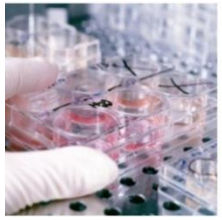
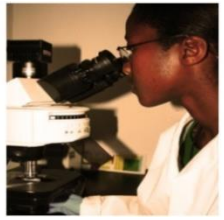
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service


Who is at risk of severe influenza in Africa?

Dr Cheryl Cohen
Centre Head: Epidemiology
Centre for Respiratory Diseases and Meningitis (CRDM)
National Institute for Communicable Diseases, a division of the National Health Laboratory Service
cherylc@nicd.ac.za

Burden of influenza

- Annually globally seasonal influenza
  - 1 billion infections, 3-5 million cases of severe disease, 300,000-500,000 deaths
- In South Africa, annually
  - 17,000-22,000 respiratory hospitalisations
  - 2500-5700 respiratory deaths
- Important to identify risk groups
  - Risk-group based vaccination strategy
  - Need to make decisions who to target with influenza vaccination

Tempia et al CID 2014, Kyelagire, Cohen et al Submitted

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

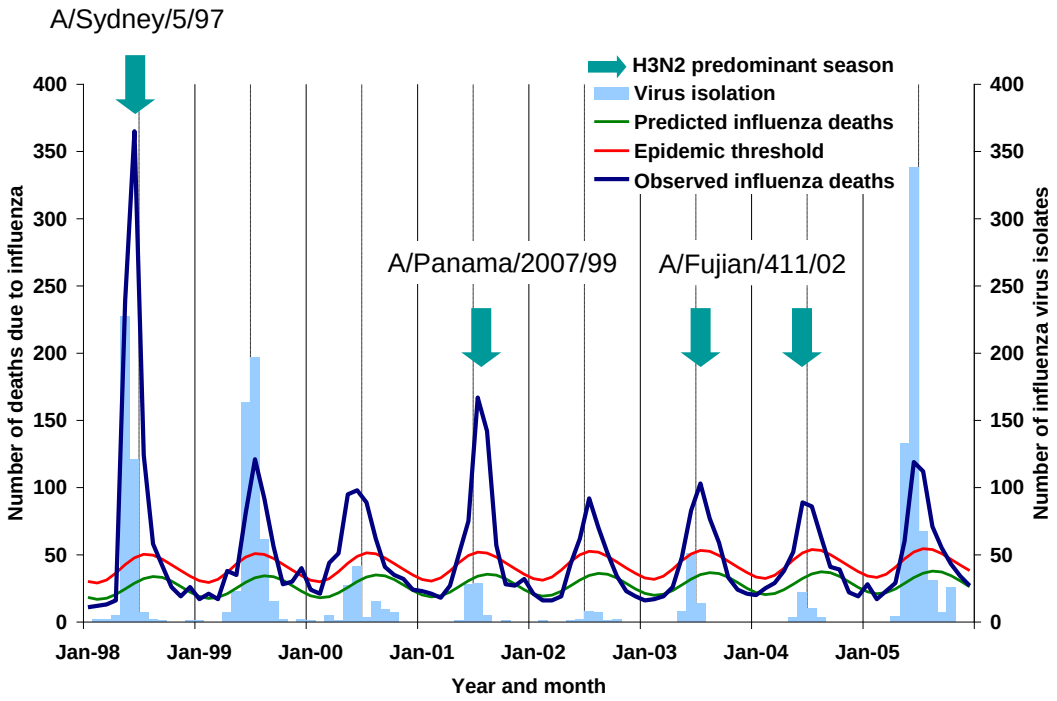
Vaccines against influenza WHO position paper – November 2012

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 programmes targeting any of these additional groups

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

Data on risk groups from sub-Saharan Africa scanty

Excess mortality rates among seniors ≥65 years are higher in South Africa than in US, 1998-2005

