Synergistic Roles of the Pneumococcus and Influenza in Disease Severity and Transmission

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RMPRU

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PCV9 Prevents Hospitalization for Pneumonia in Patients with Seasonal Influenza

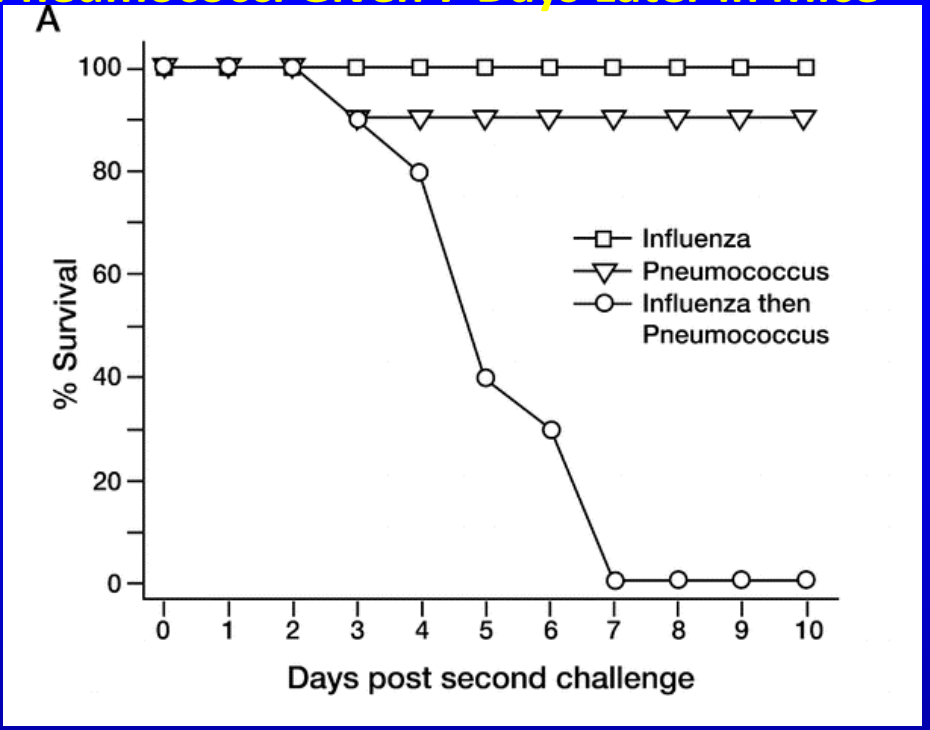
Virus	PCV9 vaccinees	Controls	Vaccine efficacy (95% CI)	P
Influenza	31	56	45 (14 to 64)	0.01

VT pneumococcal bacteremia 0 vs 1

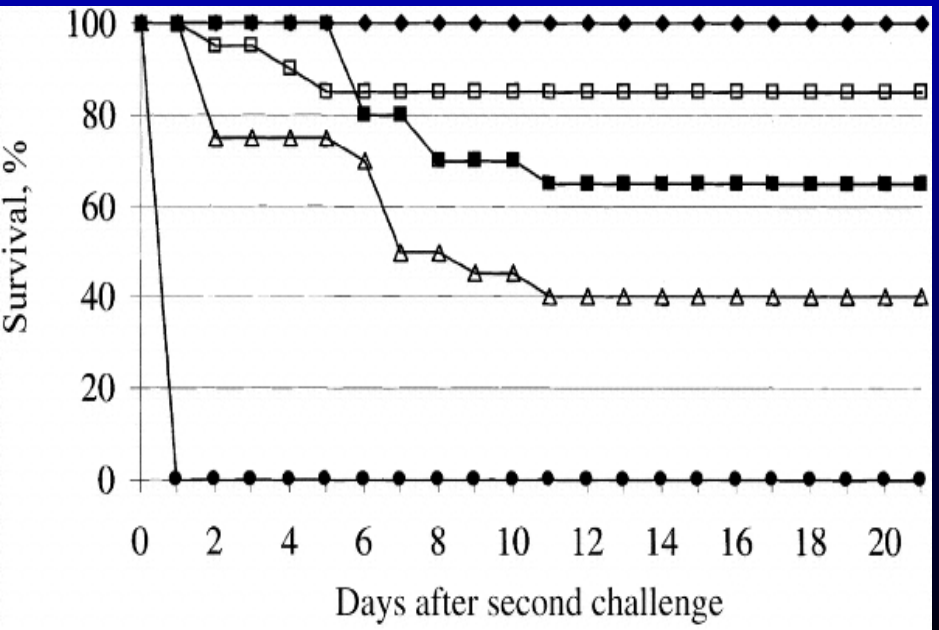
Madhi, Klugman et al. Nature Medicine 2004;10:811–13

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

Peltola and McCullers,
PIDJ, 2004,23,S87-97
0.05 MLD flu and 0.002 MLD pneumo



McCullers and Rehg,
JID, 2002, 186, 341-350
0.3 MLD flu and 0.2 MLD pneumo



Pneumococcus followed by influenza virus
PBS followed by pneumococcus
PBS followed by influenza virus

PBS followed by pneumococcus and influenza virus together

Influenza virus followed by pneumococcus.

Pneumococcus 4 Days After Influenza – Impact on Bacteremia & Lung Infection in Monkeys

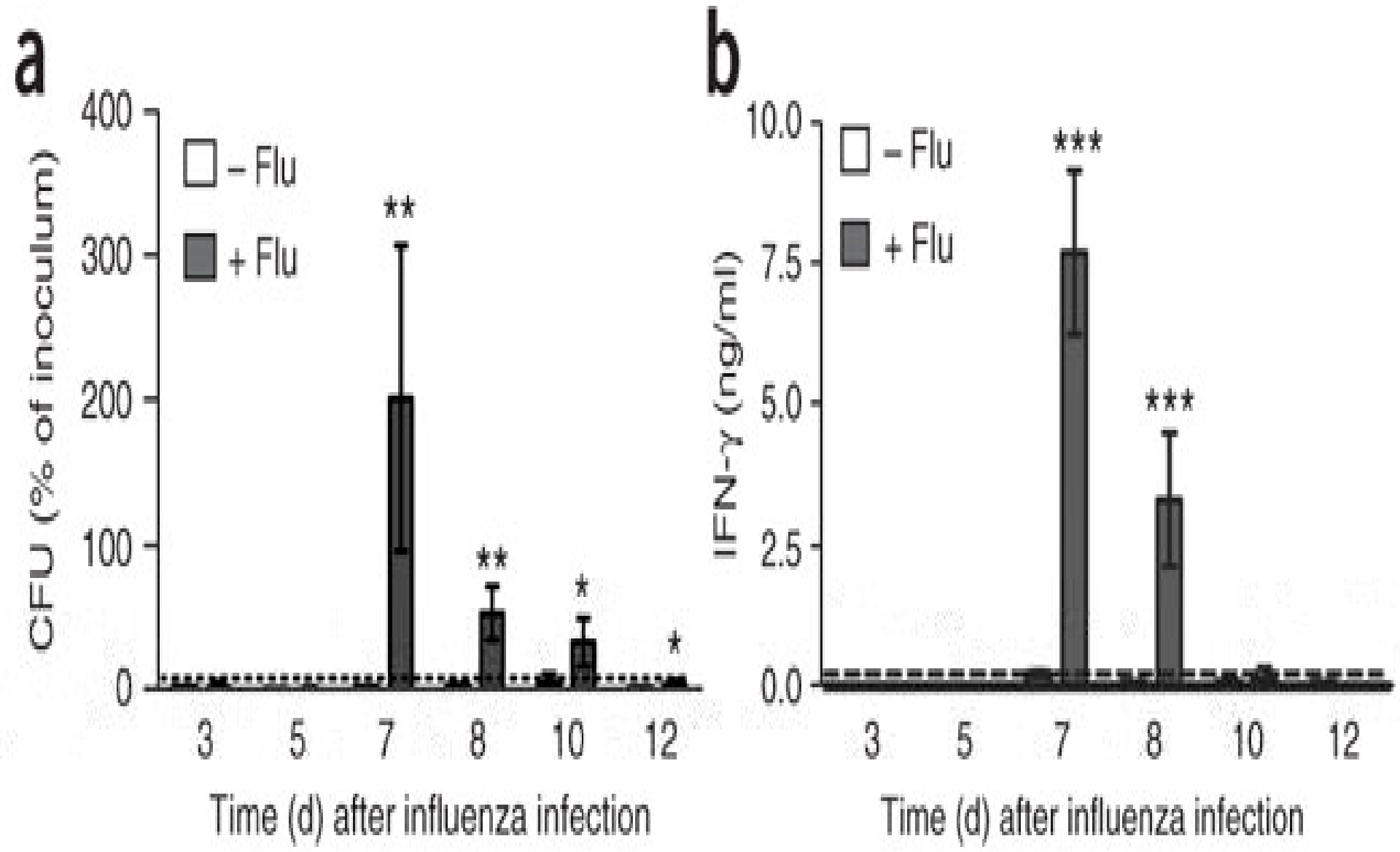
Table 2. Recovery of influenza virus and *Streptococcus pneumoniae* from monkeys at necropsy.

Organism, group*	Mean concentration in†	
	Blood	Lung
Influenza virus		
VC	0	$10^{1.0}$
BC	0	0
S	0	$10^{2.7}$
Streptococcus pneumoniae		
VC	0	0
BC	5.5×10^1	9.0×10^1
S	3.0×10^4	$>1 \times 10^5$

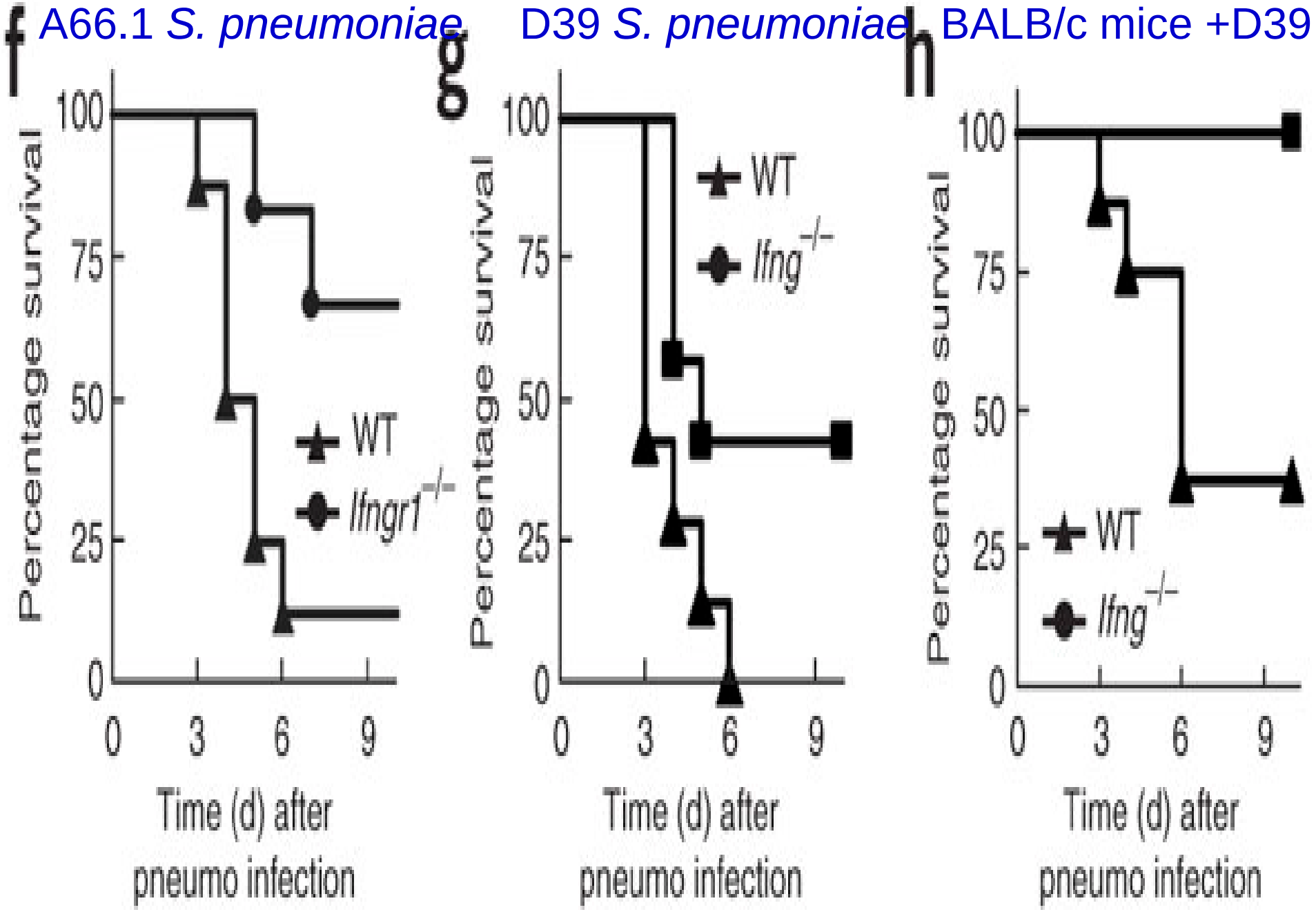
* VC = viral control; BC = bacterial control; S = sequentially infected.

