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Severe Influenza: Management and Research Challenges

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Disclosures

- Research Support°
  - Beckman Coulter, Cephied, Chimerix, Emergent BioScience, Gilead, Janssen/Johnson & Johnson, Shire
- Paid Consultation
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  - GlaxoSmithKline, Romark, Vertex
- Data & Safety Monitoring Board Participation
  - GlaxoSmithKline, Shionogi

As of 3/17/18; ° Paid to Northwestern University.

Severe Influenza

- Influenza: *Epidemiology & Seasonality*
- Severe Influenza: *Risk & Definitions*
  - Hospitalized adults
  - Immunocompromised
- Challenges to Influenza Research
  - Challenges of studies in hospitalized adults
  - Novel Scoring and Outcomes Measures

Epidemiology & Importance

Influenza: *Epidemic Impact*

- 25-50 Million influenza cases/year
- Excess mortality (25,000 excess deaths/ yr)
- Excess hospitalization (226,000/year)
- 2-3 fold increase in pneumonia rate
- Total annual costs: $25 billion in the US
- 10%: Direct costs of increased medical care
  - Superinfections, exacerbation of CHF, RAD
- 90%: Indirect costs (lost productivity, employee absenteeism)

Thompson *et al*. ***Influenza and other respiratory viruses***. 2009; 3:37-49.
Thompson *et* al. ***JAMA***. 2004;292:1333-1340. ***MMWR***. 2010; 59: 1057-1062.

Influenza: *Epidemic Impact*

Age-Specific Annual Burden of Influenza in the United States

AGE (YR)	Outpatient Visits	Hospitalized Days	Days of Productivity Lost	Life Years Lost
<5	3,728	280	5,328	11
5-17	3,718	9	6,666	3
18-49	5.270	144	10,178	36
50-64	4,329	345	6,616	92
65+	14,309	958	15,215	468
Total US Burden	31,354	3,131	44,003	611

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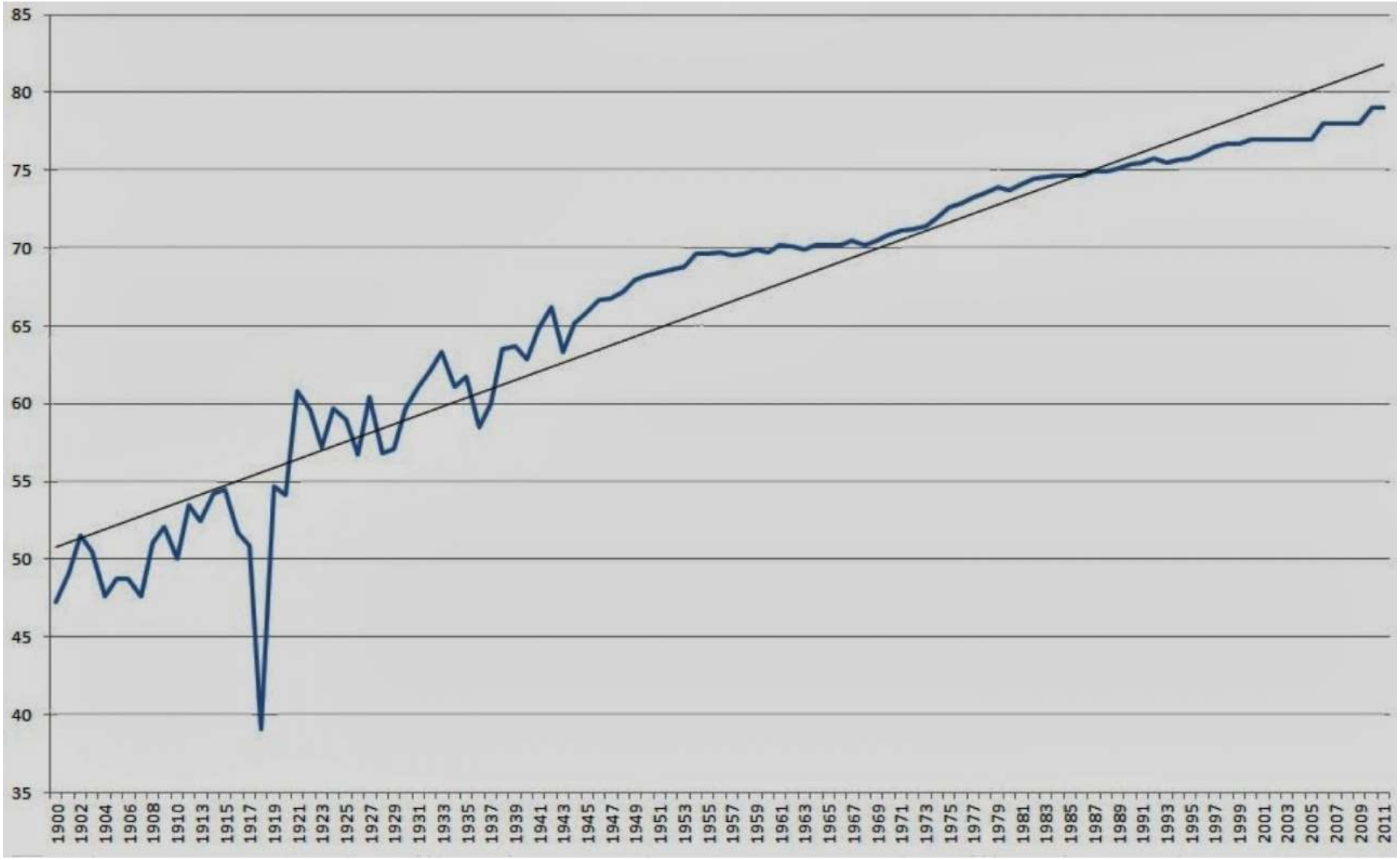
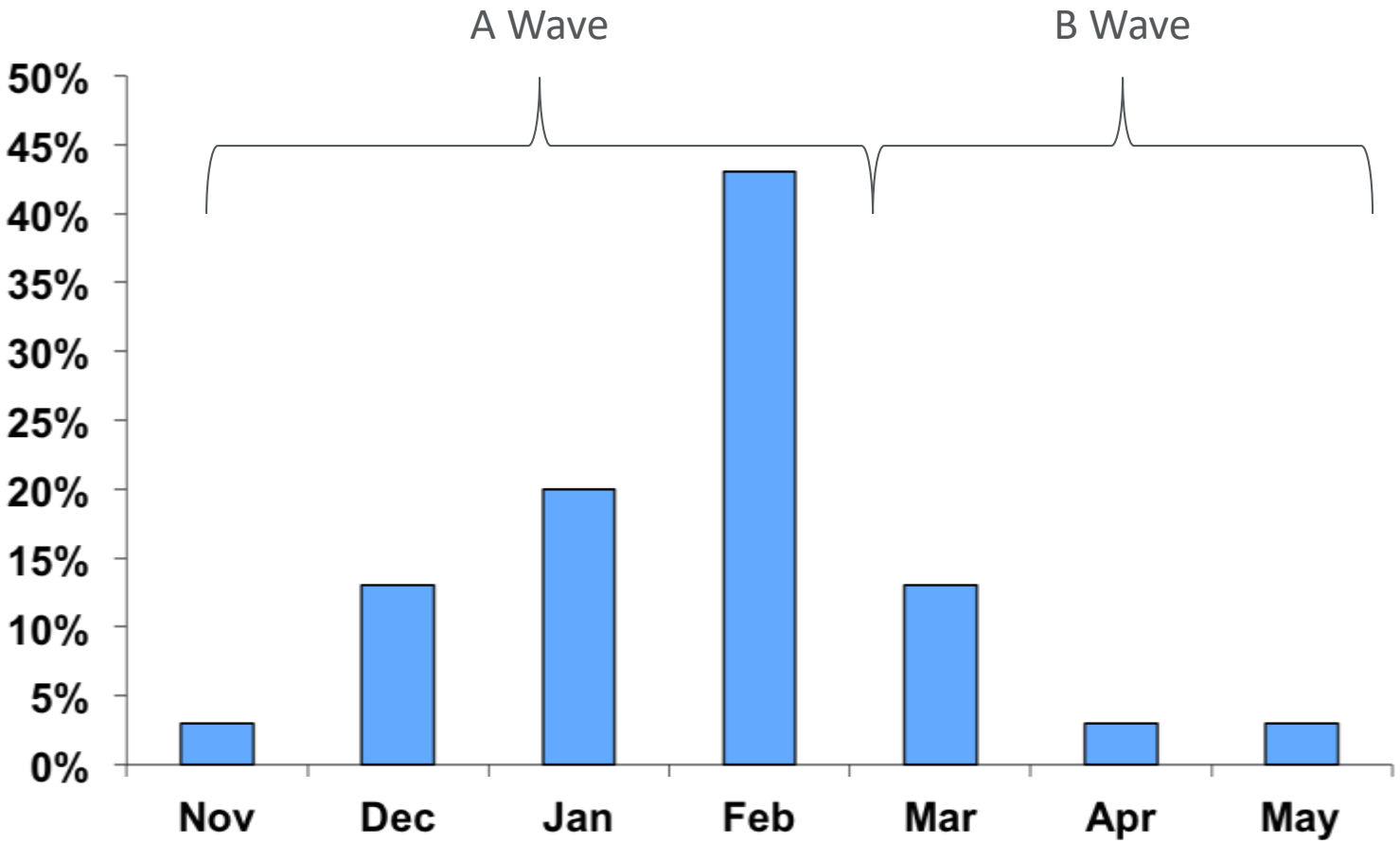
Molinari *et al*. ***Vaccine***. 2007;25:5086-5096.

