Global impact of Influenza

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CDC

Global Burden of Respiratory Disease

World	Deaths in millions	% of deaths
Ischaemic heart disease	7.25	12.8%
Stroke and other cerebrovascular disease	6.15	10.8%
Lower respiratory infections	3.46	6.1%
Chronic obstructive pulmonary disease	3.28	5.8%
Diarrhoeal diseases	2.46	4.3%
HIV/AIDS	1.78	3.1%
Trachea, bronchus, lung cancers	1.39	2.4%
Tuberculosis	1.34	2.4%
Diabetes mellitus	1.26	2.2%
Road traffic accidents	1.21	2.1%

High-income countries	Deaths in millions	% of deaths
Ischaemic heart disease	1.42	15.6%
Stroke and other cerebrovascular disease	0.79	8.7%
Trachea, bronchus, lung cancers	0.54	5.9%
Alzheimer and other dementias	0.37	4.1%
Lower respiratory infections	0.35	3.8%
Chronic obstructive pulmonary disease	0.32	3.5%
Colon and rectum cancers	0.30	3.3%
Diabetes mellitus	0.24	2.6%
Hypertensive heart disease	0.21	2.3%
Breast cancer	0.17	1.9%

Low-income countries	Deaths in millions	% of deaths
Lower respiratory infections	1.05	11.3%
Diarrhoeal diseases	0.76	8.2%
HIV/AIDS	0.72	7.8%
Ischaemic heart disease	0.57	6.1%
Malaria	0.48	5.2%
Stroke and other cerebrovascular disease	0.45	4.9%
Tuberculosis	0.40	4.3%
Prematurity and low birth weight	0.30	3.2%
Birth asphyxia and birth trauma	0.27	2.9%
Neonatal infections	0.24	2.6%

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Public health impact of influenza in United States

- **3349-48,614 deaths per year (mean 23,607)***
- **90% of deaths are in persons >65 years many with chronic, underlying conditions**
- **~75% of deaths are not coded pneumonia or influenza**
- **H3N2 predominant years cause 2.7 times as many deaths**

- **200,000 hospitalizations per year****
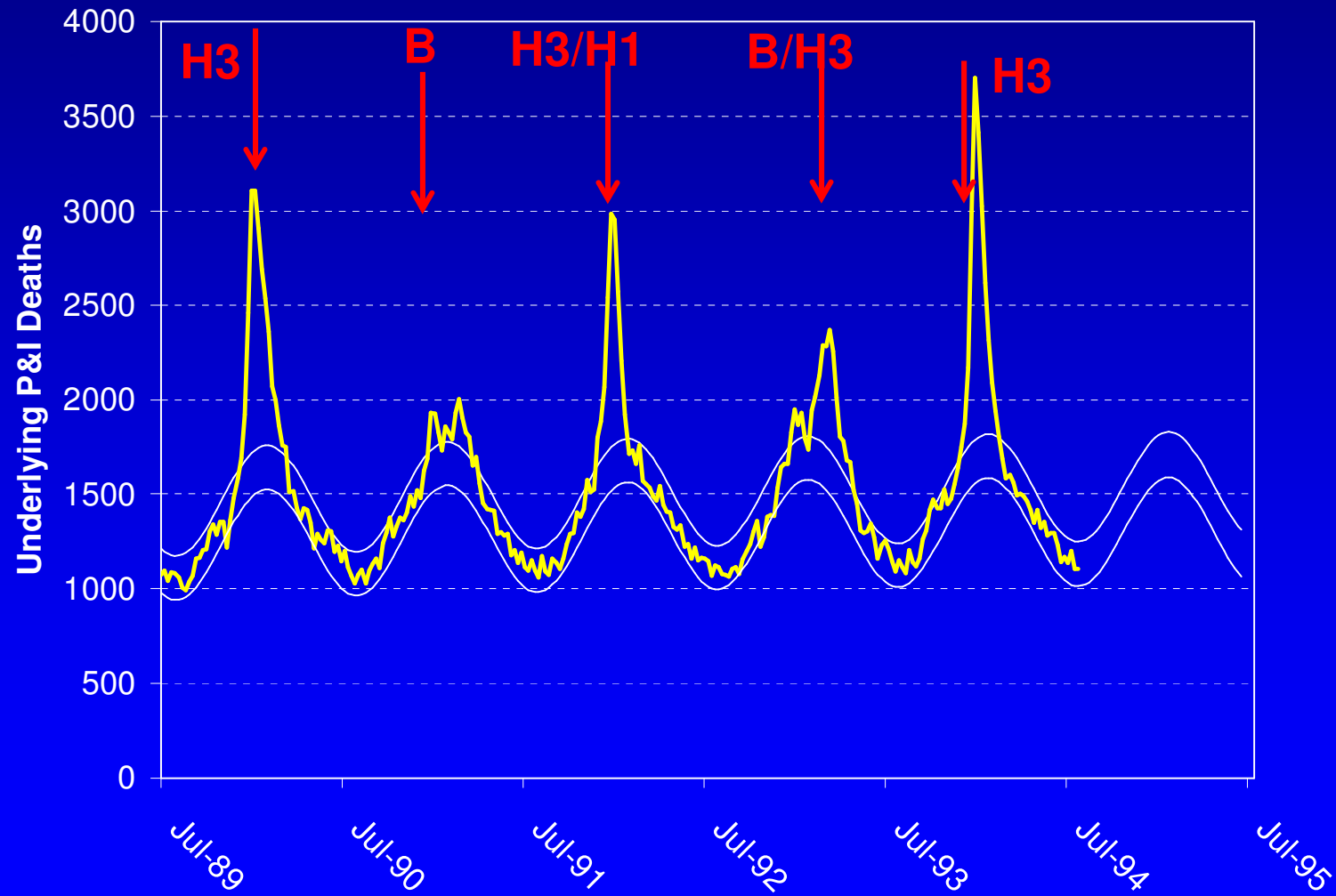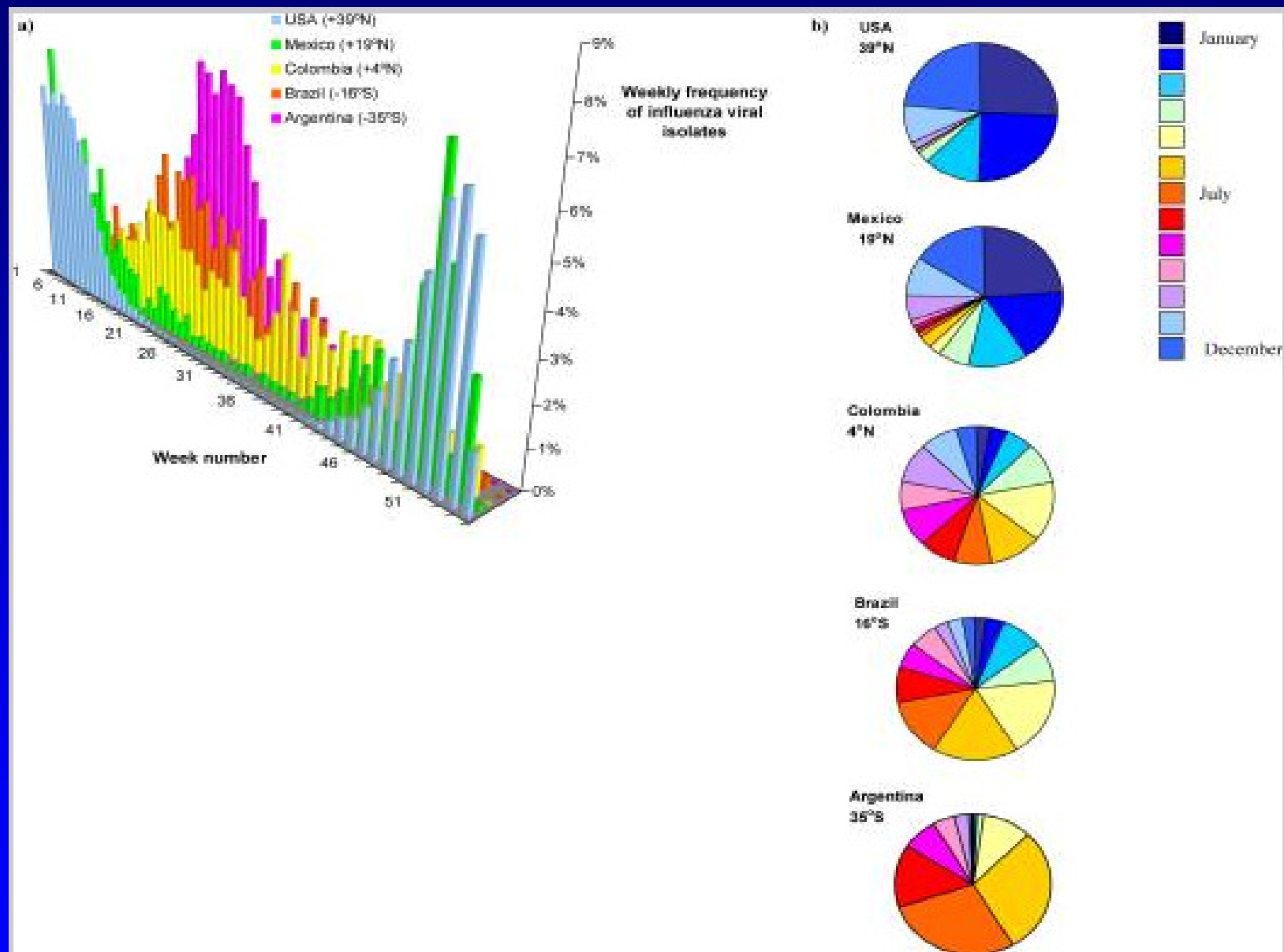- **Hospitalization rates highest in children**

