Influenza: Virus, vaccines and vaccination strategies

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PATH
A catalyst for global health

Objectives

- To understand basic influenza epidemiology and virology.
- To review the currently available influenza vaccines, and to understand the complexity of influenza vaccine development, manufacturing and distribution.
- To discuss tools and strategies to facilitate influenza prevention through vaccination in low-resource settings.

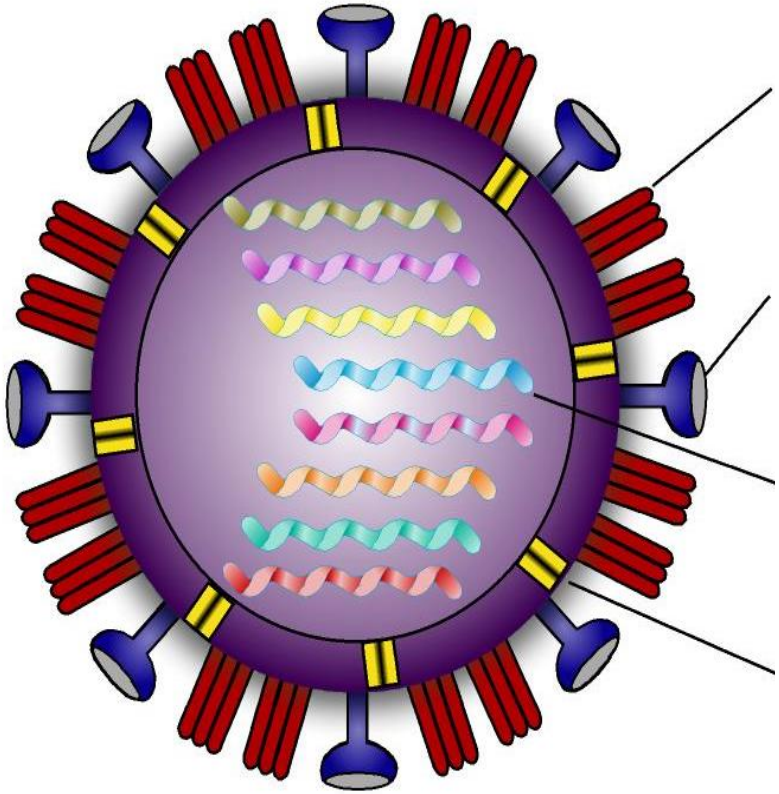
Influenza Virus

- Orthomyxoviridae family
  - Negative sense, ss RNA viruses
  - Eight separate gene segments
- Classification
  - Influenza viruses classified into types A, B, and C
- Characterized by a the emergence of distinct antigenic variants over time.
  - Lack of complete immunity to new variants is the reason we have seasonal influenza epidemics

Influenza A, B, and C Viruses

- Influenza A viruses
  - Subtypes based on surface glycoproteins
    - Hemagglutinin (HA) and Neuraminidase (NA)
    - Current human influenza A virus subtypes: H1N1, H3N2
  - Infect multiple species
    - Humans
    - Birds (wild birds, domestic poultry)
    - Other animals: pigs, horses, dogs, marine mammals, bats
- Influenza B
  - Humans only reservoir
  - Less mortality than type A
  - Associated with epidemics, not pandemics
  - Two circulating lineages (Yamagata and Victoria), resulting in expansion of influenza vaccine to include 4 antigens
- Influenza C
  - Causes mild disease, sporadic cases
  - Not included in vaccine

Influenza A Virus



Hemagglutinin (H) – 17 subtypes (attachment, penetration)

Neuraminidase (N) – 10 subtypes (release)

8 viral genes (assembly, replication)

M2 Protein (replication)

Source: AS Fauci

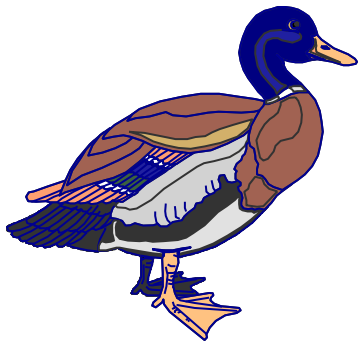
A pandemic can occur if three conditions are met

1. Emergence of novel influenza A subtype

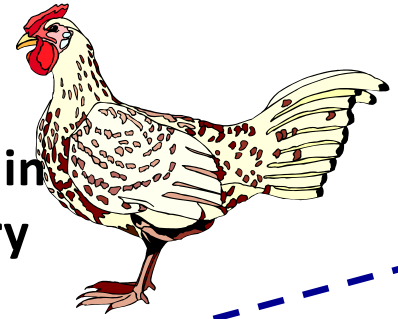
2. Efficient and sustained virus transmission occurs among humans

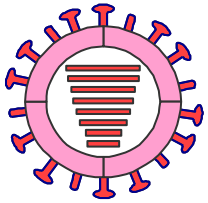
3. Infection causes disease

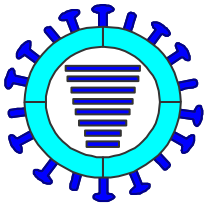
Reassortment of Influenza A Viruses



Alpha 2,3 receptors in respiratory tract



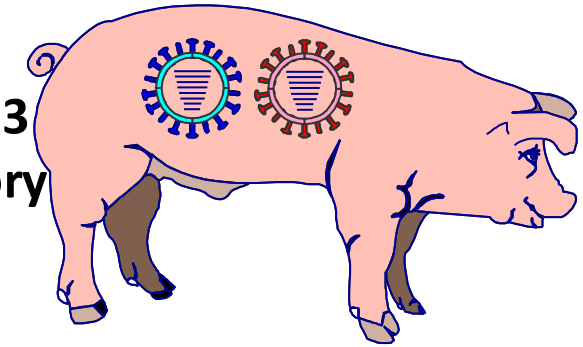


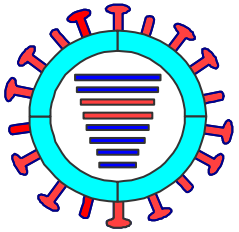


Non-human virus

Alpha 2,6 receptors

Alpha 2,6 & Alpha 2,3 receptors in respiratory tract





Reassortant virus

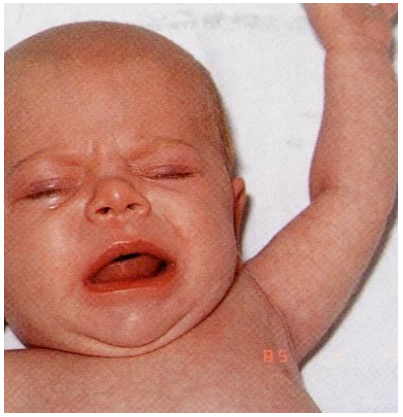
Influenza A HA and NA Subtypes

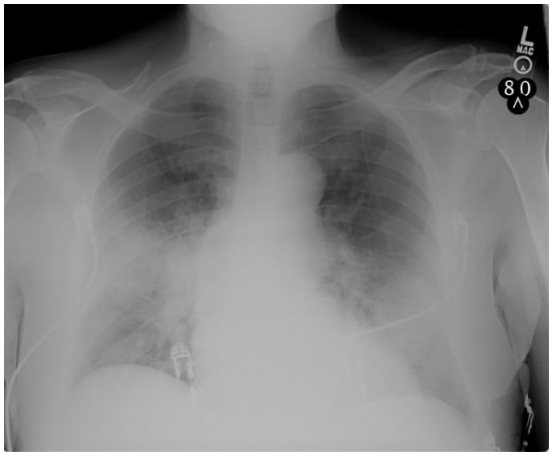
H1	human, swine, fowl
H2	human, fowl
H3	human, swine, fowl, equine, canine
H4	seal, fowl swine
H5	human, fowl
H6	fowl
H7	human, seal, fowl, equine
H8	fowl
H9	human, swine, fowl
H10	fowl
H11	fowl
H12	fowl
H13	gulls
H14	fowl
H15	gulls
H16	gulls
H17	bats

N1	human, swine, fowl
N2	human, swine, fowl
N3	fowl
N4	fowl
N5	fowl
N6	fowl
N7	seal, fowl, equine
N8	canine, fowl, equine
N9	fowl, HUMAN
N10	bat