† For influenza virus, mean concentrations are expressed in egg median infectious doses/ml; for *S. pneumoniae* concentrations are expressed in cfu/ml.

Berendt et al, *J Infect Dis* 1975;132:689-93.



Sun and Metzger, Nature Med, 2008, 14, 558 - 64

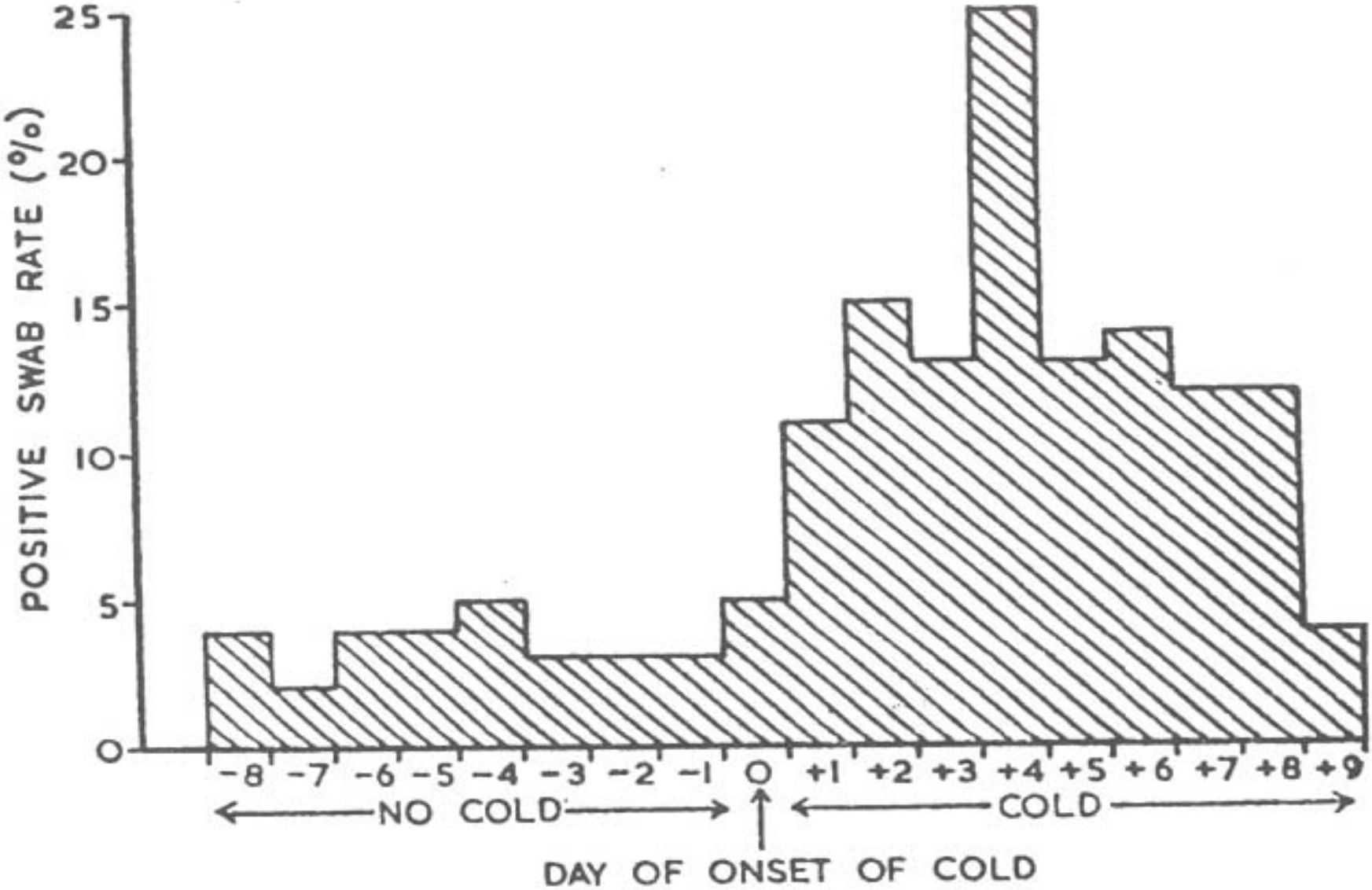


Sun and Metzger, Nature Med, 2008, 14, 558 - 64

Does influenza increase pneumococcal transmission?

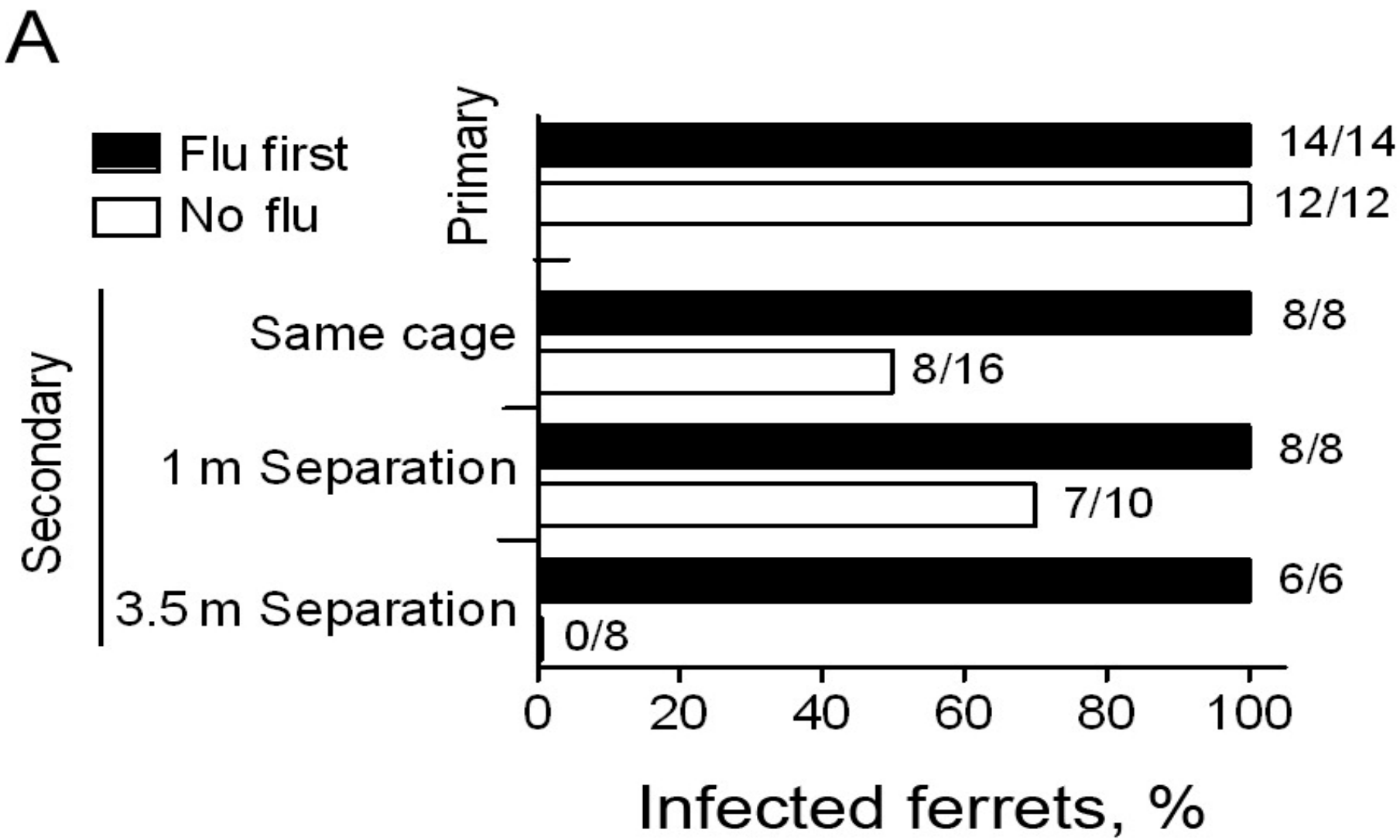
Can the pneumococcus influence influenza transmission?

Culture of *S. pneumoniae* in relation to cold onset in British families



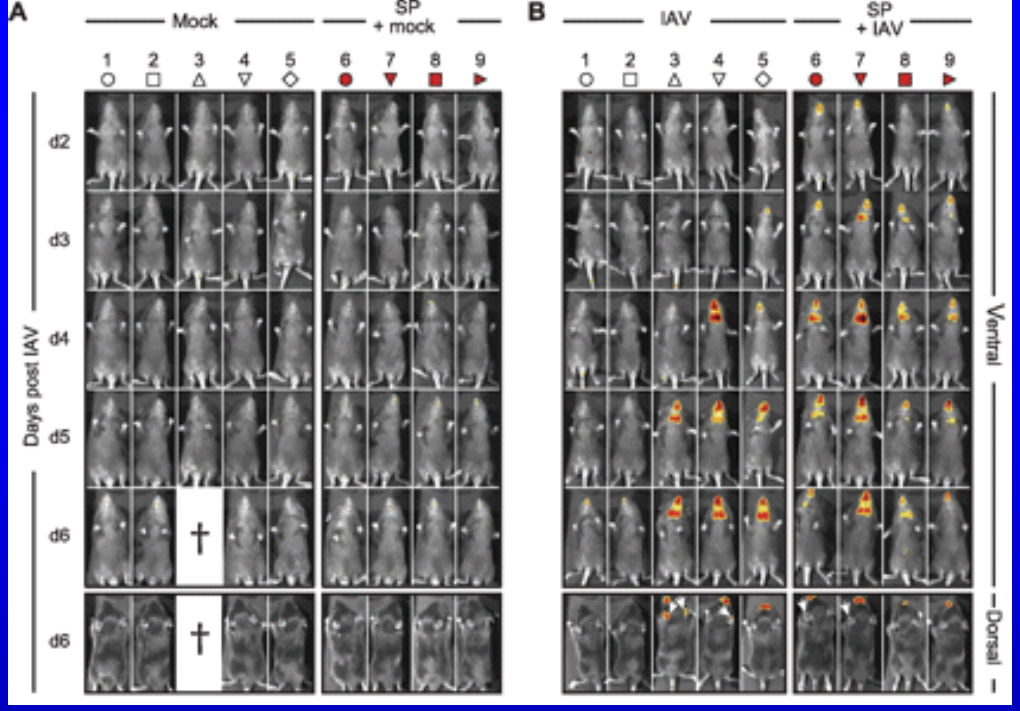
Brimblecombe et al, BMJ, 1958, 1, 119-28

