm a decline in influenza-related mortality since 1980, even as vaccination coverage increased from 15% to 65%. Paradoxically, whereas those studies attribute about 5% of all winter deaths to influenza, many cohort studies report a 50% reduction in the total risk of

ORIGINAL ARTICLE

Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children

Timo Vesikari, M.D., Markus Knuf, M.

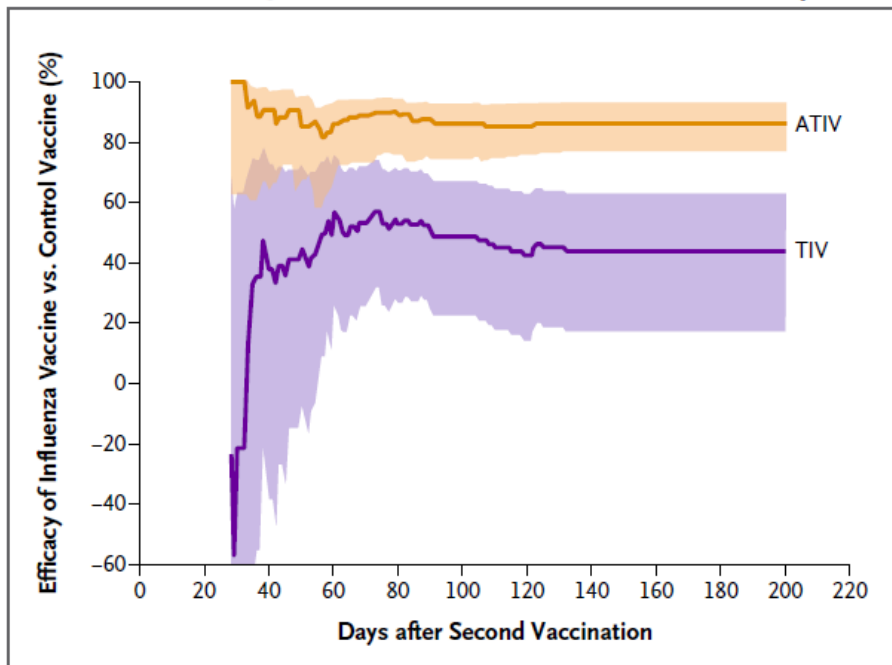


Figure 2. Efficacy of Influenza Vaccines versus Control Vaccine over Time.

The cumulative efficacy of ATIV and of TIV, as compared with control (non-influenza) vaccine, is shown. The data are for efficacy against all viral strains over time after the second dose of vaccine in children 6 to less than

- VE of TIV in children suboptimal
- VE 86% adjuvanted
- VE 43% without adjuvant
- Adjuvant slightly more reactogenic in older ages

CHALLENGES FOR INFLUENZA VACCINES AND NEW APPROACHES

Challenges for influenza vaccines

- Vaccines provide sub-optimal protection in groups at highest risk (elderly, very young, underlying illness)
- Need for annual revaccination
 - Waning protection
 - Antigenic drift
- Challenges in vaccine production and distribution
 - Complex manufacturing processes
 - Compressed production timelines
- Equity issues

What is needed?

- Need for
 - More effective vaccines
 - More rapid, efficient and reliable vaccine production technology
 - More surge capacity in the event of a pandemic
- Strategies to improve effectiveness
 - New vaccines
 - Adjuvants
 - New targets – universal vaccines
 - Strategies to optimise indirect protection
 - Maternal vaccination
 - Vaccinate healthcare workers
 - Vaccinate school children
- Multiple efforts underway to address this

Priorities for overcoming rate limiting steps in vaccine production

- Wider implementation of technologies such as reverse genetics to generate reference strains optimised to grow well in eggs
- New methods to accelerate potency and sterility testing – shorten time from strain development to vaccine release
- Preservative free multidose vials

Table 1. Current and New Approaches to Influenza-Vaccine Production.