Influenza: *An Important Impact on Life Expectancy*



Influenza: *Seasonal Epidemiology*



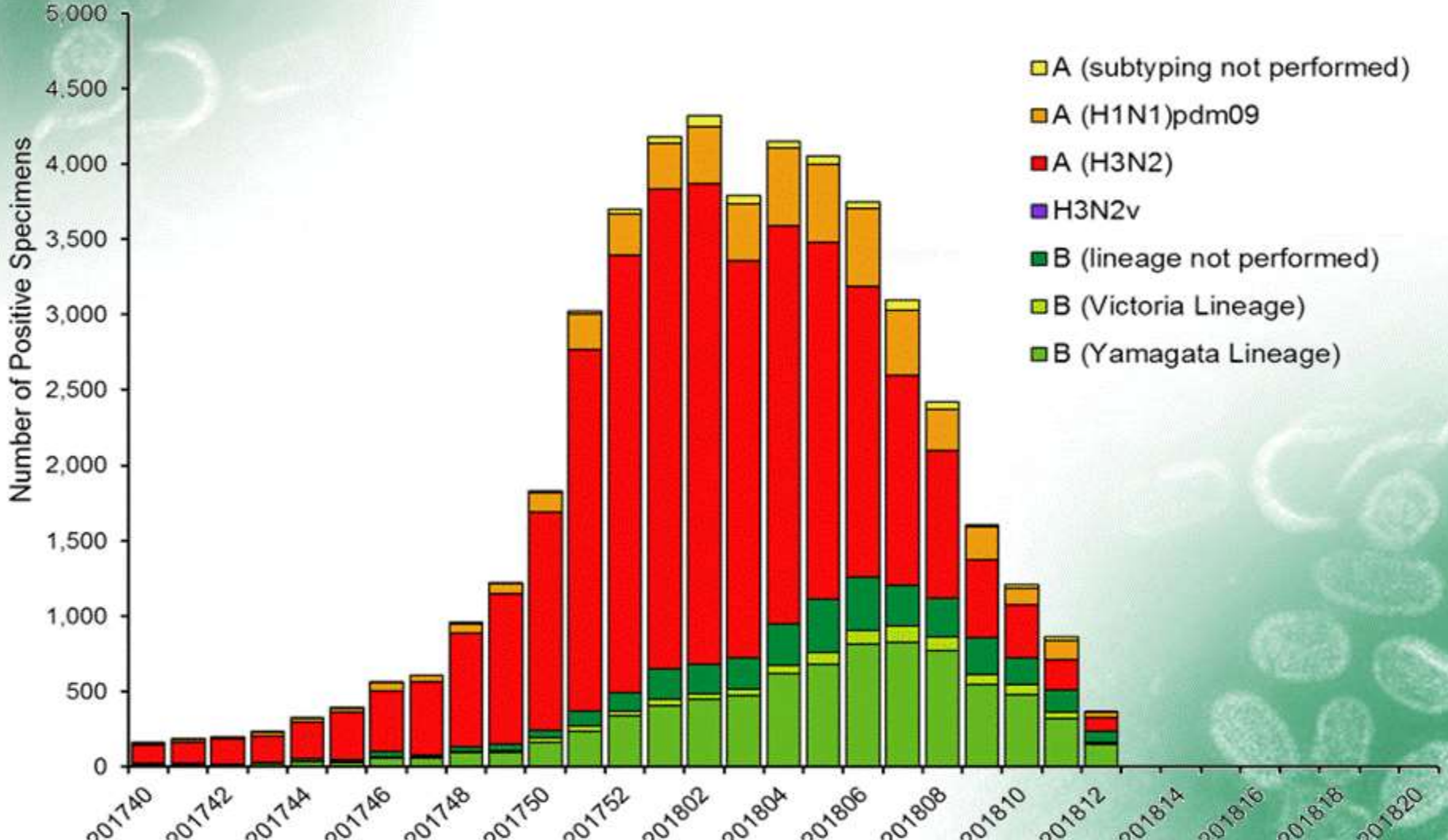
CDC. *MMWR*. July 28, 2006;55 (RR-10):1-42.

FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
Centers for Disease Control and Prevention

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2017-2018 Season

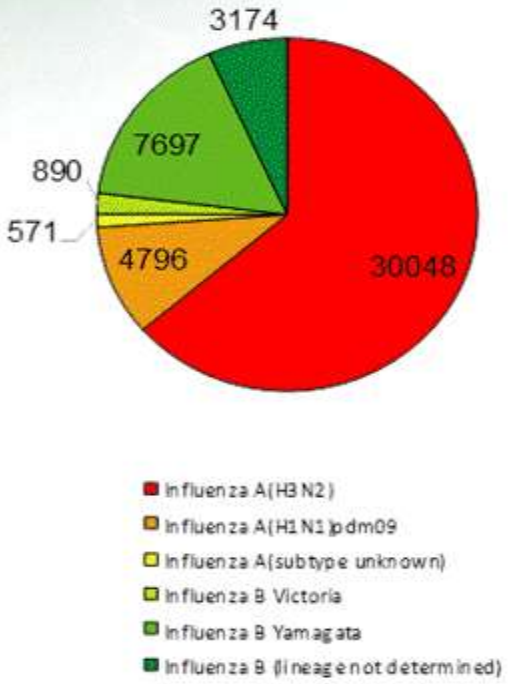


FLUVIEW

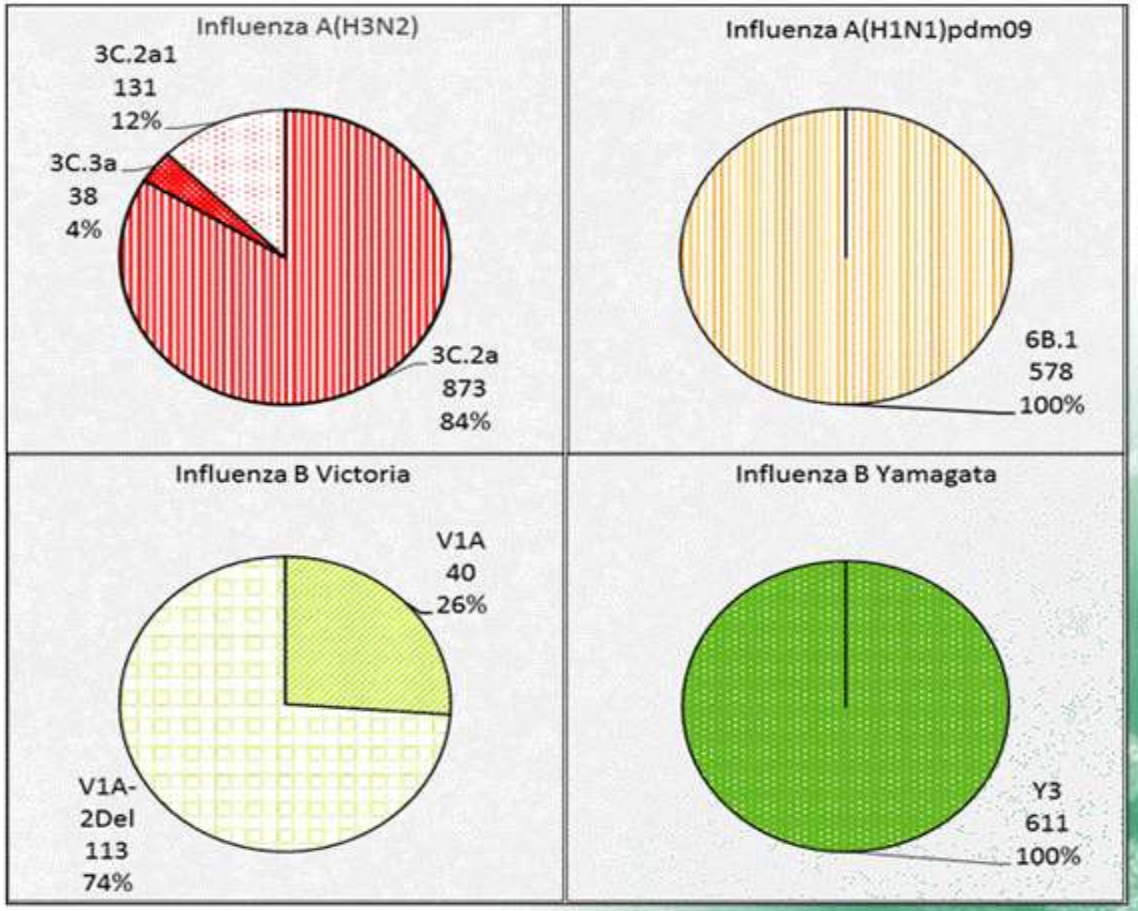
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
Centers for Disease Control and Prevention