Human Influenza - Clinical

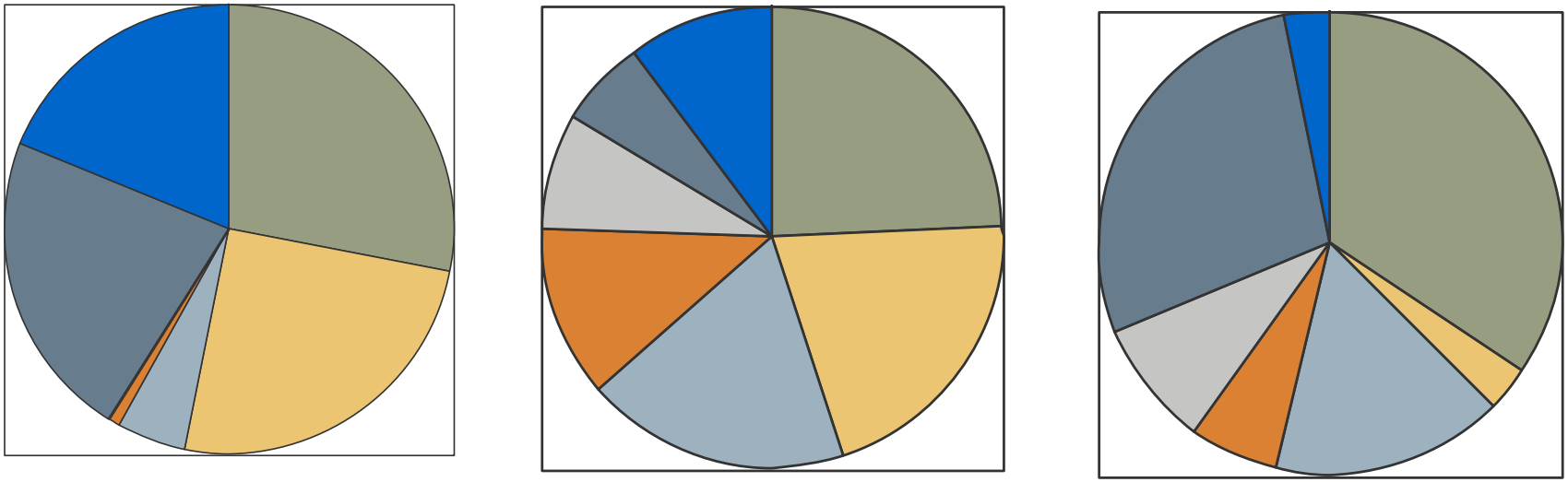
- Acute febrile respiratory illness
  - "Influenza-like illness"
    - Fever or feverish
    - Cough and/or sore throat or other manifestations (otitis)
  - More serious pulmonary manifestations
    - Primary or secondary pneumonia, croup, bronchiolitis
- Non-specific febrile illness
- Extra-pulmonary manifestations
    - Neurologic – Encephalitis, seizures
    - Myositis
    - Cardiac





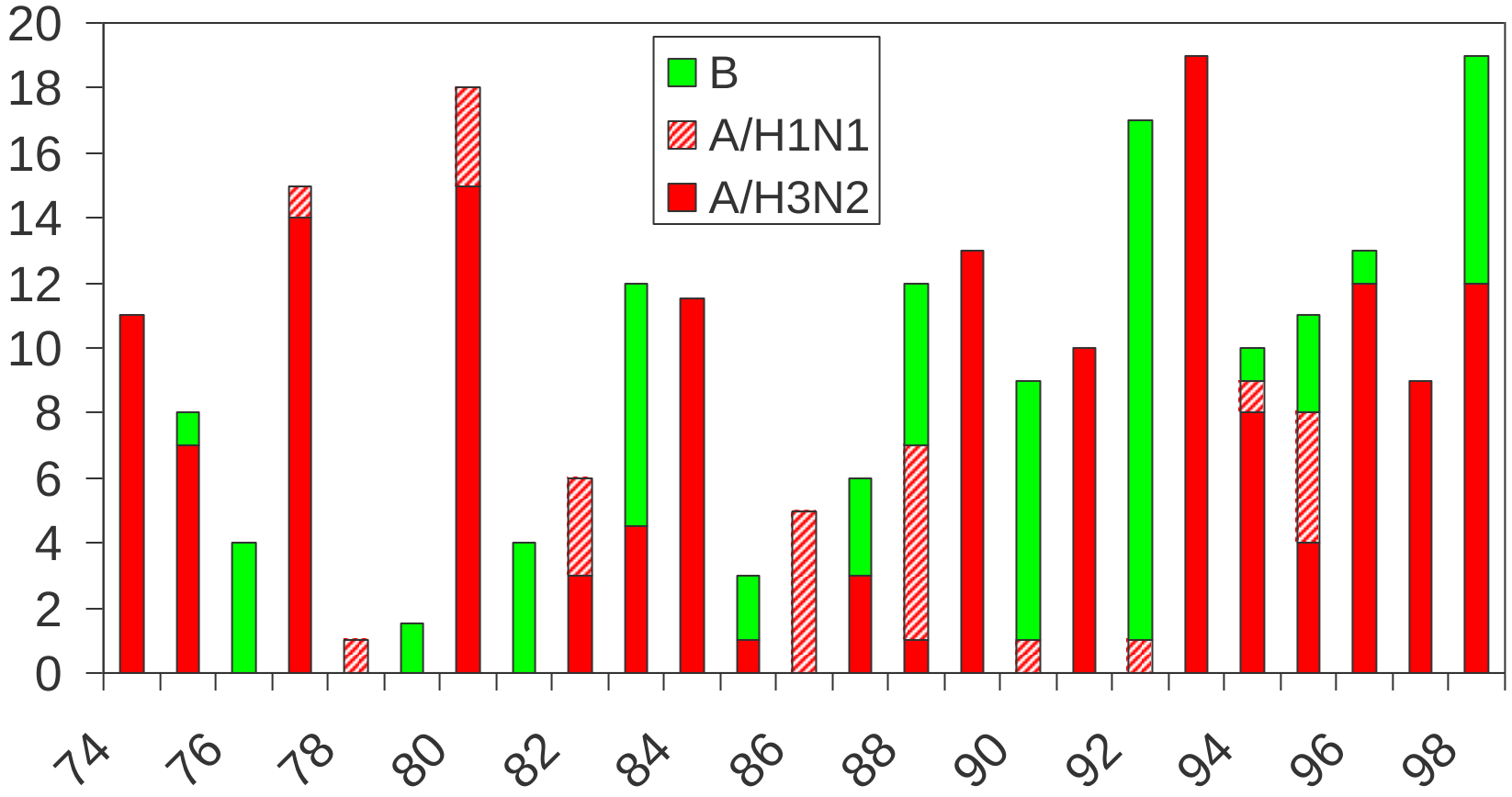
Absence of data does not equal absence of influenza!

Discharge diagnosis of children hospitalized with laboratory-documented influenza infection, by age



Poehling, et al. N Engl J Med 2006; 355:31-40.