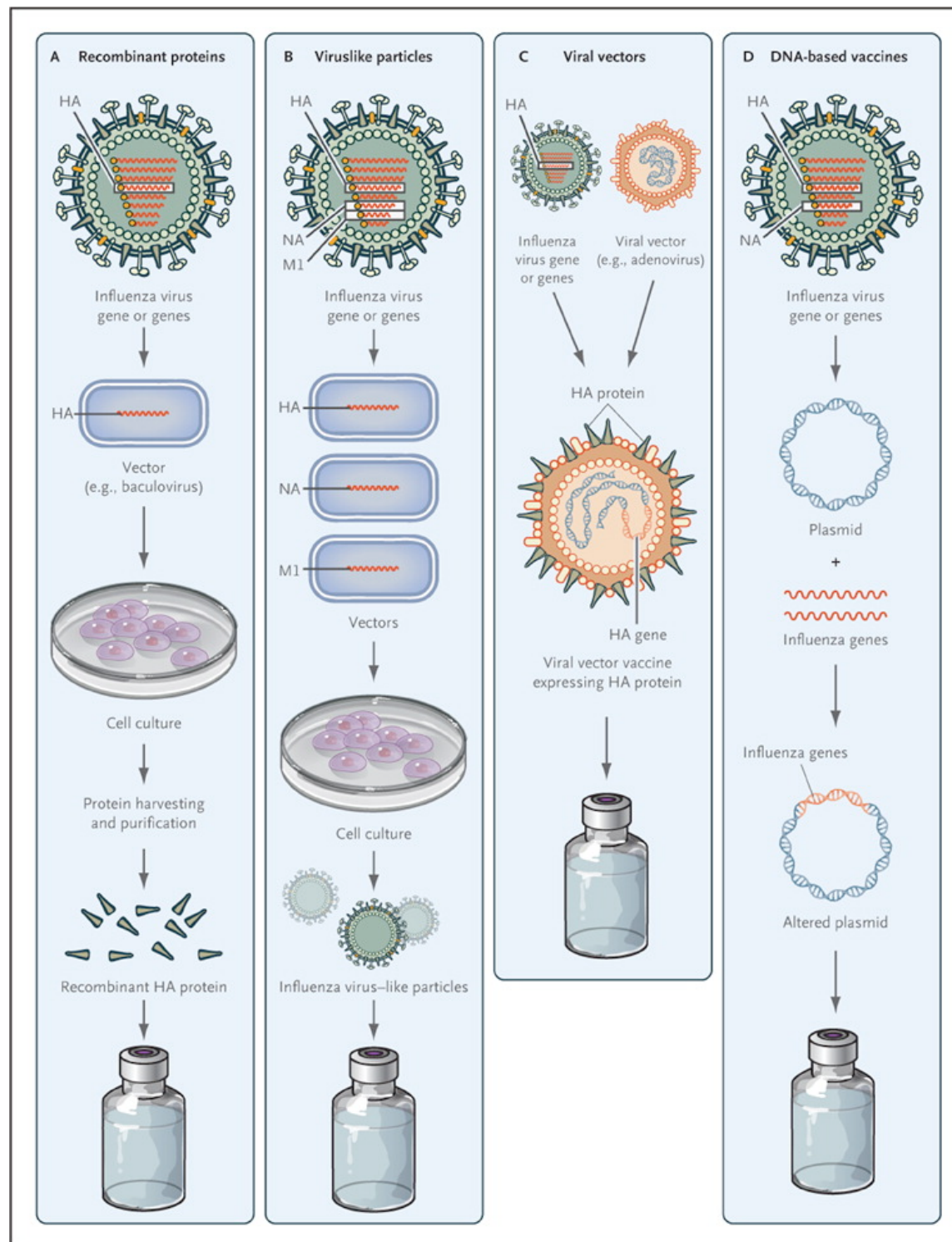
Vaccine	Stage of Development			
	Preclinical Development	Phase 1 and 2 Clinical Testing	Phase 3 Clinical Testing	Licensed or Approved
Inactivated vaccines				
Egg-based	Yes	Yes	Yes	Yes
Cell-based	Yes	Yes	Yes	In Europe but not in the United States
With adjuvant	Yes	Yes	Yes	In Europe but not in the United States
Live attenuated vaccines				
Egg-based	Yes	Yes	Yes	Yes
Cell-based	Yes	Yes	No	No
Next generation				
Recombinant proteins	Yes	Yes	Yes	No
Viruslike particles	Yes	Yes	No	No
Viral vectors	Yes	Yes	No	No
DNA-based vaccines	Yes	Yes	No	No
Universal vaccines	Yes	Yes	No	No