Influenza Positive Specimens Reported by U.S. Public Health Laboratories, Cumulative, 2017-2018 season



Sequence Results, by Genetic HA Clade/Subclade, of Specimens Submitted to CDC by U.S. Public Health Laboratories, Cumulative, 2017-2018 Season

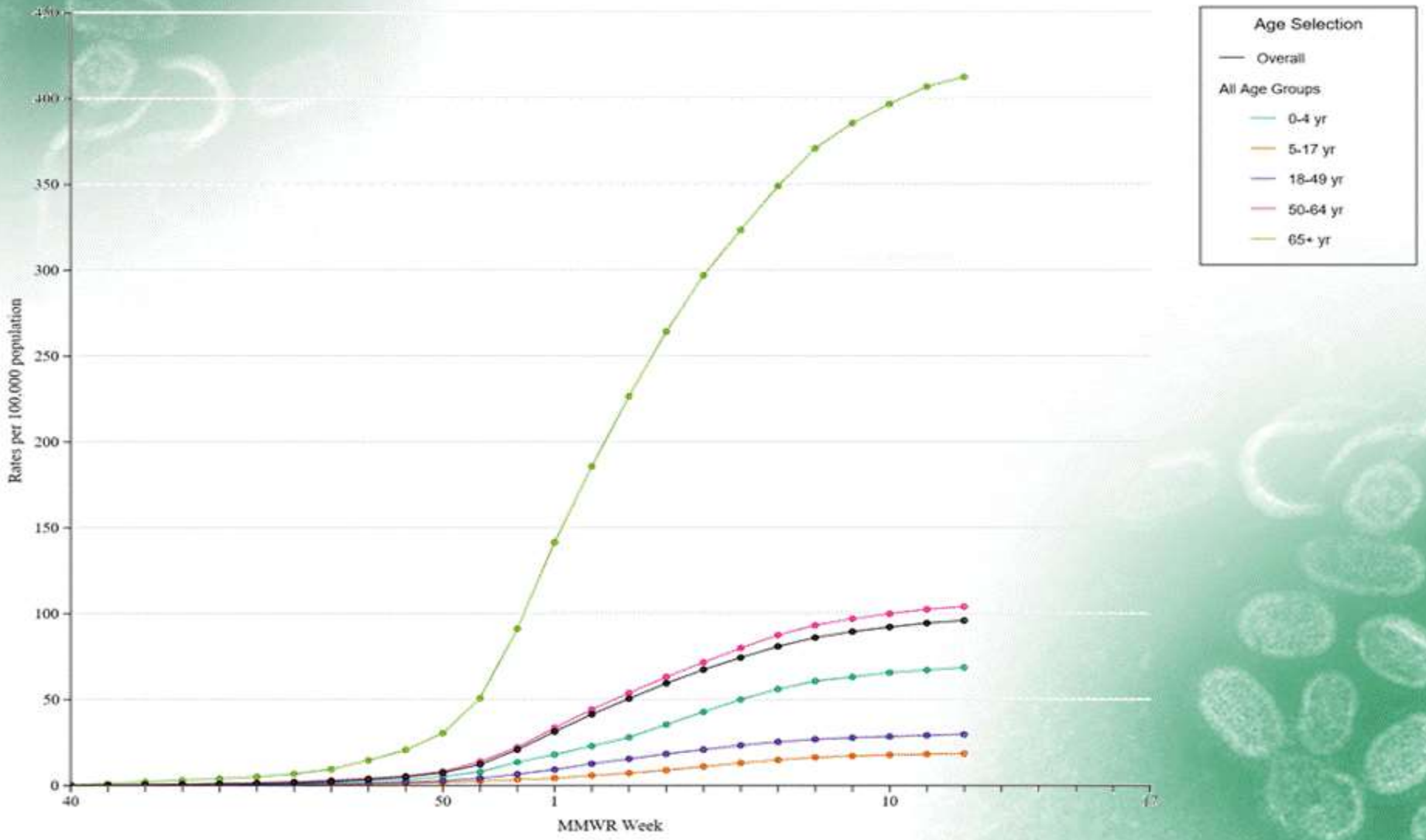


FLUVIEW

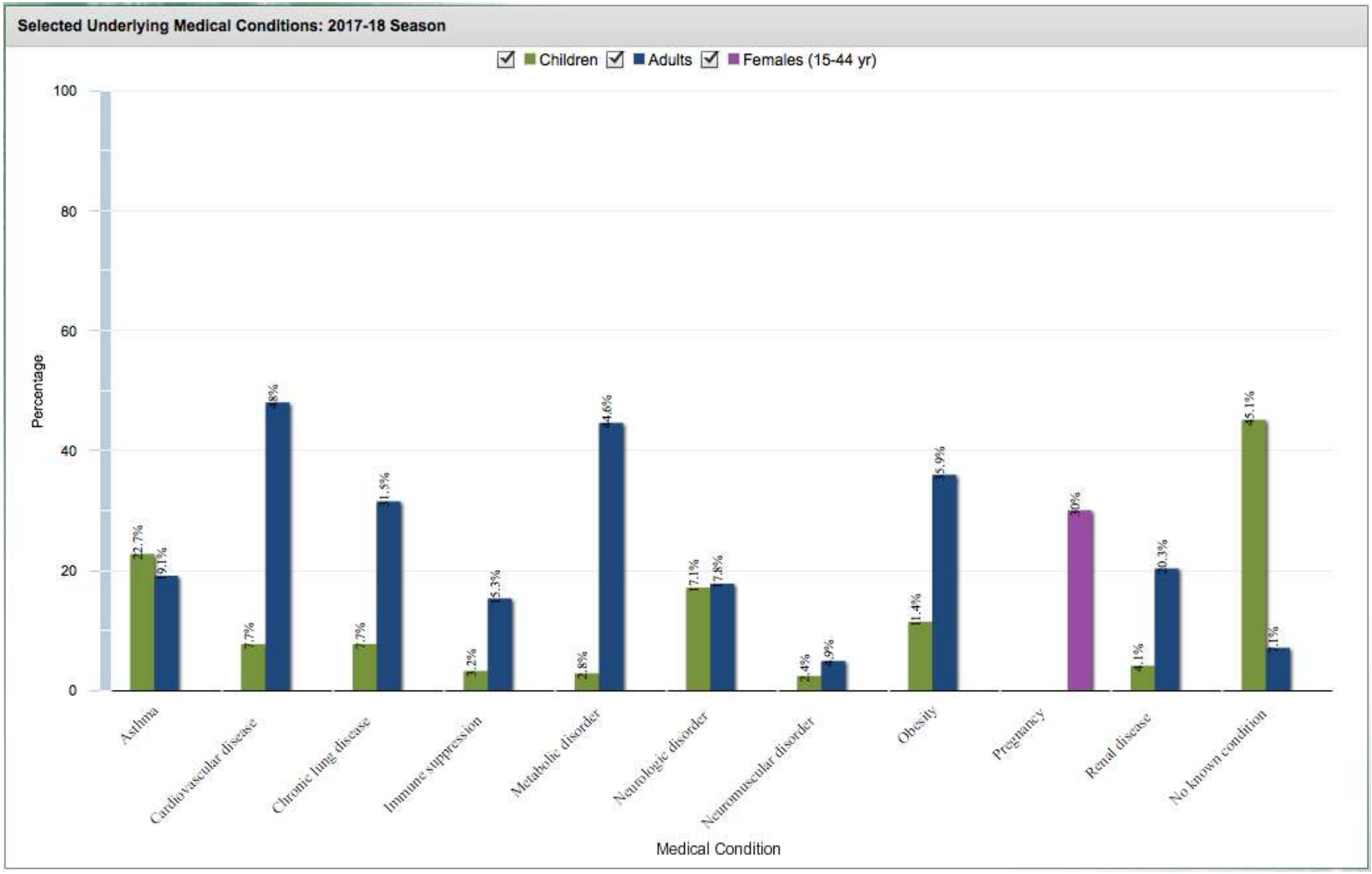
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Laboratory-Confirmed Influenza Hospitalizations