Symptomatic influenza attack rates per 100 children < 5 years

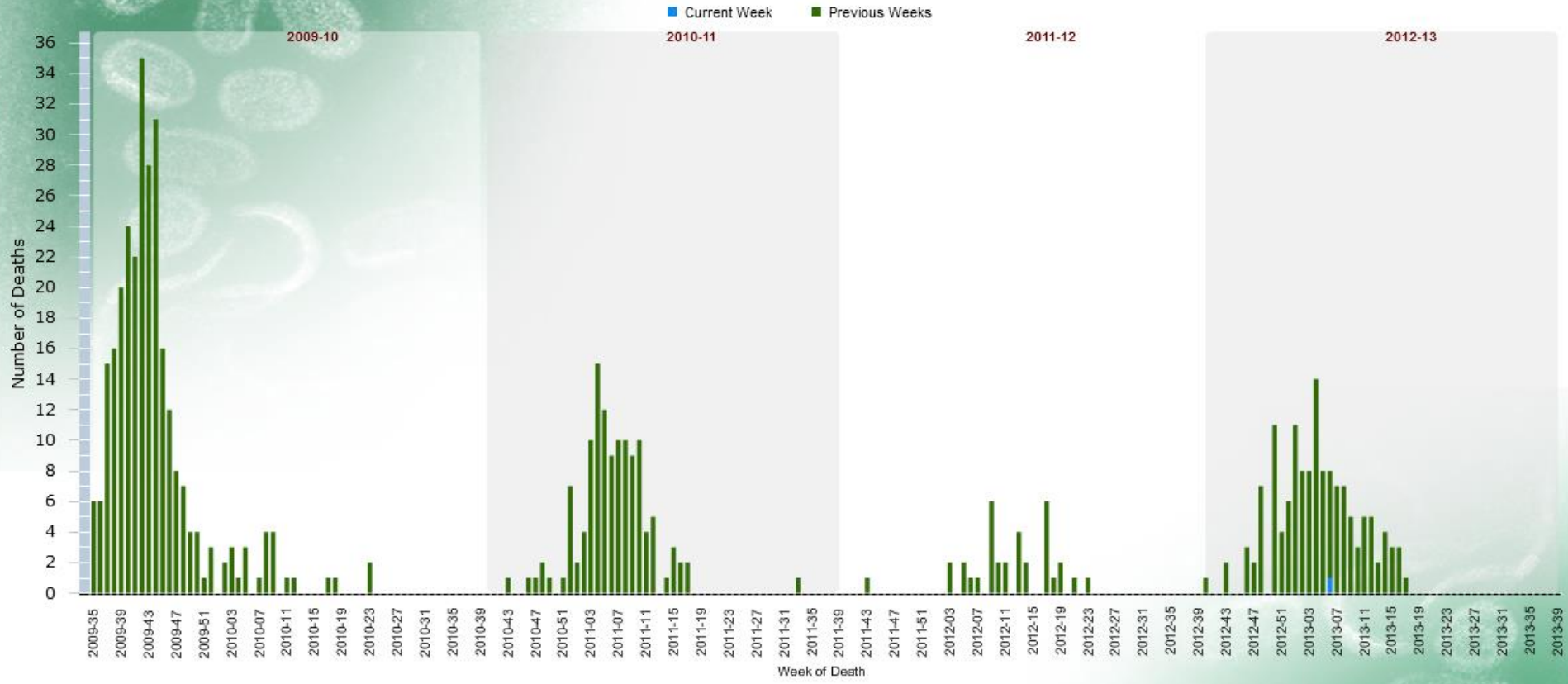


Neuzil, et al. JID 2002; 185:147.

FLUVIEW

CDC

Number of Influenza-Associated Pediatric Deaths by Week of Death



Season	Total Deaths	Deaths Reported During the Week Ending 03 May 2013
2009-10	282	0
2010-11	123	0
2011-12	34	0
2012-13	138	1

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Influenza: Global Burden

- Infection rates are highest among children, while complications, hospitalizations, and deaths from seasonal influenza are typically greatest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that confer increased risk for complications from influenza (including pregnancy).
- Highly variable from year-to-year
- Children play an important role in the spread of influenza.

Preventing influenza with vaccine: What is our goal? What are our options?

- Vaccines?
- Vaccination strategies?
- Markets?
- Manufacturers?

Photo credit: John C. Victor, PATH

Inactiviated influenza vaccine (IIV, flu shot)

- Licensed for over 60 years
- Monovalent, bivalent, trivalent and now quadrivalent
- Population: All 6 months and over
- Efficacy varies by population, season, strain
- Strong safety record, but adverse events do occur
  - RCT: sore arm
  - GBS (1976); oculorespiratory syndrome (2000); febrile seizures in young children in Western Australia (2010)

What are the major limitations of current inactivated seasonal influenza vaccines?

- Efficacy
  - Suboptimal, particularly in young children (2 doses), elderly, immunocompromised
- Limited cross-protection
- Annual, seasonal administration
- Cumbersome manufacturing process
- Supply and distribution
- Relatively high cost

Influenza vaccines, US, 2013-14

Type of Vaccine	Trade Name	Manufacturer	Age Indications	Route
IIV3: Inactivated influenza vaccine; Trivalent Note: One vaccine is produced in cell culture; this is referred to as ccIIV	Afluria®	CSL Limited	≥ 9 years	IM
	Fluarix®	GlaxoSmithKline	≥ 3 years	IM
	Flucelvax®	Novartis Vaccines	≥ 18 years	IM
	FluLaval®	ID Biomedical	≥ 3 years	IM
	Fluvirin®	Novartis Vaccines	≥ 4 years	IM
	Fluzone®	Sanofi Pasteur	≥ 6 months	IM
	Fluzone® Intradermal (9mcg HA/strain/dose)	Sanofi Pasteur	18 through 64 years	Intradermal
	Fluzone® High-Dose (60mcg HA/strain/dose	Sanofi Pasteur	≥ 65 years	IM
IIV4: Inactivated influenza vaccine; Quadrivalent	Fluarix® Quadrivalent	GlaxoSmithKline	≥ 3 years	IM
	Fluzone® Quadrivalent	Sanofi Pasteur	≥ 6 months	IM
	FluLaval®	ID Biomedical	≥ 3 years	IM
RIV3: Recombinant HA; Trivalent	FluBlok®	Protein Sciences	18 through 49 years	IM
LAIV4: Live attenuated influenza vaccine; Quadrivalent	FluMist® Quadrivalent	MedImmune	2 through 49 years	Intranasal

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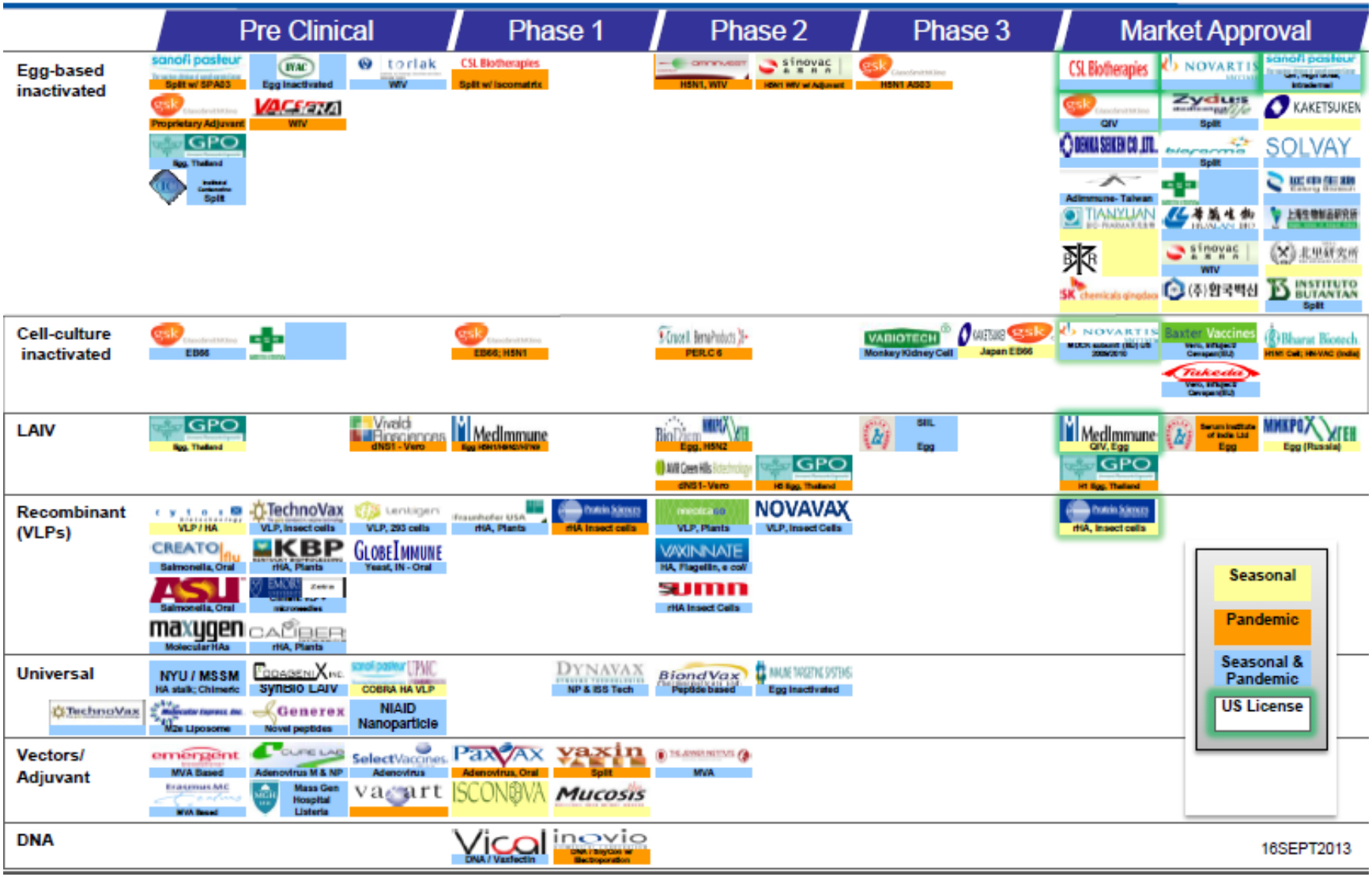
LAIV4: Live attenuated influenza vaccine; Quadrivalent	FluMist® Quadrivalent	MedImmune	2 through 49 years	Intranasal