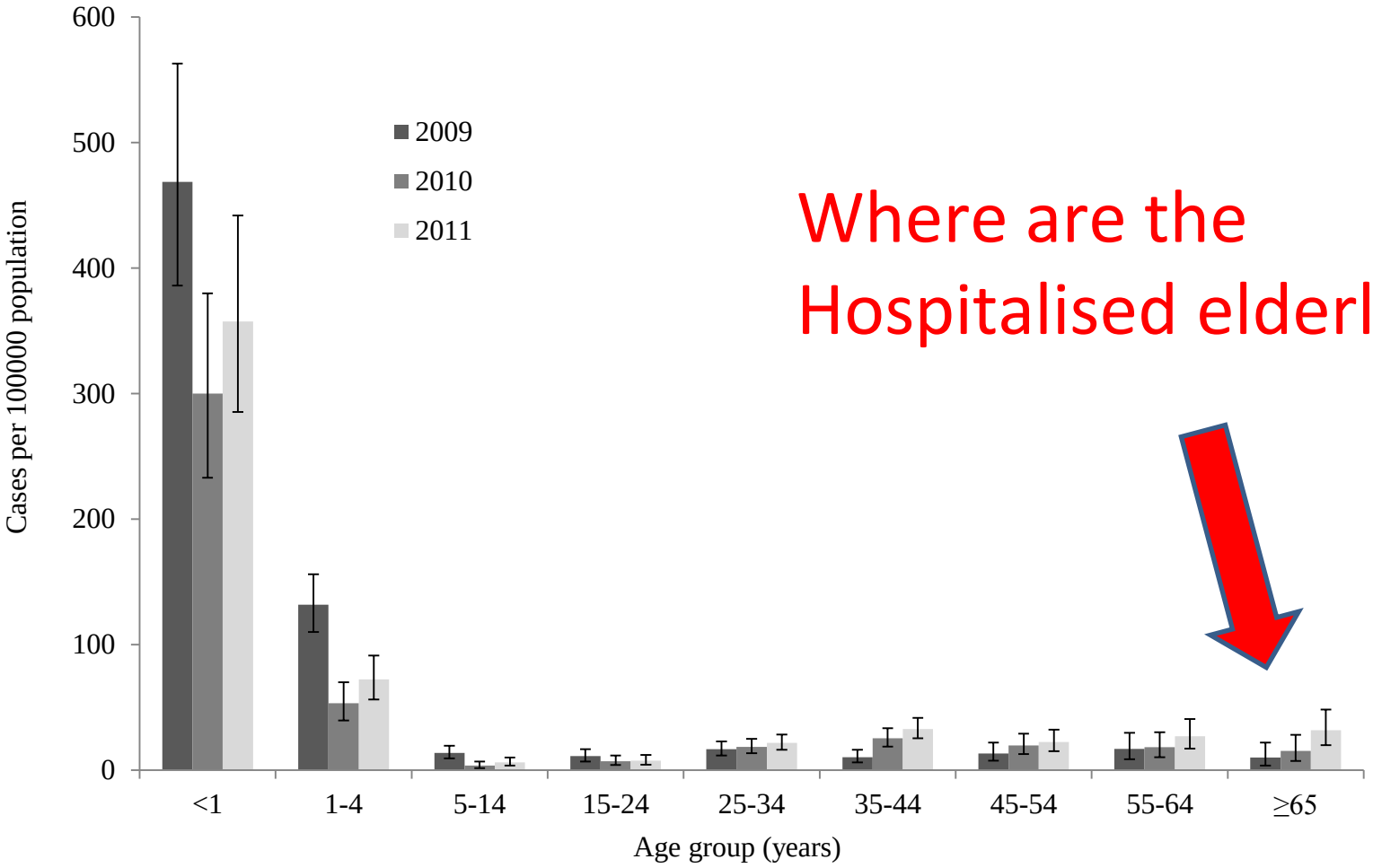


	Crude seasonal excess mortality rates per 100,000			Age-standardized rates
	South Africa	USA	RR (South Africa/USA)	RR (South Africa/USA)
P&I deaths	42	22	1.9	3.0*
Respiratory deaths	87	35	2.5*	3.5*
All cause deaths	387	112	3.5*	4.1*

* P for between-country difference <0.05

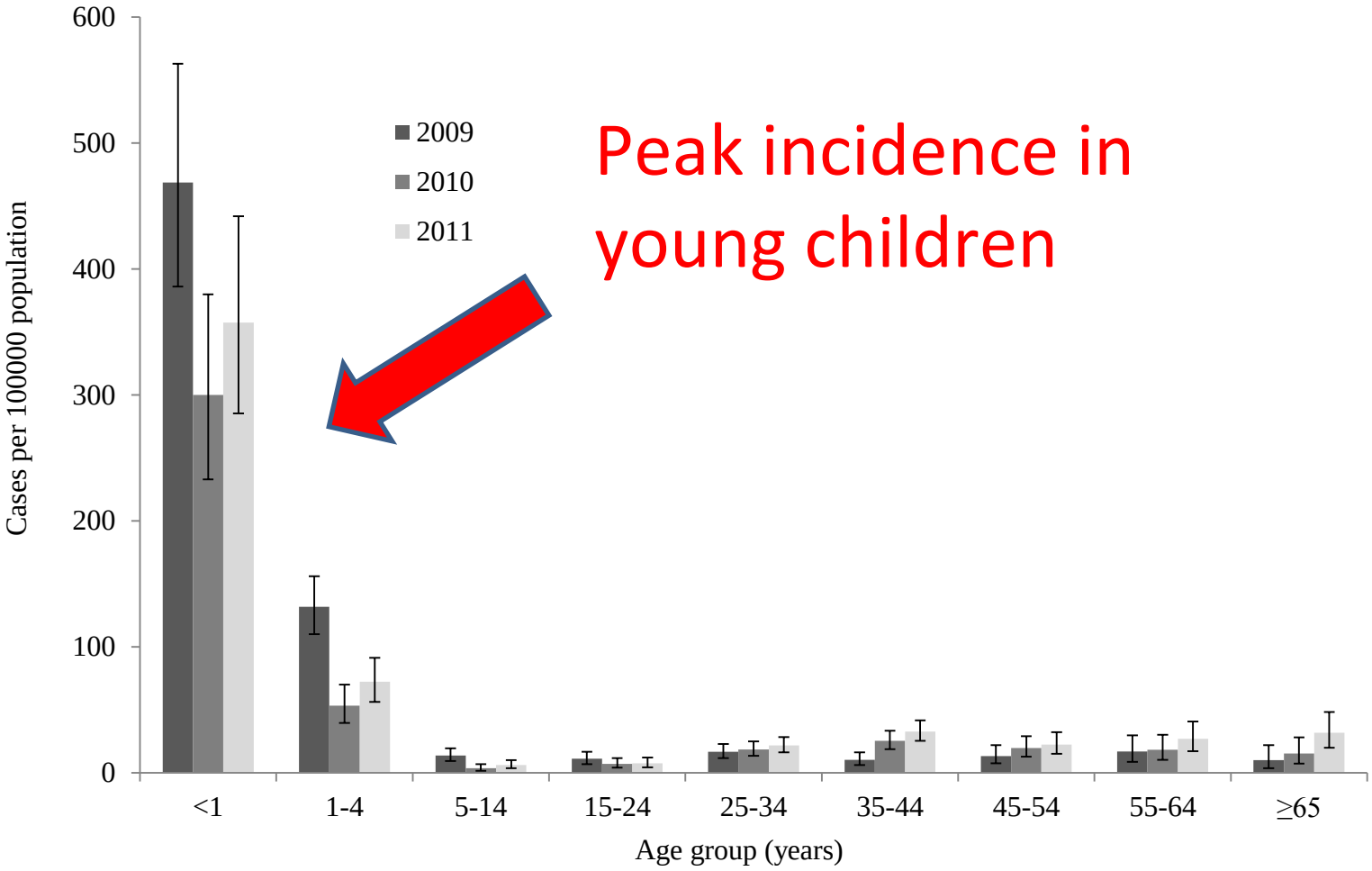
Cohen et al, Clinical Infectious Diseases 2010