Preliminary cumulative rates as of Mar 24, 2018



Laboratory Confirmed Hospitalized Influenza



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FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

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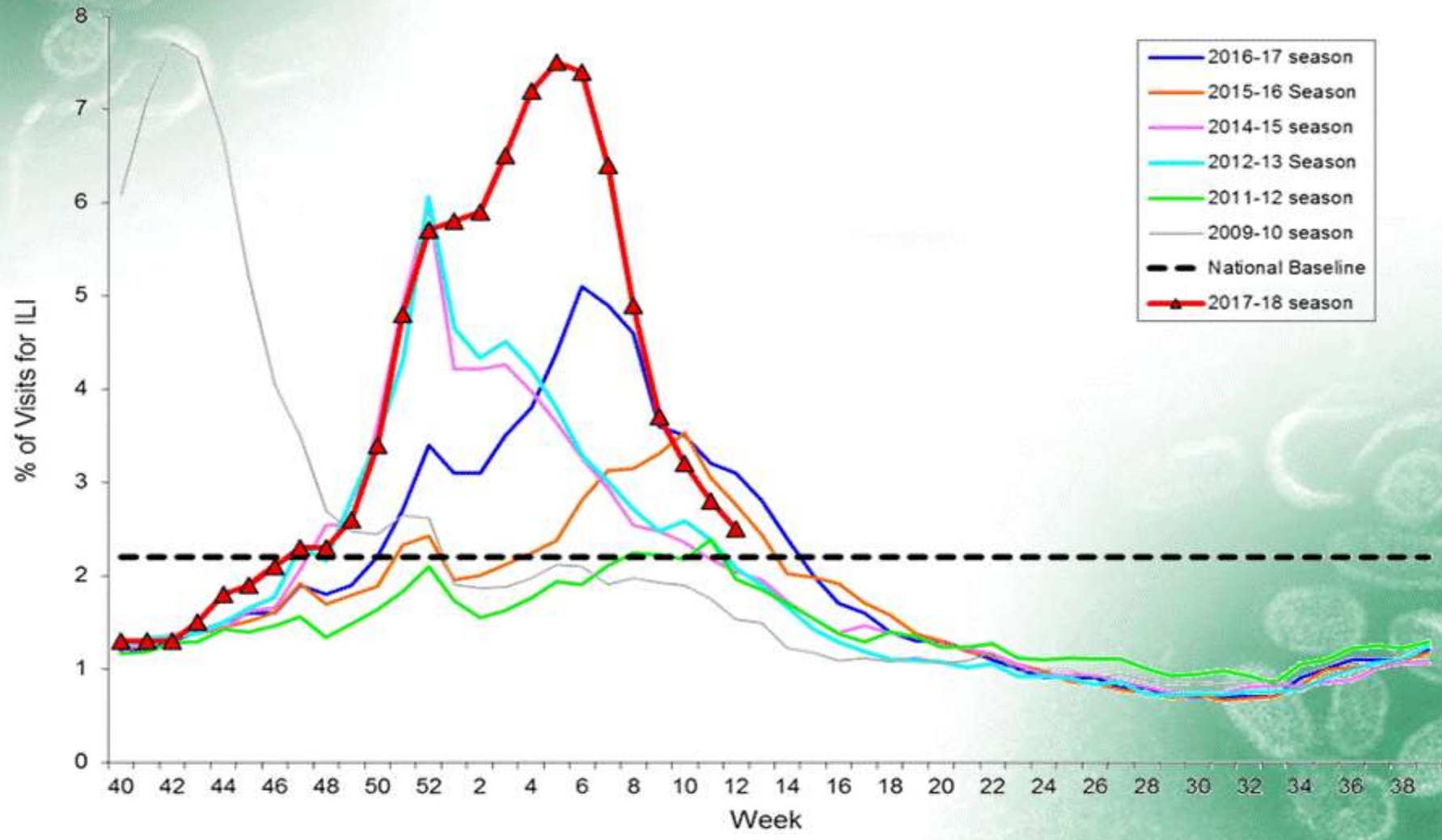
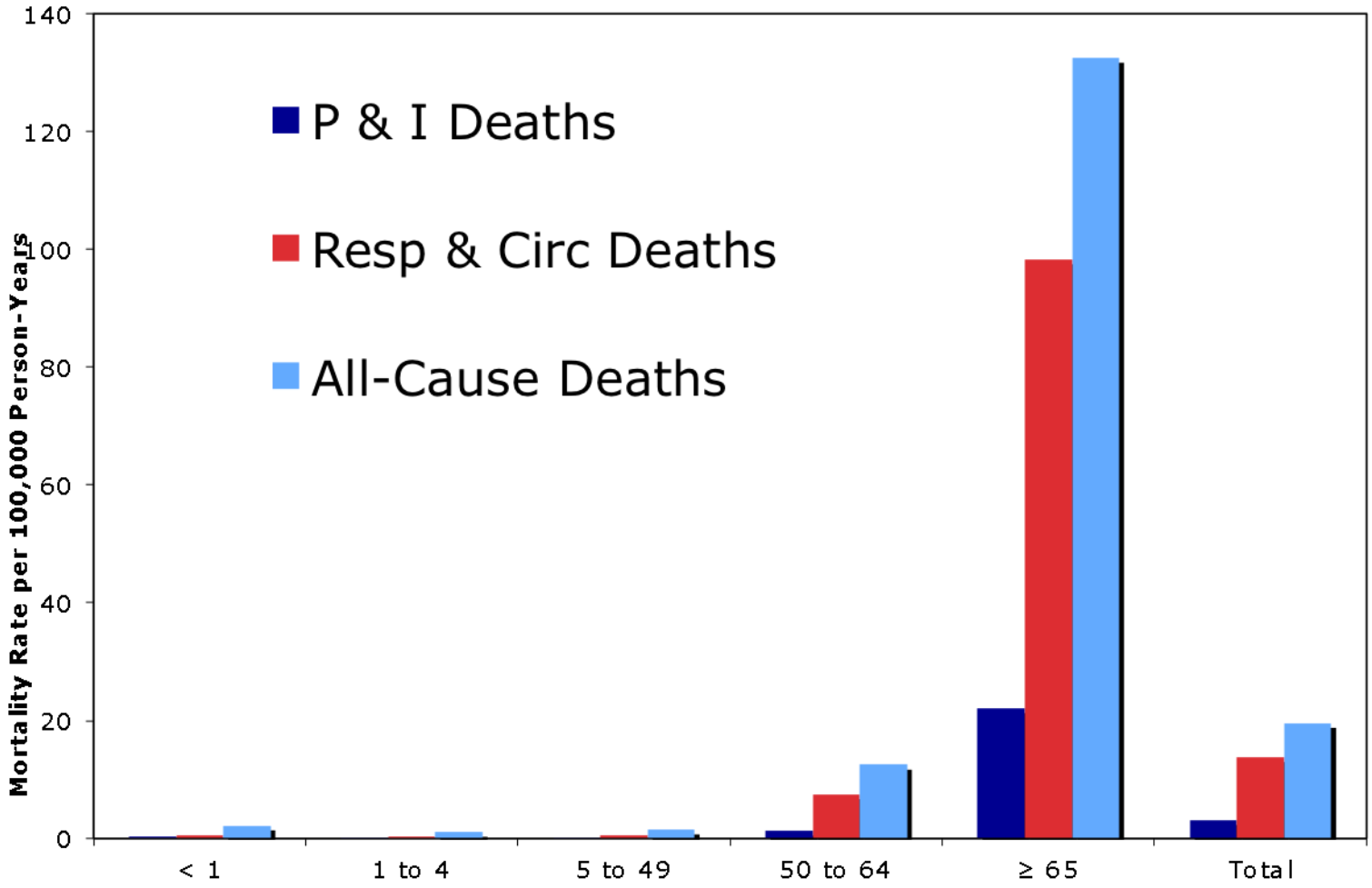
CENTERS FOR DISEASE CONTROL AND PREVENTION

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2017-2018 and Selected Previous Seasons



Seasonal Influenza: *Mortality*



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Thompson, *et al*. *JAMA*. 2003; 289:179-186.