Influenza Vaccine Landscape

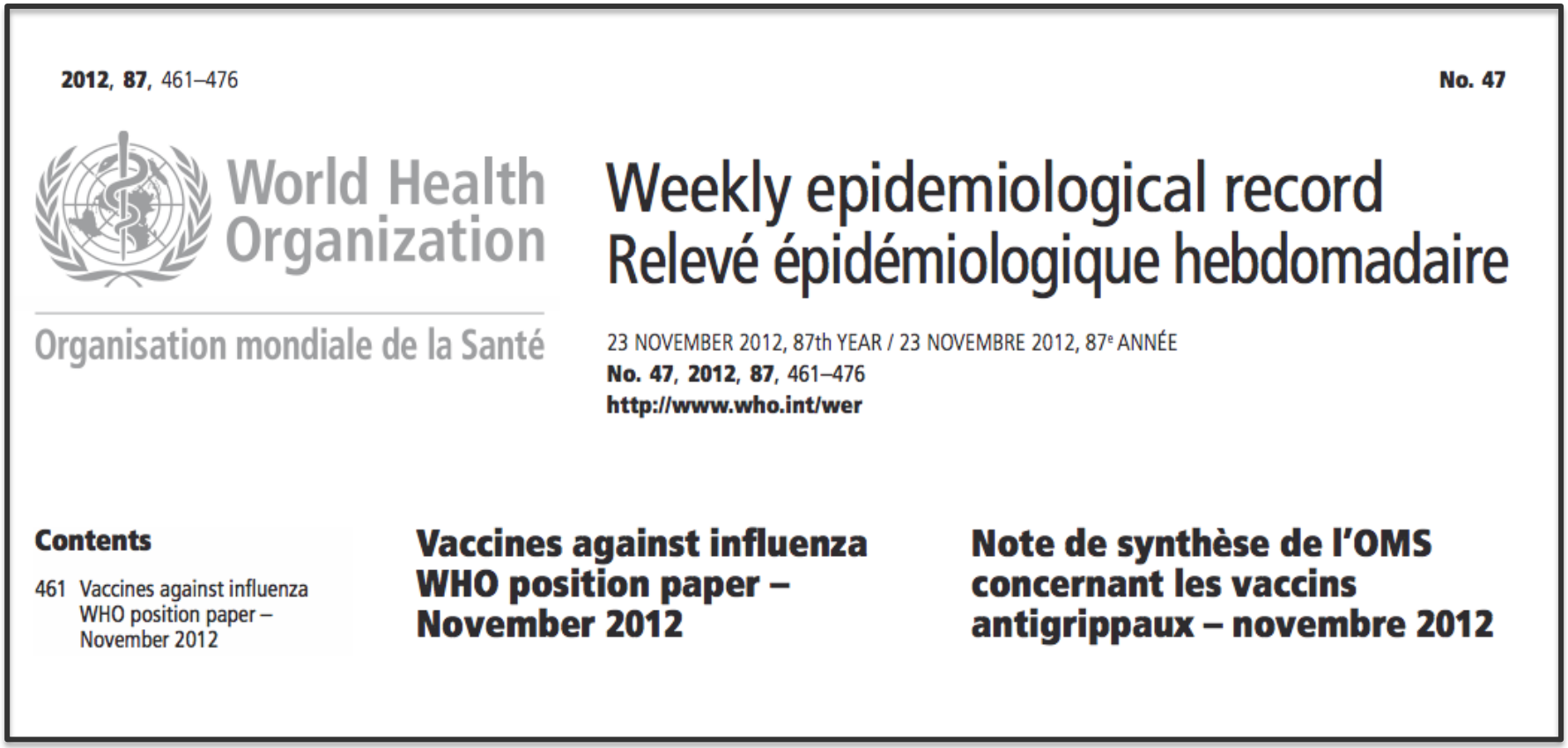


Influenza vaccine recommendations, U.S., 2014

- Routine annual influenza vaccination of all persons aged ≥6 months continues to be recommended.
- No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one product is otherwise appropriate.

Prevention and Control of Seasonal Influenza with Vaccines

Recommendations of the Advisory Committee on Immunization Practices — United States, 2013–2014



2012, 87, 461–476 No. 47

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

23 NOVEMBER 2012, 87th YEAR / 23 NOVEMBRE 2012, 87e ANNÉE
No. 47, 2012, 87, 461–476
http://www.who.int/wer

Contents

Vaccines against influenza WHO position paper – November 2012

Note de synthèse de l'OMS concernant les vaccins antigrippaux – novembre 2012

"For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that pregnant women should have the highest priority."

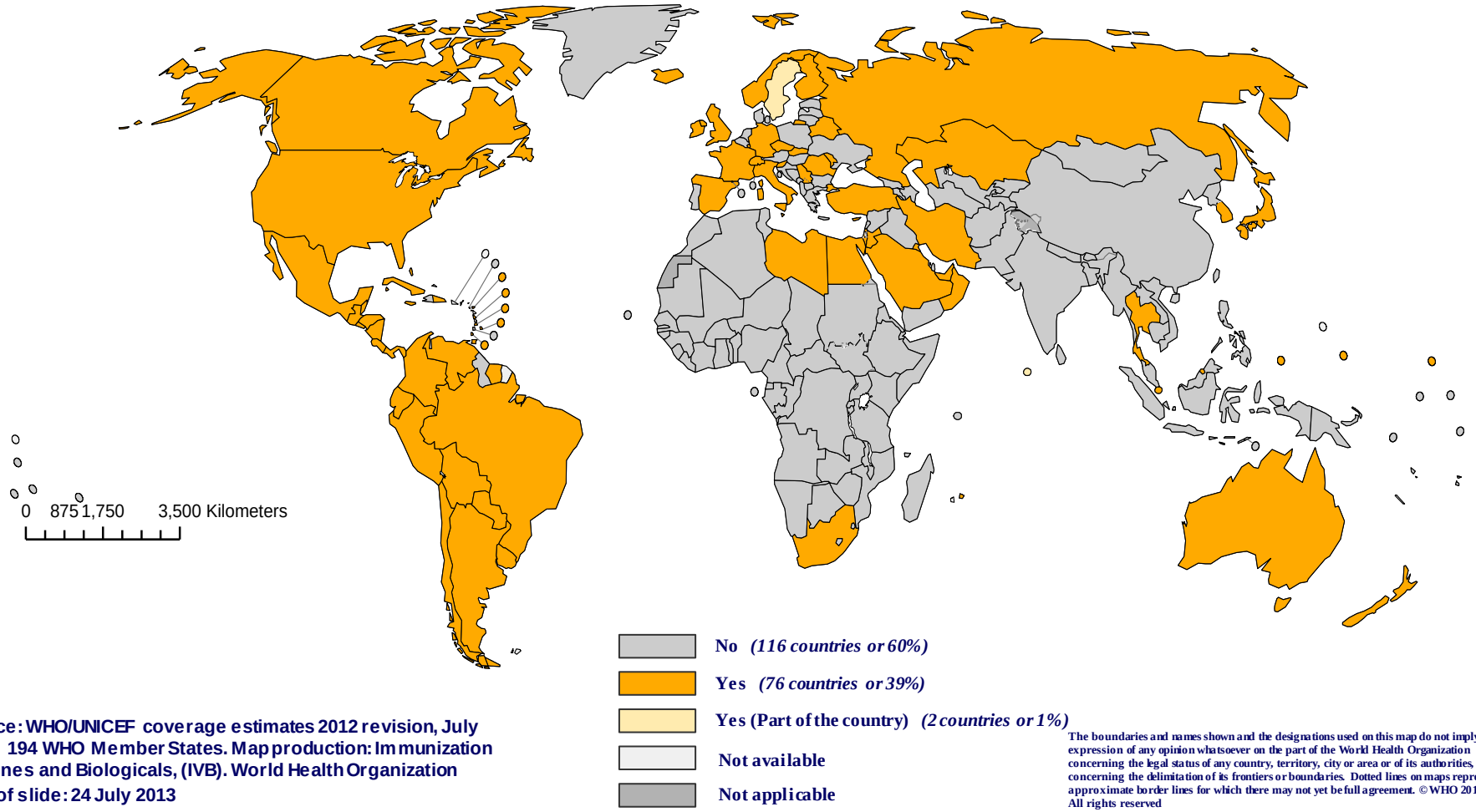
WHO. Vaccines Against Influenza, WHO position paper – November 2012. Wkly Epidemiol Rec. No. 47, 2012, 87, 461–476.