Incidence of influenza-associated pneumonia hospitalisation by age group, Soweto, South Africa, 2009-2011



Where are the Hospitalised elderly

Incidence of influenza-associated pneumonia hospitalisation by age group, Soweto, South Africa, 2009-2011



Clinical Infectious Diseases Advance Access published March 12, 2014

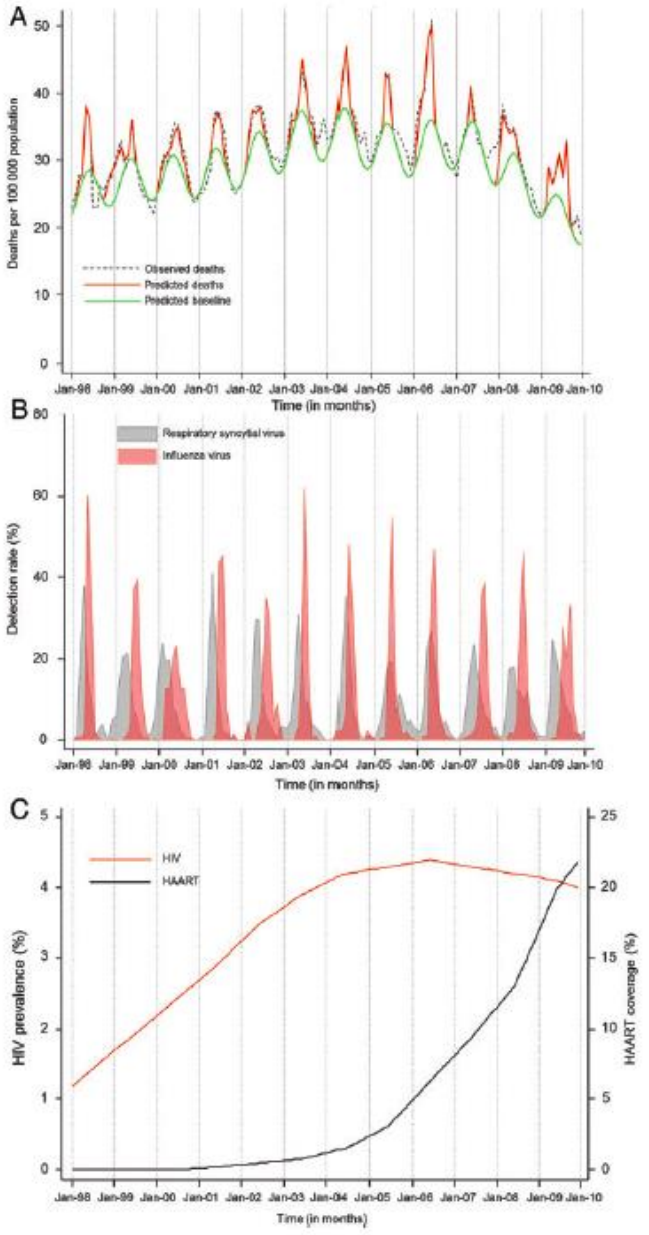
MAJOR ARTICLE

Mortality Associated With Seasonal and Pandemic Influenza and Respiratory Syncytial Virus Among Children <5 Years of Age in a High HIV Prevalence Setting—South Africa, 1998–2009

Stefano Tempia,[1,2,3] Sibongile Walaza,[3] Cecile Viboud,[4] Adam L. Cohen,[1,2] Shabir A. Madhi,[3,5,6] Marietjie Venter,[3,7] Johanna M. McAnerney,[3] and Cheryl Cohen[3,8]

Influenza-associated deaths

Cause of Death	No., Mean (95% CI)	Rate[b], Mean (95% CI)
Seasonal influenza virus		
All respiratory		
<1 y	240 (117–368)	22 (11–34)
1–4 y	212 (110–313)	5 (2–7)
<5 y	452 (227–681)	8 (4–13)



Case fatality ratio (CFR) due to influenza-associated severe ALRI in hospitalised children younger than 5 years