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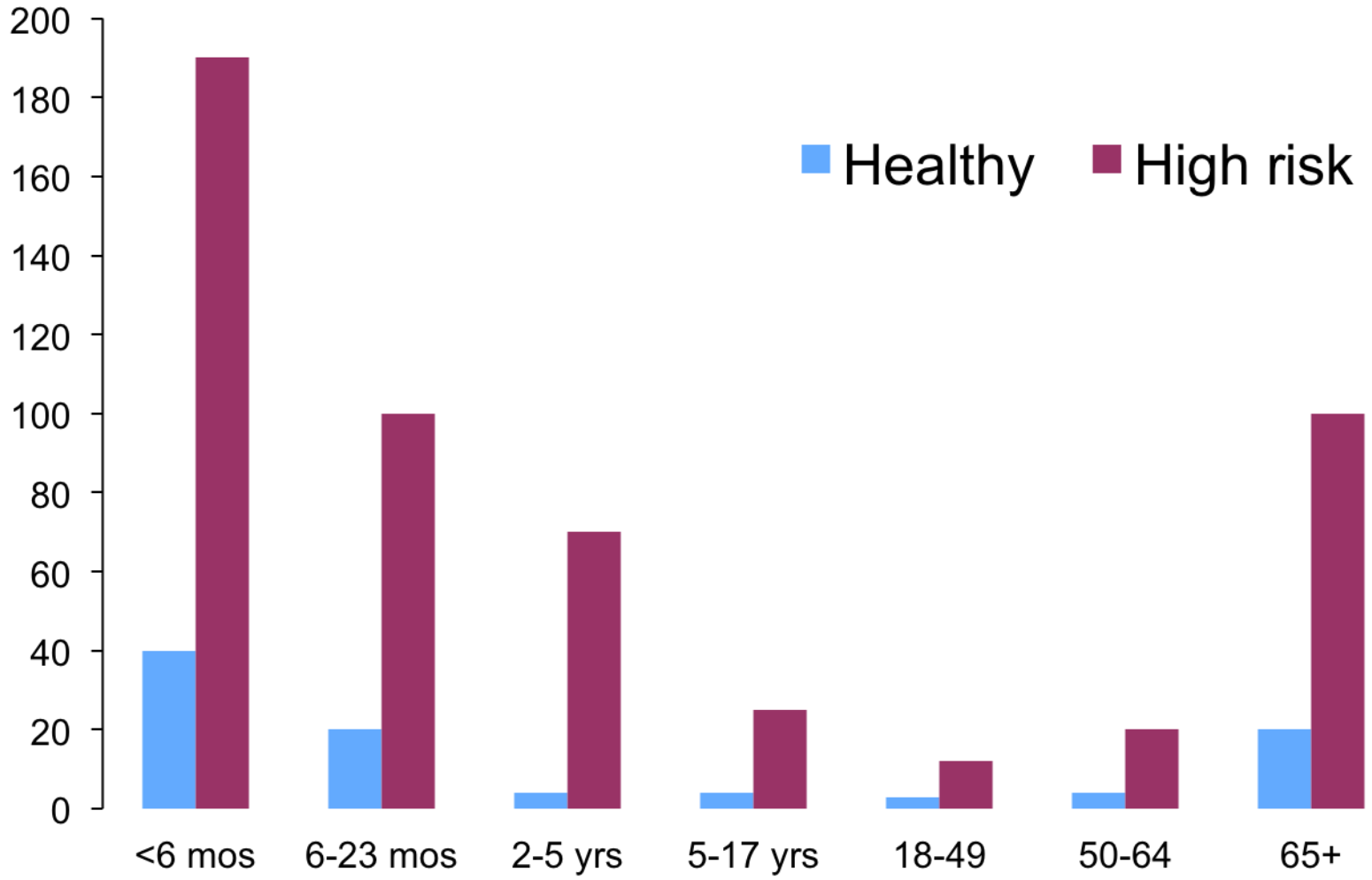
Seasonal Influenza: *Hospitalizations*



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Glezen WP. ***Am Rev Respir Dis***. 1987;136:550-555.

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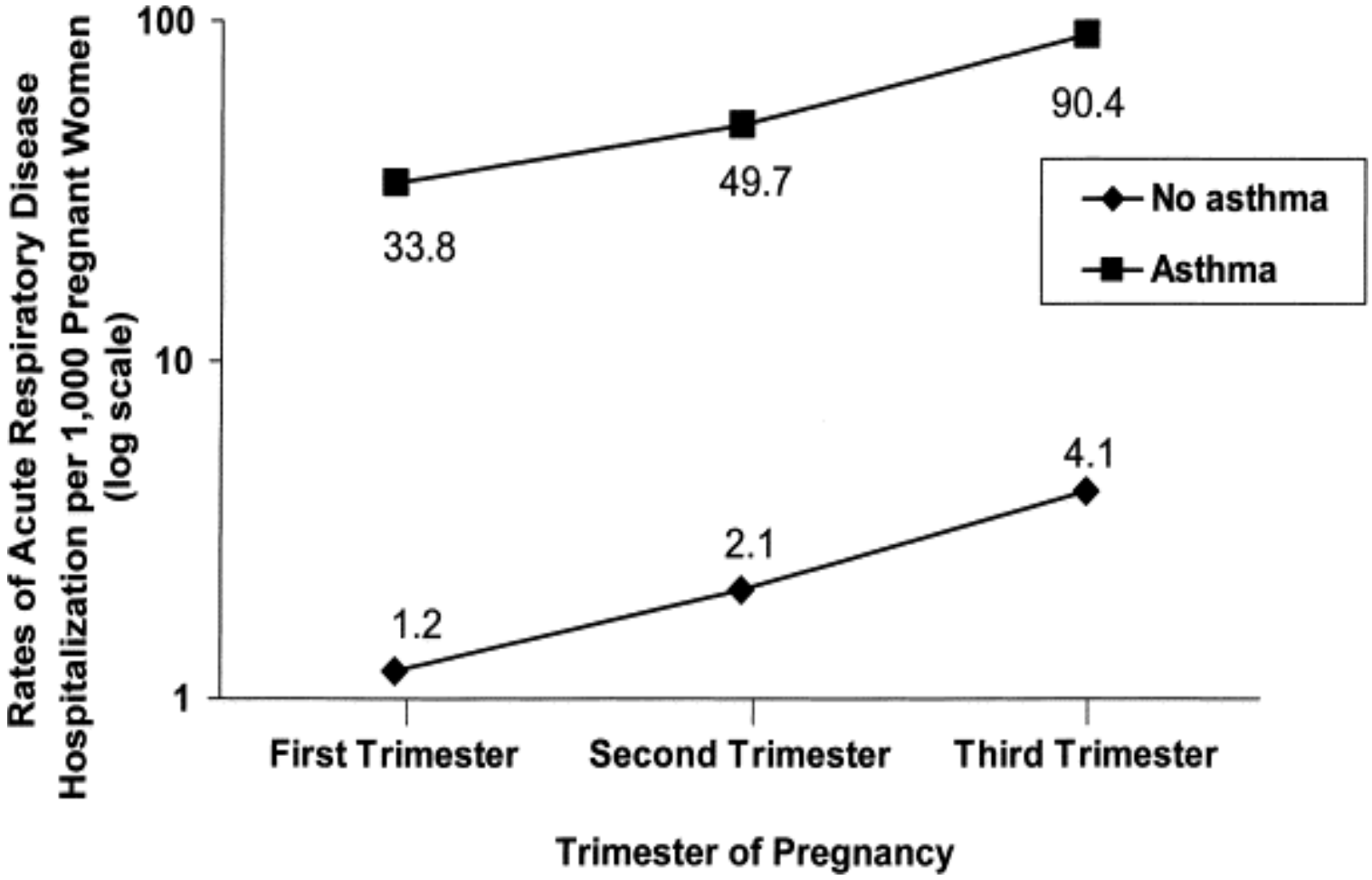
Influenza in Pregnant Women: *Hospitalization*