WHO SAGE, April 2012

- The priority accorded to pregnant women was based on "compelling evidence of substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe and effective in preventing disease in pregnant women as well as their young infants, in whom disease burden is also high."
- SAGE also supported the recommendation, in no particular order of priority, of vaccination of the following targeted populations:
  - Healthcare workers.
  - Children 6 to 59 months of age.
  - The elderly.
  - Those with high-risk conditions.

Source: WHO. WER 2012; 87: 201-16.

Countries Providing Seasonal Influenza in National Immunization Schedule, 2012



Source: WHO/UNICEF coverage estimates 2012 revision, July 2013. 194 WHO Member States. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization
Date of slide: 24 July 2013

Influenza vaccine and pregnancy

- High burden of influenza illness among pregnant women.
- Excellent immunogenicity and safety profile of TIV in women, fetuses, and infants.
- Effectiveness in infants born to vaccinated mothers.
- No good alternatives for neonates and young infants (vaccine approval at 6 months).
- Main barriers: logistics and acceptability.

Level of evidence	High resource	Low resource
Disease burden, mother	++	+
Disease burden, infant	++	+
Vaccine safety	++	+
Maternal immunogenicity	++	+
Antibody interference with routine childhood immunization	N/A	N/A
Effectiveness in pregnant women	+	+
Effectiveness in infants born to vaccinated mother	+	+

Legend:

++ Substantial information available

\+ Partial information available

– Little or no information available

N/A Not applicable

Source: Ortiz JR, Englund JA, Neuzil KM. Influenza vaccine for pregnant women in resource-constrained countries: A review of the evidence to inform policy decisions. Vaccine. 2011 Jun 15;29(27):4439-52. PMID: 21550377

Countries and territories in the Americas with policies for seasonal influenza vaccination

Number of countries with:	2004	2008	2012
- Vaccination of healthy children	6	- 22	- 25
- Vaccination of only children with chronic diseases	---	- ---	- 10
- Vaccination of elderly	12	33	38
- Vaccination of persons with chronic diseases	9	24	32
- Vaccination of health workers	3	32	37
- Vaccination of pregnant women	3	7	22

Source: Country Reports to PAHO, MOH web pages, PAHO/WHO Surveys
Note: Data was not collected from the French Departments (French Guiana, Guadeloupe, Martinique)

Effectiveness of Maternal Influenza Vaccination in Dhaka, Bangladesh

- TIV decreased respiratory illness with fever by 29% among infants and 36% among their mothers.
- Vaccine efficacy against laboratory-confirmed influenza among newborns was 63%
- Influenza attack rate in infants <6 months
  - 31% (10 RIDT and 31 seroconversion) (Henckle PIDJ 2011)

Zaman, et. al. NEJM 2008

Prevention of influenza through vaccination of mothers

ICDDR,B - Matlab, July 2006.

- 3 randomized, controlled clinical trials of trivalent, inactivated influenza vaccine for pregnant women recently completed in Mali, Nepal and South Africa
- Will examine maternal and newborn outcomes
- Funded by BMGF

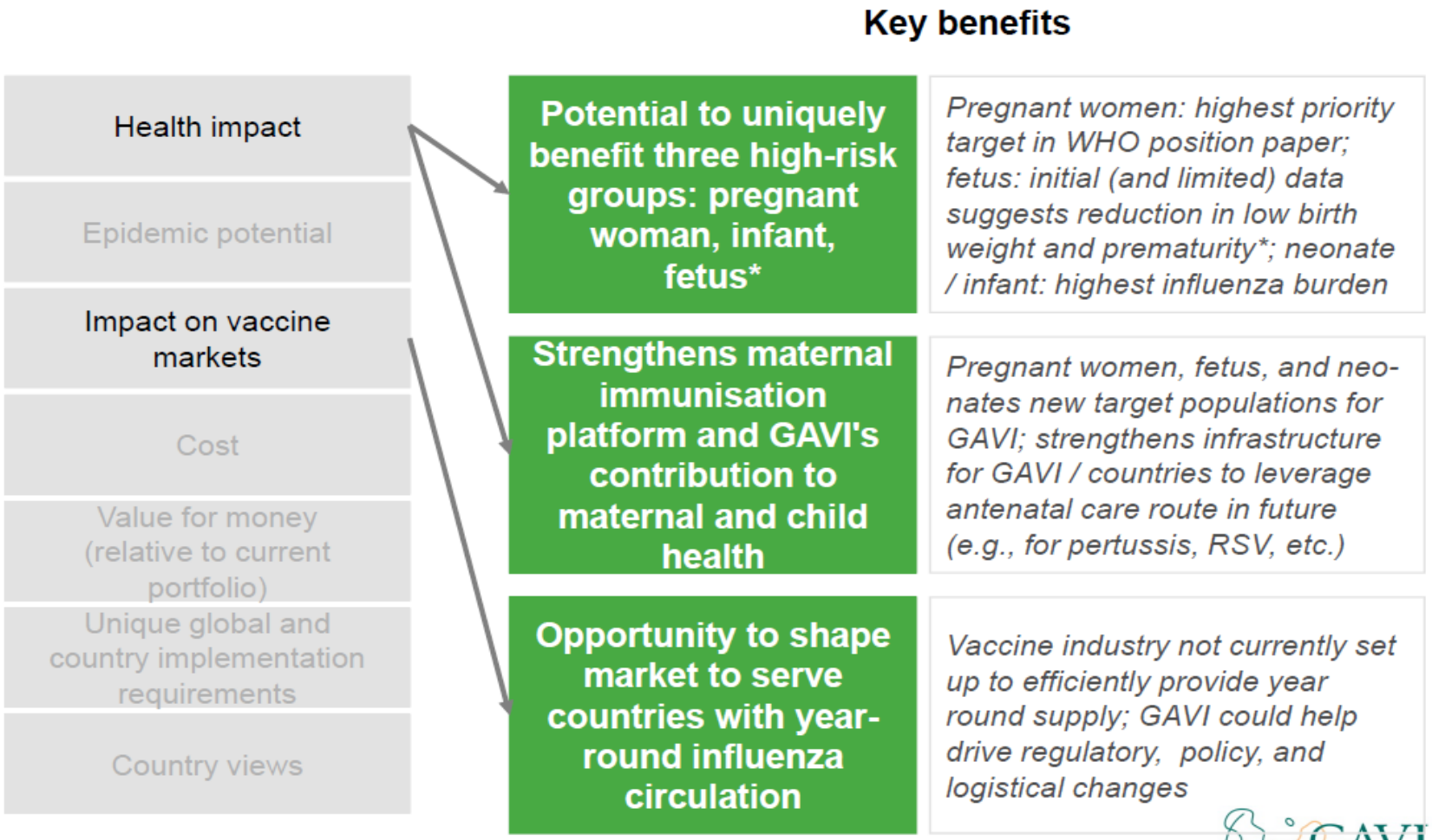
Maternal Influenza Vaccination in South Africa

- Trials in HIV-infected and HIV-uninfected cohorts
- Double-blind, randomized, placebo-controlled trial in Soweto, South Africa in 2011.
- 194 HIV-infected women between 20-34 weeks of gestational age randomized to receive either trivalent IIV or placebo IM.
- Laboratory confirmed influenza illnesses were identified in 7/99 (7.1%) IIV-recipients and 16/95 (16.8%) placebo-recipients.
- Despite low HAI antibody responses to vaccination, trivalent IIV was associated with a reduction of first episode of LCI illness (VE: 58%; 95%CI: 2.5 to 81.9; p=0.035).