Location (Reference)	Study period	Case fatality ratio (%) for influenza-associated severe-ALRI (n)
Developed countries		
CFR meta-estimate (95% CI)		***0.17 (0.08, 0.26)***
Developing countries		
Paraná State, Brazil[58]	1996-2001	6.67 (3/45)
Soweto, South Africa (Madhi et al.)	1998-2004	5.61 (10/178)
Bohol, Philippines (Lucero et al.)[2][3]	2000-2004	7.5 (3/40)
Kuala Lumpur, Malaysia[59]	2002-2007	2.59 (3/116)
Sa Kaeo and Nakhon Phanom, Thailand (Simmerman et al.)	2005-2008	0.2 (1/430)
Kilifi, Kenya (Berkley et al.)	2007	2.43 (1/41)
Bondo district, Kenya (Ope et al.)	2007-2009	4.48 (3/67)
SARI Sentinel sites, Jordan, Oman, Egypt (Dueger et al.)	2008	2.5 (2/80)
Santa-Rosa, Guatemala (Lindblade et al.)	2008	28.57 (2/7)
Takeo town, Cambodia (Vong et al.)	2008	5 (1/20)
CFR meta-estimate (95% CI)		***2.96 (0.79, 5.13)***

ALRI – Acute lower respiratory infection

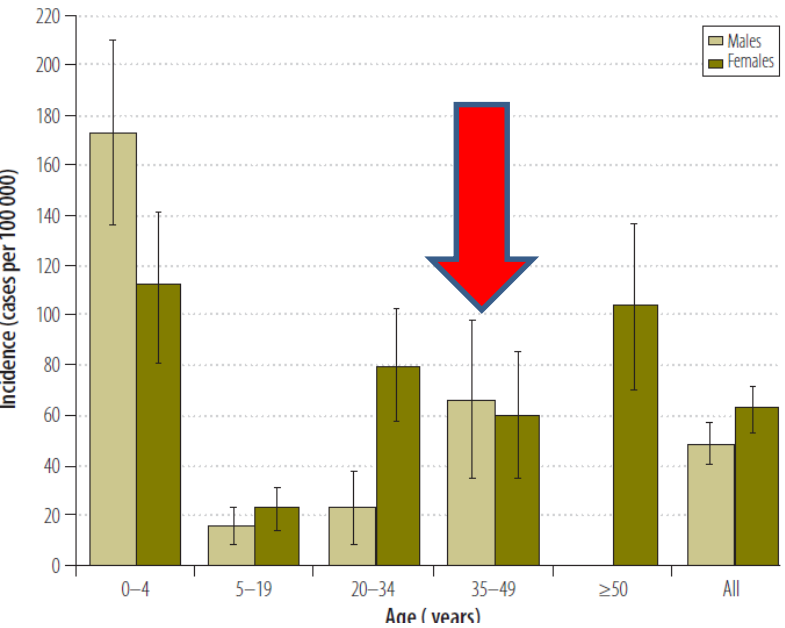
Nair et al., Lancet (2011), Vol. 378

Incidence of influenza and HIV

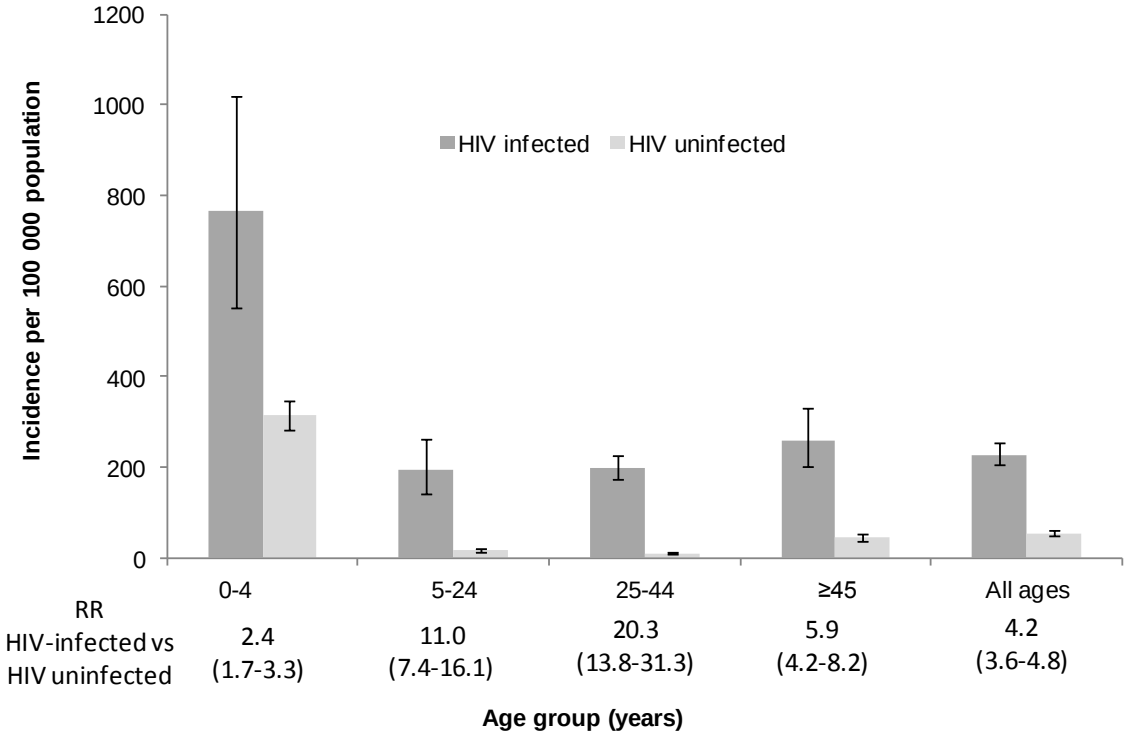
The population-based burden of influenza-associated hospitalization in rural western Kenya, 2007–2009