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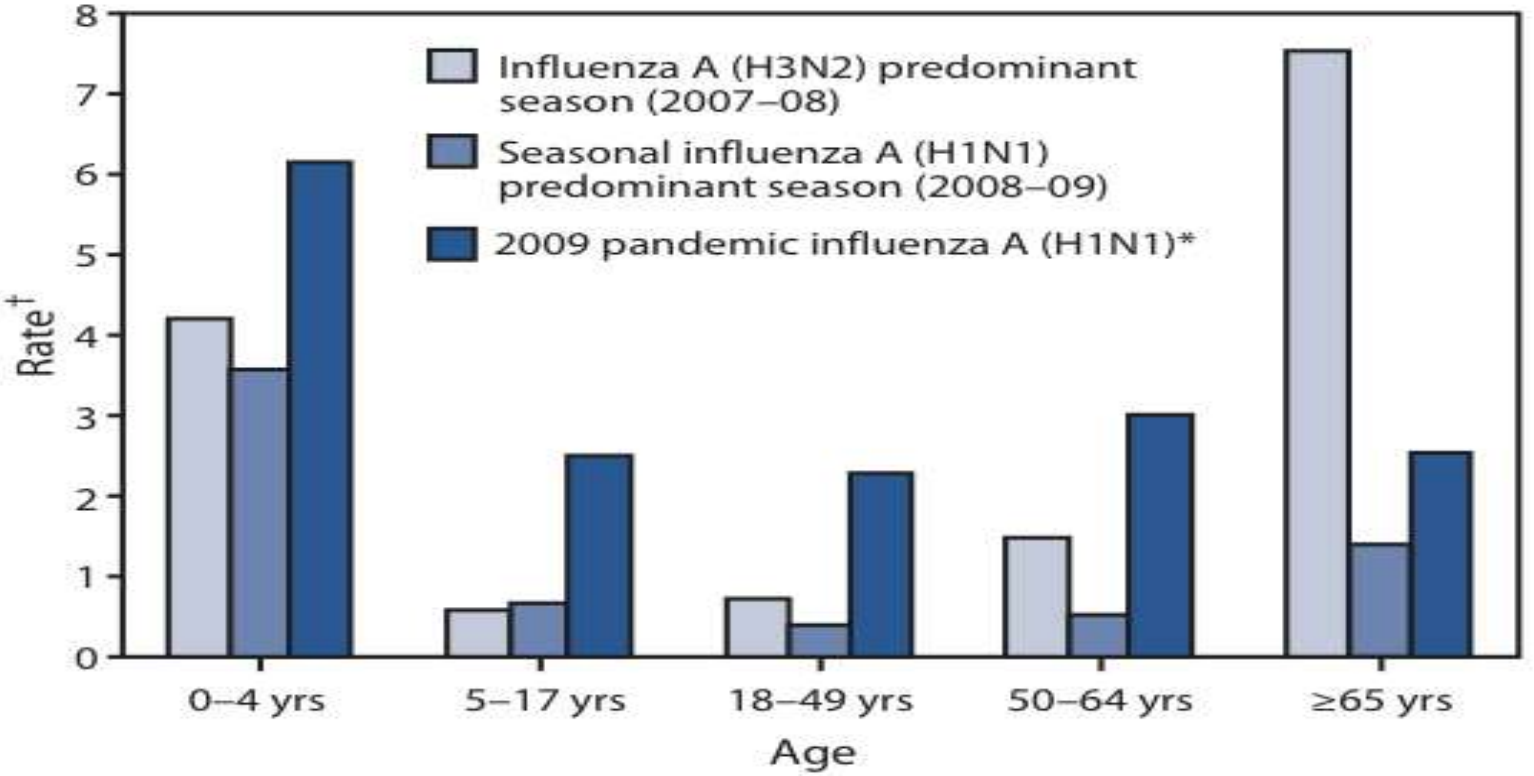
Hartert *et al*. ***Am J Obstet Gynecol***. 2003; 189: 1705-1712.

Influenza Mortality: *Trends Over Time*

FIGURE 1. Cumulative rate of hospitalizations during three influenza seasons, by age group — Emerging Infections Program, United States, 2007–2010



* 2009 Pandemic Influenza A(H1N1) hospitalization data from September 1, 2009–January 21, 2010.

† Per 10,000 population.

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Fiore *et al*. ***MMWR.*** 2010; 59: 1-47.

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Influenza Mortality: *Impact of Pandemics*

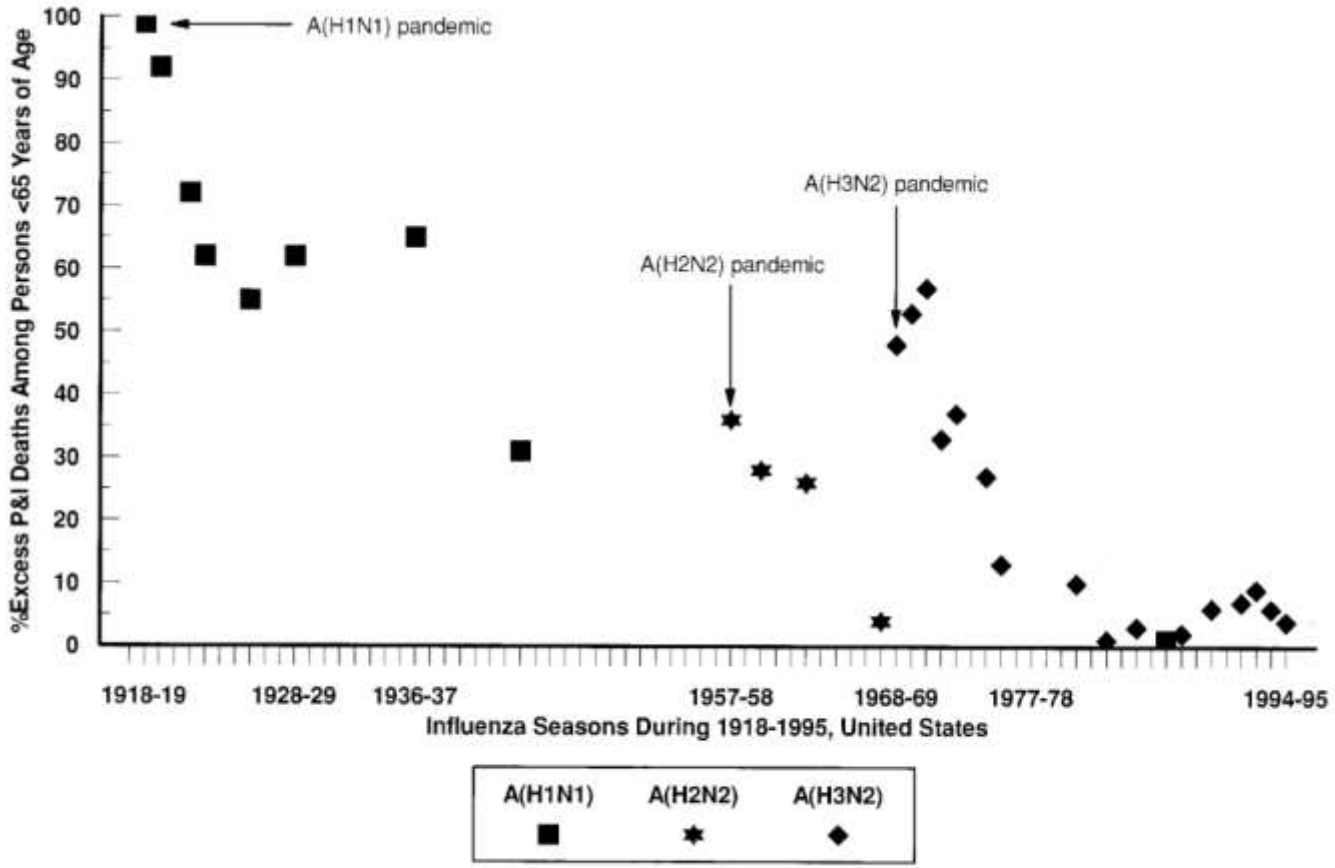

Figure 1. Age distribution of deaths associated with 3 influenza A pandemics and interpandemic seasons in United States, 1918–1995. Data from tables 1–3 are plotted graphically for influenza A (H1N1), A (H2N2), and A (H3N2). For influenza A (H1N1) seasons, only data point for 1986–1987 season was included, which was the only season when excess mortality was attributed solely to A (H1N1) viruses. Data points since 1968 are based on our analysis of pneumonia and influenza (P&I) mortality data.