CDC

Serfling Linear Regression Model

Viboud et al PLoS Med, 2006

Disease burden globally

Percentage of respiratory specimens that tested positive for influenza
By influenza transmission zone

Status as of week 03
15 – 21 January 2012
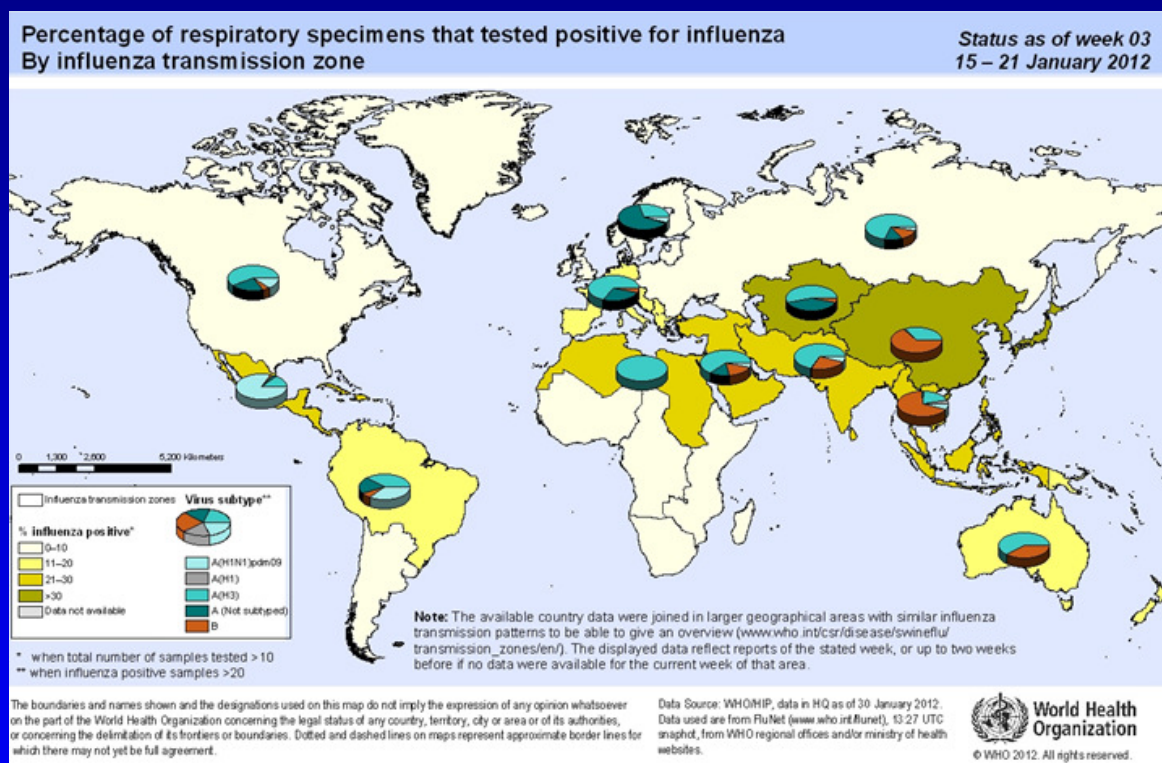
- **250-500,000 deaths* per year?**
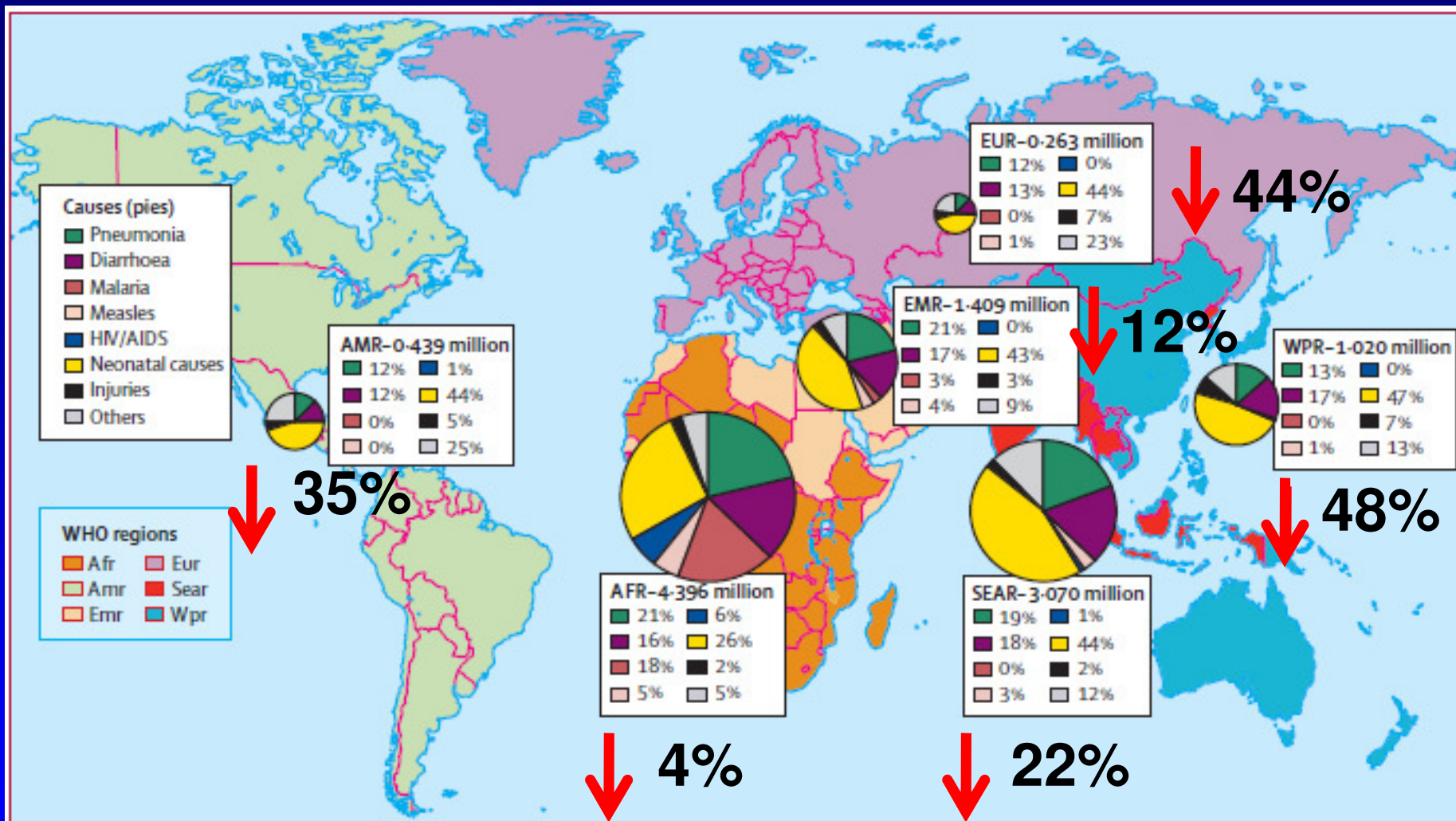- **3-5 million severe cases** per year?**

