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**Role of Pneumococcal Conjugate Vaccine (PCV) in the
Prevention of Viral-associated Pneumonia**





PNEUMONIA

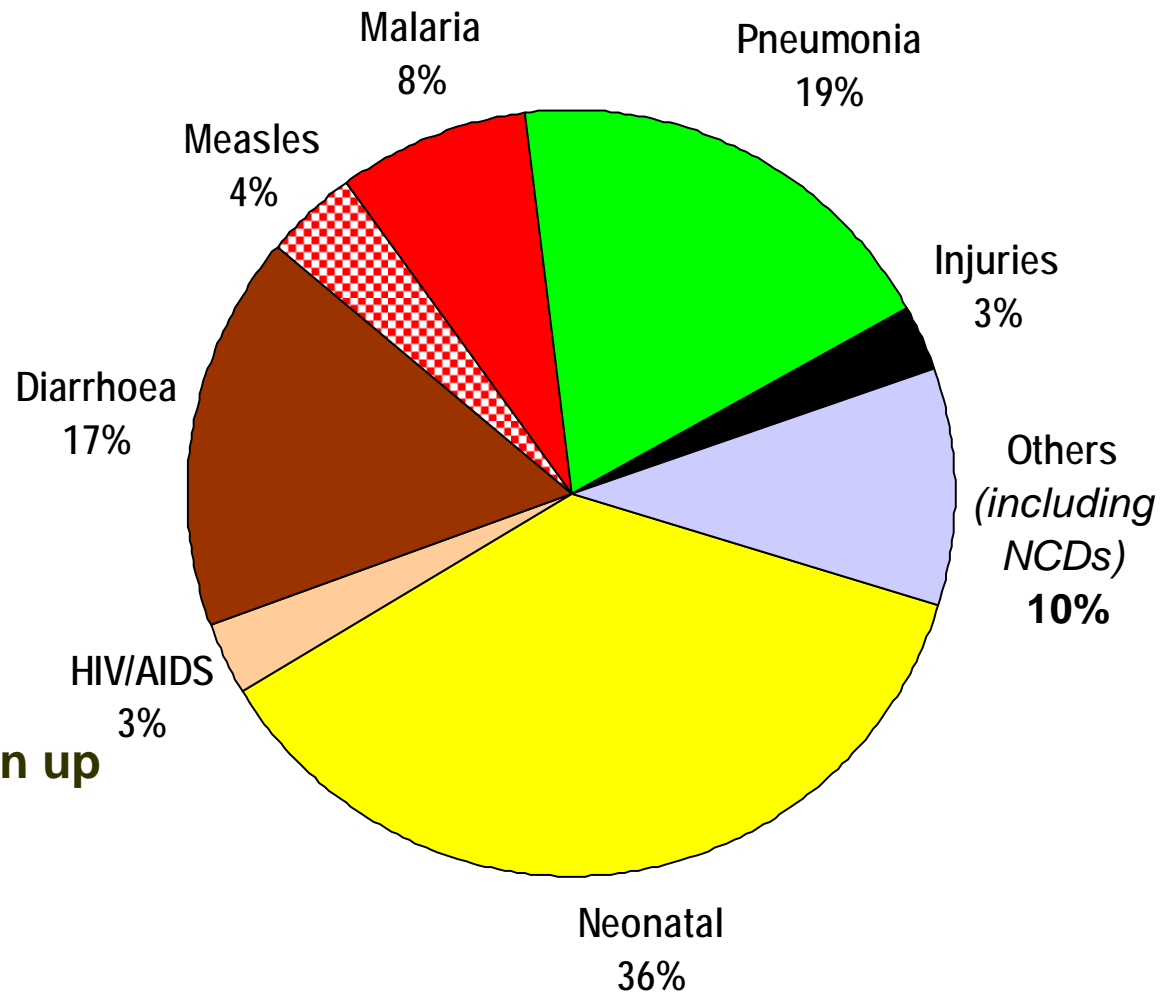
THE FORGOTTEN
KILLER OF
CHILDREN

unicef 

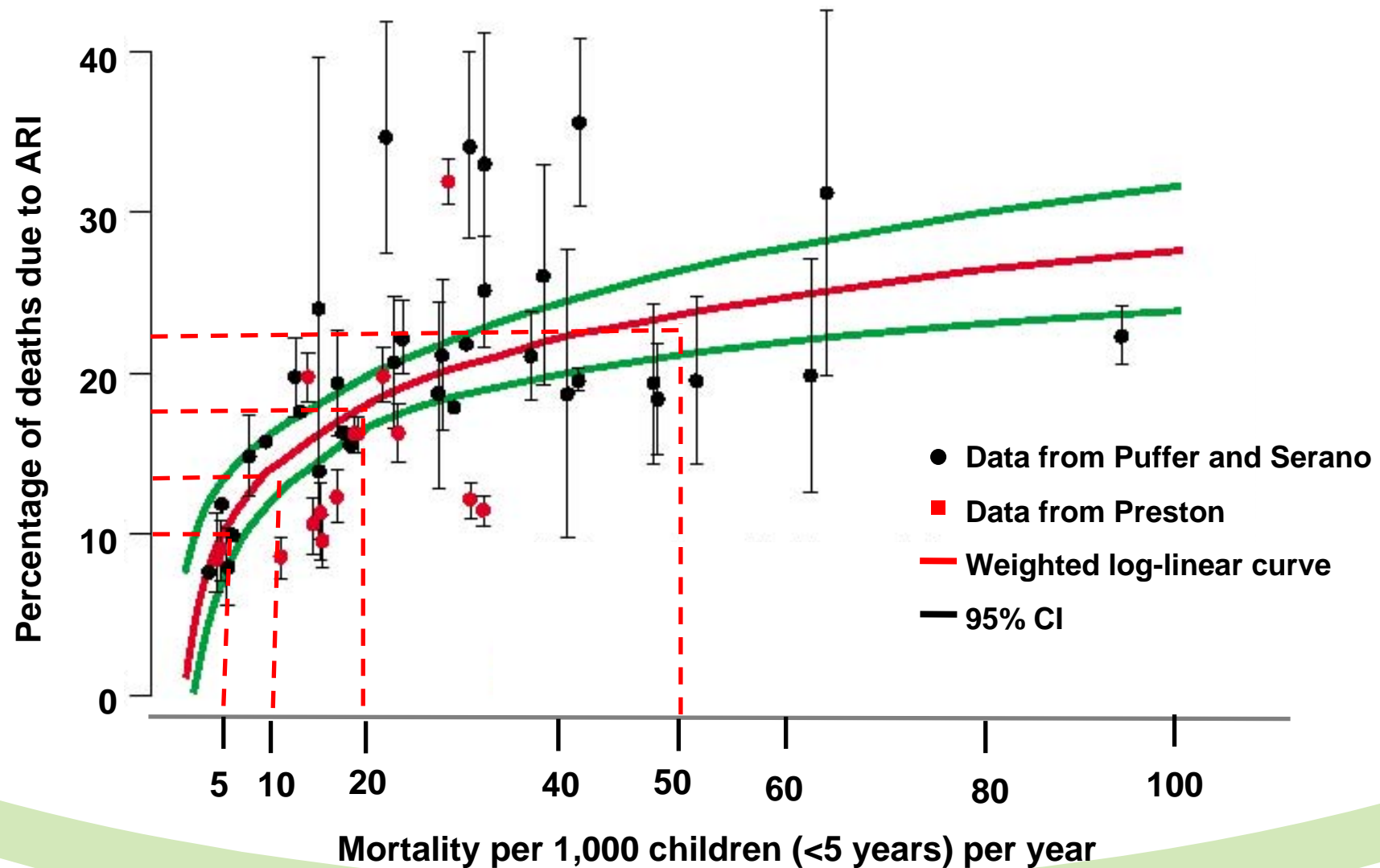
 World Health
Organization

The Causes of Global Child Mortality

- **Pneumonia (19%)**
- Diarrhoea (17%)
- Preterm birth (10%)
- **Neonatal infection (9%)**
- Birth asphyxia (8%)
- Malaria (8%)
- HIV/AIDS (3%)
- Undernutrition (present in up to 50%)



Direct Association Between Proportion of Deaths Due to Pneumonia and Childhood Mortality



Global Distribution of Childhood Pneumonia Cases

WHO REGIONS	Total population of children aged 0-4 years (in millions)	Incidence of clinical pneumonia (e/cy)	Number of pneumonia cases (in millions)
African region	105.62	0.33	35.13
The Americas	75.78	0.10	7.84
Eastern Mediterranean region	69.77	0.28	19.67
European region	51.96	0.06	3.03
South-East Asian region	168.74	0.36	60.95
Western Pacific region	133.05	0.22	29.07
Total (developing)	523.31	0.29	151.76
Total (developed)	81.61	0.05	4.08
Total (world)	604.93	0.26	155.84