Nunes et. al. Options for the Control of Influenza VIII September 2013, Cape Town.

Key influenza vaccine benefits:

Uniquely benefits three groups, strengthens maternal immunisation, catalytic market-shaping opportunities

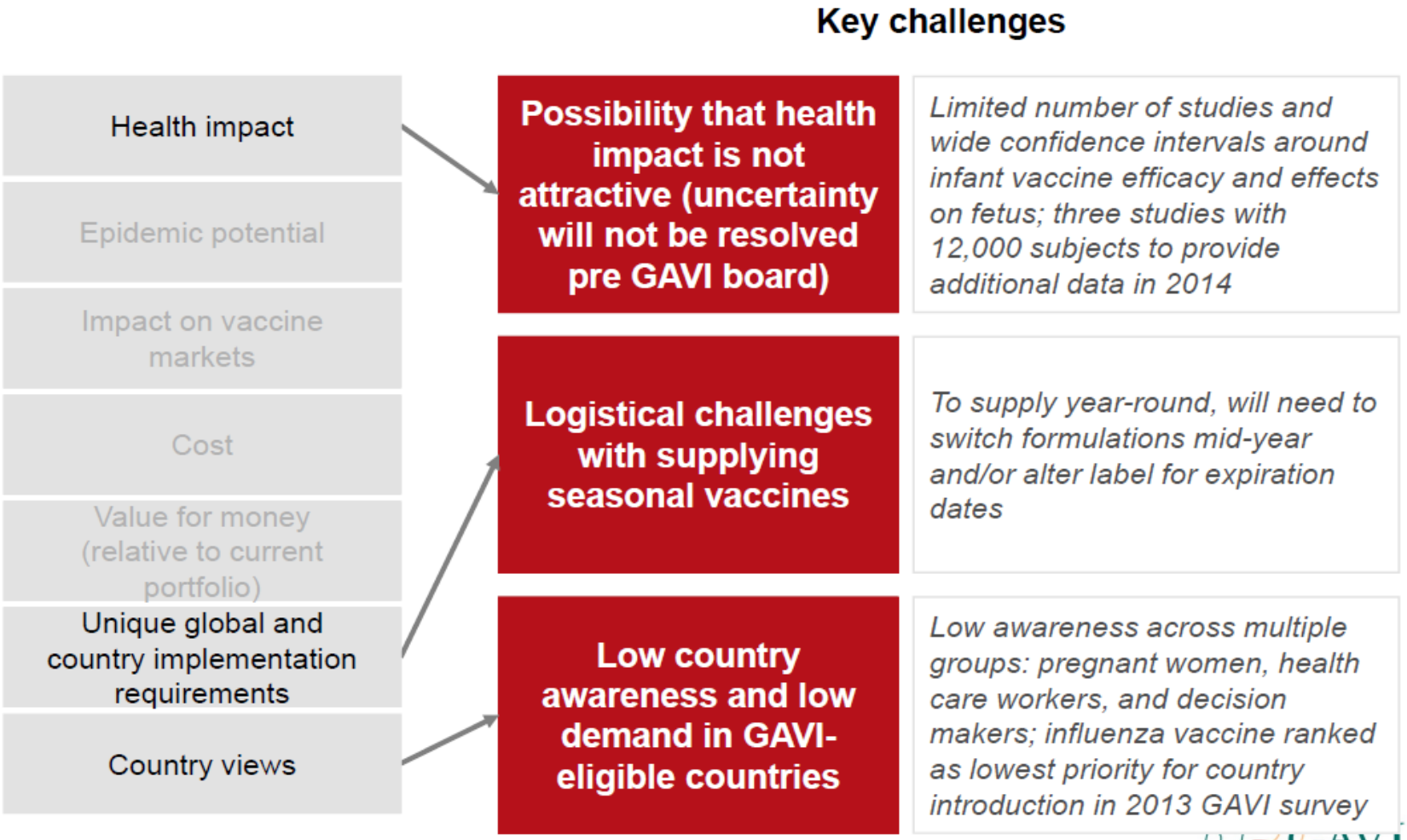


* Effects on fetus highly uncertain and not included in VIS impact estimates

Source: http://www.gavialliance.org/about/governance/gavi-board/minutes/2013/21-nov/

Key influenza vaccine challenges:

Uncertainty in impact, complex provision of year-round supply, low awareness / demand



Source: http://www.gavialliance.org/about/governance/gavi-board/minutes/2013/21_nov/

Influenza: Global burden in children < 5 years

- Limited (but increasing) data from low-resource countries.
- 2010 Global burden of disease estimates 2% of all mortality is attributable to influenza virus infection during the first 5 years of life.
- 2011 *Lancet* meta-analysis in children < 5 years estimates:
  - 20 million (95% CI 13-32) acute lower respiratory infections (ALRI).
  - 1 to 2 million severe ALRI.
  - 28,000 to 111,500 deaths.
  - 99% of early childhood influenza deaths occur in low- and middle-income countries.

Source: Lozano R, et al. *Lancet* 2012;380:2095-2128;
Nair H, et al. *Lancet* 2011;378:1917-1930.

Influenza vaccines for young children

- Children younger than 6 months of age: no available influenza vaccines approved
- Children younger than 2 years of age: inactivated, non-adjuvanted vaccines are only approved vaccines
  - Wheezing signal (< 2 years) and excess hospitalizations (< 1 year) associated with LAIV has resulted in approval for use starting at 2 years of age
- Children 2 through 4 years of age
  - Inactivated, non-adjuvanted and live-attenuated vaccines are approved

Efficacy of TIV in young children against laboratory-confirmed influenza

Study	Design	Age mos	Safety	Efficacy Lab-conf.
Gruber 1990	19 TIV (1)	3-5	No data	83% B (culture)
Heikkinen 1991	187 TIV x2 No placebo	12-36	No data	83% (culture)
Hurwitz 1995	60 TIV (2)	24-60	Well-tolerated	31% H3N2 45% B*
Neuzil/Edwards 2001	271 TIV (1)	12-60	Well-tolerated	44% H1N1 48% H3N2*
Hoberman 2003	525 TIV(2) 261 placebo	6-24	Well-tolerated	66% year 1 -7% year 2 (culture)

Efficacy of MF-59 adjuvanted versus unadjuvanted TIV in 6 to 72 month-old children

Analysis*	Cases/ Vaccinated	VE % (2-sided 95% CI)	Target	Assessment
Efficacy Against All Strains				
FLUAD vs. Non-influenza controls	13/1937 vs. 48/993	**86 (74 - 93)**	Lower CI ≥40	Met
TIV vs. Non-influenza control	50/1772 vs. 48/993	**43 (15 – 61)**		
FLUAD vs. TIV	13/1937 vs. 50/1772	**75 (55 - 87)**	Lower CI ≥10	Met
Efficacy Against Matched Strains				
FLUAD vs. Non-influenza controls	9/1937 vs. 41/993	**89 (78 - 95)**	Lower CI ≥40	Met
TIV vs. Non-influenza control	44/1772 vs. 41/993	**45 (16 - 64)**		
FLUAD vs. TIV	9/1937 vs. 44/1772	**80 (59 - 90)**	Lower CI ≥10	Met

Vesikari et al. N Engl J Med 2011;365:1406-16.