Figure 3: Number of deaths in children younger than age 5 years and their distribution by cause for the six WHO regions (yearly average for 2000–03)
Size of circle represents number of deaths in region. Afr=Africa. Amr=Americas. Emr=Eastern Mediterranean. Eur=Europe. Sear=Southeast Asia. Wpr=Western Pacific.

J Bryce et al: Lancet 2005;365:1147-52
Black et al Lancet 2010; June 2010

What might be different around the world?

- **Age structures different**

- **Low health care access and provision**

- **Malnutrition**

- **Interaction with bacterial infection**

- **Prevalence of comorbidities often unknown**
    - **E.g. Underlying asthma may be lower**
        - **TB and respiratory co-infections higher**

- **Co-morbidities different, often inadequately treated**
    - **E.g. Dengue**
        - **HIV infection with low CD4 counts**
        - **Untreated chronic obstructive pulmonary disease (COPD)**

CDC

Possible risk factors

- **HIV**

    Ope et al. PLoS One, 2011, 6(5)

    Risk factors for Hospitalized Seasonal Influenza in Rural Western Kenya

    - Odds of HIV seropositivity among adults hospitalized for influenza-associated respiratory disease compared to among community matched controls: 3.56 (95%CI =1.26-10.07)

- **Refugee populations**

    Ahmed et al BMC Infect Dis 2012 12(1)

    Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007-2010

    - **Rate of influenza-associated SARI**

        4.8 / 1000 in <5 year olds

        11.1 /1000 in <1 year olds

Interaction with *Streptococcus pneumoniae*

Table 1 Percentage efficacy of pneumococcal conjugate vaccine by per protocol analysis in fully immunized infants

Clinical diagnosis	All children[e]				HIV-uninfected children[f]				HIV-infected children[f]			
	Vaccine n = 18,245	Placebo n = 18,268	Efficacy (95% CI)	P value	Vaccine n = 17,065	Placebo n = 17,086	Efficacy (95% CI)	P value	Vaccine n = 1,180	Placebo n = 1,182	Efficacy (95% CI)	P value
Total number of pneumonia cases[a]	544	679	20 (10, 28)	0.00009	348	452	23 (11, 33)	0.0002	181	210	14 (−4, 28)	0.1
Pneumonia with alveolar consolidation[b]	251	303	17 (2, 30)	0.03	119	158	25 (4, 40)	0.02	128	140	8 (−15, 27)	0.5
Pneumonia without identified virus[c]	419	486	14 (2, 24)	0.03	252	299	16 (0, 29)	0.05	167	187	11 (−8, 26)	0.3
Any identified virus-associated pneumonia[d]	160	231	31 (15, 43)	0.0004	111	167	33 (15, 48)	0.0008	44	57	0.2 (−14, 47)	23
Influenza A	31	56	45 (14, 64)	0.01	21	32	34 (−14, 62)	0.1	9	21	57 (7, 80)	0.03
RSV	90	115	22 (−3, 41)	0.08	64	94	32 (6, 50)	0.02	22	17	−30 (−143, 31)	0.4
PIV types 1–3	24	43	44 (8, 66)	0.02	16	27	41 (−10, 68)	0.09	8	16	50 (−17, 78)	0.1
Adenovirus	14	15	7 (−94, 55)	0.9	9	13	31 (−62, 70)	0.4	5	2	−150 (−1,188, 51)	0.3

[a]First episodes are shown; thus, a child with episodes of pneumonia associated both with and without a virus are counted in that category for each first episode, but only once in the total number of pneumonia cases. [b]Alveolar consolidation (WHO-AC)[5]. [c]Includes episodes of pneumonia that tested negative for all of the respiratory viruses examined. [d]Includes the first episode of any identified virus-associated pneumonia including influenza B. [e]Includes children whose HIV status was unknown. [f]Although the number of children receiving vaccine or placebo are known, the denominators of HIV-infected and HIV-uninfected children are estimated as 6.47% and 93.53%, respectively (see **Supplementary Methods** online for the basis of this estimate).