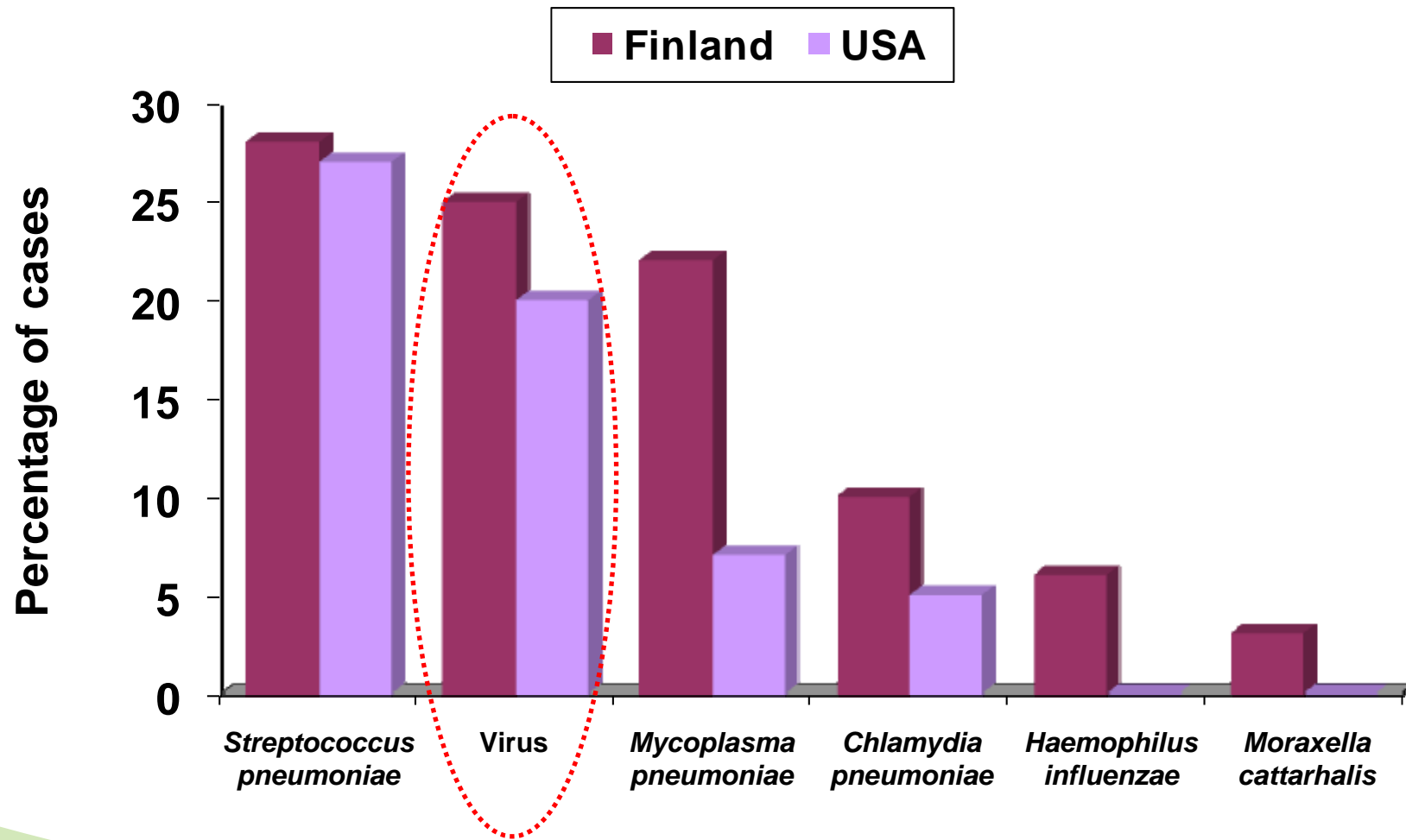


Burden of Pneumonia in Selected WHO Regions of SEAR and Western Pacific

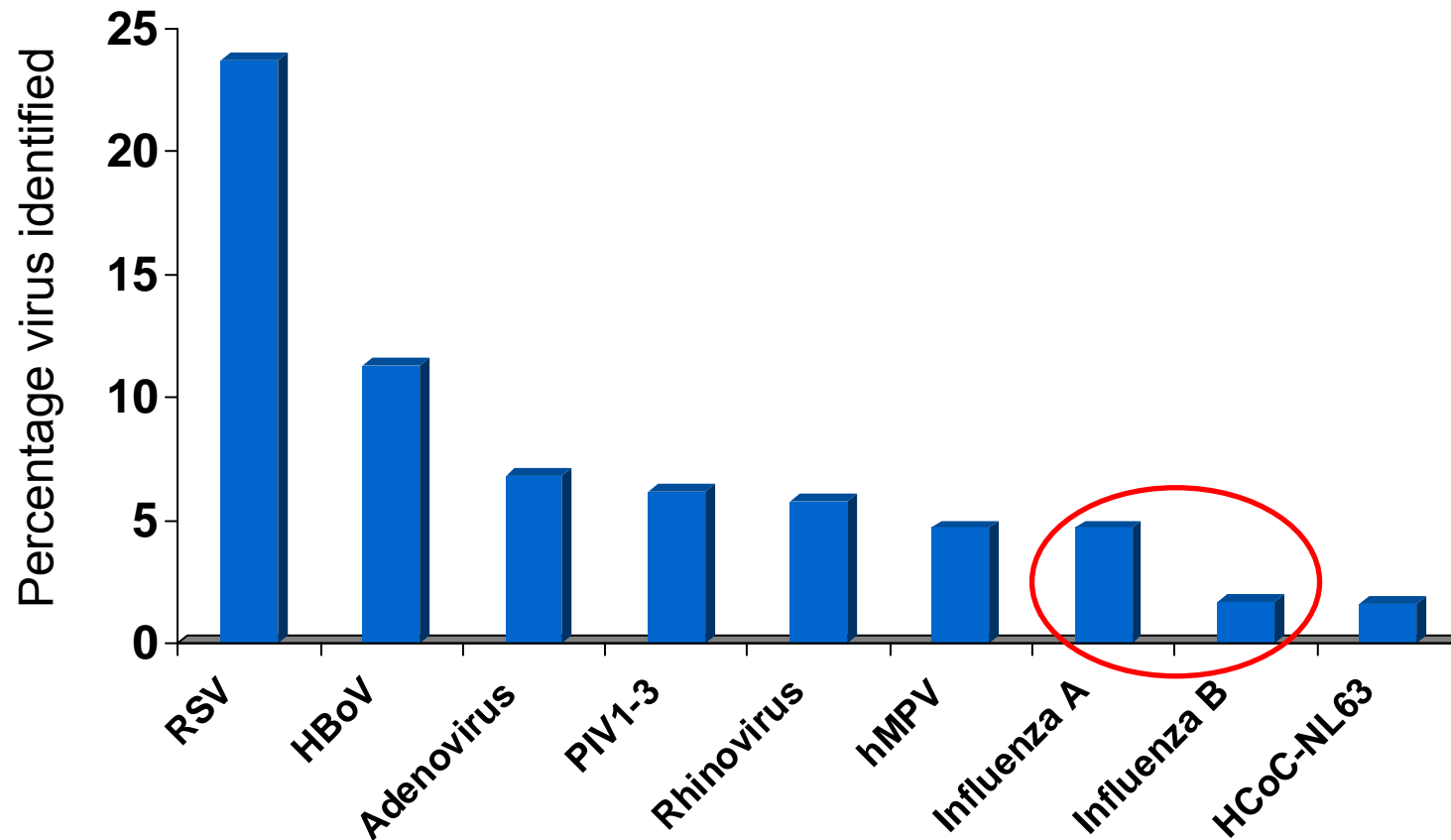
Country	Total number of children aged 0-4 yrs (millions)	Incidence of clinical pneumonia (e/cy)	Number of pneumonia cases	Number of severe pneumonia
Malaysia	2.61	0.12	314,861	27,078
Thailand	4.83	0.35	1,668,276	143,470
Philippines	9.88	0.27	2,671,370	229,740
SEAR	168.74	0.36	60,950,000	
Western Pacific region	133.05	0.22	29,070,000	

Courtesy of Igor Rudan.

Etiology of Community-acquired Pneumonia in Children From Developed Countries



Identification of Respiratory Viruses in South Korean Children With Lower Respiratory Tract Infections



High Burden of Influenza Attributable Hospitalization for Acute Cardiopulmonary Illnesses in Children in Tennessee, USA, 1974 to 1993

Age	No. of person-years	No. of hospitalizations for acute cardiopulmonary conditions per 10,000 person-years				No. of influenza-attributable hospitalizations per 10,000 person-years ^a	Average excess No. of hospitalizations per 10,000 children per year (95% CI) ^b
		Influenza	Peri-influenza				
		Season	Season	Summer	Total		
<6 mos	117,205	1,964	1,497	608	1,146	449	103.8 (89.0-118.6)
6 to <12 mos	82,997	1,117	854	403	675	233	49.6 (35.3-63.8)
1 to <3 yrs	324,900	464	387	233	325	79	18.6 (14.2-23.0)
3 to <5 yrs	302,344	232	193	138	173	43	8.6 (4.9-12.3)
5 to <15 yrs	1,207,697	120	105	86	98	22	4.1 (2.8-5.5)

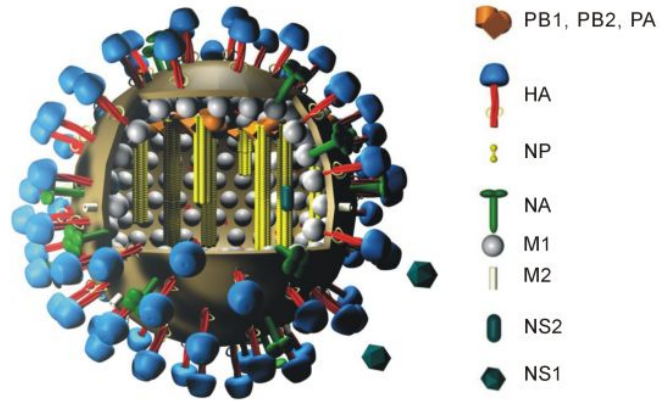
- **18% to 20% of hospitalizations for cardiopulmonary illnesses in children <3 yrs of age during winter attributed to influenza**
- **56% of deaths occur in children <1 year of age**

a. Values are differences in rates between the influenza season and the peri-influenza season (the base line values).

b. Values are weighted averages of annual excess hospitalizations for a population of 10,000 persons within the specified age group. The excess hospitalizations were calculated for each stratum by multiplying the stratum-specific difference in hospitalization rate by the proportion of the study year covered by the influenza season. CI denotes confidence interval.

c. The weighted average differences in rate between the influenza season and the peri-influenza season were calculated with stratum-specific person-years in all seasons as weights; strata were defined by age group, study year, race, and residence.

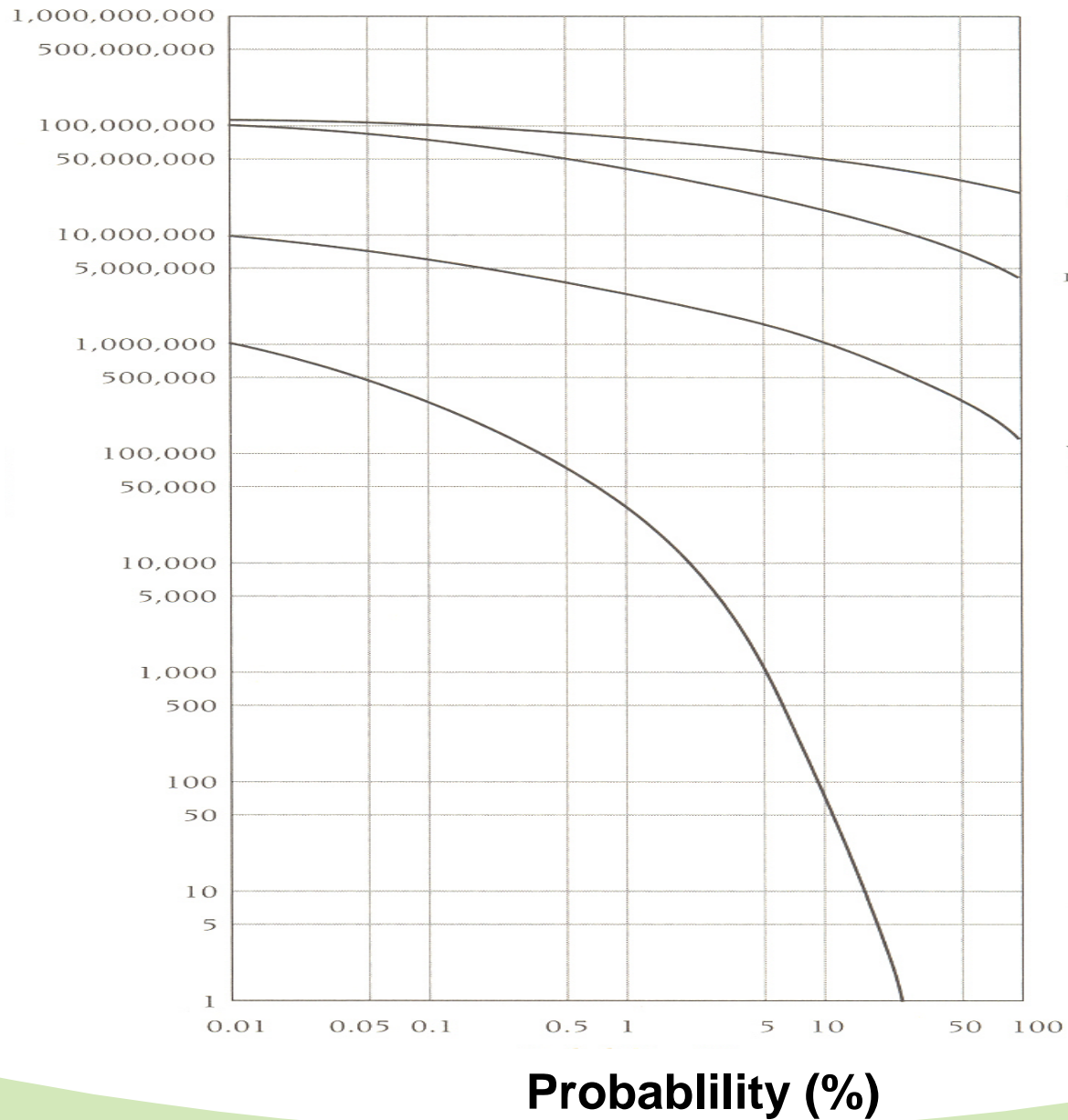
Neuzil KM, et al. *NEJM*. 2000;342:225-231.