Randomized, controlled trial of quadrivalent IIV in children 3 – 8 years: efficacy by disease severity

Table 1. Vaccine Efficacy against rt-PCR–Confirmed and Culture-Confirmed Influenza A or B According to Age and A Subtype and B Lineage.*

Cohort and Influenza Variable	QIV Group		Control Group		QIV Efficacy
	Cases	Attack Rate	Cases	Attack Rate	
	no.	%	*no.*	%	% *(95% CI)*
Total vaccinated cohort					
rt-PCR–confirmed influenza, any severity	62	2.40	148	5.73	59.3 (45.2 to 69.7)
rt-PCR–confirmed influenza, moderate-to-severe	16	0.62	61	2.36	74.2 (51.5 to 86.2)†
Culture-confirmed, rt-PCR–confirmed influenza, any severity, any seasonal strain	54	2.09	129	4.99	59.1 (41.2 to 71.5)†
Culture-confirmed, rt-PCR–confirmed influenza, any severity, vaccine-matched strain	35	1.35	66	2.55	47.7 (16.4 to 67.3)†

Source: Jain VK , et al. *NEJM* 2013;369 (26):2481-2491

Randomized, controlled trial of quadrivalent IIV in children: efficacy by age and disease severity

Per-protocol efficacy cohort stratified by age‡					
rt-PCR–confirmed influenza, any severity					
Children 3–4 yr of age	32	3.78	48	5.69	35.3 (–1.3 to 58.6)
Children 5–8 yr of age	26	1.70	80	5.15	67.7 (49.7 to 79.2)
rt-PCR–confirmed influenza, moderate-to-severe					
Children 3–4 yr of age	6	0.71	18	2.13	67.5 (18.0 to 87.1)
Children 5–8 yr of age	8	0.52	34	2.19	76.2 (48.5 to 89.0)

DOI: 10.1056/NEJMoa1215817

PICU effectiveness

Table 5. Regression model results and vaccine effectiveness based on comparison of cases and community controls (n=44 cases, 93 community controls)

	Odds Ratio (95% CI)	p	Vaccine Effectiveness (95% CI)
Full vaccination	0.18 (0.04 to 0.77)	0.02	82% (23 to 96%)
Partial vaccination	1.79 (0.50 to 6.41)	0.37	-79% (-541 to 50%)
No vaccination	Ref		
Female	0.33 (0.12 to 0.90)	0.03	
White race	4.27 (1.22 to 15.0)	0.02	
≥3 chronic health conditions	24.6 (3.81 to 158.7)	0.0008	

NOTE: From a conditional logistic regression model with cases and controls matched by age group, geographic area, and influenza risk category. Vaccination status was based on parental report for both cases and controls.

Source: Ferdinands et al JID 2014

Seasonal influenza vaccination of children in Senegal: a cluster-randomized trial

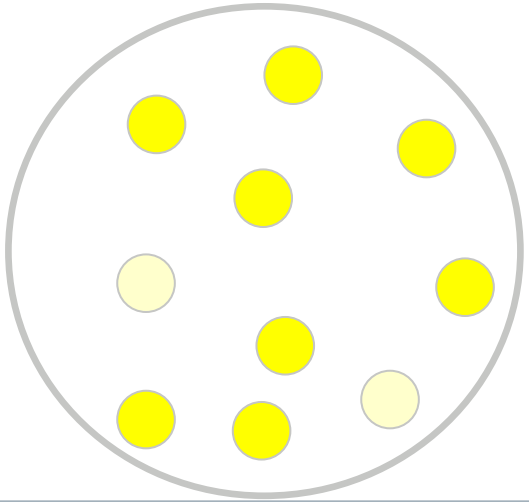
U.S. CDC Co-operative agreement; Partners: Institut de Recherch pour la Developpement; Institut Pasteur of Dakar; Presented by JC Victor, PATH, at Options for the Control of Influenza VIII September 6, 2013.

Group-randomized trials: measures of vaccine effectiveness in the population

Effectiveness Measure:	**Group Incidence Compared:**
Population or Overall:	
Total:	
Indirect:	
Direct:	

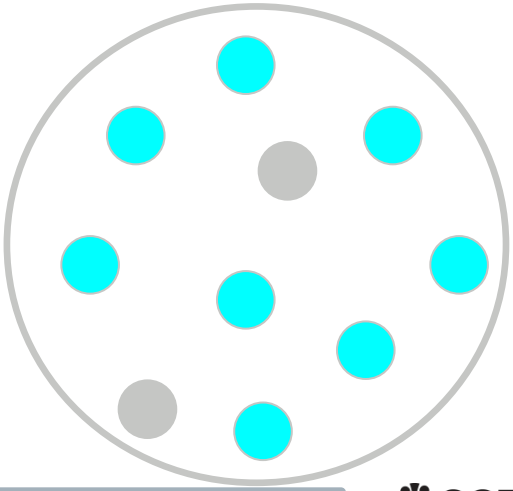
Vaccine Village

Control Village



Received flu vaccine

Did not receive flu vaccine



Received control vaccine

Did not receive control vaccine

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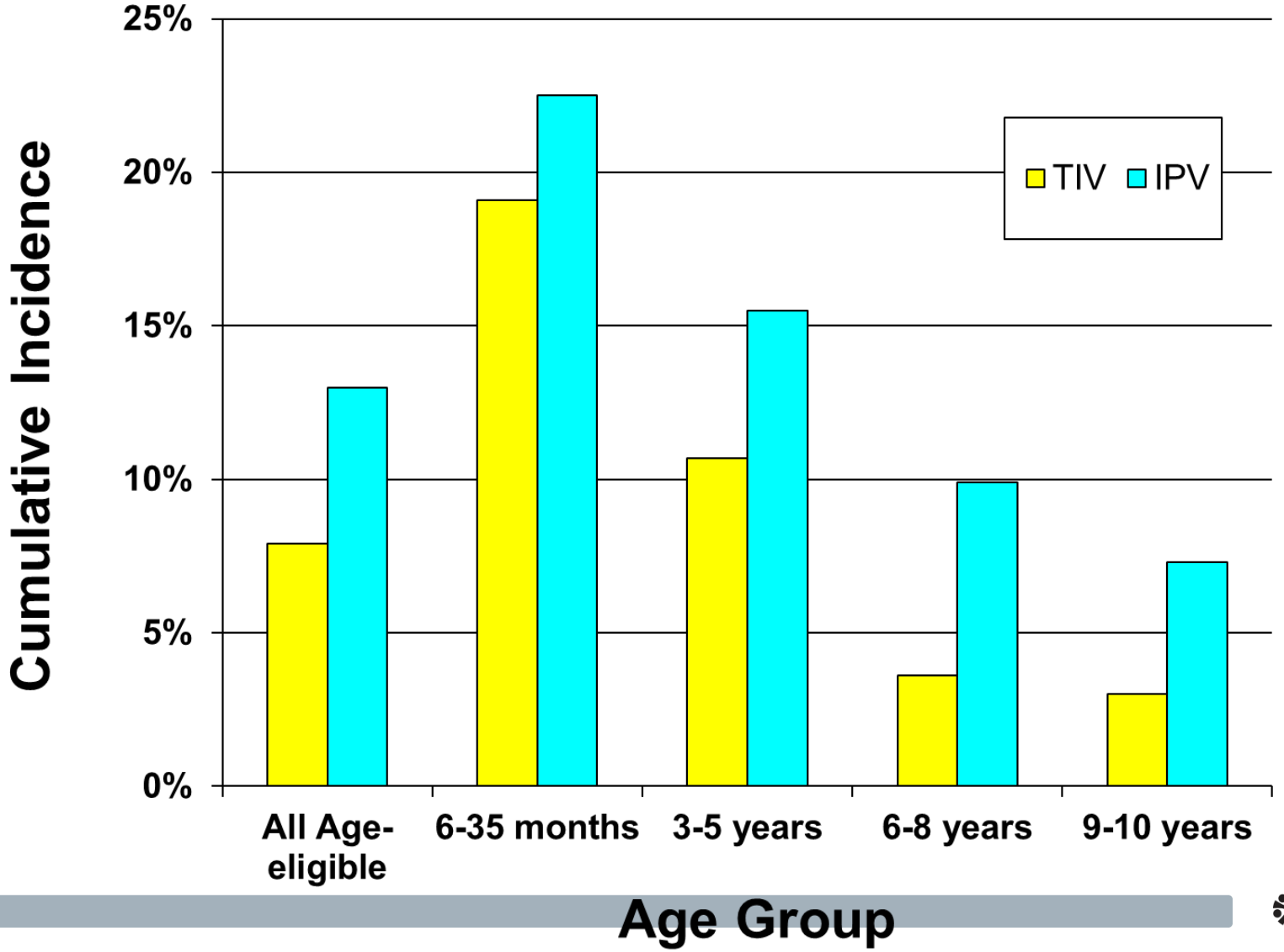
Results: incidence of A/H3N2 influenza among children participating in vaccinations