Lambert, NEJM, 2010

Reference

New approaches to influenza vaccine development

Lambert, NEJM, 2010



Trivalent Inactivated Influenza Vaccine in African Adults Infected With Human Immunodeficient Virus: Double Blind, Randomized Clinical Trial of Efficacy, Immunogenicity, and Safety

Shabir Cheryl **Efficacy and immunogenicity of influenza vaccine in HIV-infected children: A randomized, double-blind, placebo controlled trial.**

Table 2. Vaccine Efficacy in HIV-Infected Adults on Stable Antiretroviral Therapy

Shabir A. Madhi^{a,b,c}, Sylvia Dittmer^d, Locadiah Kuwanda^{b,c}, Marietjie Venter^a, Haseena Cassim^d, Erica Lazarus^d, Teena Thomas^d, Afaaf Liberty^d, Florette Treurnich^a, Clare L. Cutland^{b,c}, Adriana Weinberg^e and Avy Violari^d

Outcome	TIV N = 80	Placebo N = 77	TIV N = 175	Placebo N = 174	TIV N = 255	Placebo N = 251	Rate reduction ^b	P value	Vaccine efficacy (95% Confidence Intervals)
Influenza Virus A or B	0 (0) ^a	6 (0.39)	3 (0.09)	6 (0.18)	3 (0.06)	12 (0.24)	0.18	0.019	75.5% (9.2–95.6)
Influenza-like illness	3 (0.19)	5 (0.33)	8 (0.23)	5 (0.15)	11 (0.22)	10 (0.20)	−0.02	0.867	−7.3% (−140.5 to 64.7)
Acute respiratory illness	14 (0.89)	15 (0.98)	26 (0.76)	32 (0.95)	40 (0.80)	47 (0.96)	0.16	0.402	16.6% (−30.0 to 46.7)
Hospitalized	0	23	34	15	3	3	Not calculated		
Died	16	23	0	0	1	2			

^a Figures in parentheses are incidence per 100 person-weeks unless otherwise indicated.

^b Rate reduction per 100 person-weeks. 3. Subjects hospitalized for pneumonia and another with unknown diagnosis, both of whom died. 4. One subject each hospitalized for dilated cardiomyopathy, pneumonia and another in whom no diagnosis was established, all of whom were discharged from the hospital. 5. Subjects hospitalized for gastroenteritis and discharged well. 6. 1 Subject died. Cause of death not ascertained.

ORIGINAL ARTICLE

Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuwanda, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Florette Treurnicht, Ph.D., Justin R. Ortiz, M.D., Marietjie Venter, Ph.D., Avy Violari, M.D., Kathleen M. Neuzil, M.D., Eric A.F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (Matflu) Team*



Table 4. Efficacy of IIV3 Vaccination in Mothers and Infants until 24 Weeks after Birth, Intention-to-Treat Population.*

Efficacy End Point	HIV-Uninfected Cohort				HIV-Infected Cohort			
	IIV3 (N=1026)	Placebo (N=1023)	Vaccine Efficacy	P Value	IIV3 (N=100)	Placebo (N=88)	Vaccine Efficacy	P Value
Infants								
RT-PCR–confirmed influenza — no. (%); (95% CI)								
With inclusion of B/Yamagata	19 (1.9); (1.1 to 2.9)†	37 (3.6); (2.6 to 5.0)†‡	48.8 (11.6 to 70.4)	0.01	5 (5.0); (1.6 to 11.3)§	6 (6.8); (2.5 to 14.3)§	26.7 (–132.0 to 76.8)	0.60
Women								
RT-PCR confirmed influenza — no. (%)								
With inclusion of B/Yamagata	19 (1.8); (1.1 to 2.8)¶	38 (3.6); (2.6 to 4.9)¶	50.4 (14.5 to 71.2)	0.010	7 (7.0); (2.9 to 13.9)‖	16 (17.0); (10.1 to 26.2)‖	57.7 (0.2 to 82.1)	0.05