Madhi S and Klugman K et al, Nat Med, 2004

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Increased pandemic mortality worldwide among indigenous groups

Country or area Pandemic H1N1 influenza data sources	Deaths				
	Number (%) [1]		Rates (per 100,000)		
	Indigenous	Non-indigenous	Indigenous (c)	Non-indigenous (d)	Rate ratios (c/d)
Americas					
Canada [4]					
First Nations, Inuit and Métis	9 (11.50)	69 (88.50)	0.78	0.23	3.4
Arizona (United States) [5]					
American Indians	4 (18.18)	18 (81.82)	1.3	0.3	4.3
Brazil [2] [6,7]					
Amerindians	NA	NA	NA	NA	NA
Pacific					
Australia [8]					
Aborigines and Torres Straits Islanders	21 (11.48)	162 (88.52)	4.1	0.8	5.1
New Zealand [9]					
Māori	NA	NA	NA	NA	NA
Pacific peoples	NA	NA	NA	NA	NA
New Caledonia [10]					
Indigenous Oceanians [3]	7	1	4.93	0.93	5.3

Laruche et al Eurosurveillance 2009

Increased risk of mortality among indigenous populations in New Zealand in three pandemics
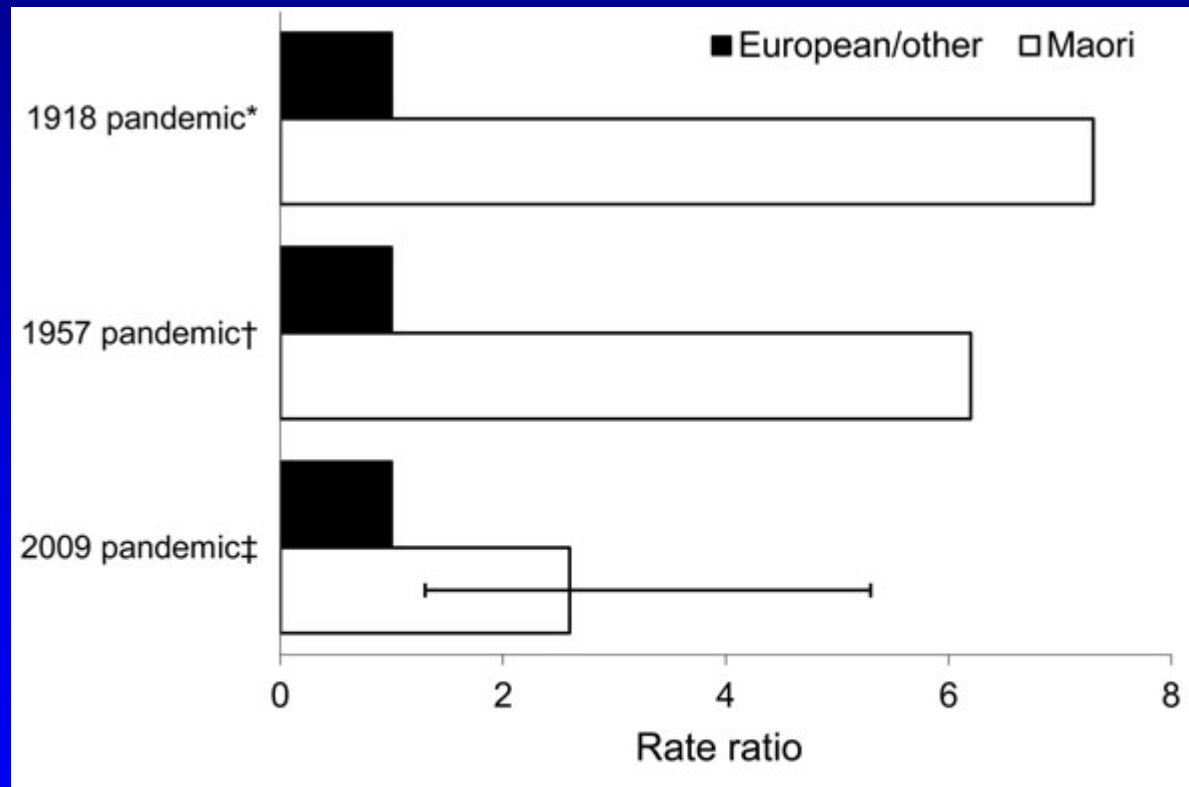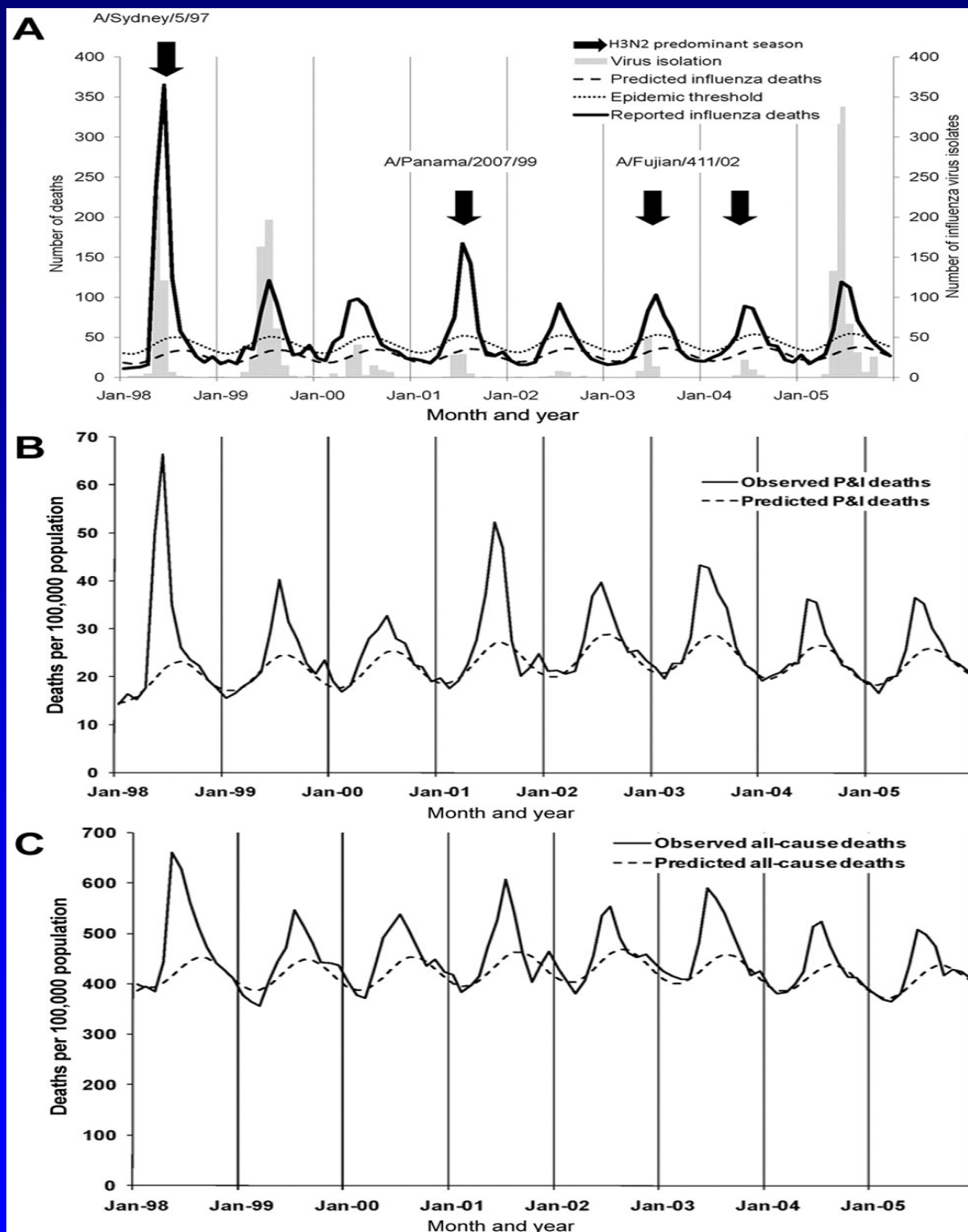

Figure 2. Mortality rate ratios (age-standardized on the basis of 2009 data) for Māori versus European/other New Zealanders (non-Māori/non-Pacific) during 3 influenza pandemics in New Zealand. *Data from (6); †official mortality rate data; ‡age-standardized to the Māori population. Error bar represents 95% CI.