Year	Subtype	Origin	Est. mortality
1830-33	???	Russia	???
1836-37	???	?Russia	???
1889-90	H2 and H3	?Russia	???
1918-19	H1N1	Europe/USA	20-40 mil
1957-58	H2N2	Southeast Asia	2 mil
1968-69	H3N2	Hong Kong	1 mil

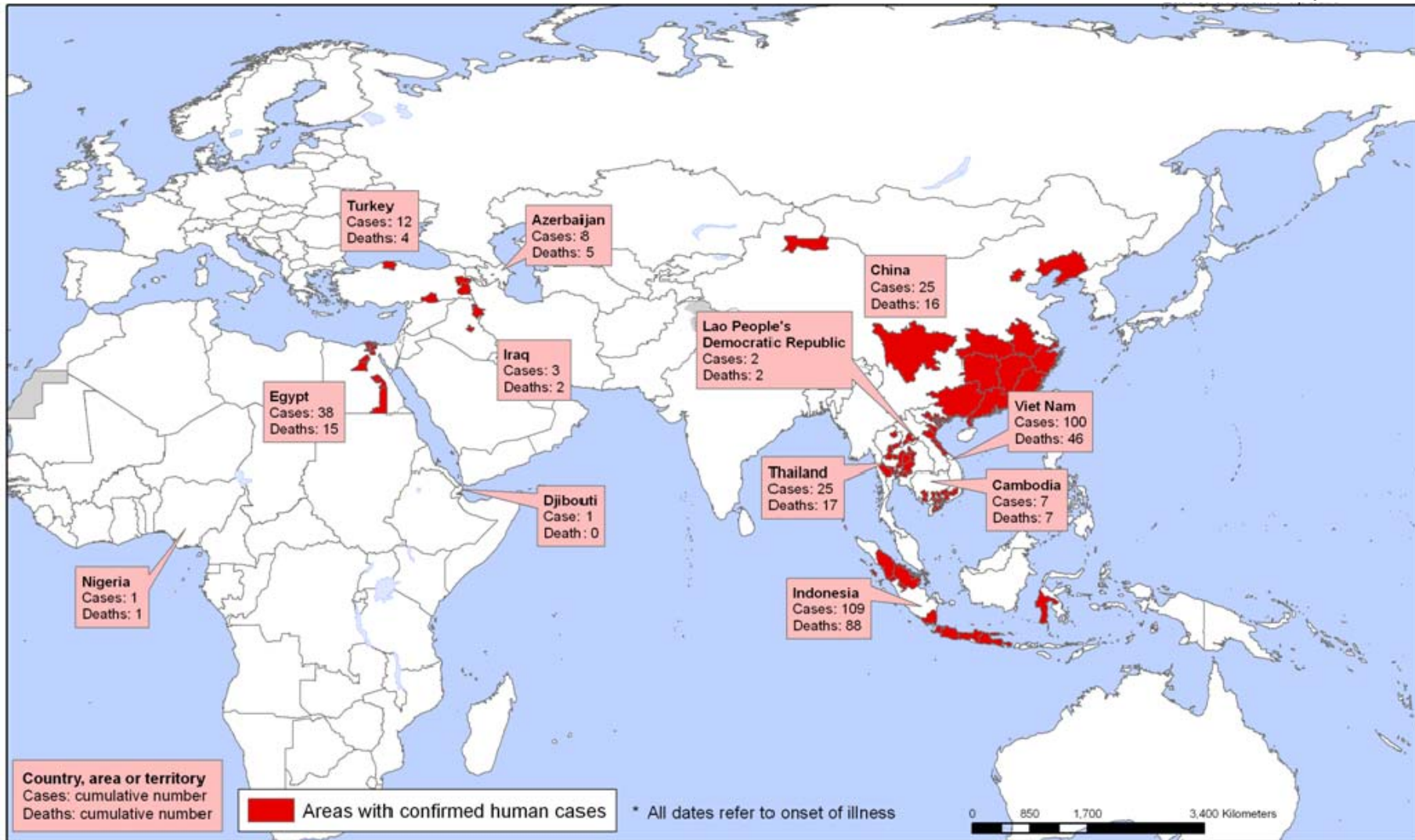


Predicted Fatalities



Areas with confirmed human cases of H5N1 avian influenza since 2003*

Status as of 17 October 2007
Latest available update

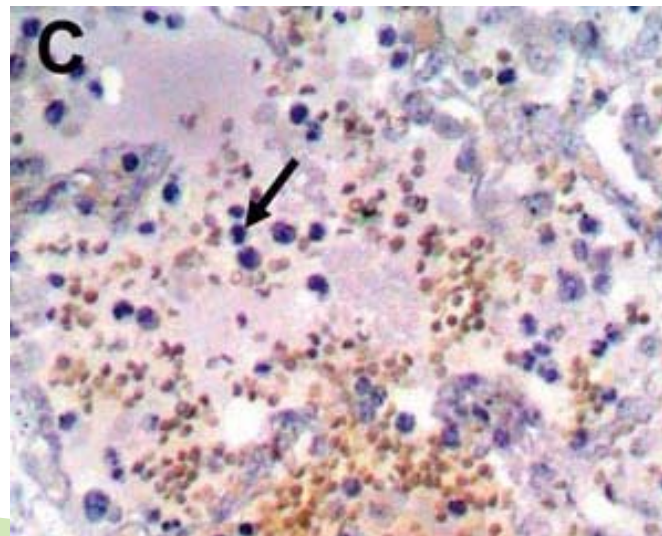
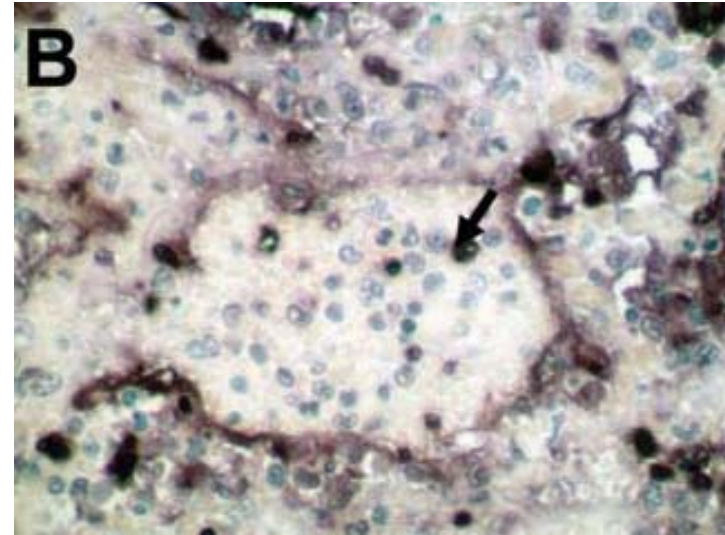
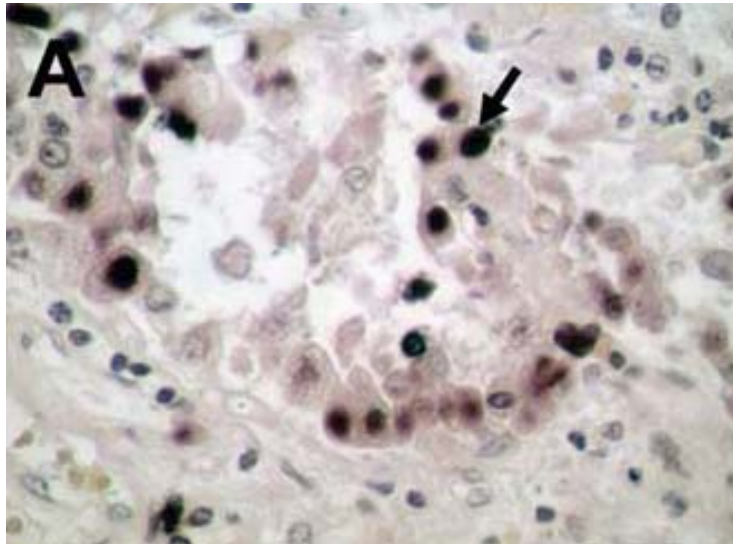


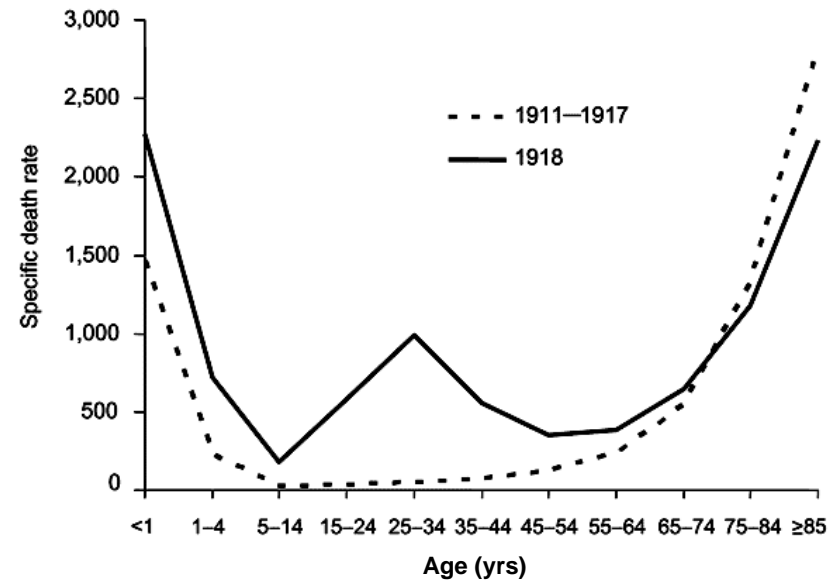
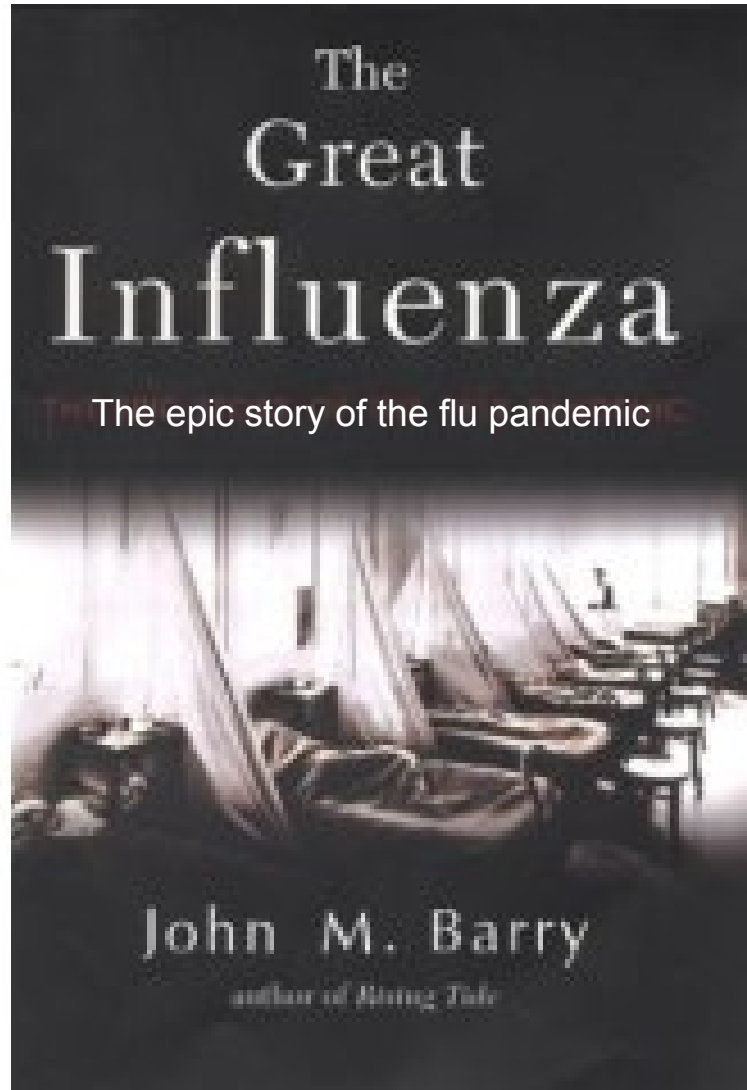
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO / Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS) World Health Organization