THE JAPANESE EXPERIENCE WITH VACCINATING SCHOOLCHILDREN
AGAINST INFLUENZA

THOMAS A. REICHERT, PH.D., M.D., NORIO SUGAYA, M.D., DAVID S. FEDSON, M.D., W. PAUL GLEZEN, M.D.,
LONE SIMONSEN, PH.D., AND MASATO TASHIRO, M.D., PH.D.

60 percent in some areas. It was clear that school attendance played an important part in amplifying the epidemic. In the aftermath, official policy on influenza vaccination in Japan was changed; the new recommendations stated that “because schoolchildren are the major disseminators of the disease, they should be immunized. Young children, elderly, high-risk patients, pregnant women and workers of essential community services may be immunized as possible.”¹³ In 1962, special programs of vaccination against influenza for schoolchildren were begun, and in 1977, legislation made such vaccination obligatory. From the mid-1970s to the late 1980s the levels of vaccine coverage among Japanese schoolchildren ranged from 50 percent to 85 percent. In 1987, however, new legislation allowed parents to refuse vaccination against influenza for their

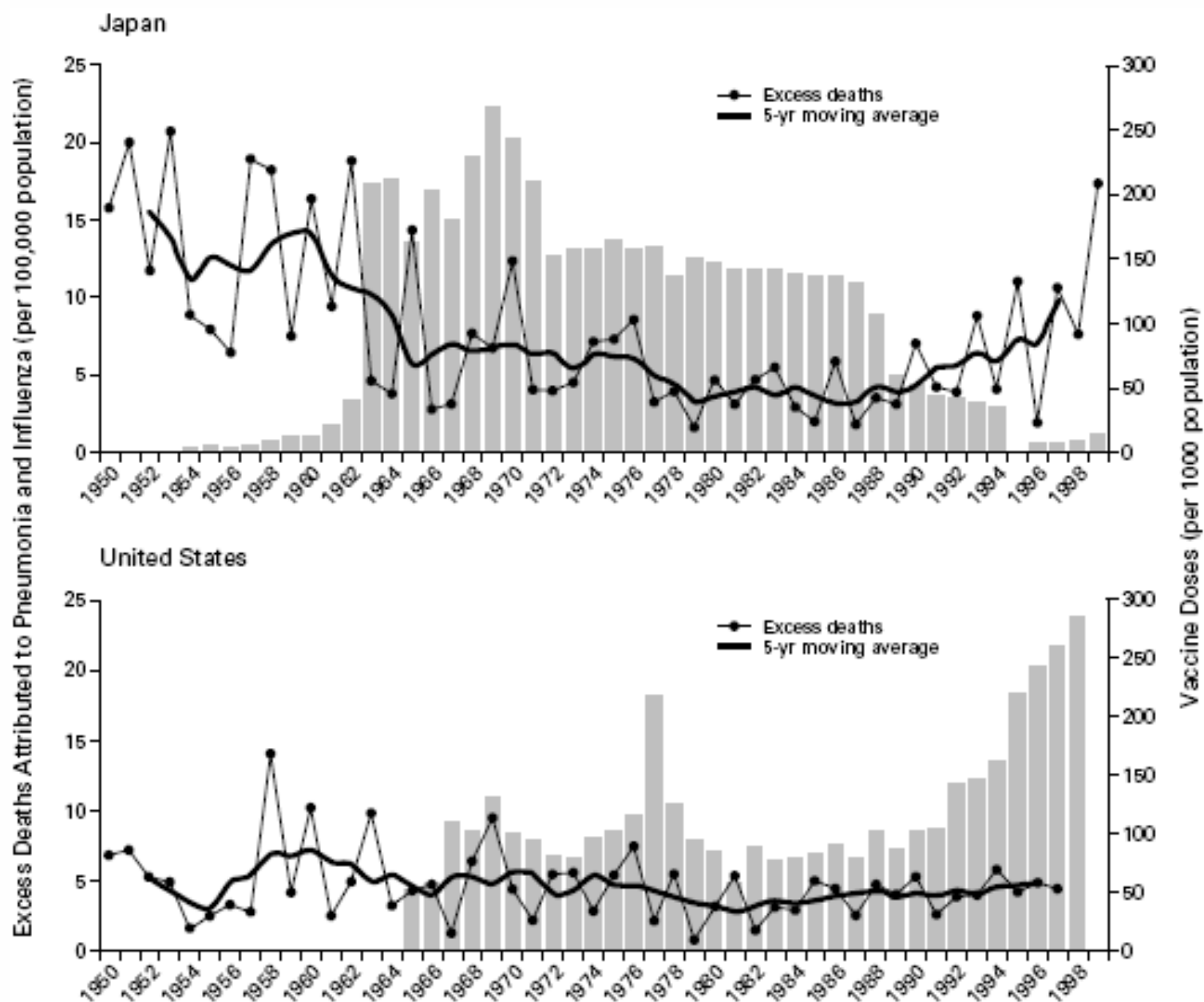


Figure 4. Excess Deaths Attributed to Pneumonia and Influenza over a 50-Year Period in Japan and the United States. The five-year moving average is also shown. The history of the rates of use of vaccine in each country is superimposed (shaded bars). Tick marks represent the beginning of the years indicated.

Science News

Flu Vaccinations Recommended For Health-care Workers

ScienceDaily (Oct. 5, 2007) — The American College of Physicians (ACP) recommends that an annual influenza vaccine should be required for every health care worker with direct patient care activities. They state that influenza vaccination of health-care workers results in improved patient safety, improved employee safety and decreased health-care expenditures.

Only 36 percent of all health care workers are immunized against influenza each year. Transmission of influenza from health care workers to patients has been documented in nearly every health care setting, and multiple studies show that 70 percent or more

See also:

Health & Medicine

- [Workplace Health](#)
- [Today's Healthcare](#)
- [Health Policy](#)

Plants & Animals