Wilson et al EIDJ, 2012

Elevated Influenza-Related Excess Mortality in South African Elderly Individuals, 1998–2005
Cheryl Cohen,et al, CID, 2010

Comparing South Africa and United States influenza-associated mortality in the elderly

Table 3. Comparison of Mean Seasonal Estimates of Influenza-Related Excess Mortality in Individuals Aged ⩾65 Years in South Africa (SA) for 1998–2005 and in the United States (US) for the 1997/1998 to 2004/2005 Seasons

Cause of death	Crude deaths per 100,000 population			Age-standardized deaths per 100,000 population[a]			Percentage excess deaths over summer baseline[b]			Percentage excess deaths over baseline winter deaths[c]		
	SA	US	P[d]	SA	US	P[d]	SA	US	P[e]	SA	US	P[e]
All causes	340 ± 143	112 ± 62	<.001	545 ± 190	133 ± 79	.01	19 ± 9	8 ± 4	<.001	16 ± 6	6 ± 3	<.001
All respiratory causes	87 ± 45	35 ± 21	.008	124 ± 62	35 ± 21	.02	38 ± 23	26 ± 13	<.001	25 ± 11	14 ± 8	<.001
Pneumonia and influenza	42 ± 21	22 ± 13	.08	63 ± 35	21 ± 13	.03	50 ± 36	44 ± 25	<.001	29 ± 14	20 ± 11	<.001
Cerebrovascular disease	40 ± 14	7 ± 5	<.001	54 ± 20	7 ± 5	<.001	18 ± 5	6 ± 4	<.001	16 ± 4	4 ± 3	<.001
Diabetes	20 ± 5	3 ± 2	<.001	25 ± 6	3 ± 2	<.001	14 ± 3	8 ± 3	<.001	13 ± 3	5 ± 3	<.001
Ischemic heart disease	12 ± 4	25 ± 20	.036	15 ± 6	24 ± 20	.40	10 ± 4	8 ± 6	<.001	9 ± 3	6 ± 4	<.001
Cancer	3 ± 4	7 ± 4	.221	6 ± 5	7 ± 4	.83	1 ± 2	2 ± 1	<.001	1 ± 2	2 ± 1	<.001

NOTE. Data are rate per 100,000 population or percentage ± standard deviation of annual estimates.

[a] Standardized to the US population in 2000.
[b] Percentage increase over the summer baseline equals the ratio of excess death rates during epidemic months divided by baseline expected death rates during summer. Summer is defined as January, February, November, and December in South Africa and May–August in the United States.
[c] Percentage increase over the winter baseline equals the ratio of excess death rates during epidemic months divided by baseline expected death rates during the same months, as prediced by the seasonal model.
[d] Negative binomial regression.
[e] Logistic regression.

Elevated Influenza-Related Excess Mortality in South African Elderly Individuals, 1998–2005
Cheryl Cohen et al, CID, 2010

Comparing rates of influenza-related all-cause mortality in different settings (per 100,000 person-years)

Country	>65 years	All Ages	Reference
United States	133	20	Thompson et al*
Hong Kong	136	16	Wong et al†
Singapore	168	15	Chow et al‡
Australia	116	Not done	Newall AT ‖
South Africa	**545**	Not done	Cohen et al§

* Thompson et al JAMA 2003
† Wong et al Clin Infect Dis 2004
‡ Chow et al Emerg Inf Dis 2006
‖ Newall et al Epidem Infect 2008
§ Cohen et al Clin Infect Dis 2011

Estimate of global influenza burden among children <5 years of age

➤ **ALRI**
  – **Incidence (active surv) in developing countries = 35/1000/y**
  – **Incidence (passive surv) in industrialised countries = 12/1000/y**
  – **Possible 3-fold increase risk in low-resource setting**

➤ **Severe ALRI**

  – **Incidence in developing countries = 1.65 /1000/y**
  – **Incidence in industrialised countries = 1.18/1000/y**
  – **1.4 times increased risk in low-resource setting**