Impact of Influenza on Pneumococcal Acquisition in Ferrets

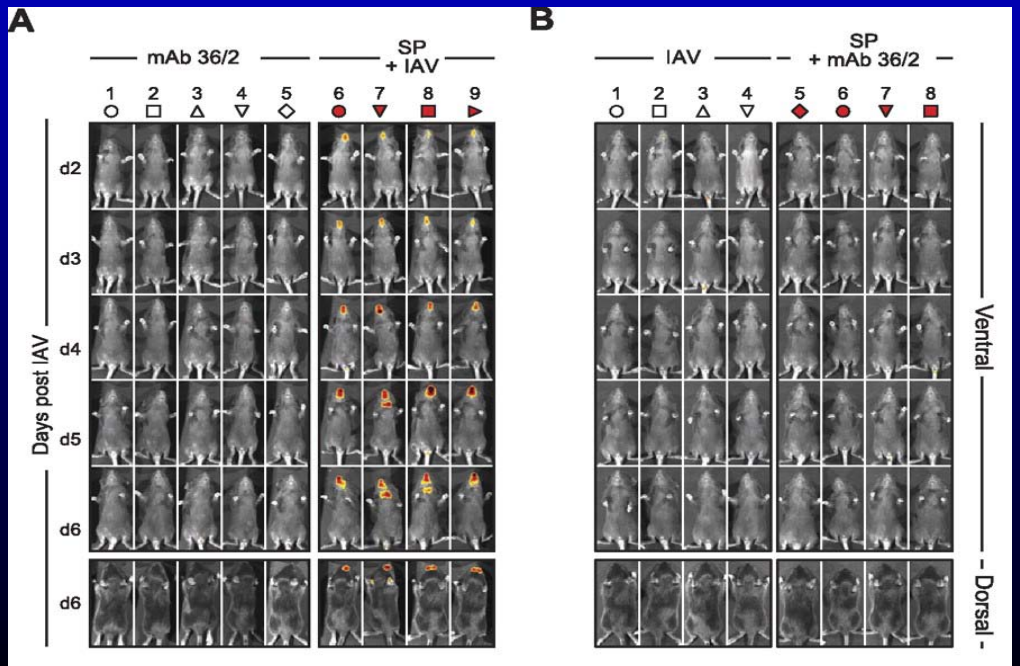


McCullers et al, JID 2010, 202, 1287 - 95

Transmission Studies in Infant Mice



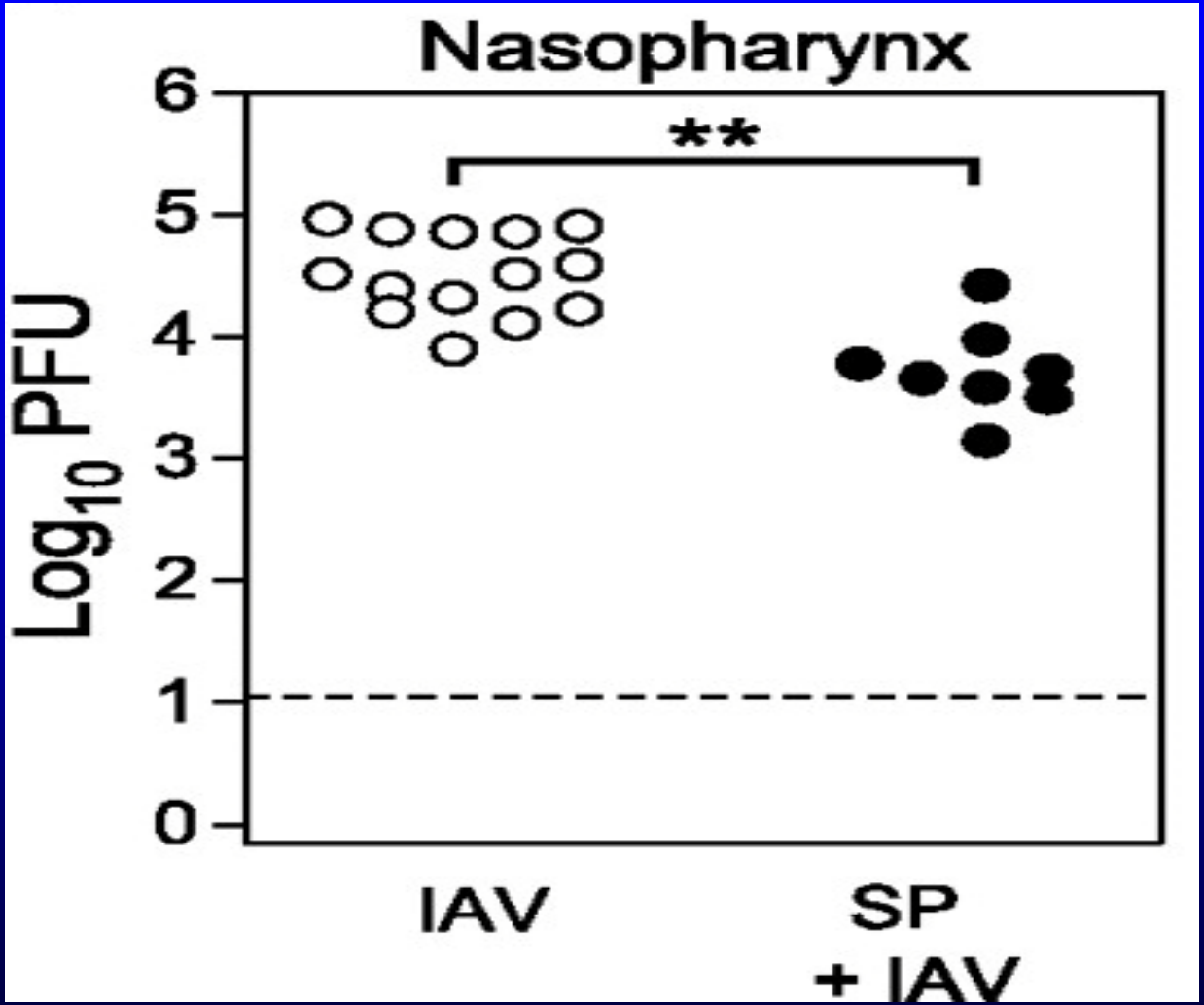
Red symbols indicate index infant mice and open symbols are littermates



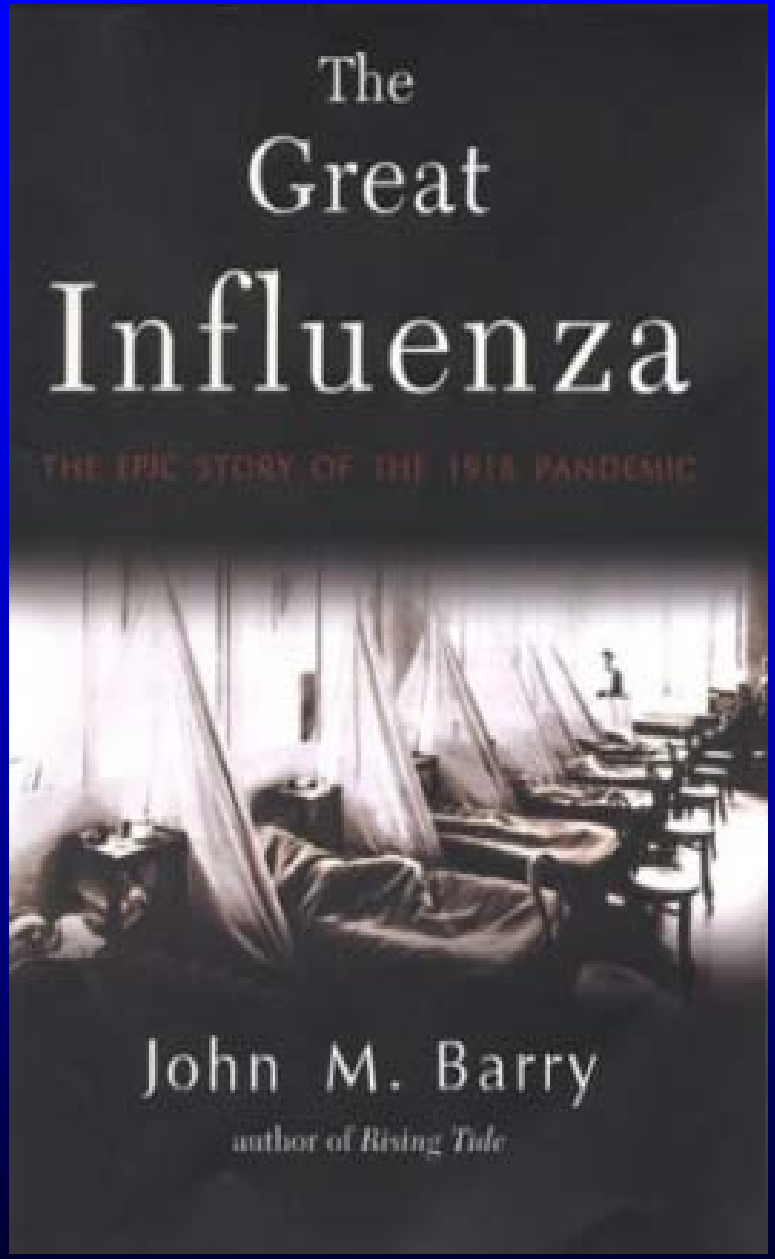
Data show transmission to littermates only if both index mice AND littermates are infected with Flu

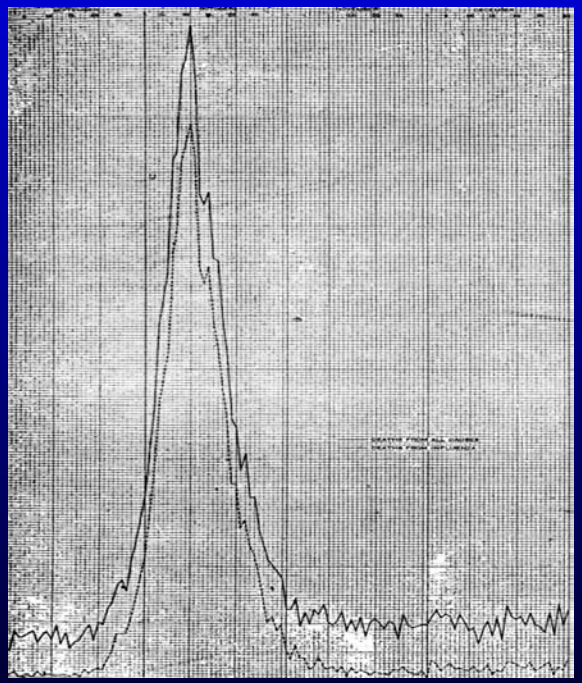
Diavatopoulos et al, FASEB J, 2010, 24, 1789-98

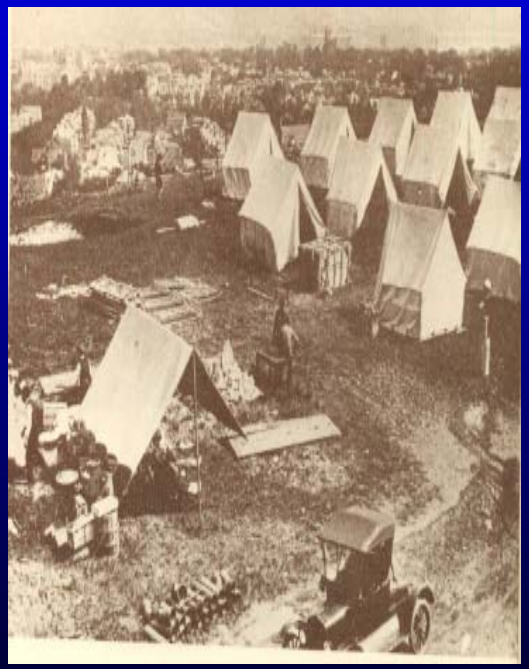
Serotype 19F Pneumococci Given 3 Days Prior to Flu A Decrease Flu Density in NP of Infant Mice



Diavatopoulos et al, FASEB J, 2010, 24, 1789-98


The
Great
Influenza
THE EPIC STORY OF THE 1918 PANDEMIC
John M. Barry
author of Rising Tide

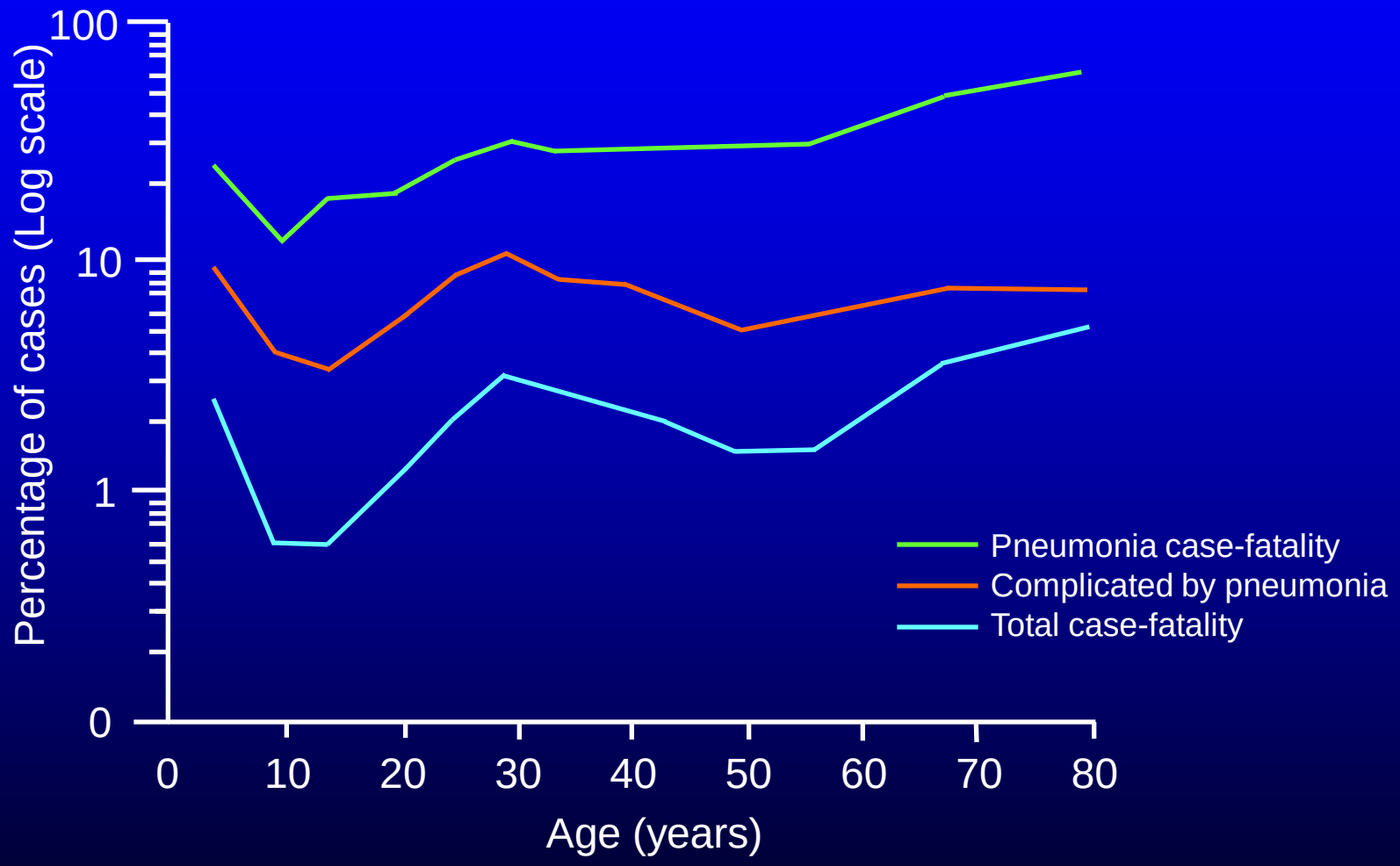




www.stanford.edu/group/virus/uda/fluresponse.html
and www.ninthday.com/spanish_flu.htm [accessed 10/18/04]