- [Bird Flu Research](#)

Related Stories

Johns H Vaccina

2005) — epidemic mandato the best staff from

FDA Inv Influenz and Drug of potent vaccine i

Flu Vac With Hi 2005) —



NEWS RELEASE

EMBARGOED UNTIL 12:00 NOON EST ON THURSDAY, JAN. 25

NOTE: TELECONFERENCE THURSDAY, JAN. 25 AT 12 NOON EST. CALL-IN INFORMATION AT THE BOTTOM OF THIS RELEASE

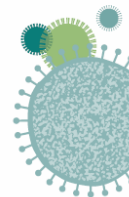
Contact: Steve Baragona, (703) 299-0412, sbaragona@idsociety.org

Flu Experts Call for Mandatory Shots for Health Care Workers

Issue Comprehensive Set of Principles to Prepare for Seasonal, Pandemic Flu

ALEXANDRIA, VA—The top professional society of infectious diseases experts is insisting that all physicians, nurses, and other health workers caring for patients be vaccinated against influenza each year or decline in writing. It is the strongest call yet to plug a critical weakness in the nation's flu

Are your health care workers vaccinated against influenza?



Infectious Disease Experts Call for Mandatory Influenza Vaccination for Health Care Workers

The Infectious Disease Society of America (IDSA) is insisting that all physicians, nurses, and other health care workers caring for patients be vaccinated against influenza each year or decline vaccination in writing.

This call to action is part of a broader set of pandemic and seasonal influenza planning principles issued by the group to complement the Pandemic and All-Hazards Preparedness Act enacted by Congress and the Administration in December 2006. IDSA's principles support many of the new law's concepts, and provide additional directions and a level of specificity not found in the Act.

Point: Mandatory Influenza Vaccination for All Health Care Workers? Seven Reasons to Say "No"

Mark Finch

Brown and Toland Medical Group, San Francisco, California

(See the counterpoint by Backer on pages 1144-7)

(IDSA) is issuing the call to a new set of recommendations to an inevitable influenza pandemic, a real threat of seasonal influenza.

assessments to date on the major threats. IDSA intends its principles to complement the nation's efforts in enacting the law in December 2006. IDSA's principles are included in the new law, but provide a level of specificity not found in the Act.