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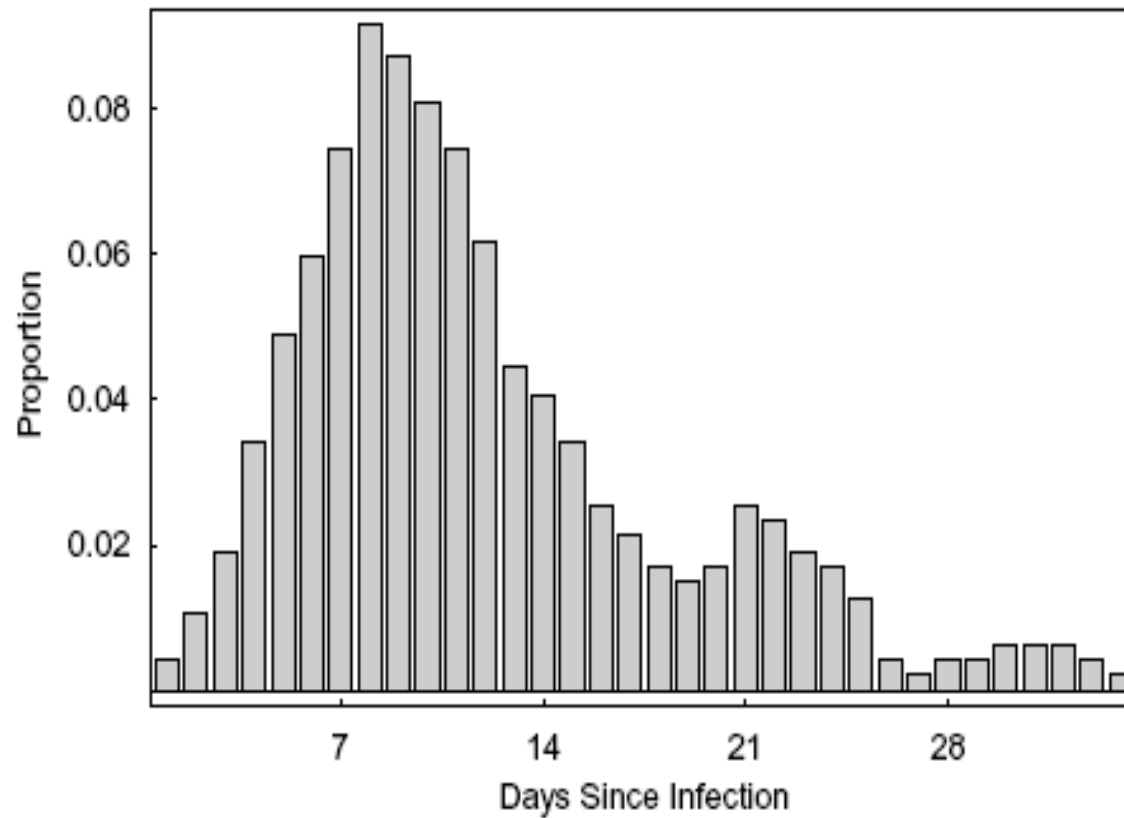
H5N1 Associated With Diffuse Alveolar Damage and Apoptosis of Alveolar Macrophages and Leukocytes



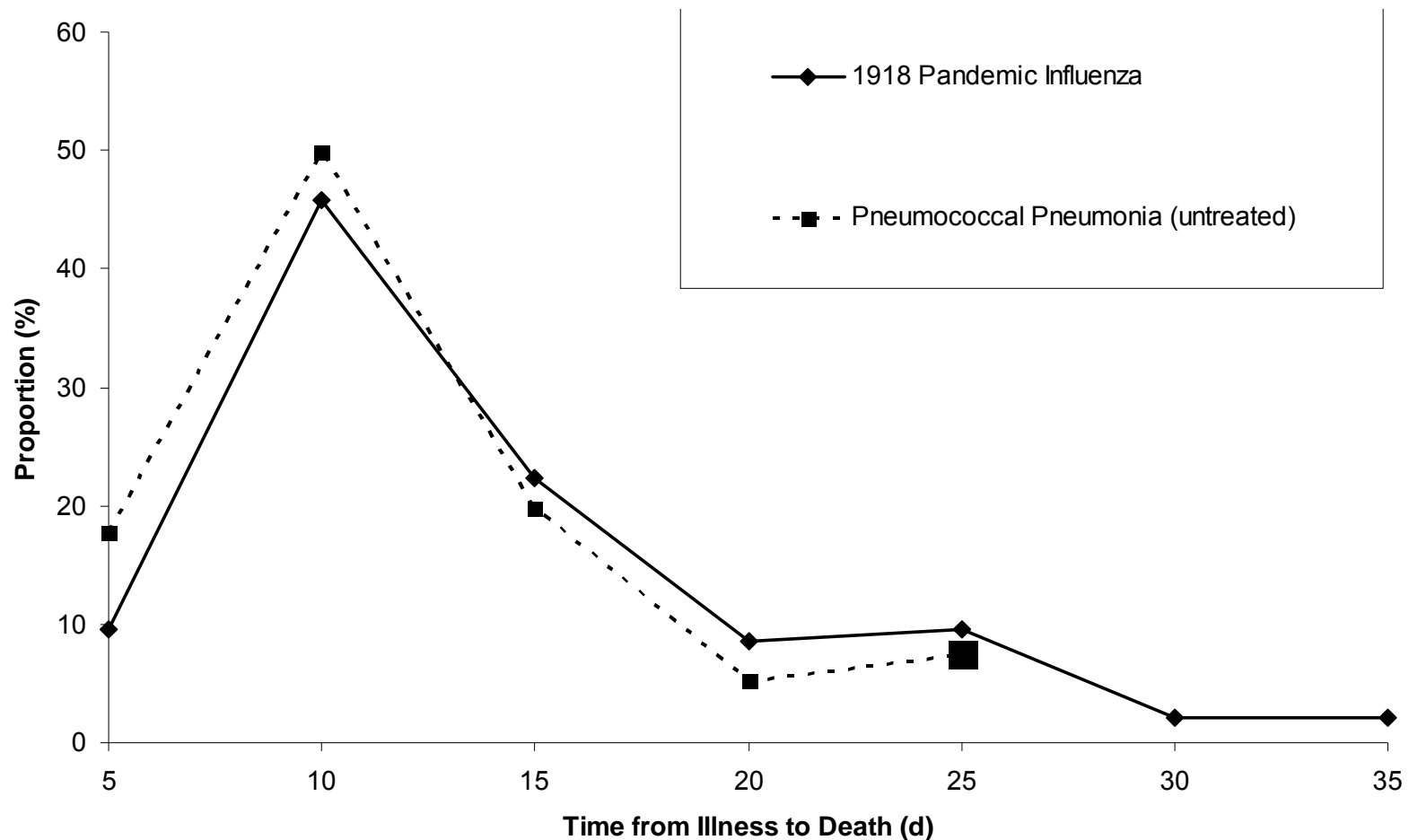


**(Archives yearbook for South
African history)**
by H. Phillips

Timeline Post Infection of Influenza Deaths: 1918 Epidemic



Similarity in Time-to Death Distribution During 1918 Influenza Pandemic and In Untreated Pneumococcal Pneumonia (among those who die within 35 days)



C. E. Mills, J. M. Robins, M. Lipsitch, *Nature* **432**, 904 (Dec 16, 2004).

O. Klotz, in *Studies on epidemic influenza*. (Pittsburgh Univ. School of Medicine., Pittsburgh, 1919).

W. G. MacCallum, in *Johns Hopkins Hospital Reports*. (Johns Hopkins Press, Baltimore, 1921), vol. XX.

S. B. Wolbach, *Johns Hopkins Hospital Bulletin* **338**, 104 (1919).

R. C. Tilghman, M. Finland, *Archives of Internal Medicine* **59**, 602 (1937).

Mills, Klugman, Lipsitch unpublished

Did Bacterial Infection (esp. the Pneumococcus) Play a Major Role in Mortality During the 1918 Influenza Epidemic?

Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness

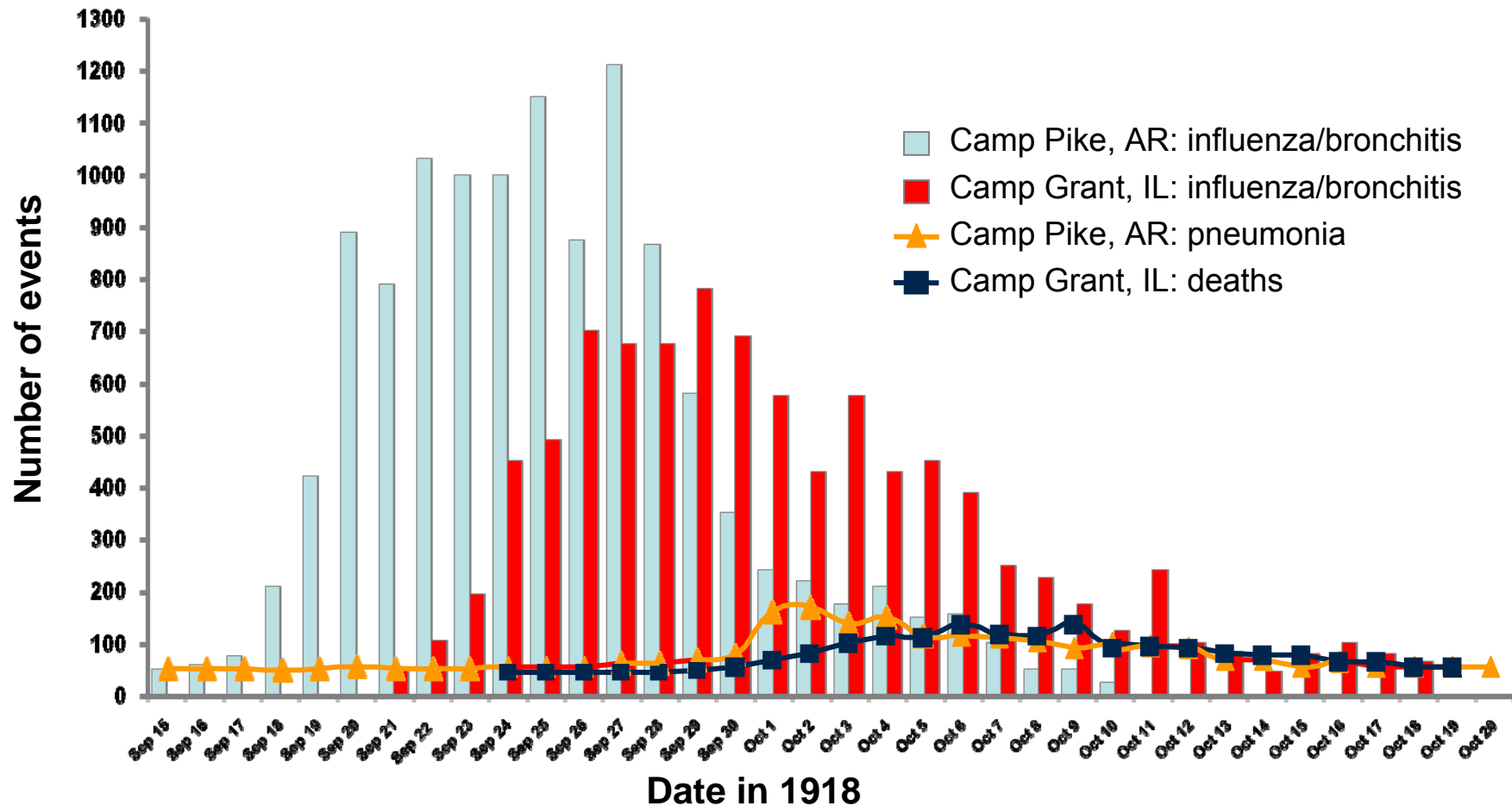
John F. Brundage

Lancet Infect Dis. 2006;6:303-312.

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john.brundage@amedd.army.mil

ILI Followed by Pneumonia and/or Death



“The influenza paves the way for the pneumonia, if it does not actually cause it” Soper GA, *JAMA*. 1918;71.

Opie, et al. *JAMA*, 1919;72:556–565.

Synnott, Clark. *JAMA*. 1918;71:1816-1821. Brundage. *Lancet Infect Dis*. 2006;6:303-312.

1918 Influenza Epidemic in US Military: Heart Blood Cultures Postmortem

- In nine postmortem examinations at Camp Logan, TX, pneumococci were the most frequently recovered organisms from lungs (44%), pleural cavities (67%), and heart blood (33%)¹
- Pneumococci were isolated from 65% of 80 postmortem cultures of heart blood at Camp Devens, MA²
- Postmortem cultures of lung and heart blood specimens from 280 fatal pneumonia cases at Camp Custer, MI, revealed that 28% of each were positive for pneumococcus³

“without exception the deaths from the respiratory epidemic have been due to secondary bacterial pneumonia. In no instance has a case come to necropsy in which death occurred from influenza infection alone”³

1. Hall, et al. *JAMA*.1918;71:1986-1987.

2. Spooner, et al. *JAMA*.1919;72:155-159.

3. Blanton, Irons. *JAMA*.1918;71:1988-1991.

1918 Influenza Epidemic: Blood Cultures From Living Patients

- **Blood cultures were made from 15 severe presumed influenza cases in British and American troops— 5 (33%) grew pneumococci¹**
- **45 (50%) of 90 blood cultures of living patients at Camp Grant, IL, revealed “a Gram-positive diplococcus in pure strain without exception ... all the morphologic and cultural characteristics of a pneumococcus”²**
- ***S. pneumoniae* grew from blood of 50 of 111 (45%) of soldiers with influenza – associated pneumonia in Camp Beauregard, LA (5 type I; 7 type II; 7 type IIa; 12 type III and 19 type IV). 44/50 (88%) died.³**
- **Total = 100 / 216 = 46%**

1. Muir, Wilson. *BMJ*. 1919;1:3-5.

2. Hirsch, McKinney. *JAMA*. 1918;71:1735-1736.

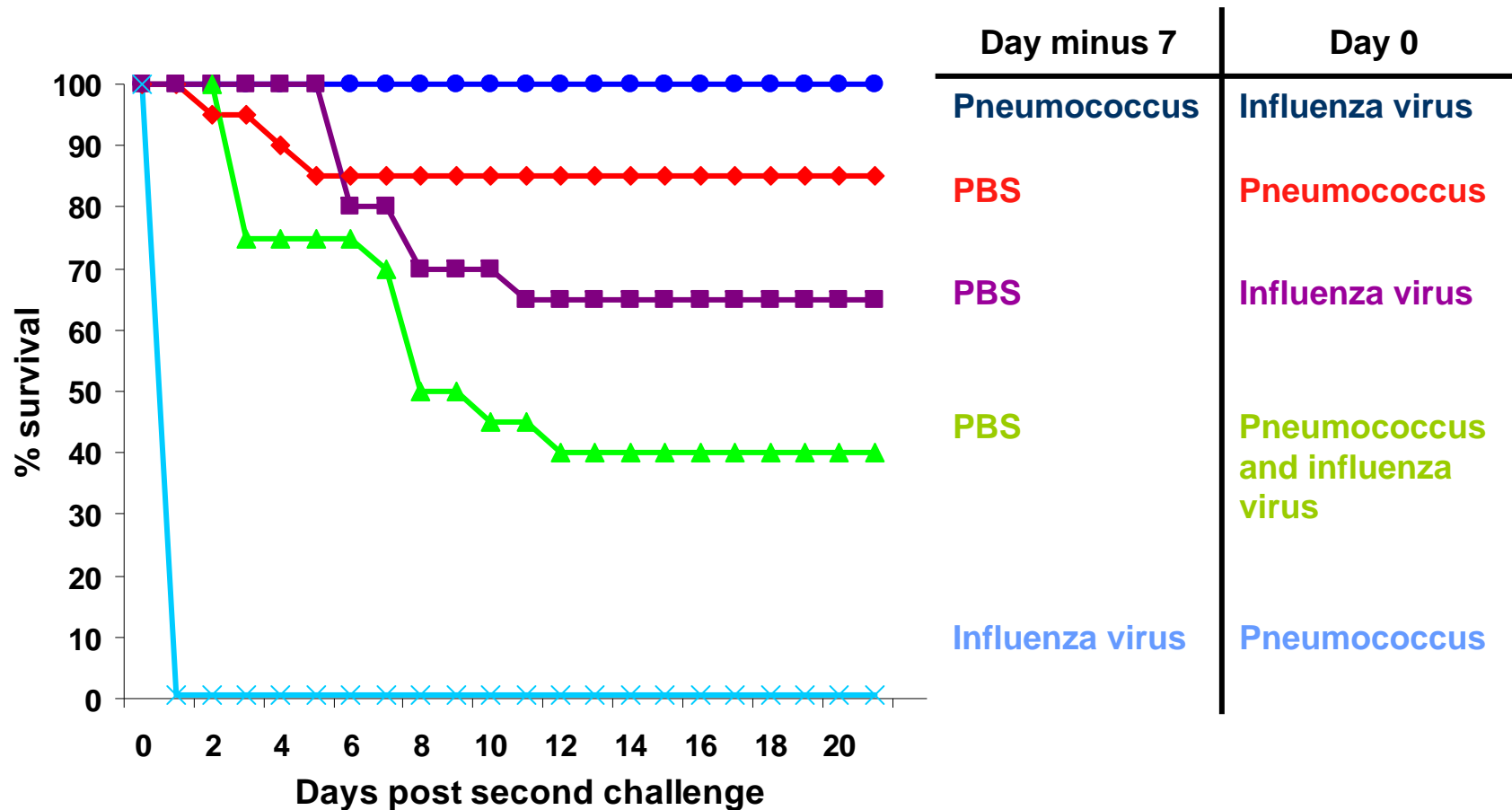
3. McClelland and Captain, *Amer J Clin Sci*, 1919, 158, 80-7



Exploring the Interactions of Influenza-bacterial Infections: Animal-model Studies



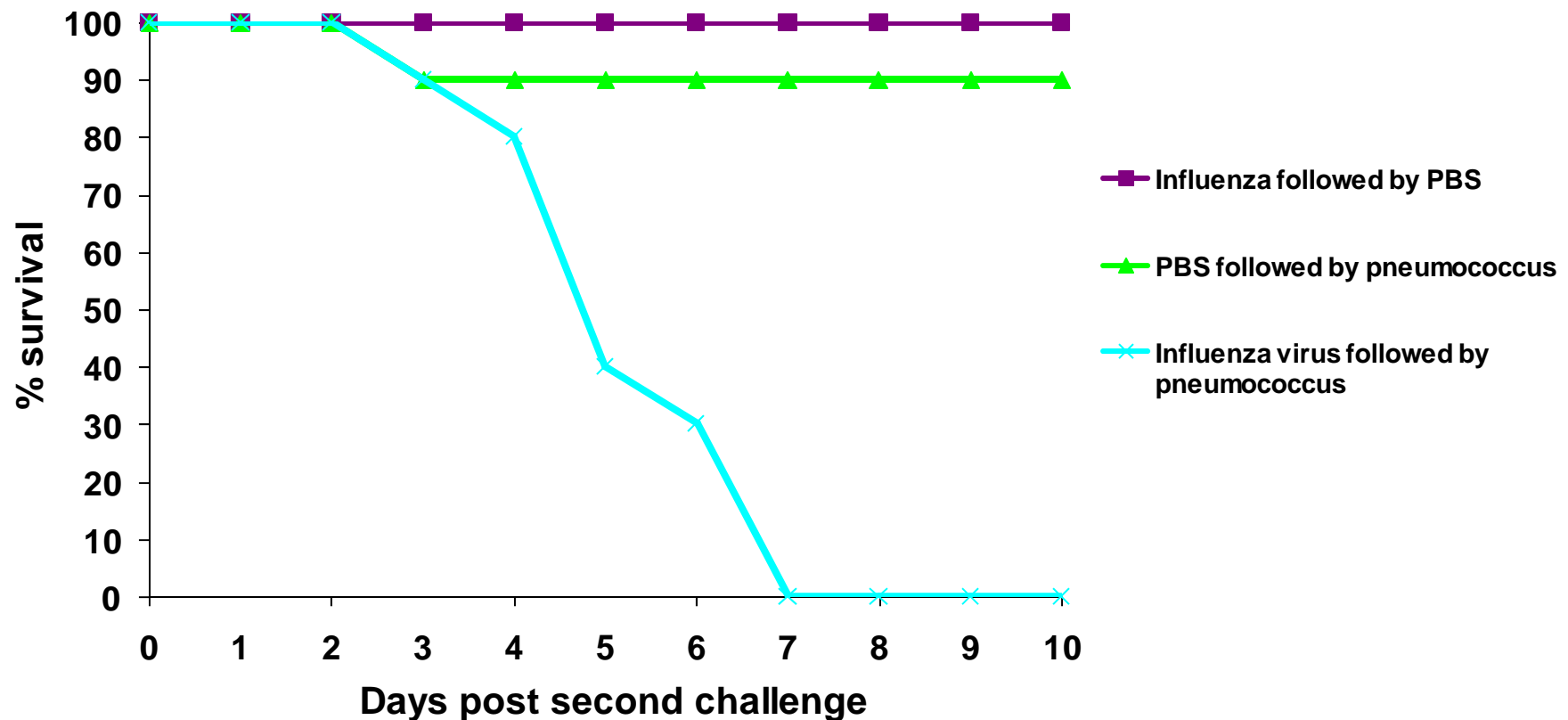
Synergistic Lethality of Influenza Plus Pneumococci Given 7 Days Later in Mice