Daniel R Feikin,[a] Maurice O Ope,[b] Barrack Aura,[a] James A Fuller,[c] Stella Gikunju,[a] John Vulule,[d] Zipporah Ng'ang'a,[e] M Kariuki Njenga,[a] Robert F Breiman[a] & Mark Katz[a]

Fig. 2. **Age- and gender-specific annual influenza-associated hospital admissions (per 100 000 people), Bondo district, Kenya, June 2007–May 2009**



Incidence (per 100 000) of influenza-associated ALRI by HIV infection status, SARI surveillance, South Africa, 2009

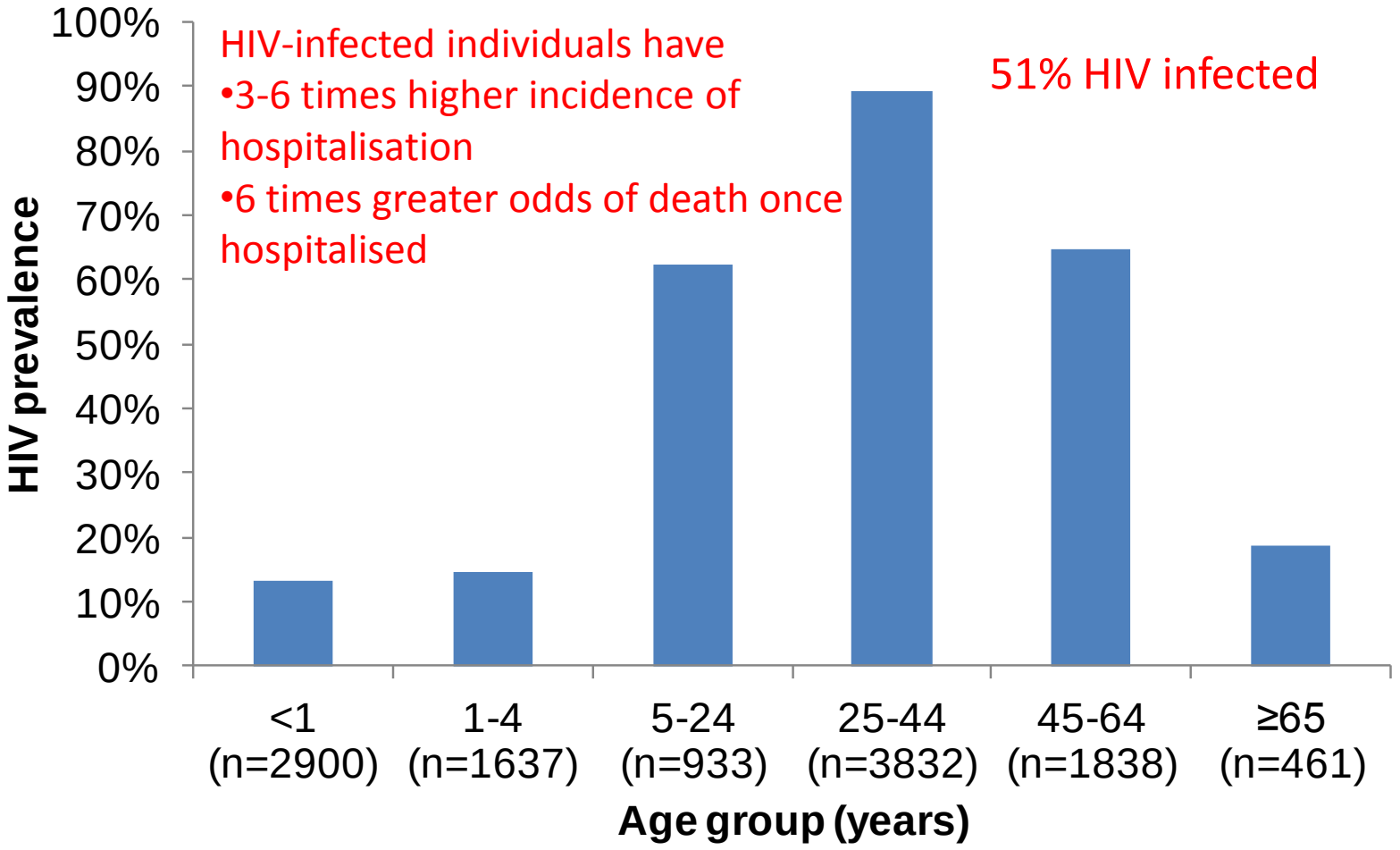


HIV-infected individuals have 6 times greater odds of death once hospitalised

Feikin et al. Bull WHO 2012

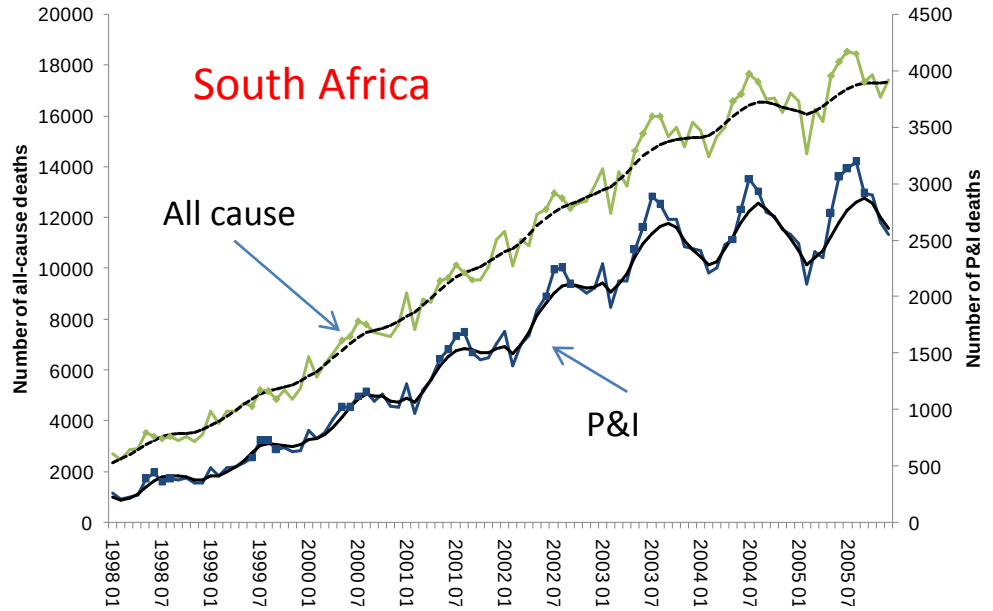
Options for the control of influenza 2010. Cohen et al.

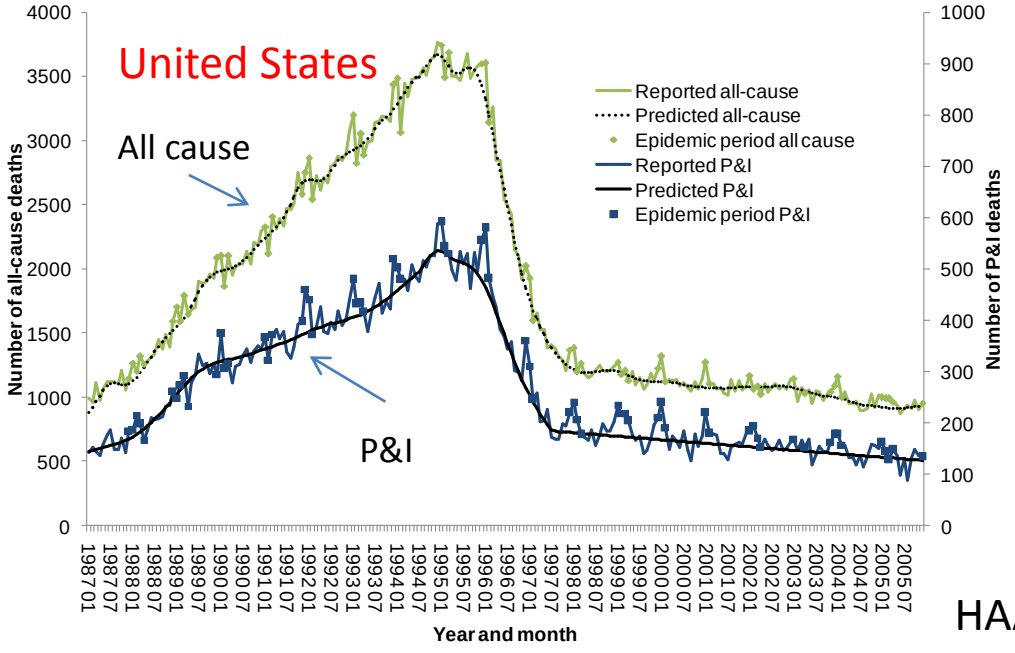
HIV prevalence by age group in patients with influenza-associated acute lower respiratory-tract infection, South Africa, 2009-2011