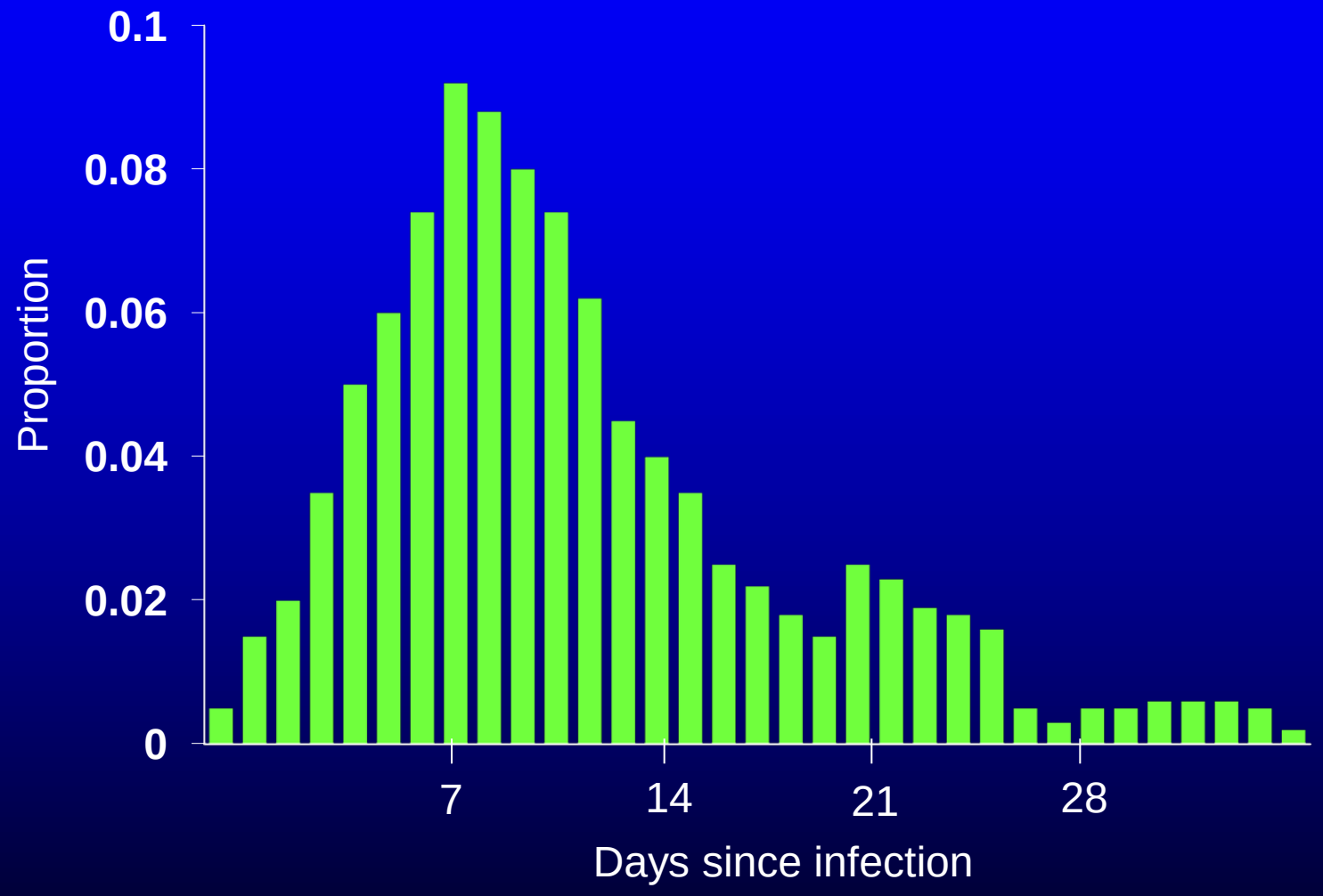
Did bacterial infection (especially the pneumococcus) play a major role in mortality during the 1918 influenza epidemic?

Age-related complications of pneumonia and death, and case fatality rate, 1918–1919 pandemic



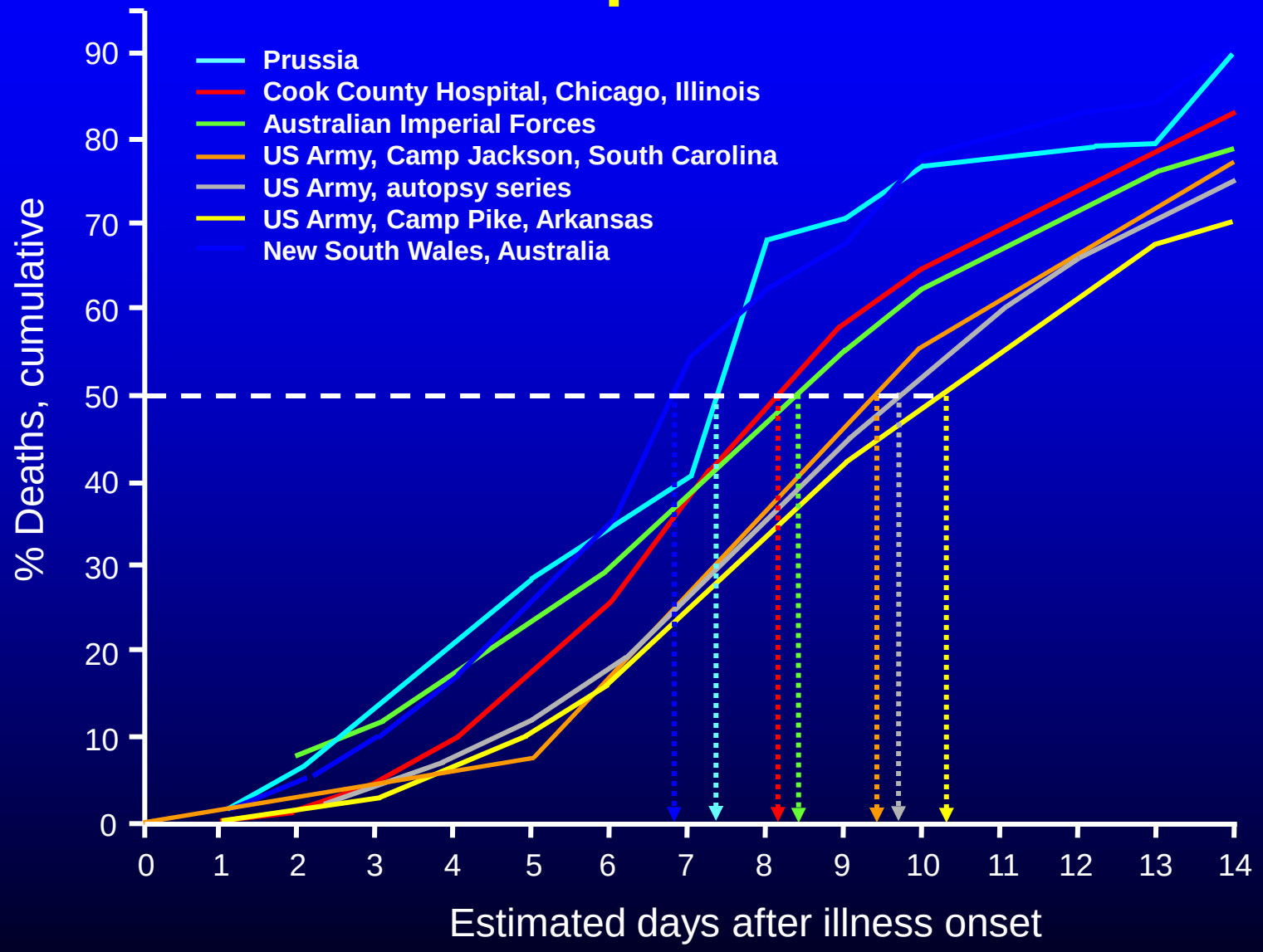
Nicholson, Human Influenza, In Nicholson, Webster, Hay, Textbook of Influenza, Blackwell; Oxford 1998:p237

Timeline post-infection of influenza deaths: 1918 epidemic



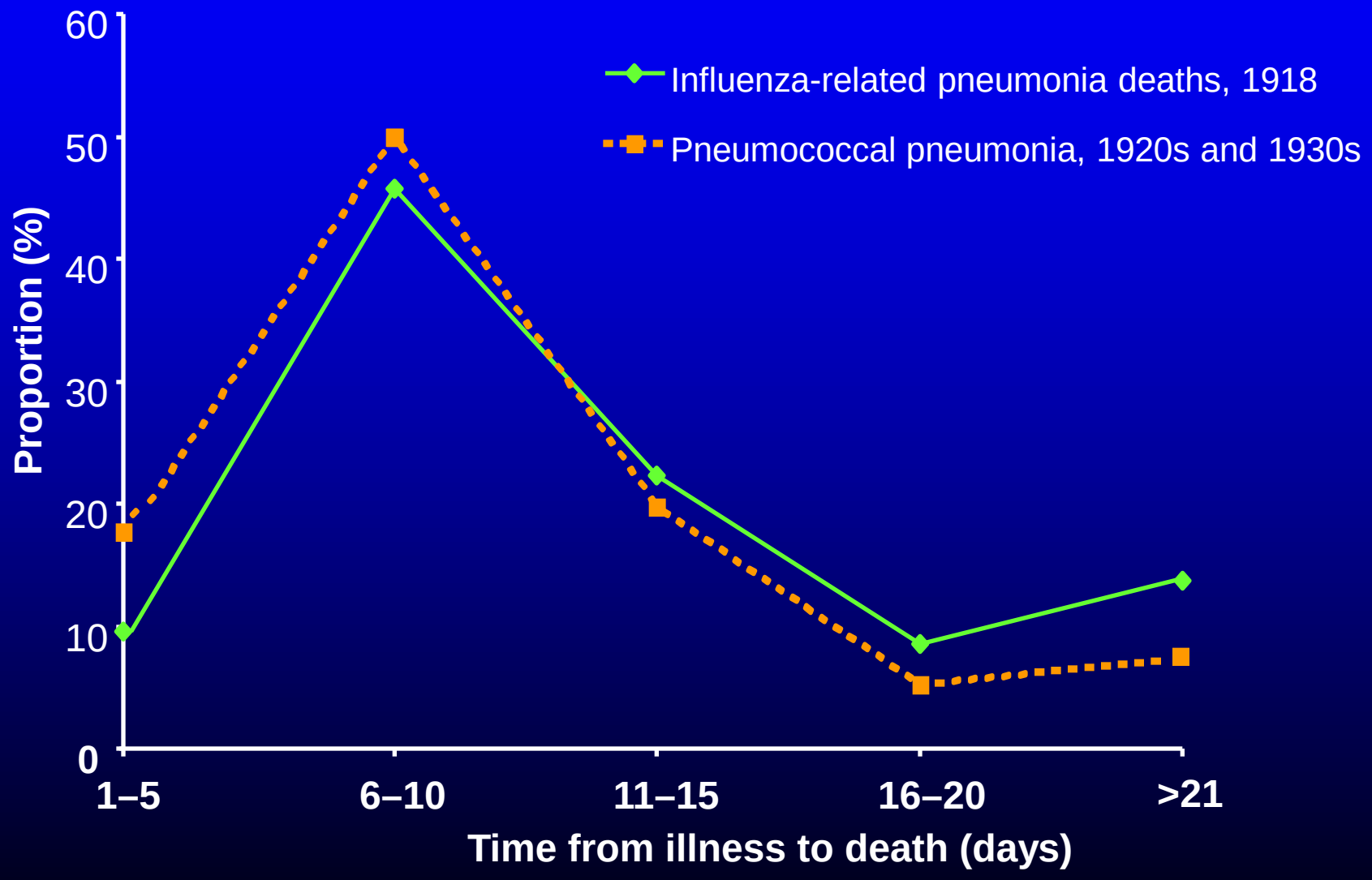
Mills et al. *Nature* 2004;432:904–6, Supplementary fig 2