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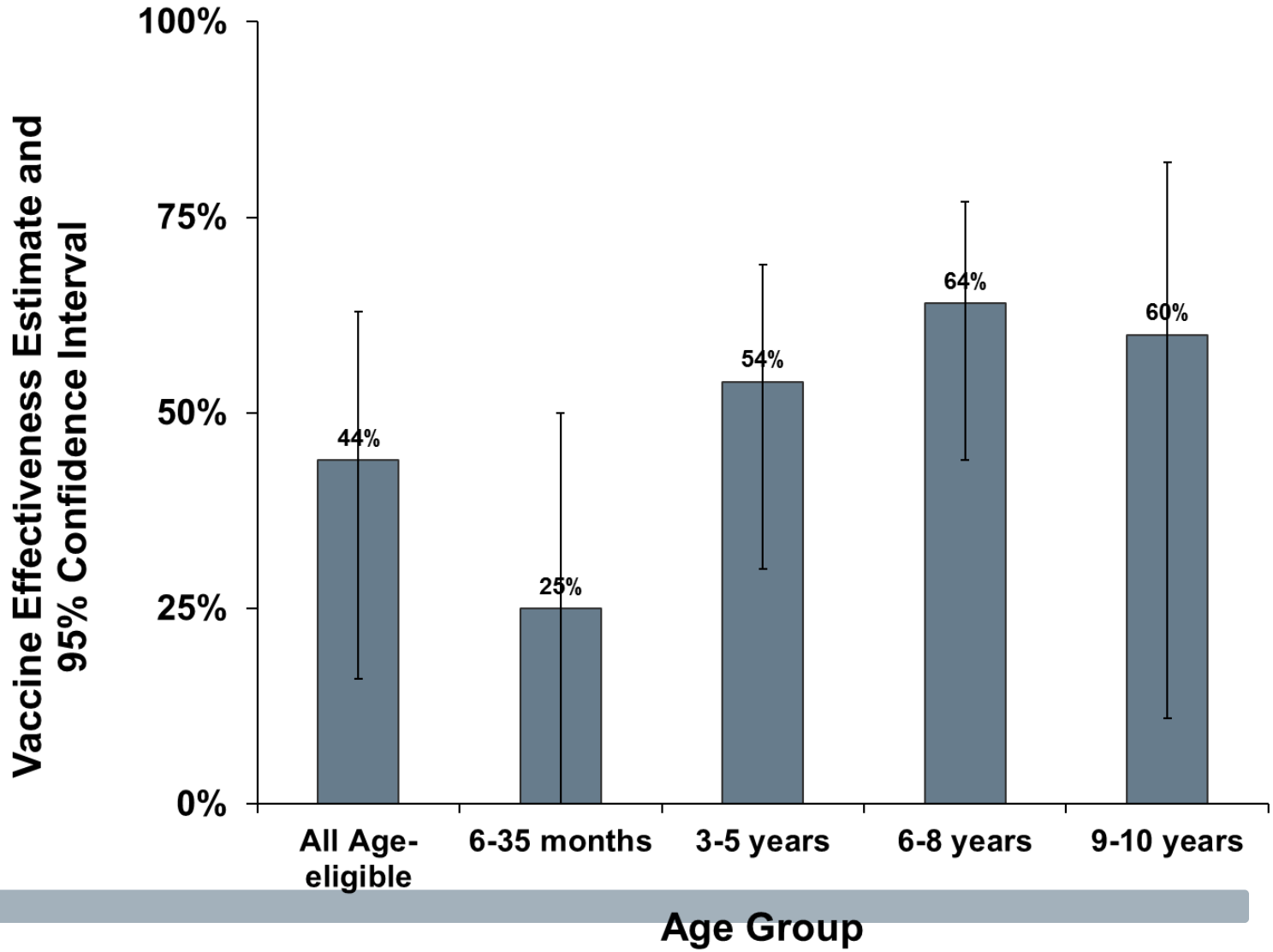
Results: effectiveness against A/H3N2 among participating children (total effectiveness)



PATH

Influenza prevention in children in low resource settings: Rationale for LAIV

- Public health need: Young children at high risk for severe influenza outcomes.
- LAIV may be better choice than current, unadjuvanted, inactivated vaccines for seronegative (unprimed) individuals.
  - LAIV superior to inactivated influenza vaccine (IIV) in RCTs in young children.
  - Potentially better cross- protection (antigenic drift variants).
- Egg-based production of LAIV can be achieved in higher yield and at lower cost as compared to inactivated vaccines.
- Enhanced feasibility: Intranasal delivery and potentially single dose for all ages.

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Relative efficacy of LAIV (Ann Arbor) versus trivalent, inactivated influenza vaccine (TIV) by age and strain

Age, months (*n*)	All strains* Relative efficacy, % (95% CI)	H1N1* Attack rate, %		H1N1* Relative efficacy, % (95% CI)	H3N2* Attack rate, %		H3N2* Relative efficacy, % (95% CI)	B* Attack rate, %		B* Relative efficacy, % (95% CI)
		LAIV	TIV		LAIV	TIV		LAIV	TIV	
6–23 (3686)	56 (40–68)	0·1	0·3	67 (–56 to 95)	0·7	4·1	83 (70–91)	2·3	2·7	15 (–29 to 43)
24–35 (2612)	57 (40–69)	0·1	0·3	78 (–79 to 99)	1·0	5·6	82 (68–90)	2·8	3·0	10 (–42 to 43)
36–47 (846)	42 (5–66)	0	2·3	100 (63–100)	1·7	3·4	48 (–29 to 81)	4·1	4·8	12 (–69 to 55)
48–59 (708)	56 (25–75)	0	2·0	100 (47–100)	1·1	4·0	76 (22–95)	5·0	7·5	25 (–37 to 60)

LAIV, live attenuated influenza vaccine; TIV, trivalent inactivated influenza vaccine.
*Regardless of antigenic match to vaccine.

Source: Belshe RB, et al. *Influenza Other Respi Viruses*. 2010;4(3):141-145.

Preferential recommendation for LAIV in young children in the United Kingdom, Canada, Germany, Israel.

Vaccine 29S (2011) A16–A21

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A pandemic influenza vaccine in India: From strain to sale within 12 months

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Fig. 2. Intranasal spray device for administration of H1N1 pandemic vaccine.

PATH-sponsored SIIL trivalent LAIV clinical trials in Bangladesh and Senegal

Senegal

- Clinical efficacy

Site PI

Dr. Aldiouma Diallo, Institut de Recherche pour le Développement

Funder

CDC

Bangladesh

- Safety and immunogenicity
- Clinical efficacy

Site PI

Dr. Abdullah Brooks

Icddr,b/Johns Hopkins University

Funder

BMGF

Goal: To provide data to guide policy in low resource countries

Trial objectives

- Assess safety outcomes, including wheezing, in young children.
- Demonstrate efficacy against laboratory-confirmed influenza outcomes.
- Demonstrate burden of illness/risk-benefit ratio in low-resource populations.
- Assess immunogenicity and post-vaccination shedding outcomes.

Research questions remain

- What is the effect of priming (original antigenic sin?) on future vaccine responses?
- What is the effect of vaccination over multiple years?
- What is the duration of vaccine protection?
- Will effects differ by type of vaccine (non-replicating vs live attenuated?)
- How do we best measure indirect protection in different settings/environments?

Influenza Vaccines in Low-resource Settings

- Influenza is a disease of global importance
  - We have a lot to learn about seasonal in most of the world
  - Burden of illness studies, particularly focusing on the contribution of influenza to severe disease (e.g. pneumonia) are critical
  - Absence of data does not equal absence of influenza
- Initial strategies should consider WHO recommendations, burden of illness and programmatic feasibility
- Vaccines can reduce the impact of influenza – but we need to employ appropriate tools and strategies so that all can benefit.
  - Choice of vaccine will depend on overall prevention goals

What does the (near) future hold?

- HA-based non-relicating vaccines and live-attenuated vaccines will be our primary options in the near-term.
- More influenza vaccine manufacturers throughout the world will enter the influenza vaccine marketplace.
- Vaccination schedules will become more detailed— e.g. different vaccines for different age groups and risk groups.

What must we do to prepare for the future?

- Continue strong surveillance programs.
- Continue research, development and comparative trials of novel vaccines.
- Continue research on understanding natural influenza infection and natural and vaccine-induced immunity.
- Countries with vaccination programs should focus on increasing vaccine coverage and should continue to monitor safety and effectiveness of different vaccines in different age groups.