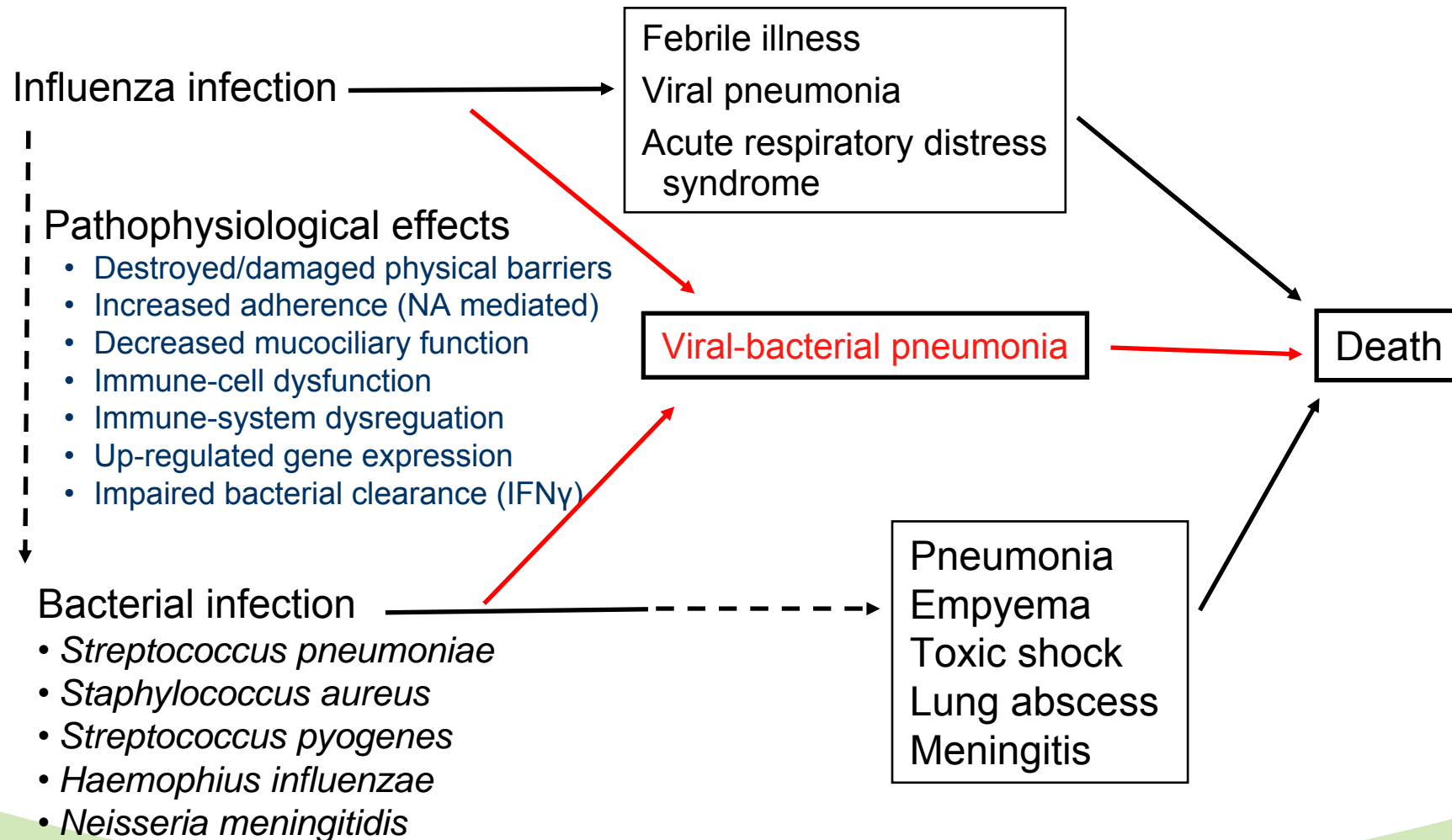
0.3 MLD₅₀ influenza and 0.2 MLD₅₀ *S. pneumoniae*

Synergistic Lethality of Influenza Plus Pneumococci Given 7 Days Later in Mice

0.05 MLD₅₀ influenza and 0.002 MLD₅₀ *S. pneumoniae*



Pathophysiological Interactions Between Influenza and Bacterial Respiratory Pathogens and Clinical Expression





High Prevalence of Bacterial Co-infections Among Children With Viral-associated Acute Otitis Media

Bacterial species	Respiratory syncytial virus N=48 (%)	Parainfluenza virus N=15 (%)	Influenza virus N=10 (%)
<i>S. pneumoniae</i>	8 (17)	1 (7)	8 (80)
<i>H. influenzae</i>	10 (21)	5 (33)	2 (20)
<i>M. cattarhalis</i>	6 (13)	5 (33)	3 (30)
Any bacteria	22 (46)	10 (67)	8 (80)

Role of Mixed Viral/Bacterial Etiology in Hospitalized Children With Pneumonia

- Children with preceding (7-28 d) influenza-like illness **12.4-fold (95% CI 1.7-30.6)** more likely to develop severe pneumococcal pneumonia¹
- **30%** of 254 children had evidence of **mixed bacterial/viral** infection²
- Serological evidence of **bacterial infection** was found in 0 of 24 children with PIV and croup but in 4 (**31%**) of children with **PIV and LRT**³
- **Bacterial serology** was positive in **39%** of hospitalized children with **RSV infection and pneumonia** or otitis
- **31%** of episodes of **pneumococcal** community-acquired pneumonia diagnosed by culture and PCR were **co-infected** with a **virus**⁴

1. O'Brien KL, et al. *CID*. 2000;30:784-789.

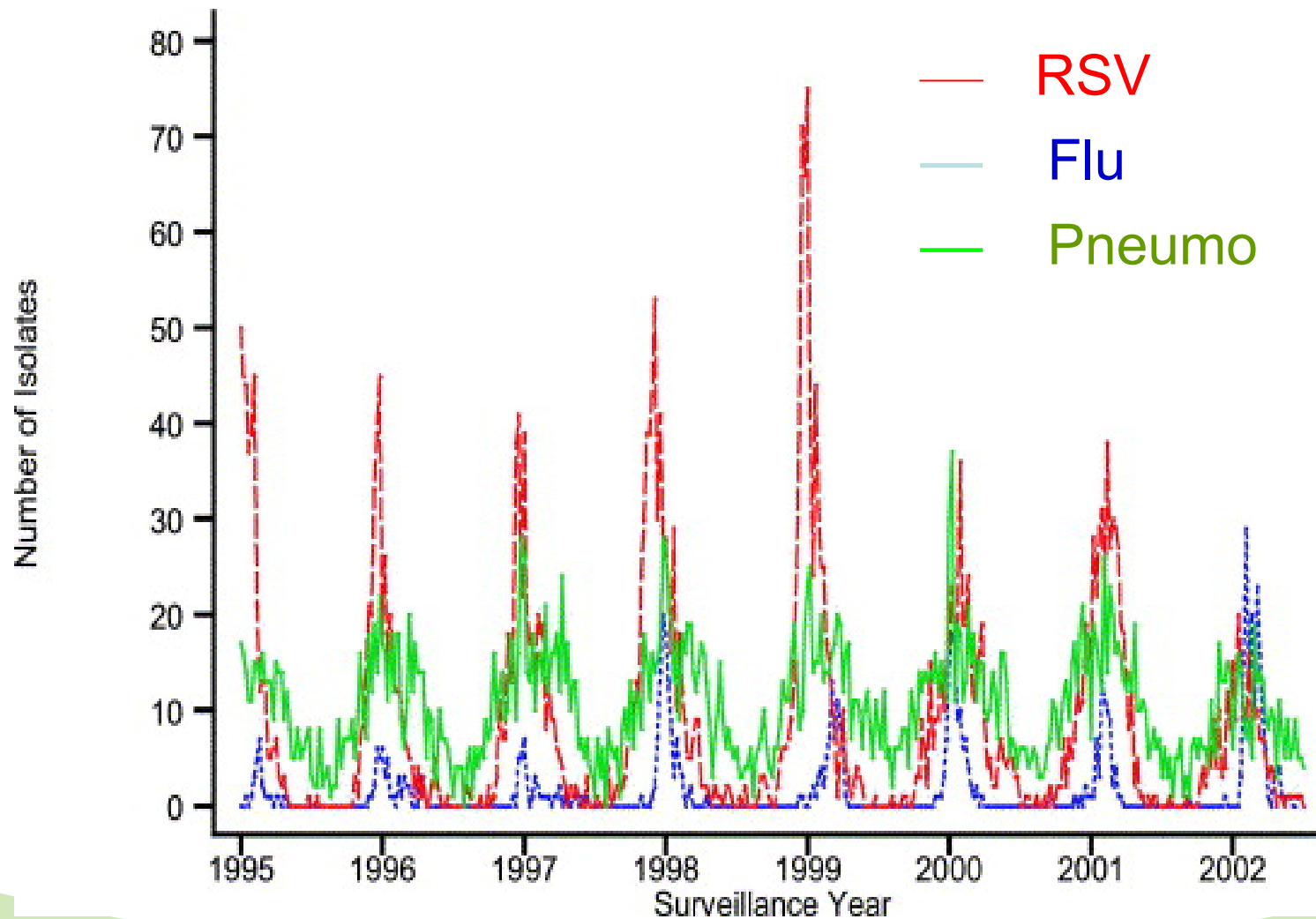
2. Juven, et al. *PIDJ*. 2000;19:293-298.