Timeline post-infection of influenza deaths: 1918 epidemic



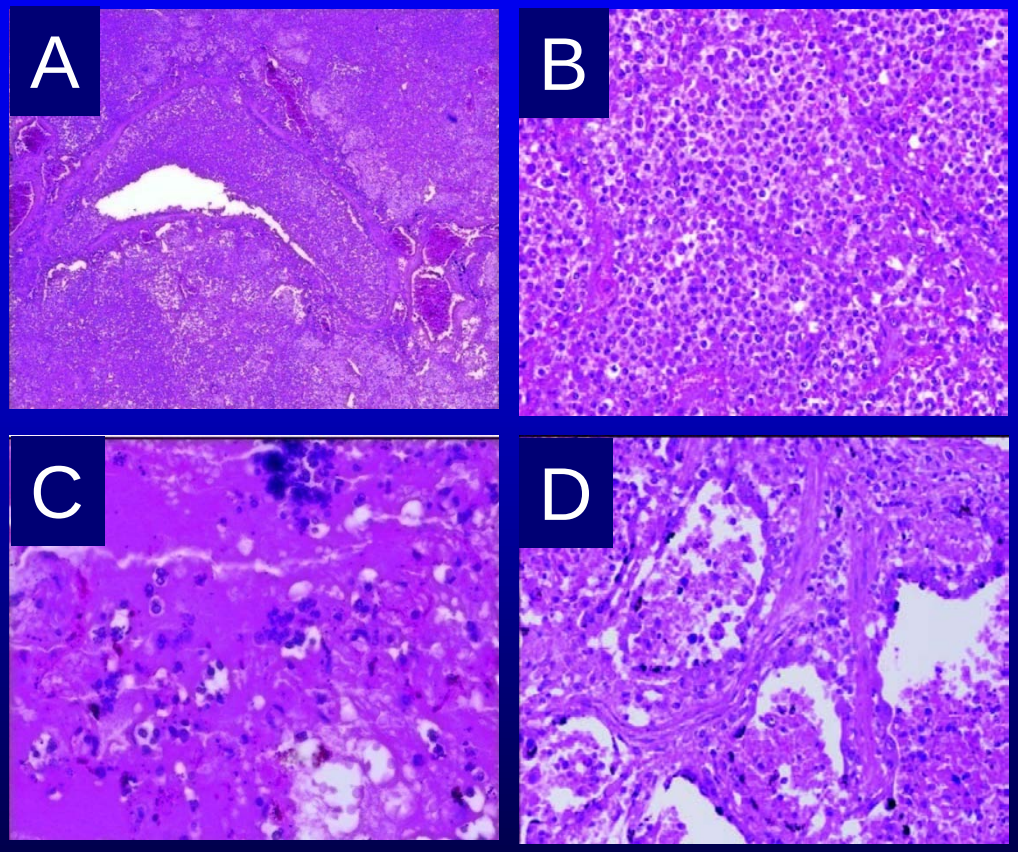
Brundage and Shanks. *EID* 2008;14:1193–99

Time to death distribution



Klugman et al. *EID* 2009;15:346–7

1918 pneumonia deaths due to bacterial infection – 58 autopsies reviewed in 2008



A: Typical picture of severe, widespread bacterial bronchopneumonia

B: Massive infiltration of neutrophils in the airspaces of alveoli associated with bacterial bronchopneumonia

C: Bronchopneumonia with intra-alveolar edema and hemorrhage

D: Bronchopneumonia with evidence of pulmonary repair

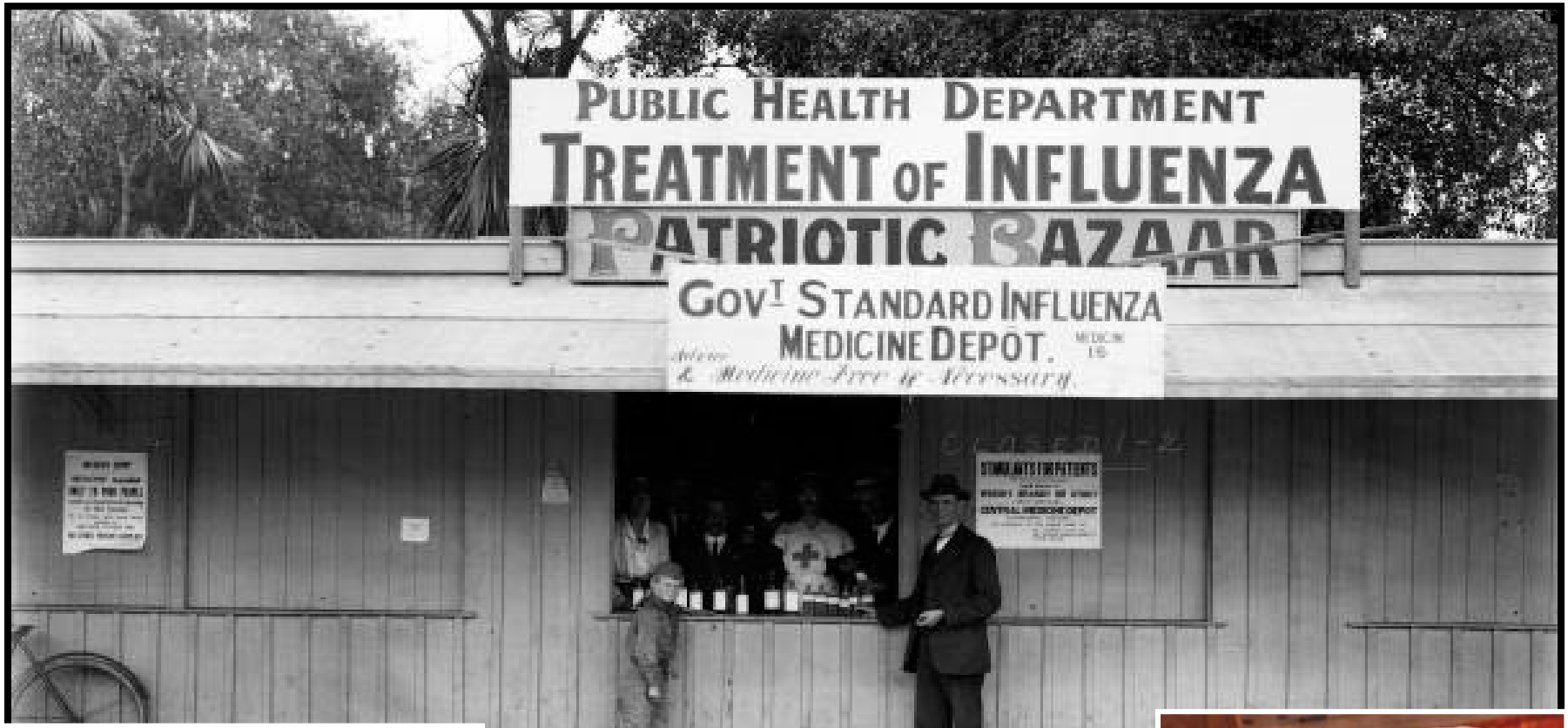
Morens et al. *JID* 2008;198:962–70

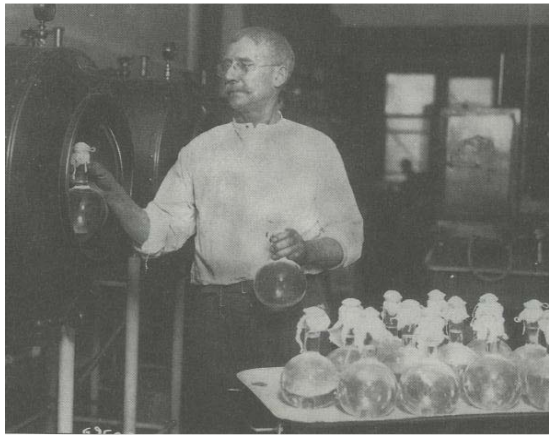
Positive Blood Cultures in Pneumonia Cases During 1918 Pandemic

Table 1. Culture Results for Patients during the 1918 Pandemic, According to Type of Culture and Pneumonia Status at the Time of Culture.*

Type of Culture and Population	No. of Studies	Positive Cultures	No. Positive for Pneumococci	No. Positive for Hemolytic Streptococci	No. Positive for *Staphylococcus aureus*	No. Positive for Other or Undetermined Bacteria
		no./total no. (%)				
Antemortem blood cultures						
Patients without pneumonia						
Military	5	0/323	0	0	0	0
Civilian	5	1/86 (1)	0	1	0	0
Total	10	1/409 (<1)	0	1	0	0
Patients with pneumonia						
Military	16	290/2042 (14)	238	49	2	3
Civilian	8	81/323 (25)	36	32	2	11
Total	24	371/2365 (16)	274	81	4	14
Patients with documented, subsequently fatal pneumonia						
Civilian	3	18/45 (40)	8	1	0	9
Antemortem pleural-effusion and lung cultures						
Military	5	182/224 (81)	140	55	0	10
Civilian	2	45/61 (74)	9	31	1	5
Total	7	227/285 (80)	149	86	1	15

Chien, Klugman, Morens, NEJM, 2009, 361,2582-3

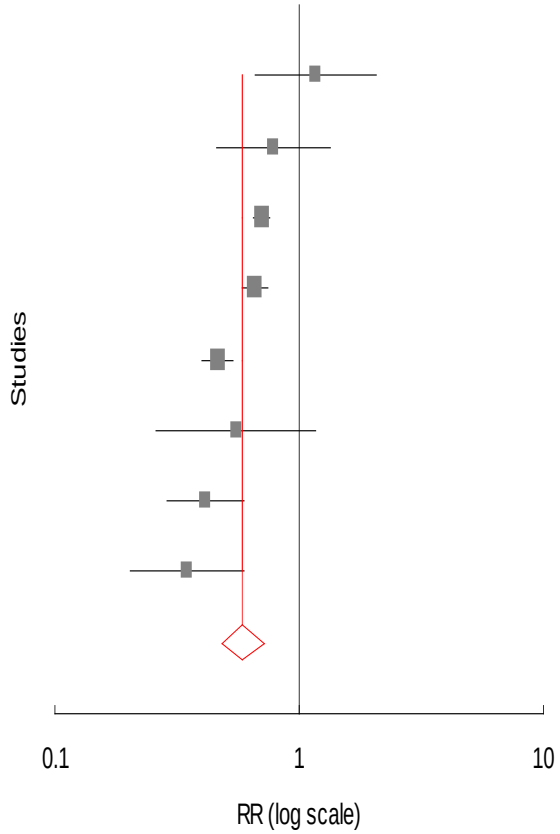




Picture Courtesy of David Morens, NIH

Meta – Analysis of Pneumococcal Vaccine Studies – Impact on Pneumonia Hospitalization

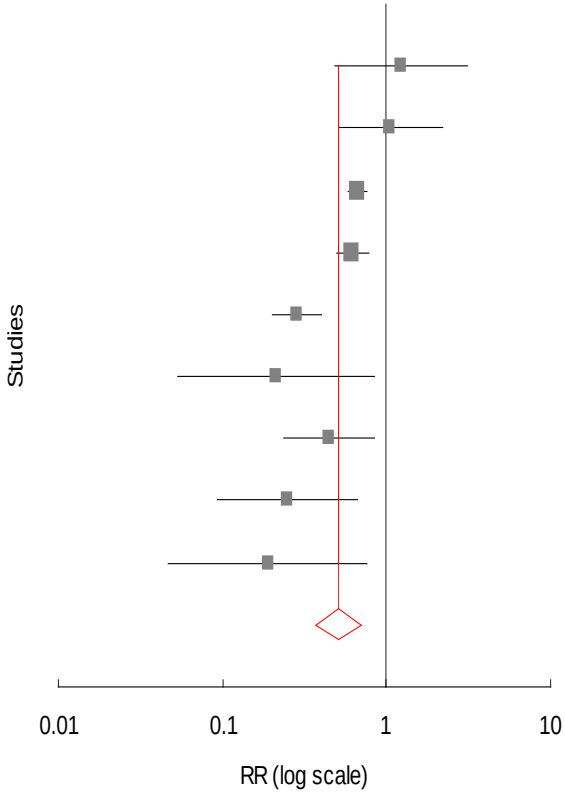
Study ID	Year	Exposed n[e](E=1)/n[e]	Control n[c](E=1)/n[c]	Weight (%)	Association measure with 95% CI
McCoy	Civilian	23/119	17/103	7.00%	1.17 (0.66 to 2.07)
Waters	Civilian	13/89	88/471	8.00%	0.78 (0.46 to 1.34)
Rosenow	Civilian	745/13666	7534/97258	21.00%	0.7 (0.65 to 0.76)
Cadham	Civilian	300/5203	1869/21285	20.00%	0.66 (0.58 to 0.74)
Cherry	Civilian	180/1148	676/2002	19.00%	0.46 (0.4 to 0.54)
Erye	Military	9/92	17/96	5.00%	0.55 (0.26 to 1.18)
Leishman	Military	26/221	583/2059	12.00%	0.42 (0.29 to 0.6)
Cadham	Military	17/282	41/238	8.00%	0.35 (0.2 to 0.6)
META-ANALYSIS:		1313/20820	10825/123512	100%	0.59 (0.49 to 0.71)