➤ **By age**
  – **<2 year old at higher risk (1-2 fold) than 2-4 year olds**

Nair et al. Lancet 2011

CDC

Estimate of global influenza burden among children <5 years of age

➢ **Global number of ALRI= 20 million episodes**

    – **13% of all childhood ALRI***

    – **Pneumococcus-associated ALRI = 14 million****

    – **Hib-associated ALRI = 8 million[†]**

    – **RSV (using similar methods) = 34 million[‡]**

➢ **Global number of severe ALRI = 1 million episodes**

    – **7% of all childhood severe ALRI**

*Rudan I et al Bull WHO 2008
**O'Brien K et al Lancet 2009
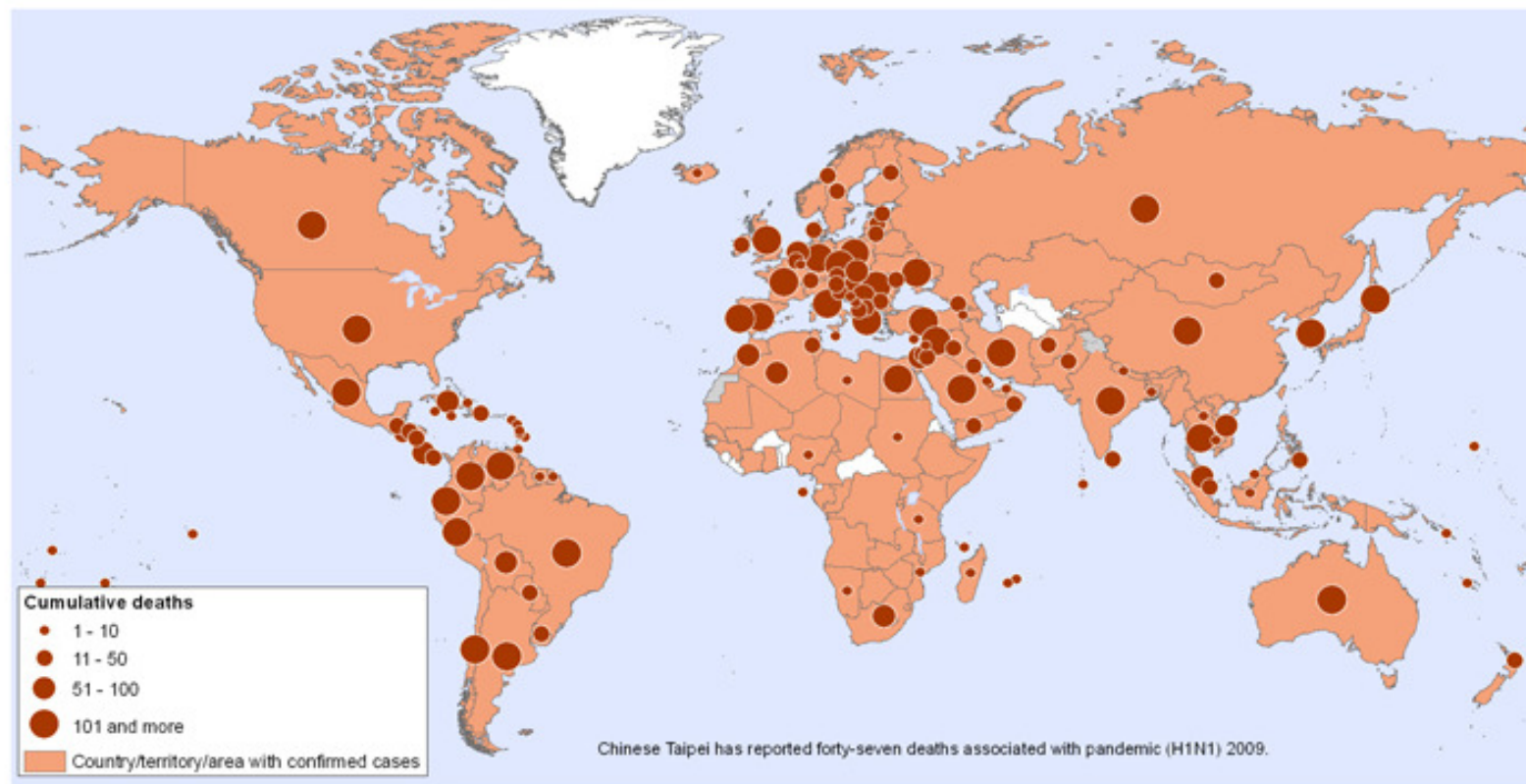**† Watt J et al Lancet 2009**
‡ Nair H et al Lancet 2010

CDC

Development of Respiratory Mortality Multiplier (RMM)

Median LRTI Mortality Rate Ratio*

WHO Mortality Stratum†

Legend:
- ◆ Africa
- ■ Americas
- ▲ Mediterranean
- ✕ Europe
- ✳ Southeast Asia
- ● Western Pacific

X-axis categories:
- Low Adult and Child Mortality
- Low Child and High Adult Mortality
- High Adult and Child Mortality
- High Child and Very High Adult Mortality
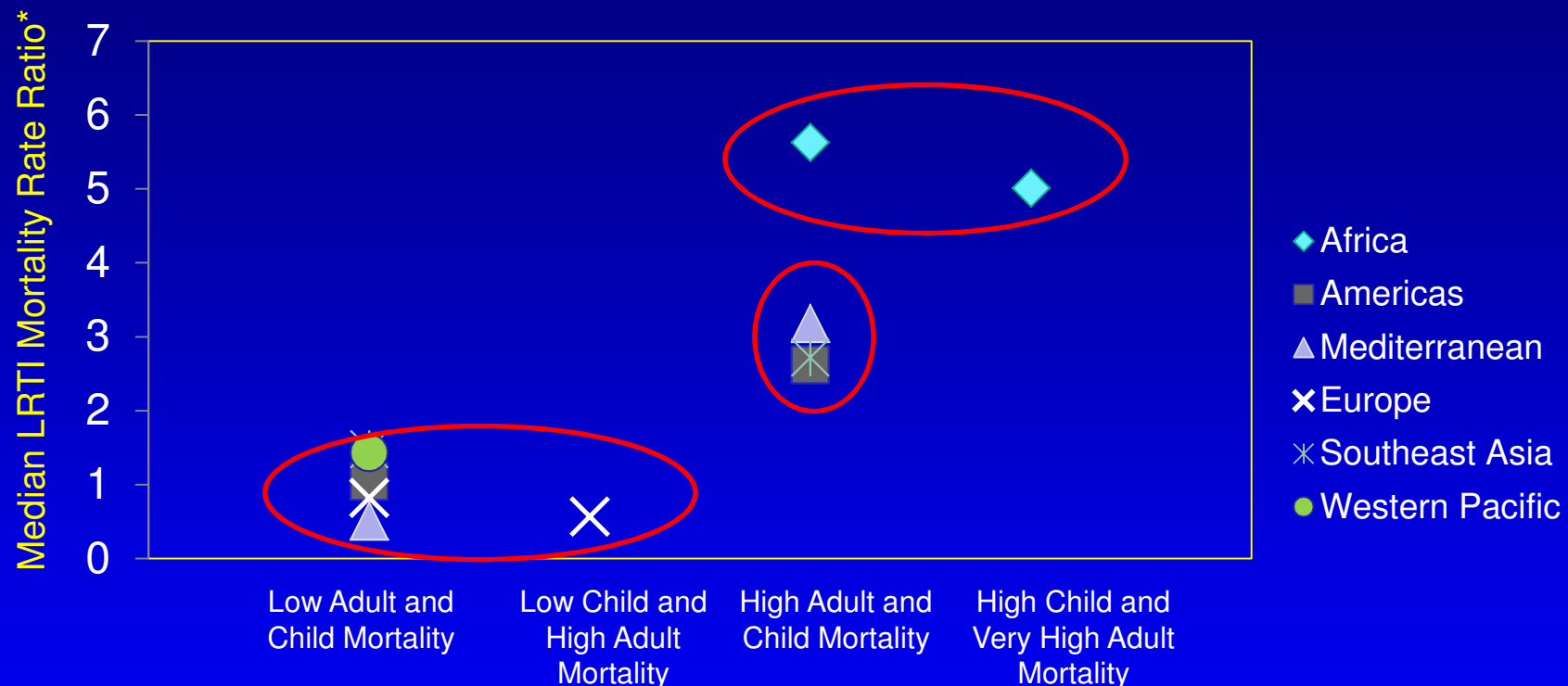
*LRTI mortality rate ratio calculated by comparing the LRTI mortality rate in each country with the median LRTI mortality rate of countries with very low child and adult mortality

†World Health Organization. List of Member States by WHO Region and Mortality Stratum (Available at: http://www.who.int/whr/2004/annex/topic/en/annex_member_en.pdf).