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Simonsen *et al*. ***J Infect Dis.*** 1998; 178: 53-60.

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Influenza: *Risk Groups*

Table 1. Risk Factors for Complications of or Severe Illness with 2009 H1N1 Virus Infection.*

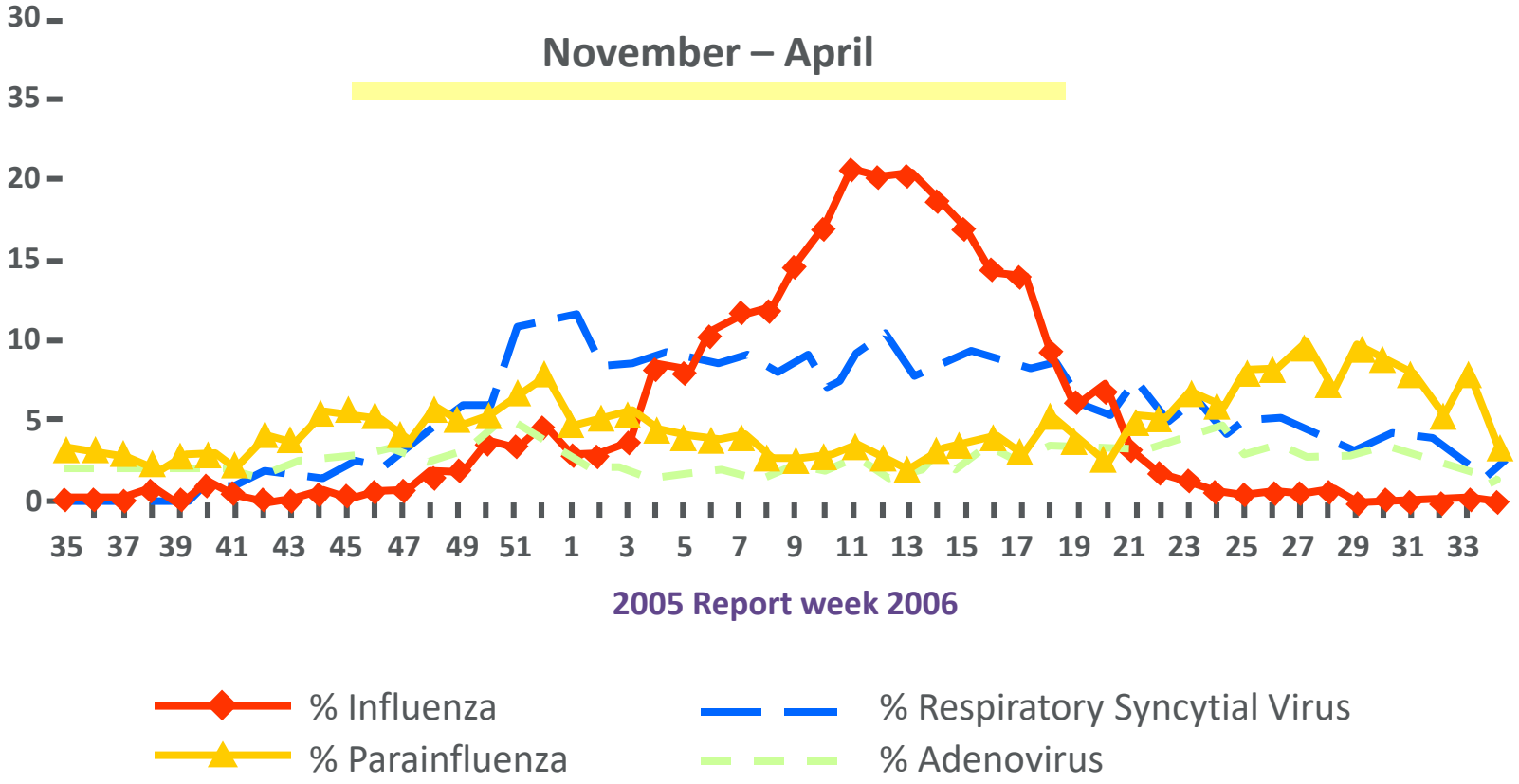
Risk Factor	Examples and Comments
Age <5 yr	Increased risk especially for children <2 yr of age; highest hospitalization rates among children <1 yr
Pregnancy	Risk of hospitalization increased by a factor of 4 to 7, as compared with age-matched nonpregnant women, with highest risk in third trimester
Chronic cardiovascular condition	Congestive heart failure or atherosclerotic disease; hypertension not shown to be an independent risk factor
Chronic lung disorder	Asthma or COPD, cystic fibrosis
Metabolic disorder	Diabetes
Neurologic condition	Neuromuscular, neurocognitive, or seizure disorder
Immunosuppression	Associated with HIV infection, organ transplantation, receipt of chemotherapy or corticosteroids, or malnutrition
Morbid obesity†	Suggested but not yet proved to be an independent risk factor for complications requiring hospitalization or ICU admission and possibly for death
Hemoglobinopathy	Sickle cell anemia
Chronic renal disease	Renal dialysis or transplantation
Chronic hepatic disease	Cirrhosis
Long history of smoking	Suggested but not yet proved to be an independent risk factor
Long-term aspirin therapy in children	Risk of Reye's syndrome; drugs containing salicylates should be avoided in children with influenza
Age ≥65 yr	Highest case fatality rate but lowest rate of infection

* COPD denotes chronic obstructive pulmonary disease, HIV human immunodeficiency virus, and ICU intensive care unit.
† Morbid obesity is defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 40 or more.

WHO Writing Committee. ***NEJM.*** 2010;362: 1708-1719.