Chien, Klugman, Morens, JID, 2010, 202, 1639-48

Meta – Analysis of Pneumococcal Vaccine Studies – Impact on Deaths

Study ID	Year	Exposed n[e](E=1)/n[e]	Control n[c](E=1)/n[c]	Weight (%)	Association measure with 95% CI
McCoy	Civilian	10/119	7/103	7.00%	1.24 (0.49 to 3.13)
Watters	Civilian	8/89	40/471	10.00%	1.06 (0.51 to 2.18)
Rosenow	Civilian	276/13666	2951/97258	20.00%	0.67 (0.59 to 0.75)
Cadham	Civilian	85/5203	563/21285	19.00%	0.62 (0.49 to 0.77)
Cherry	Civilian	36/1148	218/2002	17.00%	0.29 (0.2 to 0.41)
Minaker	Civilian	2/111	3716/43671	4.00%	0.21 (0.05 to 0.84)
Erye	Military	38/1008	11/130	11.00%	0.45 (0.23 to 0.85)
Cadham	Military	5/282	17/238	7.00%	0.25 (0.09 to 0.66)
Leishman	Military	2/221	98/2059	4.00%	0.19 (0.05 to 0.77)
META-ANALYSIS:		462/21847	7621/167217	100%	0.51 (0.37 to 0.69)



Chien, Klugman, Morens, JID, 2010, 202, 1639-48

Pneumococcal Vaccines and Flu Preparedness

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 infection 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 symptoms (*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

www.sciencemag.org SCIENCE VOL 316 6 APRIL 2007

Published by AAAS

Klugman and Madhi, Science, 2007, 316, 49 – 50.

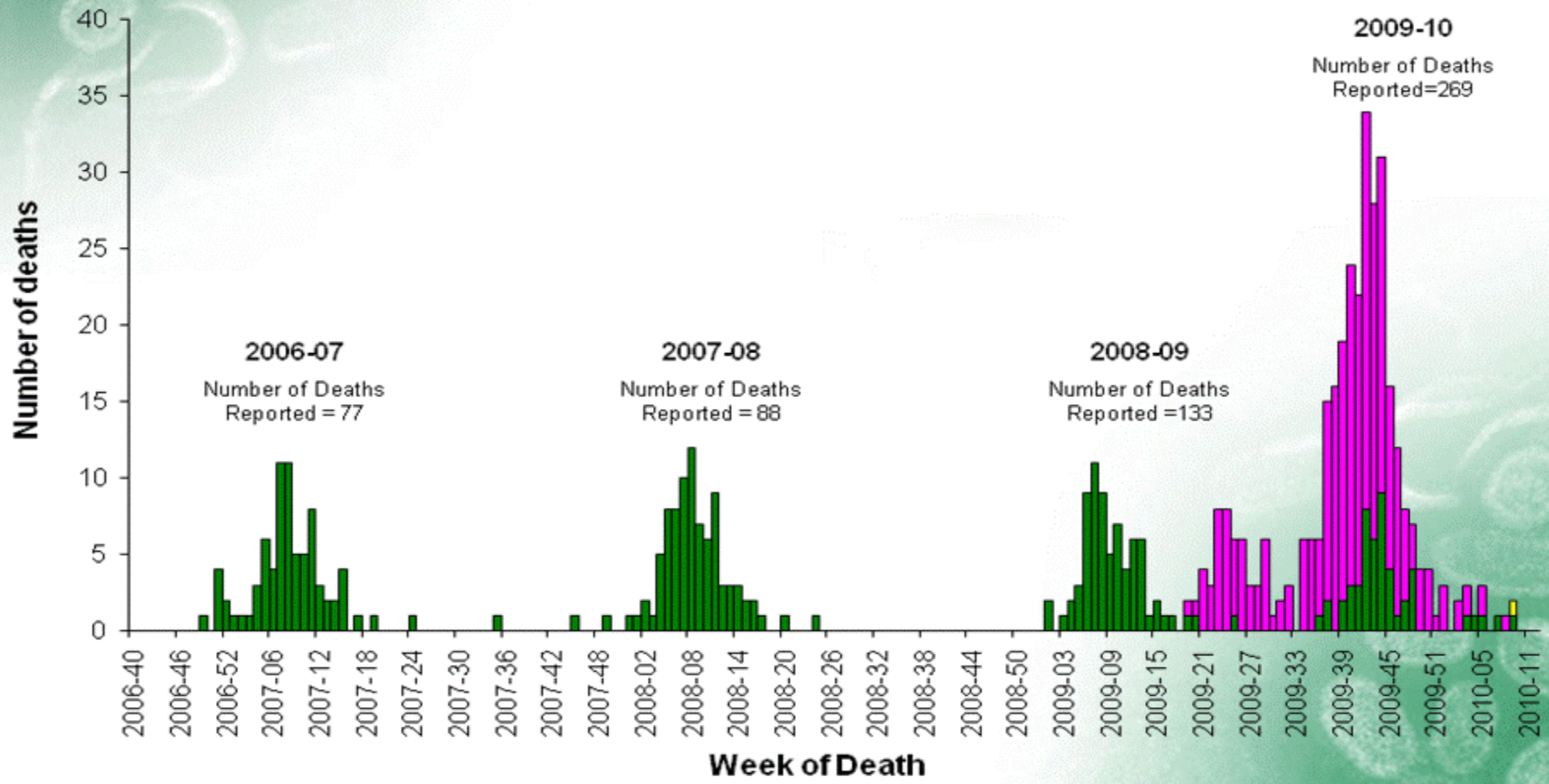
What was the role of bacterial infections in deaths and severe disease during the 2009 H1n1 influenza A pandemic?

2009 H1N1 Pandemic Autopsy Studies

FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
Centers for Disease Control and Prevention

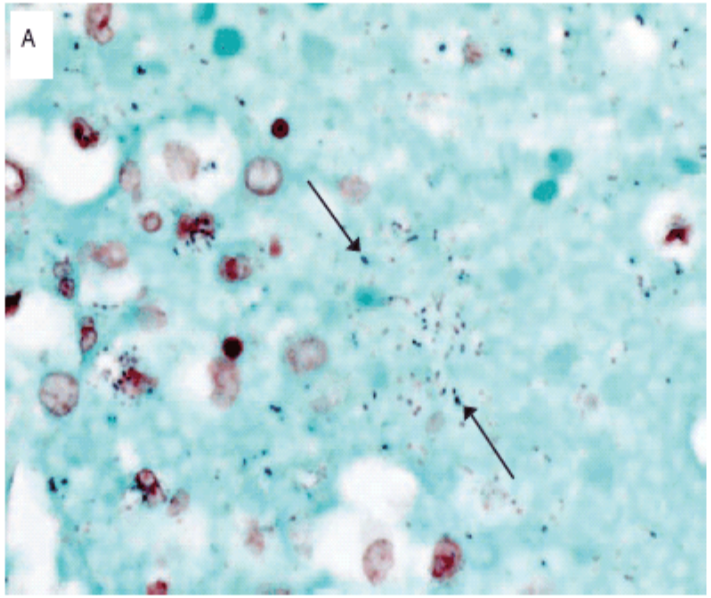
Number of Influenza-Associated Pediatric Deaths by Week of Death: 2006-07 season to present

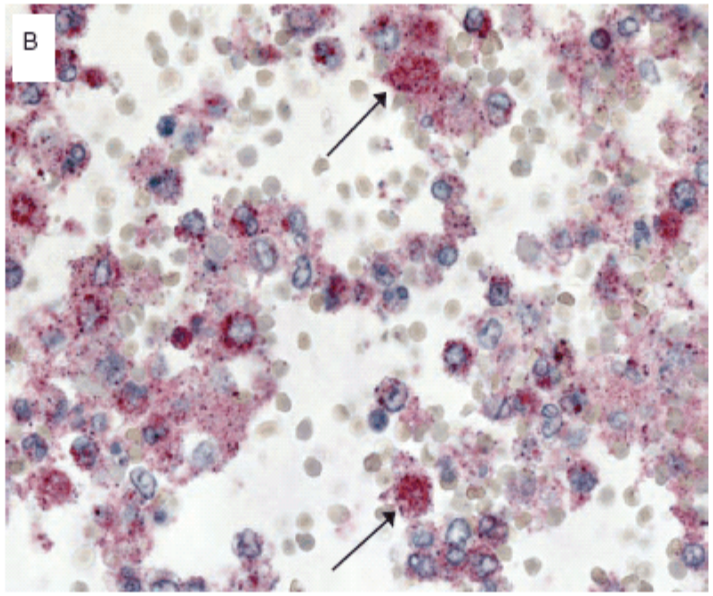


Update on Pediatric Deaths Through March 27, 2010

- Among the 269 deaths in children, 144 children had specimens collected for bacterial culture from normally sterile sites and 49 (34.0%) of the 144 were positive
- "Pneumococci were" identified in 11 (22.4%) of the 49 children, and *Staphylococcus aureus* was identified in 14 (28.6%) of the 49 children. Four *S. aureus* isolates were sensitive to methicillin, nine were methicillin resistant, and one did not have sensitivity testing performed. Thirty-two (65.3%) of the 49 children with bacterial coinfections were five years of age or older, and 17 (34.7%) of the 49 children were 12 years of age or older.

http://www.cdc.gov/flu/weekly/ Accessed 6 April 2010





Bacterial Infections Lung Tissue of 22 / 77 US Patients (29%) Who Died of H1N1 Pandemic Influenza

10 *S. pneumoniae* (no confirmed VT pneumo) (15B/C; 19A; 10F/10C/33C; 15A/F; 11A/D; 6A/B x 2)
7 *S. aureus*
6 *S. pyogenes*
2 *S. mitis*
1 *H. influenzae*
4 Co - infections

(A) Lillie- Twort Gram stain of lung tissue
(B) Immunohistochemical staining of multiple *S. pneumoniae*

MMWR Oct 3, 2009

34 Autopsies of Proven Pandemic H1N1 Deaths in New York

- 62% were 15 to 50 years old
- Comorbidity was found in 91% (obesity BMI > 30) in 72%
- Histologic (Gram stain) and microbiologic (culture or PCR) evidence of bacterial co – infection in 55%
- 30 had post mortem cultures or PCR
- 10/30 (33%) were positive
- 7/10 pneumococci; 3 GAS;1 MRSA (1pt had both pneumo and GAS)

Gill et al, Arch Pathol Lab Med, 2010, 134, 235 - 243

Autopsy Study H1N1 2009 Deaths - Brazil

- Among 21 patients who had died of confirmed H1N1 bacterial co –infection was found by bronchial aspirate or tissue PCR in 8 patients (38%), including 5/6 with necrotizing bronchiolitis.
- There was marked interferon gamma expression
- Six of the 8 bacteria were *Streptococcus pneumoniae*.

Mauad et al, Am J Resp Crit Care med, 2010, 181, 72-9.

Bacterial Infections Associated with Pediatric Mortality from 2009 H1N1 - UK

- Bacterial co-infection was clinically presumed in 14 (20%) deaths and confirmed in a further 14.
- The most common sites of bacterial infection were the lung (20), blood (six), and cerebrospinal fluid (two).
- Pathogens most frequently isolated were group A *Streptococcus* (three cases), *S pneumoniae* (three cases), *S aureus* (three cases), and *Haemophilus influenzae* (three cases).
- Excluding long-term inpatients, pre-hospital antibiotics had been given to 23 of the 65 children who died (35% of deaths). All inpatients received antibiotics.