Dawood et al Lancet submitted

Global 2009 H1N1-Associated Respiratory Deaths by Age and WHO Region

WHO Region	All Ages		0-17 years		18-64 years		>64 years	
	n	(IQ Range)	n	(IQ Range)	n	(IQ Range)	n	(IQ Range)
Africa	66,300	(32,600-161,500)	25,800	(11,000-68,200)	36,000	(19,300-63,000)	4,500	(2,300-12,300)
America	18,700	(9,800-42,700)	4,200	(1,800-20,900)	11,500	(6,300-20,000)	3,000	(1,700-8,600)
Eastern Mediterranean	20,000	(9,600-95,100)	6,500	(2,600-22,700)	11,800	(6,200-19,000)	1,700	(800-51,700)
Europe	17,200	(9,100-38,600)	2,500	(1,000-18,800)	10,400	(5,800-19,000)	4,300	(2,300-12,100)
Southeast Asia	65,200	(31,400-153,500)	17,900	(7,100-78,600)	40,600	(21,000-64,000)	6,700	(3,300-17,900)
Western Pacific	33,000	(17,500-72,700)	6,000	(2,600-38,800)	21,600	(11,900-39,000)	5,400	(3,000-15,300)
Global	220,400	(110,000-564,100)	62,900	(26,100-248,000)	131,900	(70,500-224,000)	25,600	(13,400-117,900)

30%

30%

1

WHO August 2005

"Based on data from industrialized countries, and listed in order of priority"

1. Residents of institutions for elderly people and the disabled.

2. Elderly, non-institutionalized individuals with chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies.

3. All individuals >6 months of age with any of the conditions listed above.

4. Elderly individuals above a nationally defined age limit, irrespective of other risk factors.

5. Other groups defined on the basis of national data and capacities, such as contacts of high-risk people, pregnant women, health-care workers and others with key functions in society, as well as children 6–23 months.

CDC

Different vaccine strategies
Maternal Immunization
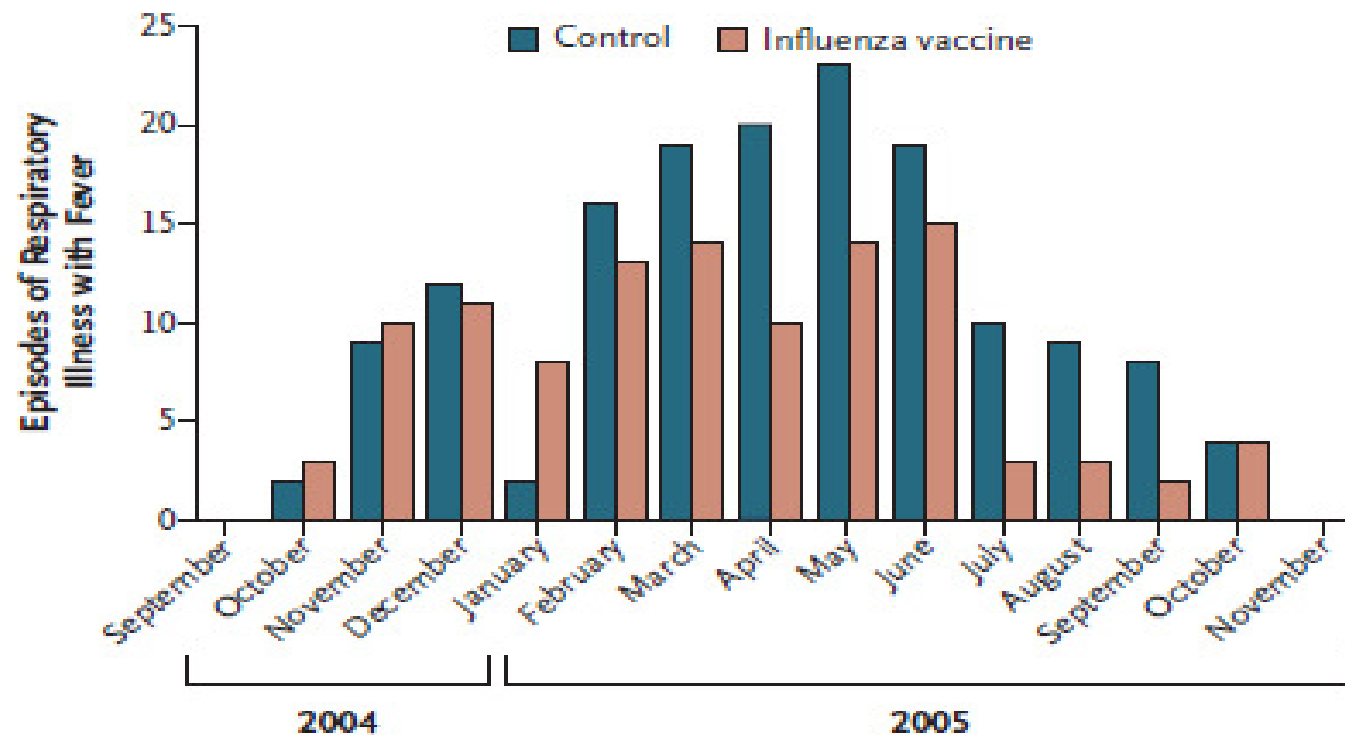
VE=29% (all febrile respiratory illness
VE=62% (Influenza +ve cases

Figure 3. Episodes of Respiratory Illness with Fever in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.
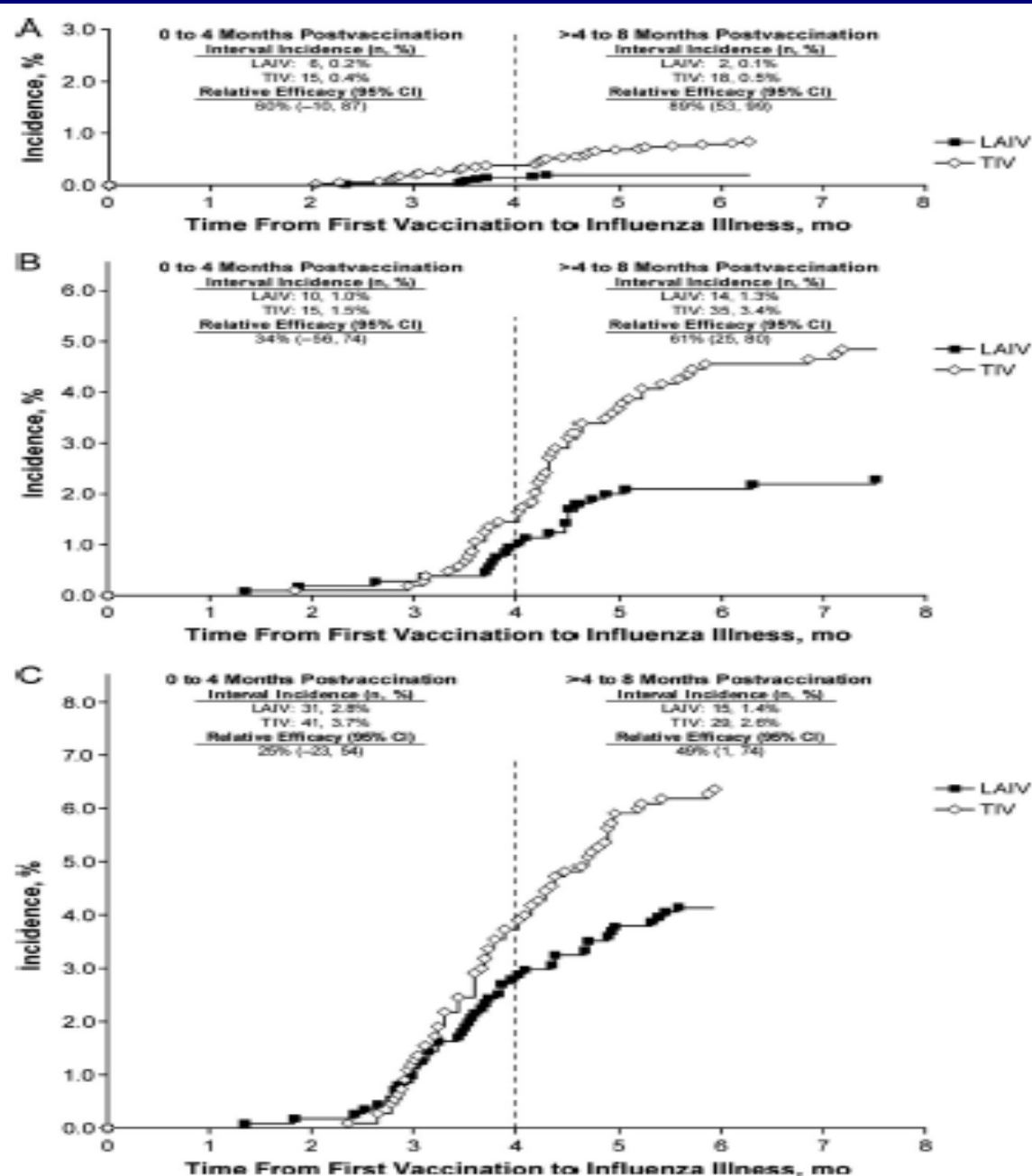Data were recorded from September 2004 to November 2005 for all ages in each vaccine group.