Cohen et al Emerging Infectious Diseases 2014

Mortality burden of influenza in adults with AIDS





- In South Africa, excess mortality rates in adults (25-54 years) with AIDS
  - Similar to US adults with AIDS pre-HAART (150-200X greater than age peers)
- In the US, excess mortality rates in adults with AIDS
  - Declined 3 to 6 fold post-HAART
  - Post-HAART still elevated (40-70 times) compared to general population

Cohen et al CID 2012

HAART – Highly active antiretroviral therapy

Are HIV exposed uninfected infants at increased risk?

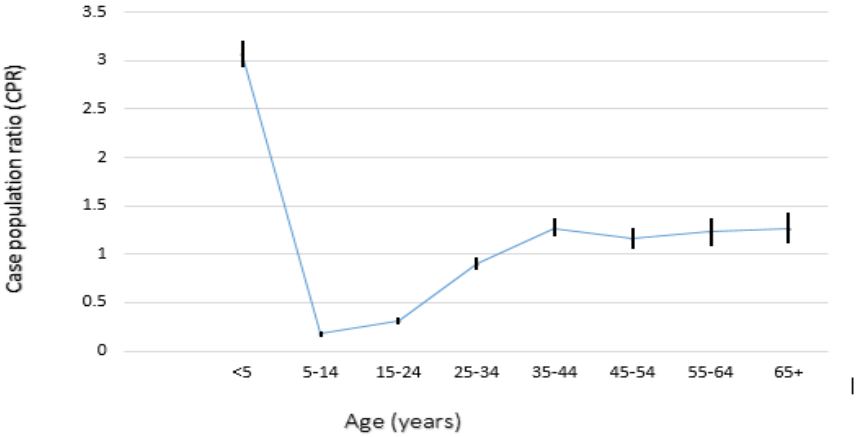
Incidence rates, incident rate ratios and case-fatality ratios among children <6 months of age hospitalised with influenza-associated severe acute respiratory illness (SARI), in Soweto, South Africa, 2010-2011