Sachedina, Donaldson, Lancet 2010, 376, 1846 - 54

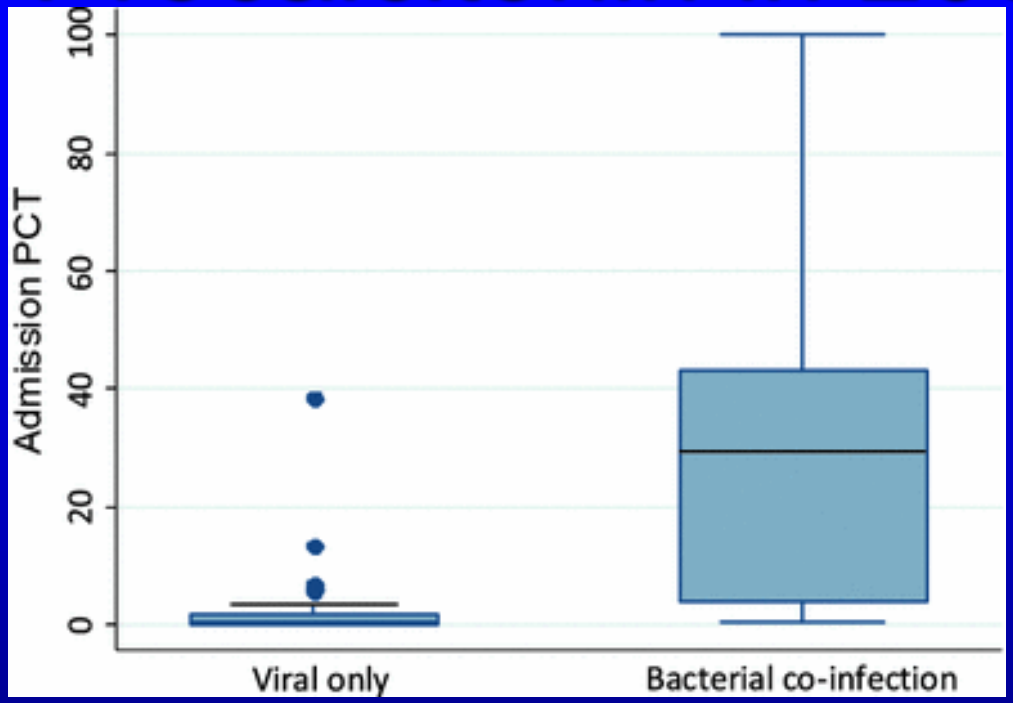
2009 H1N1 Pandemic Disease Severity

NP Pneumo by Mass Tag PCR Predicts 2009 H1N1 Severity - Argentina

- Pneumo was found in 22/39 (56%) of cases who were hospitalized (19) or died (20)
- Rate in mild cases from community was 40/160 (25%)
- Severe disease occurred mostly in the young (<6) or old (>55) (54% vs 13%)
- When considering low risk by age (6 – 55 year olds) severe disease was predicted by pneumo in NP (OR 7.4 CI 2.7 – 20) but when adjusted for comorbidity and RSV OR increased to 125 (17-928)

Palacios et al, PLoS One, 2009, 4, e8540

Procalcitonin in 2009 H1N1 Flu



French ICU study of severely ill
patients with proven H1 N1 and no previous antibiotics

Bacteria identified in 46% - mostly pneumo
Streptococcus pneumoniae (*n* = 26, 54%), *Staphylococcus aureus* (*n* = 13, 17%), group A *Streptococcus* (*n* = 4, 8%) and other microorganisms (*n* = 5, 11%).

PCT levels of 0.8 µg/l or more were associated with a more severe outcome (invasive ventilation and/or death in ICU) (OR 7; 95% CI 1.75–28.4; *P* = 0.001).

Cuquemelle et al, Intensive Care Med, 2011, 37, 796 - 800

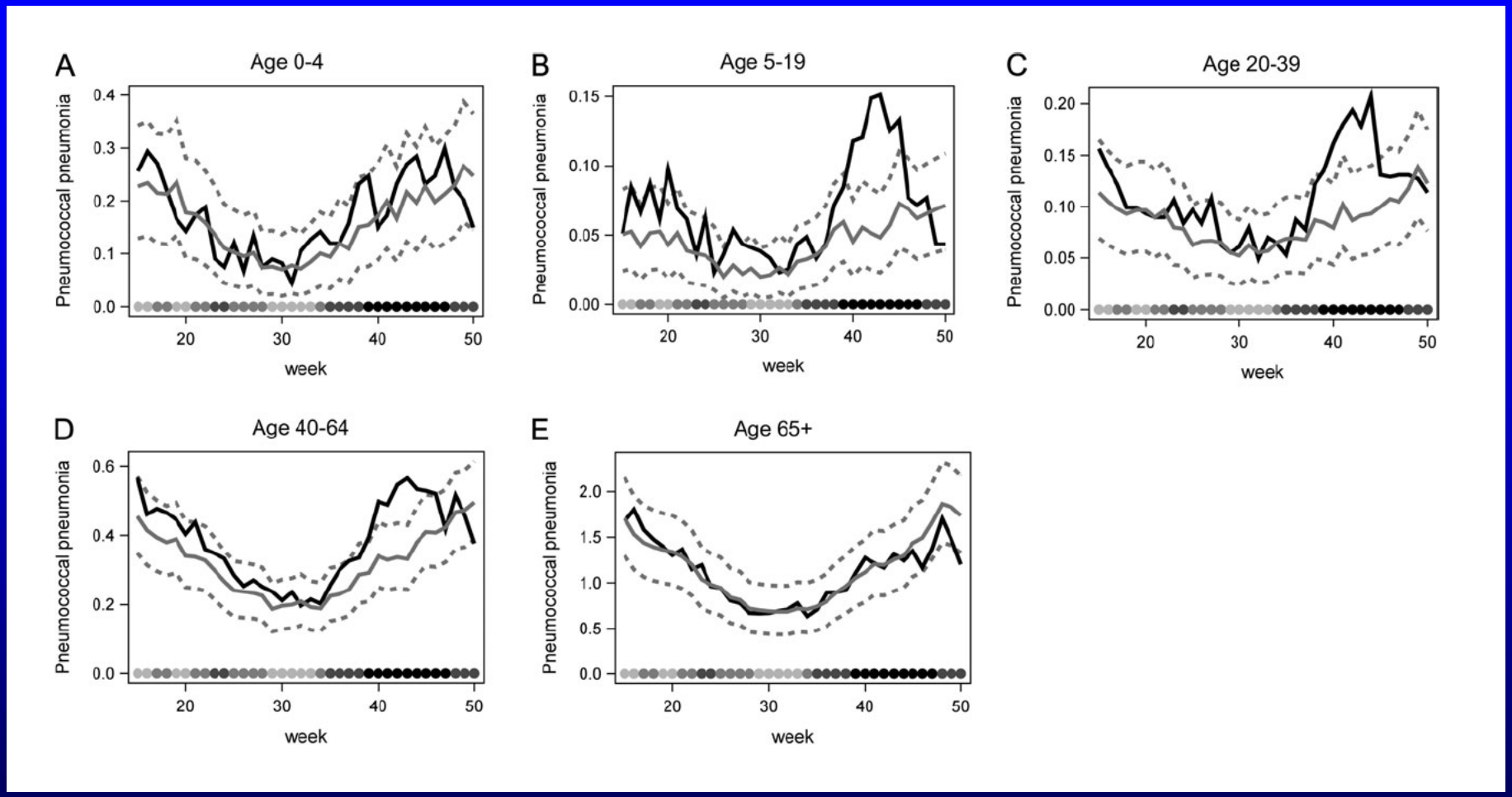
Pneumococcal Co-Infection (Majority By ICT) in Spanish Adults with 2009 H1N1 and at Least One High Risk Condition

- Of 100 patients 14 had pneumo (8 ICT (Binax) only; 5/6 remaining ICT positive + BC (2) or sputum culture (4). These patients compared to the remaining 86 had:
- Pneumonia 9 vs 15 (64% vs 17% $p<0.001$)
- Hospital admission 12 vs 21 (86% vs 24% $p<0.001$)
- ICU admission 2 vs 2 (14% vs 2% $p = 0.034$)
- CURB-65 $\geq$ 2 5 vs 3 (36% vs 4% ($p<0.001$)
- Higher CRP (190.7 mg/L vs. 26.6 mg/L; $p <0.001$).

Masia et al, EID, 2011, 17, 1475-8

2009 H1N1 Pandemic Impact on Pneumonia Admissions and on IPD Burden

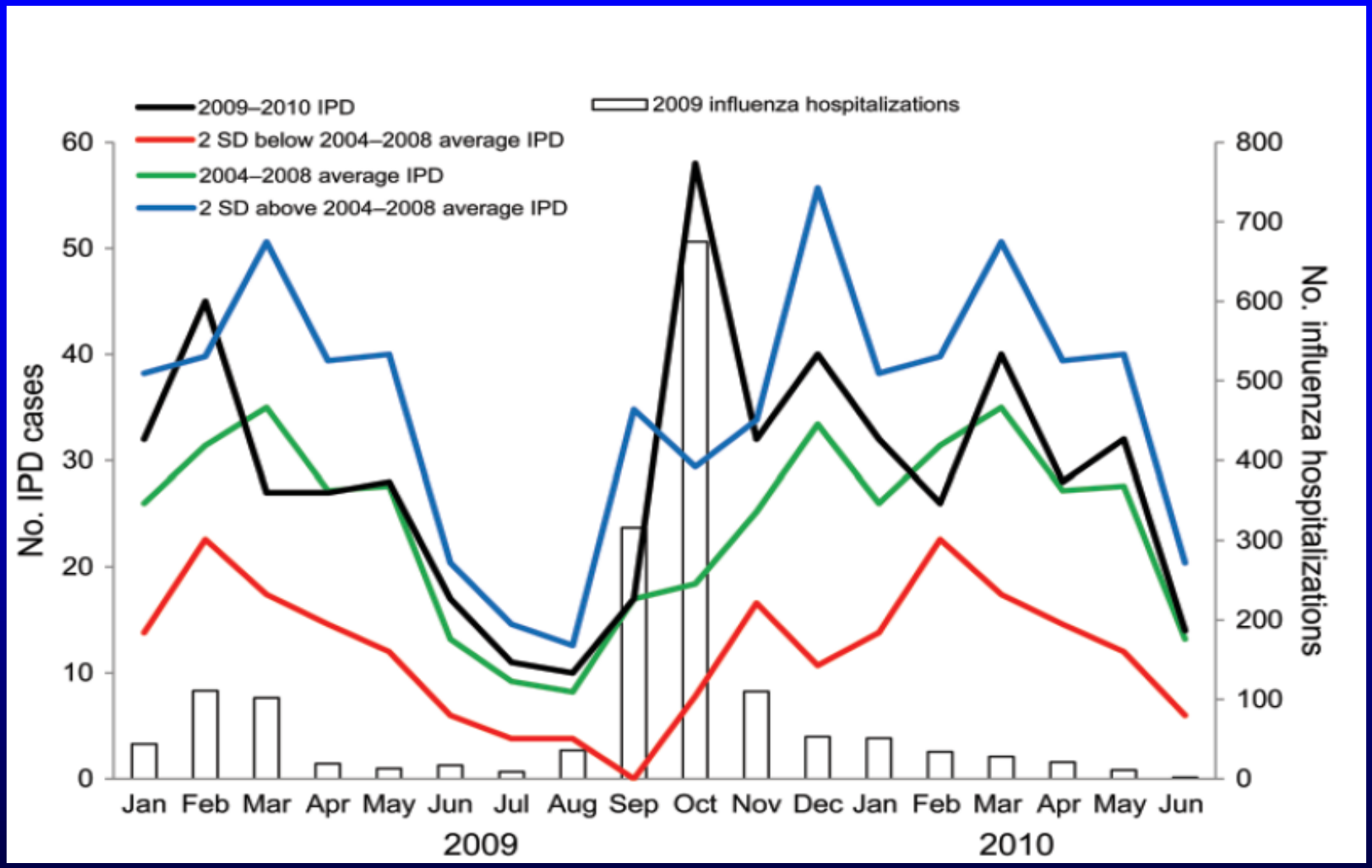
Excess Pneumococcal Pneumonia Hospitalizations in 2009 Compared to 2003 – 8 Baseline - US



Note excess pneumococcal pneumonia hospitalization associated with flu activity in 5 – 64 year olds compared to 95% CI of previous seasons with no excess in the elderly