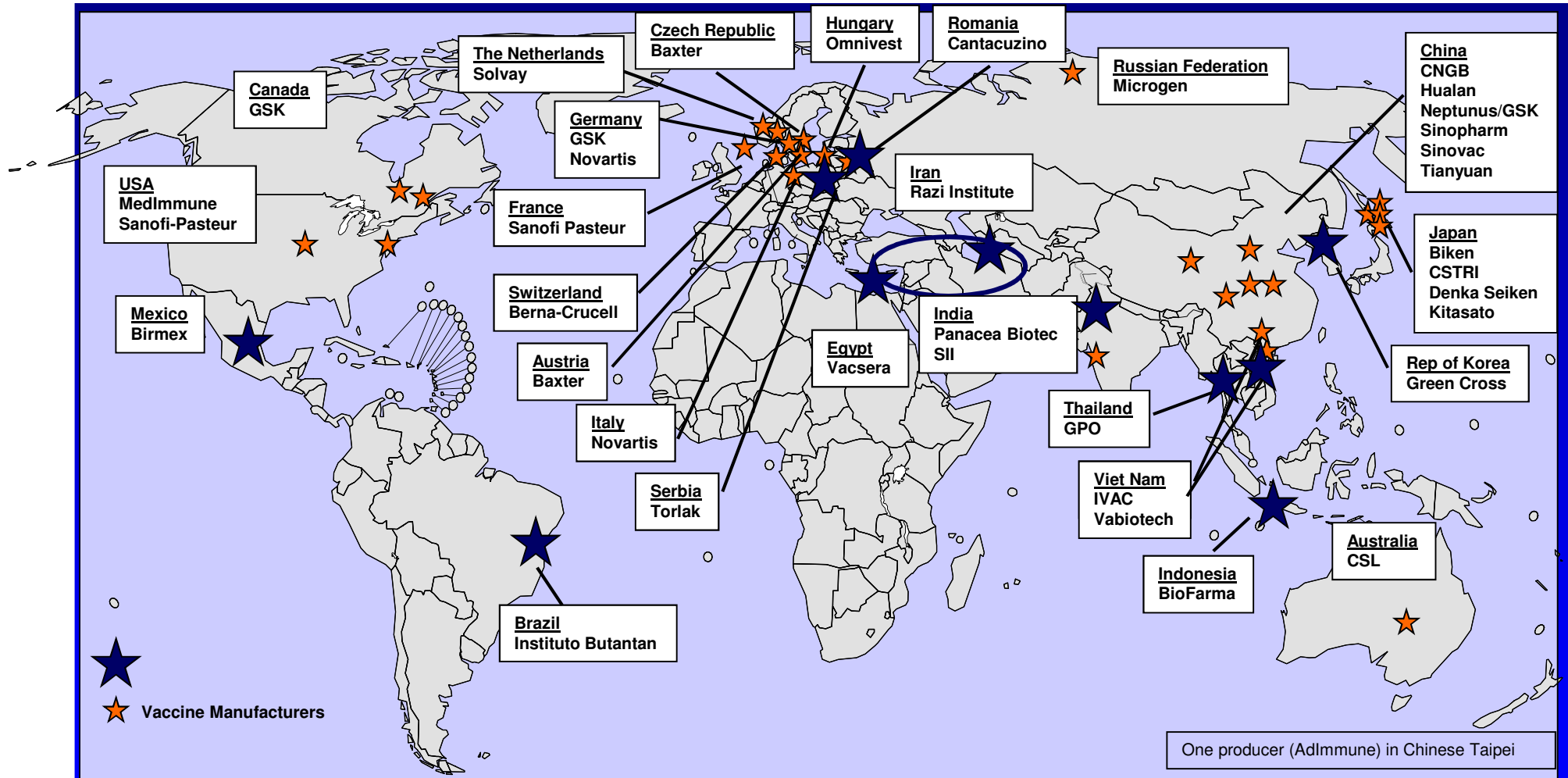Zaman et al, NEJM, 2008

65% vs 89%

34% vs 61%

25% vs 46%

**Ambrose et al.
Pediatr Infect Dis J,
2010**

Influenza Vaccine Manufacturers
(January 2010; Actual and Potential)

The Netherlands
Solvay

Czech Republic
Baxter

Hungary
Omnivest

Romania
Cantacuzino

Russian Federation
Microgen

China
CNGB
Hualan
Neptunus/GSK
Sinopharm
Sinovac
Tianyuan

Canada
GSK

Germany
GSK
Novartis

Iran
Razi Institute

Japan
Biken
CSTRI
Denka Seiken
Kitasato

USA
MedImmune
Sanofi-Pasteur

France
Sanofi Pasteur

Switzerland
Berna-Crucell

India
Panacea Biotec
SII

Rep of Korea
Green Cross

Mexico
Birmex

Austria
Baxter

Egypt
Vacsera

Thailand
GPO

Italy
Novartis

Viet Nam
IVAC
Vabiotech

Serbia
Torlak

Australia
CSL

Indonesia
BioFarma

Brazil
Instituto Butantan

★ Vaccine Manufacturers

One producer (AdImmune) in Chinese Taipei

CDC

Being serious about pandemic influenza

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Being serious about seasonal influenza