Organism	Incidence rates per 100 000 population	Incidence rate ratio (IRR)	CFR n/N (%)	OR
HUU	412 (325-515)	Reference	1/64 (2)	Reference
HEU	503 (354-693)	1.2 (0.8-1.8)	2/33 (6)	4.1 (0.4-46.6)
HIV infected	2516 (1300-4394)	**6.1 (3.0-11.3)**	2/10 (20)	**15.8 (1.3-193.9)**

HUU – HIV unexposed uninfected, HEU – HIV exposed uninfected, HI – HIV infected
CI – confidence interval

Evaluation of influenza risk factors in South Africa comparing prevalence among cases to population prevalence

Risk factor	CPR (Age adjusted)
High risk	
History of previous smoking	3.8
HIV infection	3.6
Children <5 years of age	3.09
Asthma	2.45
History of previous admission in the past 12 months	2.07
Moderate risk	
Tuberculosis	1.85
HAART	1.62
Elderly (>65 years)	1.4
Mining	1.32
No risk	
Male sex	0.85
Malnutrition	0.78
Completion of 3rd dose of Pneumococcal Conjugate Vaccine 7	0.74



Relative prevalence of risk conditions among Hospitalised patients with influenza-associated SARI compared to the South African population **CPR – Case population ratio**

		Prevalence in the general population	
		Low <10%	**High >10%**
Case population ratio (CPR)	**Low <2.0**	Elderly 65+ years (5%, 1.27) Non-completion of 3rd dose of PCV 7 (5.8%%) History of mining(3.3%, 1.34) Tuberculosis (11.4%, 1.85)	Males (48.7%, 0.85) Alcohol (27.7%, 0.51) HAART (31%, 1.62)
	High 2.0 +	Previous history of admission in the past 1year (9.1%, 2.07) Previous history of smoking (4%, 3.82) Asthma (4.1%, 2.45)	HIV (12.1%, 3.61) Children <5 years (11%, 3.07)

The strength of association and public health relevance of the various risk conditions identified in this study

Kyegalire R, et al. In preparation

Associations of co-infections and co-morbidities prevalent in Africa with increased severity or incidence of influenza: A systematic review

Co-infection or co-morbidity	Prevalence in Africa	Association with increased severity or incidence of influenza	Quality of evidence of association with influenza	Systematic review included in this analysis
Dengue	Medium	Yes	Limited	Yes
Hemoglobinopathies, namely sickle cell disease	High	Yes	Medium	Yes
HIV	High	Yes	High	No
Malaria	High	Yes	Medium	Yes
Malnutrition	High	Yes, but studies have shown mixed results	Medium	Yes
Measles	Medium	Yes, but studies have shown mixed results	Limited	Yes
Meningococcal disease	High (in some countries)	Yes (as a consequence of influenza infection)	High	Yes
Pneumococcal disease	High	Yes (as a consequence of influenza infection)	High	No
Pneumocystis jirovecii pneumonia (PCP)	High (among HIV infected)	Unknown	Limited	Yes
Tuberculosis	High	Yes	Medium	No
Underlying medical conditions, such as diabetes mellitus and asthma	High	Yes	High	No

Cohen A, et al. Submitted

Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: Epidemiology and factors associated with fatal cases

B N Archer (bretta@nicd.ac.za)[1,2], C Cohen[1,3], D Naidoo[1], J Thomas[1,3], C Makunga[1], L Blumberg[1,4], M Venter[1,5], G A Timothy[3], A Puren[1,4], J M McAnerney[1], A Cengimbo[1], B D Schoub[1,4]

Selected clinical characteristics of pandemic H1N1 influenza-associated deaths, South Africa, 28 April - 12 October 2009 (n=91*)

Factor	Frequency of factor / Number of cases withdata available	%
HIV infection	17 / 32	53
Pregnancy or puerperium	25 / 88	28
Obesity	16 / 73	22
No co-morbidities identified	16 / 76	21
Diabetes	11 / 72	15
Cardiac disease†	9 / 71	13
Active tuberculosis (TB)	7 / 72	10

† Cardiac disease includes: previous stents, mitral stenosis, cardiomyopathy, congestive cardiac failure, previous valvular replacement, recent myocardial infarction, and previous cardiac bypass surgery; excludes hypertension.
* Patients may have had multiple factors.
HIV: human immunodeficiency virus.

Euro Surveillance.2009;14(42):pii=19369. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19369

Numbers of individuals in groups targeted for influenza vaccination in South Africa, 2011

Target group	Number
Children ≤5 years	5 189 528
Adults ≥65 years	2 538 955
All pregnant women	852 831
Pregnant women (HIV-uninfected)	595 276
Pregnant women (HIV-infected)	257 555
HIV-infected (5-64 years, not pregnant)	5 023 017
Tuberculosis and without HIV infection (5-64 years)	138 953
Specific high-risk underlying conditions (5-64 years)	6 643 032
Health care workers	72 000
TOTAL	**20 458 316**

Currently < 1 million doses annually in public sector
Risk-group based vaccination challenging

Population 2011 - 51.7 million

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 (+-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

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

How effective are influenza vaccines in young children?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