Weinberger et al, JID, 7 Dec 2011 advance access

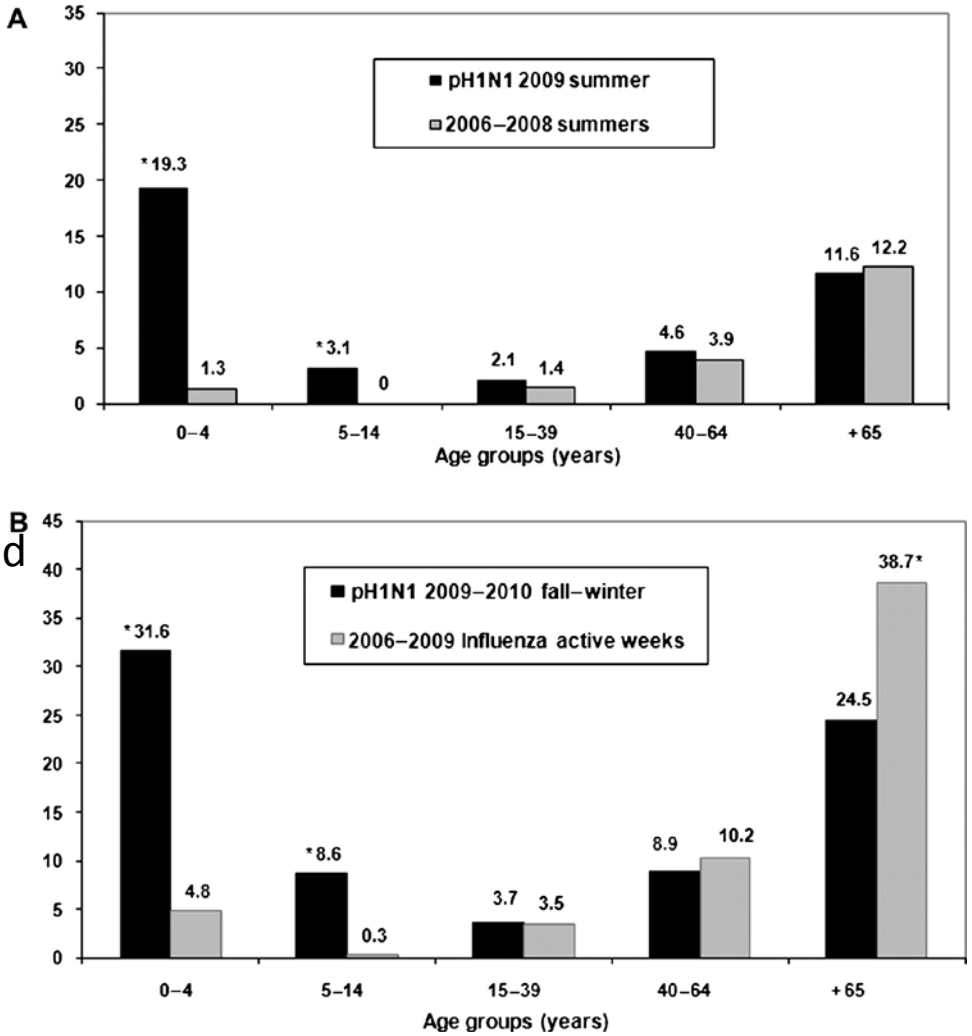
Impact of 2009 H1 N1 on IPD, Denver



Nelson et al, EID, 2012, 18, 208-16

Eight Israeli Hospitals: *Streptococcus pneumoniae* bacteremia rates (per 100 000 person-years), in differing age groups during the study years at the summers (A) and the winters (B).

Note that a potential
Confounder is that
Several fold higher
Numbers of blood
Cultures were performed
During the pandemic



Tasher D et al. Clin Infect Dis. 2011;53:1199-1207

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Clinical Infectious Diseases

Pneumococcal pneumonia /1000 in 1918 – like pandemics

	$R_E = 1.8$		$R_E = 1.5$		$R_E = 1.2$	
Pneumococcal carriage	**No PCV**	**PCV**	**No PCV**	**PCV**	**No PCV**	**PCV**
5%	1.96	1.08	1.47	0.81	0.73	0.40
10%	3.78	2.08	2.85	1.57	1.42	0.78
20%	7.00	3.85	5.31	2.92	2.68	1.47
40%	11.74	6.45	9.05	4.98	4.68	2.57

1918 flu had 40% carriage;
No PCV and no oseltamivir
To reduce RE from 1.8 to 1.2
Pneumonia rate 11.74 /1000

Today in young adults a similar virus would lead to a pneumonia rate 10 fold lower Ie. 1/1000 and mostly treatable with antibiotics

No. needed to prophylax to prevent a case of pneumococcal pneumonia

	$R_E = 1.8$		$R_E = 1.5$		$R_E = 1.2$	
Pneumococcal carriage	**No PCV**	**PCV**	**No PCV**	**PCV**	**No PCV**	**PCV**
5%	188.6	343.0	201.6	366.5	222.0	403.6
10%	98.8	179.6	105.1	191.1	115.1	209.3
20%	54.4	99.0	57.4	104.4	62.1	112.9
40%	33.9	61.7	35.2	63.9	36.9	67.1

Wen, Levin, Klugman
PLoS One. 2012;7:e29219

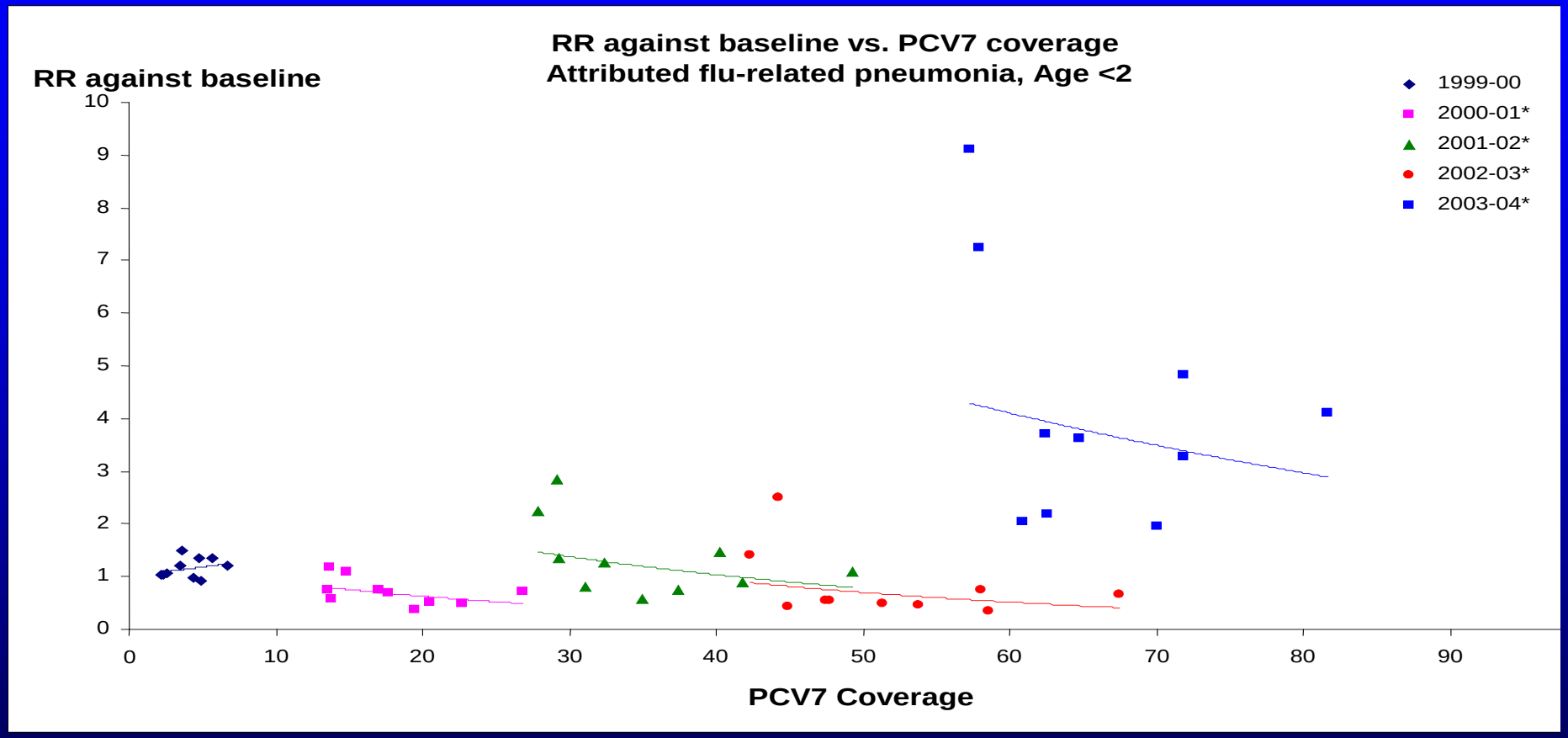
Back to Seasonal Flu and Pneumo

Flu Vaccine Reduces Bacterial Pneumonia in Flu Season

- "In the season cohort (2,368 patients) CAP in vaccinated patients was significantly less severe according to most analysed parameters (CURB index ≥1: OR 0.76, 95% CI 0.60–0.98; procalcitonin ≥2.0 $ng \cdot mL^{-1}$: OR 0.53, 95% CI 0.35–0.81; procalcitonin ≥0.5 $ng \cdot mL^{-1}$: OR 0.71, 95% CI 0.51–0.99) and these patients showed a significantly better overall survival within the 6-month follow-up period (HR 0.63, 95% CI 0.45–0.89). Within the off-season cohort (2,632 patients) there was no significant influence of vaccination status on CAP severity or disease outcome".
- Of the flu vaccinated 28% received PPV compared to 2.5% of those unvaccinated for flu – yet the benefits of reduced pneumonia severity and mortality were confined to flu season

Tessmer et al, Eur Resp J, 2011, 38,147-53

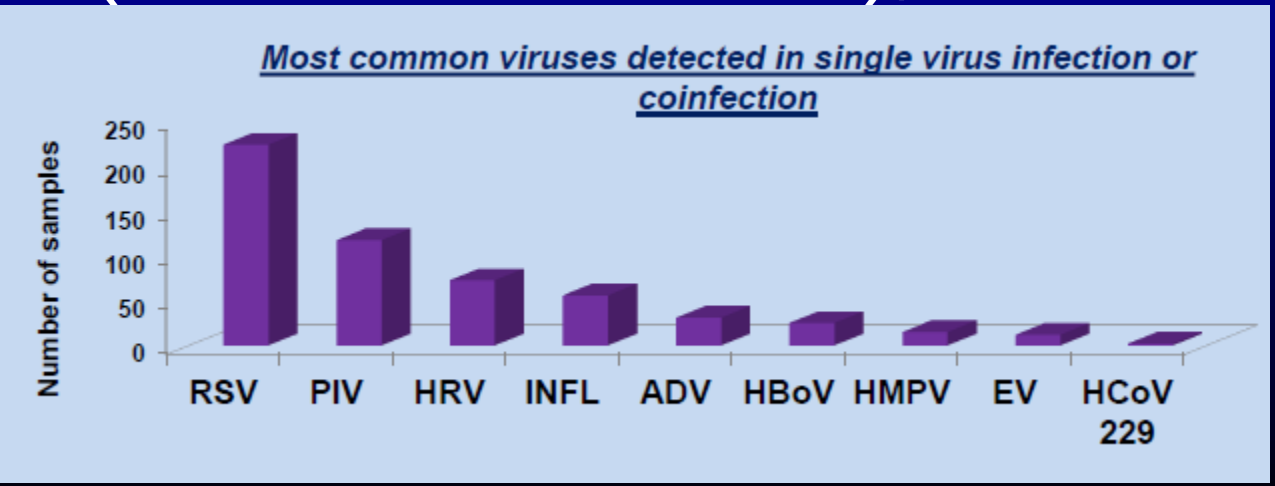
PCV7 Coverage Versus RR of Influenza Hospitalization By State



Simonsen, …., Klugman, mBio, 2011, e00309-10

PCV Reduces Viral Assocated Hospitalization

- In a population of 566 children with URTI or LRTI in whom microarray detection of viruses was performed, viruses were detected in 70% (RSV 57% >Paraflu 30% >rhino 18% >flu 14% >adeno 8% > Boca 6%).
- Receipt of PCV reduced hospitalization by 48% (95% CI 19% - 67%); P= 0.004



Kuoni et al, ICAAC 2012, Late Breaker Poster G3-1563a, p329

Diagnostic Options For Influenza

- Rapid assays
  - With high specificity and short assay time, good for triaging patients
  - May want to confirm negatives due to lower sensitivity
- PCR
  - Highly sensitive and specific
  - Higher cost and turn-around-time may hamper use as a triaging agent
- DFA
  - Sensitive and specific
  - Labor intensive, requires dedicated people & equipment
- Viral culture
  - Sensitive and specific
  - Long turn-around time

Diagnostic Tests for Pneumonia

- Sputum Culture
  - Highly sensitive
  - Must qualify samples due to significant saliva contamination
  - May take a day to over a week, depending on microorganism
- Blood Culture
  - Highly specific
  - Not highly sensitive
- Urinary Antigen
  - Same day results
  - Available for *S. pneumoniae* and *Legionella pneumophila*

Conclusions

- There is significant evidence that the majority of deaths during the 1918 pandemic were associated with the synergistic lethality of bacterial infections – mainly the pneumococcus
- For the 2009 H1N1 pandemic, data suggest a significant role for bacterial pathogens in at least a third of deaths; in severity of the disease and the pandemic increased presumed bacterial pneumonia admissions and IPD
- Pneumococcal vaccines may reduce the mortality and morbidity associated with viral respiratory infections including pandemic influenza and should be considered as an essential part of pandemic flu planning
- Urinary ICT enhances detection of co – infection in adults
- Antibiotics may be an essential part of the management of influenza-associated pneumonia, but prophylaxis even in those with proven influenza in the community, is not advised