Safety considerations

- Seasonal influenza vaccines generally safe
- Vaccines safe in pregnant women although most manufacturers state safety not proven
- 1976 Swine flu outbreak in US, GBS association, still unclear whether real
- 2009 H1N1 narcolepsy in Sweden, Finland, Iceland

Conclusion

- Influenza of public health importance
 - Seasonal and pandemic burden
- Vaccines are the best way to prevent influenza
- BUT reduced effectiveness in risk groups
- And production challenges
- Enormous efforts to address this
- Need to promote influenza vaccination in Africa and rapidly take on new technologies as they become available
- Indirect protection may be useful

QUESTIONS

Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children

Pedro A. Piedra^{a,b,*}, Manjusha J. Gaglani^c, Claudia A. Kozinetz^b, Gayla Herschler^d, Mark Riggs^d, Melissa Griffith^d, Charles Fewlass^d, Matt Watts^d, Colin Hessel^e, Julie Cordova^e, and

W. Paul Clancy^{a,b}

intervention and comparison sites during the influenza outbreaks. Baseline age-specific MAARI rates per 100 persons for the influenza season were comparable between the intervention and comparison communities. In the subsequent three influenza seasons, the age groups 35–44, 45–54, 55–65 and >64 years experienced reductions in MAARI rates in the intervention communities. In adults ≥ 35 years of age, significant reductions in MAARI of 0.08 (95% CI: 0.04, 0.13), 0.18 (95% CI: 0.14, 0.22) and 0.15 (95% CI: 0.12, 0.19), were observed in the influenza seasons for vaccination years 1, 2 and 3, respectively. No consistent reduction in MAARI rates was detected in the younger age groups. Vaccination of approximately 20–25% of children, 1.5–18 years of age in the intervention communities resulted in an indirect protection of 8–18% against MAARI in adults ≥ 35 years of age.

Effectiveness of School-Based Influenza Vaccination

[Original Articles]



The NEW ENGLAND
JOURNAL of MEDICINE
ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG

King, James C. Jr.; Stoddard, Jeffrey J.; Gaglani, Manjusha J.; Moore, Kristine A.; Magder, Laurence; McClure, Elizabeth; Rubin, Judith D.; Englund, Janet A.; Neuzil, Kathleen.

Results: In all, 47% of students in intervention schools received live attenuated influenza vaccine. As compared with control-school households, intervention-school households had significantly fewer influenza-like symptoms and outcomes during the recall week. Paradoxically, intervention-school households (both children and adults) had higher rates of hospitalization per 100 persons than did control-school households. However, there was no difference in the overall hospitalization rates for children or adults in households with vaccinated children, as compared with those with unvaccinated children, regardless of study-group assignment. Rates of school absenteeism for any cause (based on school records) were not significantly different between intervention and control schools.

Immune response

- Protection from natural infection
 - HA-specific antibodies (serum & mucosa)
 - Antibodies against NA, conserved proteins
 - T cell responses correlate with reduced disease severity

Vaccines for influenza

- Vaccination is the primary strategy for influenza prevention and control
- First population scale use in US military in 1945
- Vaccine effectiveness affected by:
 - Antigenic match to circulating virus
 - Recipient age
 - Recipient health status
- More effective vaccines needed
 - Elderly, children, underlying illness

Seasonal influenza vaccines

- Trivalent
 - A H3N2
 - A H1N1
 - B – 2 lineages Yamagata and
- Strains selected 6 months before the season
- WHO meeting
- Best guess of strains for next year
- Other factors e.g. Growth in eggs

Process of vaccine production

- Strains selected
- Vaccine reference strains developed (hybrid viruses with egg-growing lab strain) – weeks
- If low yield then further egg adaption needed (serial passage)
- Amplify virus in hundreds of millions of embryonated chicken eggs (each individually inoculated with each virus type)
- Inactivate and purify
- Formulate package and distribute