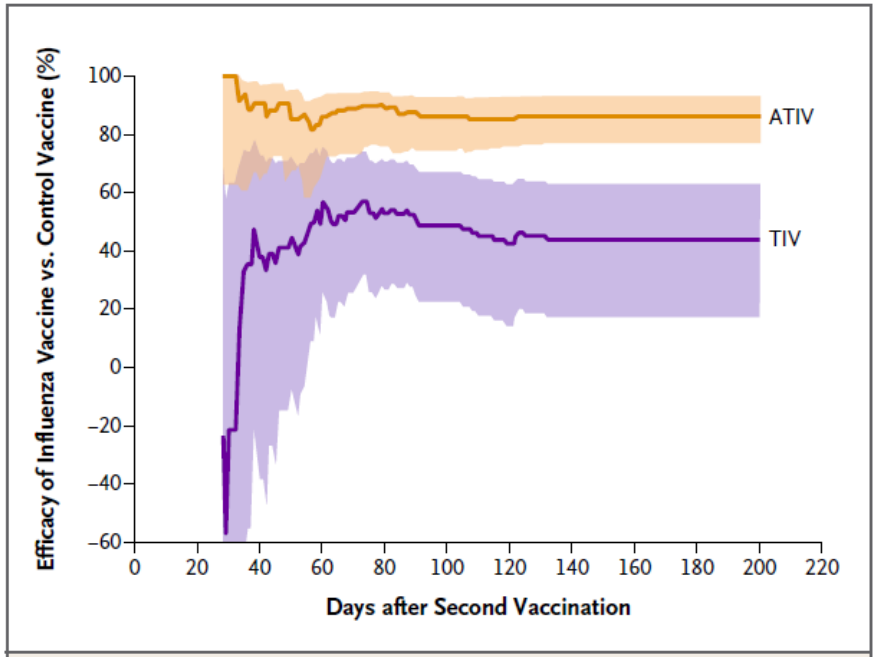


Figure 2. Efficacy of Influenza Vaccines versus Control Vaccine over Time.
The cumulative efficacy of ATIV and of TIV, as compared with control (non-

- VE of TIV in children reduced
- VE 86% adjuvanted
- VE 43% without adjuvant
- Adjuvant slightly more reactogenic in older ages
- Adjuvanted vaccines mre costly and limited availability in Africa

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.

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]

Table 2. Vaccine Effi … V-Infected Adults on Stable Antiretroviral Tr…

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.

Clinical Infectious Diseases 2011;52(1):128-137

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.

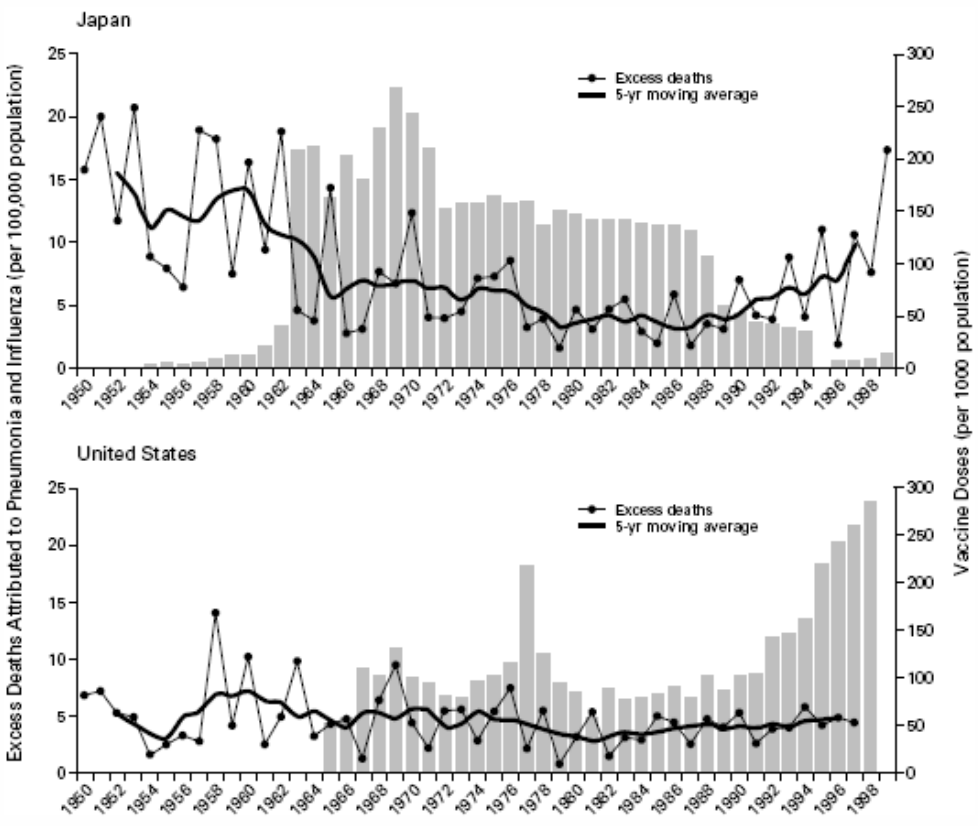


Figure 4. Excess Deaths Attributed to Pneumonia and Influenza over a 50-Year Period in Japan and the United States. The five-year moving average is also shown. The history of the rates of use of vaccine in each country is superimposed (shaded bars). Tick marks represent the beginning of the years indicated.

IDSA

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

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.

Conclusions

- Risk groups in Africa similar to elsewhere
- Some risk groups e.g. HIV much more important
- Data lacking on some key risk groups
- Need for more effective influenza vaccine
- Challenges for risk-group based vaccination
- Indirect protection may be useful in some settings