3. Korppi M, et al. *Scand J Infect Dis*. 1990;22(3):307-312.

4. Korppi, et al. *PIDJ*. 1989;10:687-692.

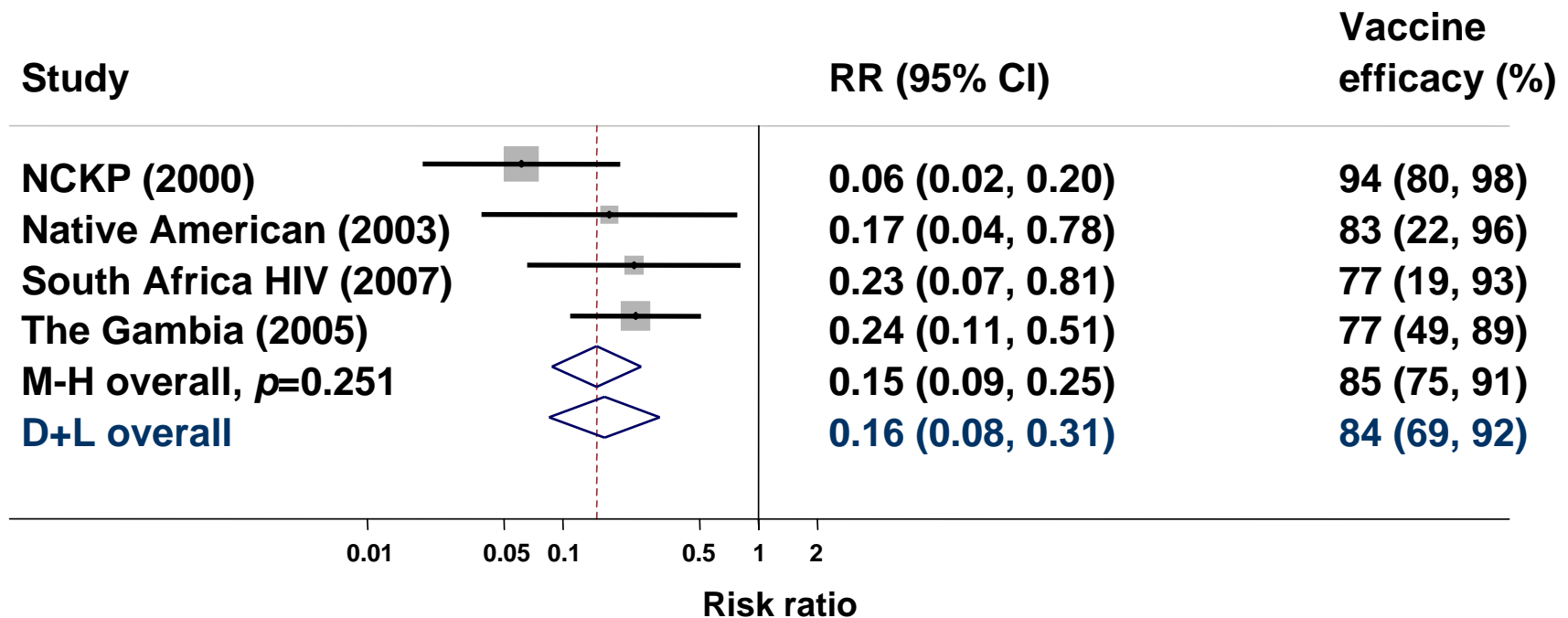
5. Michelow, et al. *Pediatrics*. 2004;113:701-707.

Pneumococcal Disease is Broadly Increased in Winter by RSV and Influenza and Probably Also by Other Respiratory Viruses (hMPV, Rhino)

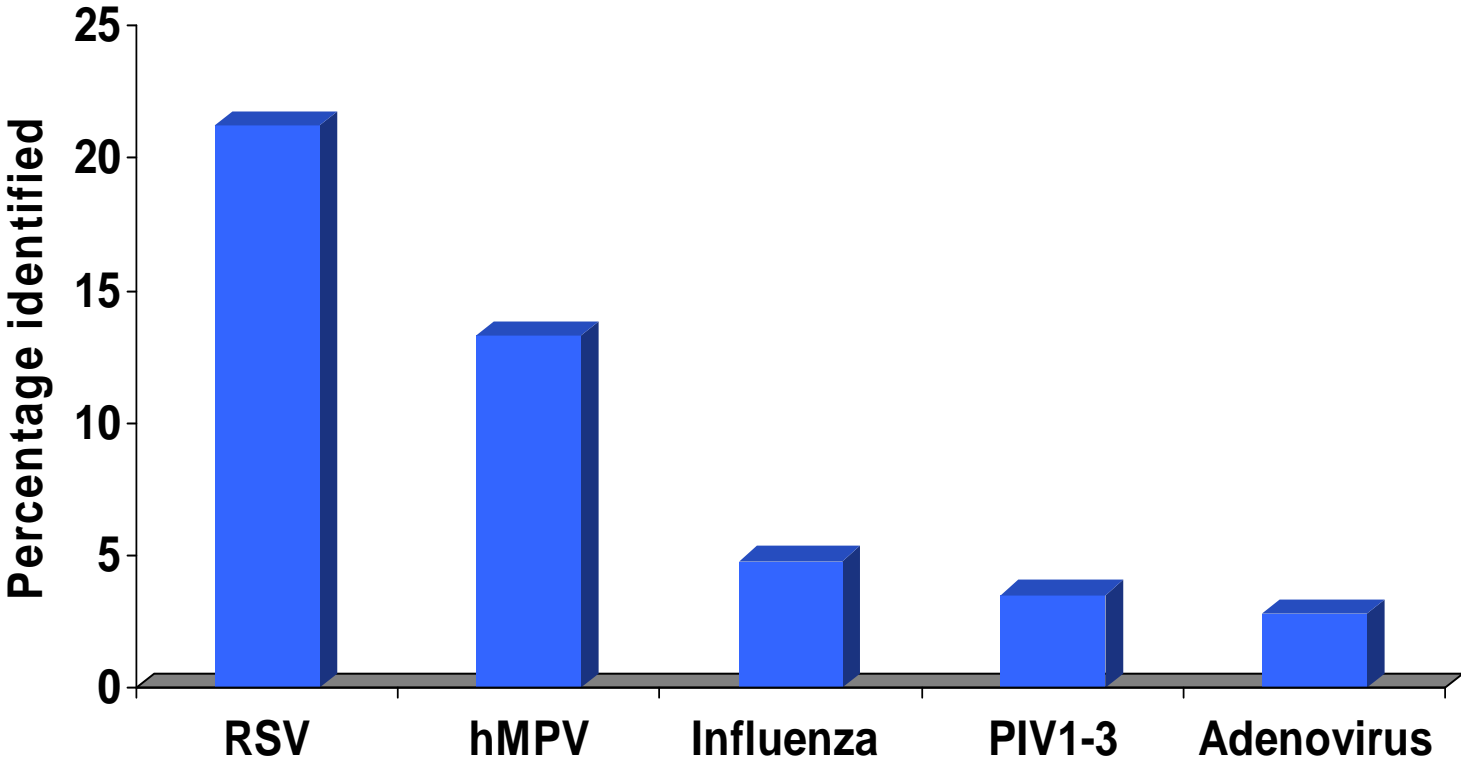


Meta-analysis: PCV Efficacious Against Vaccine-serotype-specific Invasive Pneumococcal Disease (IPD) in Randomized, Controlled Trials

7v vaccine type IPD HIV negative



Respiratory Viruses Identified in Children Hospitalized for Community-acquired Pneumonia in the Absence of PCV Immunization



Madhi SA, et al. *PIDJ*. 2007.

Low Prevalence of Concurrent Pneumococcal Bacteraemia in Children With Viral Pneumonia

Virus identified	HIV infected		HIV uninfected	
	PCV	Placebo	PCV	Placebo
Influenza A	6.7	5.3	0	2.4
RSV	0	0	0	0.6
PIV1-3	0	0	5.6	0
All	6.3	11.1	0	0

PCV study in S. Africa: <5% of pneumococcal pneumonia prevented had pneumococcal bacteremia³

Madhi SA, Klugman KP. *Nature Med.* 2004;10:811-813.

Madhi SA, et al. *J Infect Dis.* 2006;193;9:1236-1243.

Madhi SA et al. *C Infect Dis* 2005; 40: 1511-1518

PCV Reduced the Incidence of Viral-associated Pneumonia Hospitalization in Children

Virus	PCV	Placebo	Efficacy	95% CI	<i>p</i> -value
Influenza A/B	31	56	45	14-64	0.01
PIV1-3	24	43	44	8-66	0.02
hMPV	26	62	58	34-73	0.001
RSV	90	115	22	-3-41	0.08

- At least **one third of children** hospitalized for **pneumonia** in whom a **virus** is identified have **concurrent infection due to VT pneumococcus**
- Study provides a **minimal estimate** of **contribution of pneumococcal co-infection**; re:
 - PCV only likely to be preventing <50% of all pneumococcal pneumonia
 - **Additional role of non-vaccine serotypes**

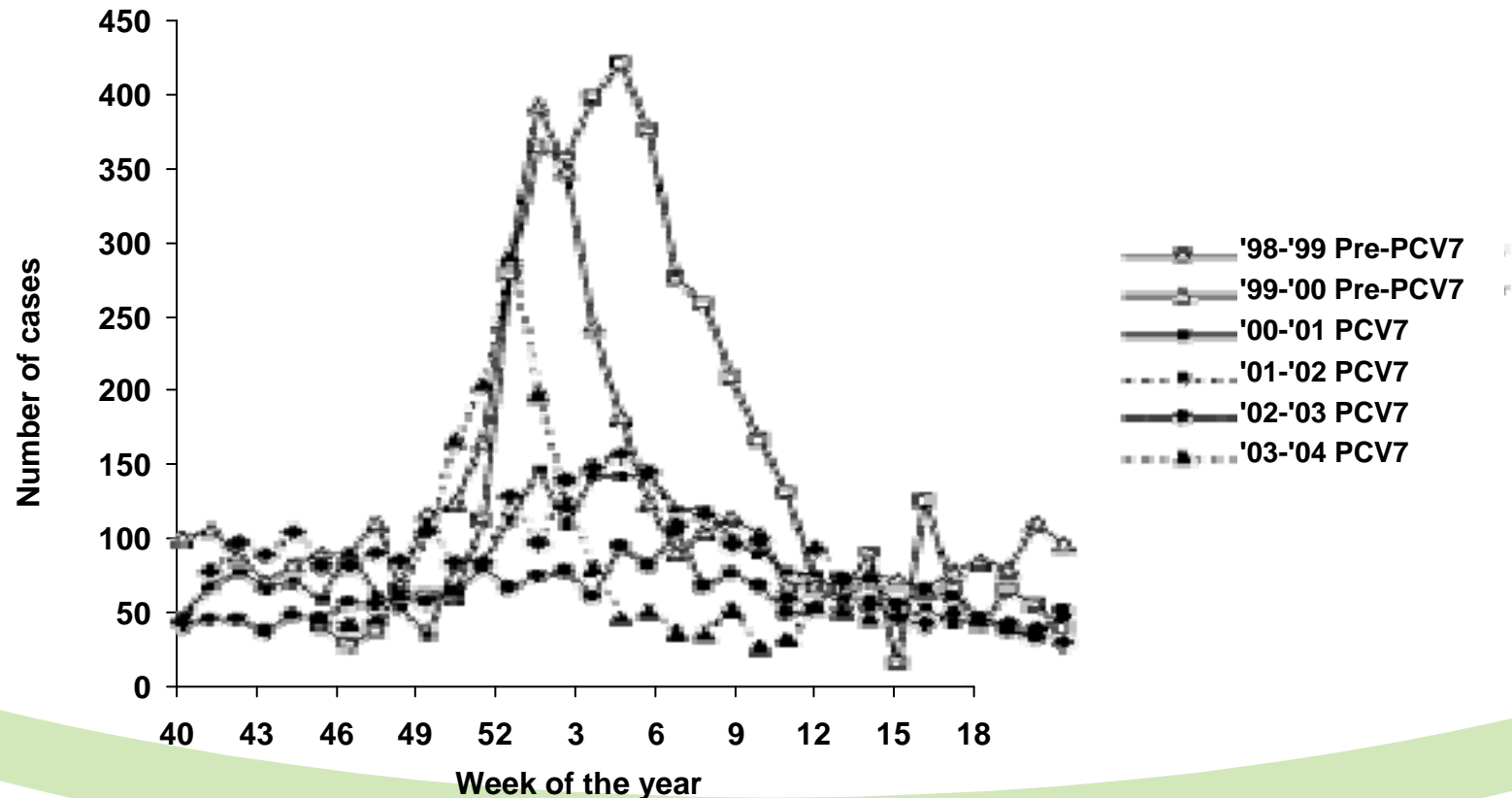
Madhi SA, Klugman KP. *Nature Med.*2004;10:811-813.

Madhi SA, et al. *J Infect Dis.* 2006;193;9:1236-1243.

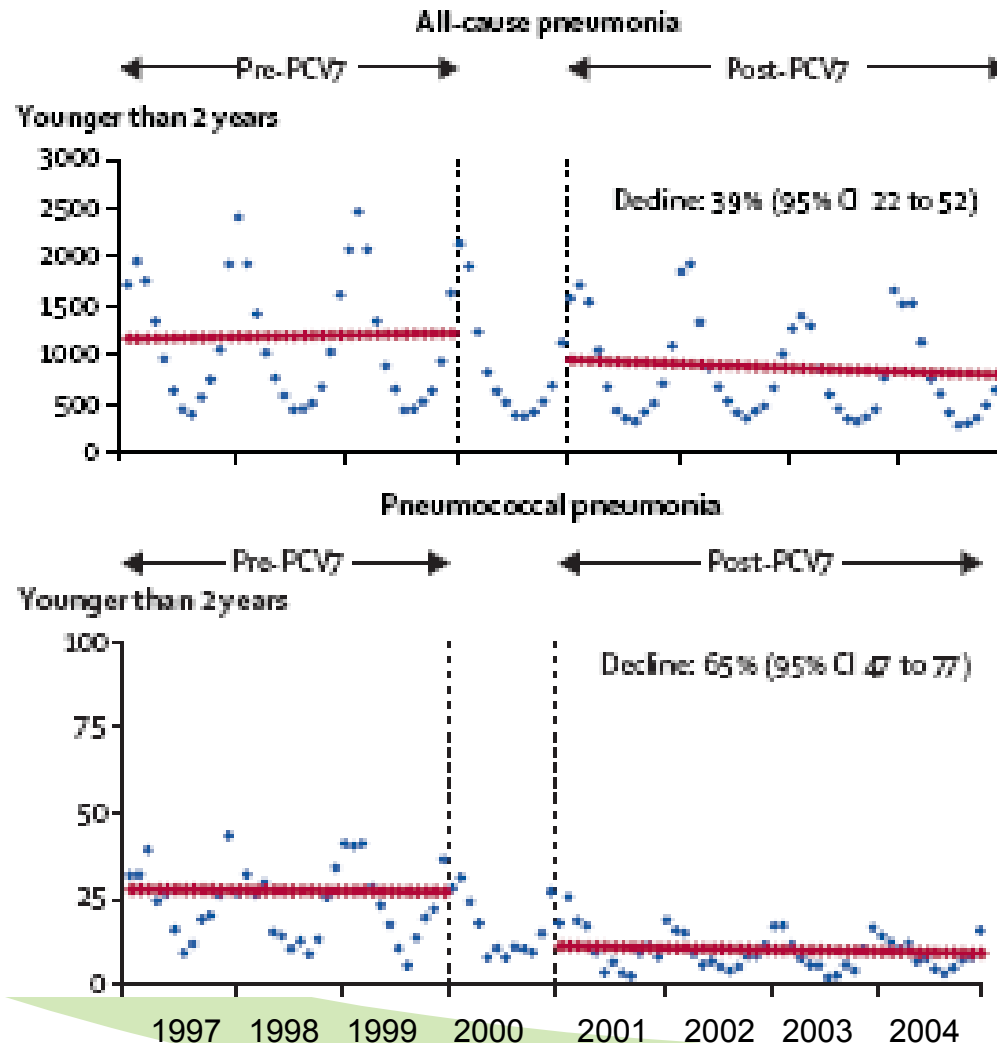
“Reduction” in Emergency Department Visits and/or Hospitalization for Influenza-like Illness Following Introduction of PCV in US

Author’s conclusion: Less severe influenza epidemics may have contributed to reduction in IPD during post-vaccine era

???Did PCV result in less hospitalization for ILI by protecting against superimposed pneumococcal infections in influenza infected individuals



Decline In Pneumonia Admissions After PCV7 Introduction: Children



- Time series analysis
- Nationwide Inpatient Sample
- Rates of all-cause pneumonia dropped 39% (-506/100,000) by 2004 in children <2 yrs
- 29 fold higher reduction in cases of clinical pneumonia compared to observed reduction in “pneumococcal pneumonia”

Does Influenza (Viral) Infection Increase the Risk of Pneumococcal (Bacterial) Disease?

“No one doubts that epidemic influenza is due to a specific organism, yet in hardly any other disease do we meet with such a variety of lesions and complications, produced by various organisms of common occurrence apart from influenza. Apparently the explanation is that the specific organism leads to a diminished resistance of the bronchial mucosa, and thus bacterial growth extends to the finest tubules, and bronchopneumonia frequently follows”

Pneumococcal Vaccines and Flu Preparedness

CREDIT: PETER HOEY

INFLUENZA-ASSOCIATED MORTALITY IN THE next five decades is likely to exceed that of any other global catastrophe (1, 2). The role of secondary bacterial infections and the need for bacterial vaccines are not mentioned in the U.S. Department of Health and Human Services Pandemic Influenza Plan (2). The evidence that pneumococcal infec-

tion played a major role in the 1918 influenza pandemic is substantial, but seems to have been forgotten (3). In two studies, culturable pneumococci could be found in the peripheral blood of 50 of 105 living soldiers with influenza, during the pandemic in the United States and the UK (4, 5), and from 55 of 89 heart blood cultures taken from U.S. soldier influenza victims immediately after death (6, 7). Roughly 1/3 of deaths during the 1918 pandemic occurred more than 2 weeks after the onset of symp-

toms (8). Blood culture and time of death both suggest a role for the pneumococcus in a substantial fraction of the deaths of these young soldiers.

The role of conjugate pneumococcal vaccine in reducing influenza-associated morbidity has recently been demonstrated (9). Children who received the vaccine and then developed laboratory-confirmed influenza were at 45% less risk of hospitalization due to the influenza-associated pneumonia than were children who had not received the

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Vaccination of children with PCV may be important in combating influenza (and other respiratory viral) associated morbidity and mortality

Concluding Remarks

- **Pneumonia** is a leading cause of childhood morbidity and mortality and **most common manifestation** of **severe pneumococcal disease**.
- **Pneumococcal co-infections** play a **central role** in precipitating severe pneumonia following **respiratory viral infections** in animal-model and human studies.
- **Pneumococcal conjugate vaccine** able to **reduce** burden of hospitalization for **viral-associated pneumonia** by at least one-third.
- **Prevention and management** of pneumococcal disease should form part of **strategy in reducing respiratory virus related complications** and in **influenza pandemic planning**.



PCV as a “Probe” Provides a Minimum Estimate of The Burden of Pneumococccal Pneumonia

$$0.75 \times \frac{VT - NVT}{(0.75 - 0.25)} = 37.5\%$$
$$= 0.5$$

Proportion of
endpoint due to
S. pneumoniae

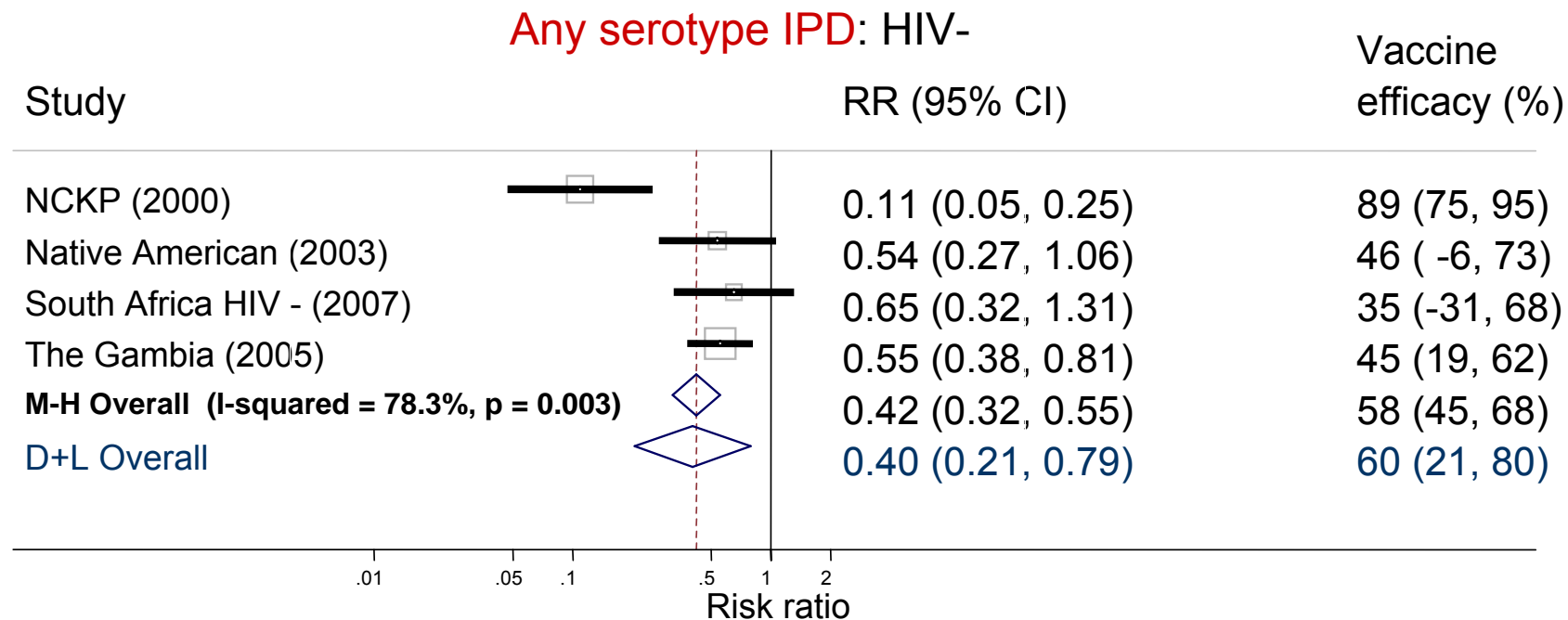
Proportion of disease
due to *S. pneumoniae*
prevented, **irrespective
of serotype.**

Number of simplifying assumptions are made for using PCV as a probe to determine the burden of pneumococcal pneumonia:

- **All of pneumococcal pneumonia present as a specified endpoint.**
- **VE against pneumococcal pneumonia is the same as VE against IPD.**

Meta-analysis: PCV Efficacious Against Any Serotype IPD in Randomized-Controlled Trials (HIV-)

Klugman KP et al. In Pneumococcal Vaccines: The Impact of Conjugate Vaccine; 2008; Chapter 21



Inference: i. Probable differences in total protection against non-bacteremic pneumococcal pneumonia between African and USA-NC children.

ii. PCV only allows for probing of 35-45% of pneumococcal pneumonia preventable with PCV-9. in Africa

PCV Efficacy Studies Under-estimate the Role of Pneumococcus As a Cause of Radiologically Confirmed Pneumonia.

	USA	South Africa (HIV-)	The Gambia
CXR Pneumonia	100	100	100
Proportion of CXR due to pneumococcus	0.75	0.75	0.75
Measured VE against all IPD	89% (75; 95)	35% (-31; 68)	45% (19; 62)
Expected VE (based on IPD) against CXR pneumonia	67%	26%	34%
Measured VE against CXR pneumonia	26% (11; 46)	25% (4; 40)	35% (20; 43)
Expected VE against CXR pneumonia if 100% efficacy against Pnc	29%	75%	75%