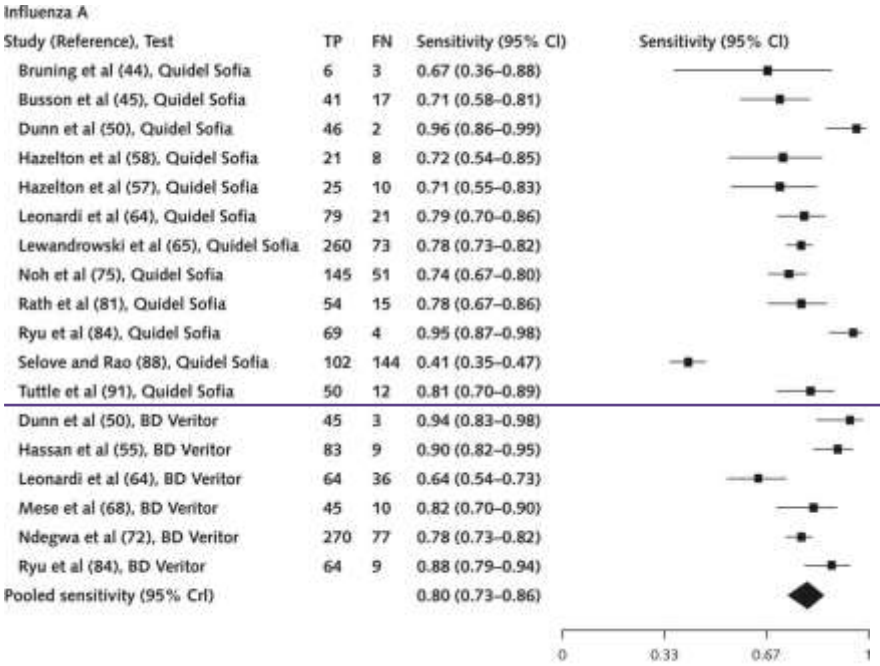
Influenza: *Diagnosis & Surveillance*

Influenza-Like Illness



Contemporary Rapid Diagnostics: *A Step Forward*

Digital Immunoassays: Influenza A vs. B



Influenza A

Study (Reference), Test	TP	FN	Sensitivity (95% CI)
Bruning et al (44), Quidel Sofia	6	3	0.67 (0.36–0.88)
Busson et al (45), Quidel Sofia	41	17	0.71 (0.58–0.81)
Dunn et al (50), Quidel Sofia	46	2	0.96 (0.86–0.99)
Hazelton et al (58), Quidel Sofia	21	8	0.72 (0.54–0.85)
Hazelton et al (57), Quidel Sofia	25	10	0.71 (0.55–0.83)
Leonardi et al (64), Quidel Sofia	79	21	0.79 (0.70–0.86)
Lewandrowski et al (65), Quidel Sofia	260	73	0.78 (0.73–0.82)
Noh et al (75), Quidel Sofia	145	51	0.74 (0.67–0.80)
Rath et al (81), Quidel Sofia	54	15	0.78 (0.67–0.86)
Ryu et al (84), Quidel Sofia	69	4	0.95 (0.87–0.98)
Selove and Rao (88), Quidel Sofia	102	144	0.41 (0.35–0.47)
Tuttle et al (91), Quidel Sofia	50	12	0.81 (0.70–0.89)
Dunn et al (50), BD Veritor	45	3	0.94 (0.83–0.98)
Hassan et al (55), BD Veritor	83	9	0.90 (0.82–0.95)
Leonardi et al (64), BD Veritor	64	36	0.64 (0.54–0.73)
Mese et al (68), BD Veritor	45	10	0.82 (0.70–0.90)
Ndegwa et al (72), BD Veritor	270	77	0.78 (0.73–0.82)
Ryu et al (84), BD Veritor	64	9	0.88 (0.79–0.94)
Pooled sensitivity (95% CrI)			0.80 (0.73–0.86)

Influenza B

Study (Reference), Test	TP	FN	Sensitivity (95% CI)
Bruning et al (44), Quidel Sofia	4	6	0.40 (0.17–0.69)
Busson et al (45), Quidel Sofia	6	5	0.55 (0.28–0.79)
Dunn et al (50), Quidel Sofia	51	1	0.98 (0.90–1.00)
Hazelton et al (58), Quidel Sofia	2	4	0.33 (0.10–0.70)
Hazelton et al (57), Quidel Sofia	4	8	0.33 (0.14–0.61)
Leonardi et al (64), Quidel Sofia	26	2	0.93 (0.78–0.98)
Lewandrowski et al (65), Quidel Sofia	211	34	0.86 (0.81–0.90)
Rath et al (81), Quidel Sofia	3	1	0.75 (0.30–0.95)
Ryu et al (84), Quidel Sofia	55	5	0.92 (0.82–0.97)
Selove and Rao (88), Quidel Sofia	18	30	0.38 (0.26–0.52)
Tuttle et al (91), Quidel Sofia	64	25	0.72 (0.62–0.80)
Dunn et al (50), BD Veritor	49	3	0.94 (0.84–0.98)
Hassan et al (55), BD Veritor	21	3	0.88 (0.70–0.96)
Leonardi et al (64), BD Veritor	22	6	0.79 (0.61–0.90)
Mese et al (68), BD Veritor	50	18	0.74 (0.62–0.83)
Ndegwa et al (72), BD Veritor	46	26	0.64 (0.52–0.74)
Ryu et al (84), BD Veritor	49	11	0.82 (0.70–0.90)
Pooled sensitivity (95% CrI)			0.77 (0.65–0.85)

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Merckex *et al*. ***Annal Int Med***. 2017;167: 394-409.

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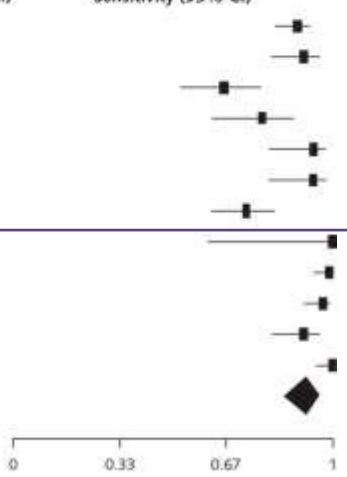
Contemporary Rapid Diagnostics: *A Step Forward*

Rapid NAAT: Influenza A vs. B

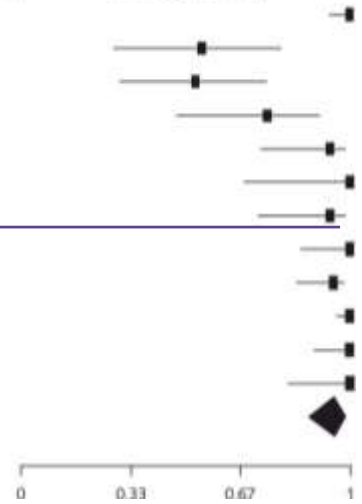
Influenza A

Study (Reference), Test	TP	FN	Sensitivity (95% CI)
Bell and Selvarangan (19), Alere	103	13	0.89 (0.82–0.93)
Busson et al (45), Alere	53	5	0.91 (0.81–0.96)
Chiarella et al (46), Alere	31	16	0.66 (0.52–0.78)
Hazelton et al (57), Alere	28	8	0.78 (0.62–0.88)
Hurtado et al (59), Alere	30	2	0.94 (0.80–0.98)
Nguyen Van et al (73), Alere	30	2	0.94 (0.80–0.98)
Nolte et al (76), Alere	56	21	0.73 (0.62–0.82)
Binnicker et al (41), cobas Liat	6	0	1.00 (0.61–1.00)
Chen et al (18), cobas Liat	79	1	0.99 (0.94–1.00)
Chen et al (18), cobas Liat	94	3	0.97 (0.91–0.99)
Melchers et al (67), cobas Liat	51	5	0.91 (0.81–0.96)
Nolte et al (76), cobas Liat	77	0	1.00 (0.95–1.00)
Pooled sensitivity (95% CrI)			0.92 (0.85–0.96)



Influenza B

Study (Reference), Test	TP	FN	Sensitivity (95% CI)
Bell and Selvarangan (19), Alere	58	0	1.00 (0.94–1.00)
Busson et al (45), Alere	6	5	0.55 (0.28–0.79)
Chiarella et al (46), Alere	8	7	0.53 (0.30–0.75)
Hazelton et al (57), Alere	9	3	0.75 (0.47–0.91)
Hurtado et al (59), Alere	16	1	0.94 (0.73–0.99)
Nguyen Van et al (73), Alere	8	0	1.00 (0.68–1.00)
Nolte et al (76), Alere	15	1	0.94 (0.72–0.99)
Binnicker et al (41), cobas Liat	21	0	1.00 (0.85–1.00)
Chen et al (18), cobas Liat	42	2	0.95 (0.84–0.99)
Chen et al (18), cobas Liat	100	0	1.00 (0.96–1.00)
Melchers et al (67), cobas Liat	30	0	1.00 (0.89–1.00)
Nolte et al (76), cobas Liat	16	0	1.00 (0.81–1.00)
Pooled sensitivity (95% CrI)			0.95 (0.87–0.99)



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Merckex *et al*. ***Annal Int Med***. 2017;167: 394-409.

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Contemporary Rapid Diagnostics: *A Step Forward*

Table 2. Overall and Subgroup Analyses of Pooled Rapid Test Accuracy Estimates for Influenza A and B, by Index Test Type*

Index Test Type	Influenza A		Influenza B	
	Pooled Sensitivity (95% CrI), %	Pooled Specificity (95% CrI), %	Pooled Sensitivity (95% CrI), %	Pooled Specificity (95% CrI), %
Overall				
Traditional RIDTs (94 influenza A studies; 30 influenza B studies)	54.4 (48.9 to 59.8)	99.4 (99.1 to 99.7)	53.2 (41.7 to 64.4)	99.8 (99.7 to 99.9)
DIAs (18 influenza A studies; 17 influenza B studies)	80.0 (73.4 to 85.6)	98.3 (97.4 to 98.9)	76.8 (65.4 to 85.4)	98.7 (97.5 to 99.4)
Rapid NAATs (12 influenza A studies; 12 influenza B studies)	91.6 (84.9 to 95.9)	99.2 (98.6 to 99.7)	95.4 (87.3 to 98.7)	99.4 (98.9 to 99.8)
Difference in sensitivities, overall				
Traditional RIDTs vs. DIAs	**−25.5 (−33.4 to −17.0)**	–	**−23.5 (−37.9 to −7.7)**	–
Traditional RIDTs vs. rapid NAATs	**−37.1 (−44.2 to −28.6)**	–	**−41.7 (−54.0 to −28.5)**	–
DIAs vs. rapid NAATs	**−11.5 (−19.5 to −2.9)**	–	**−18.2 (−30.6 to −6.9)**	–

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Merckex *et al*. ***Annal Int Med***. 2017;167: 394-409.

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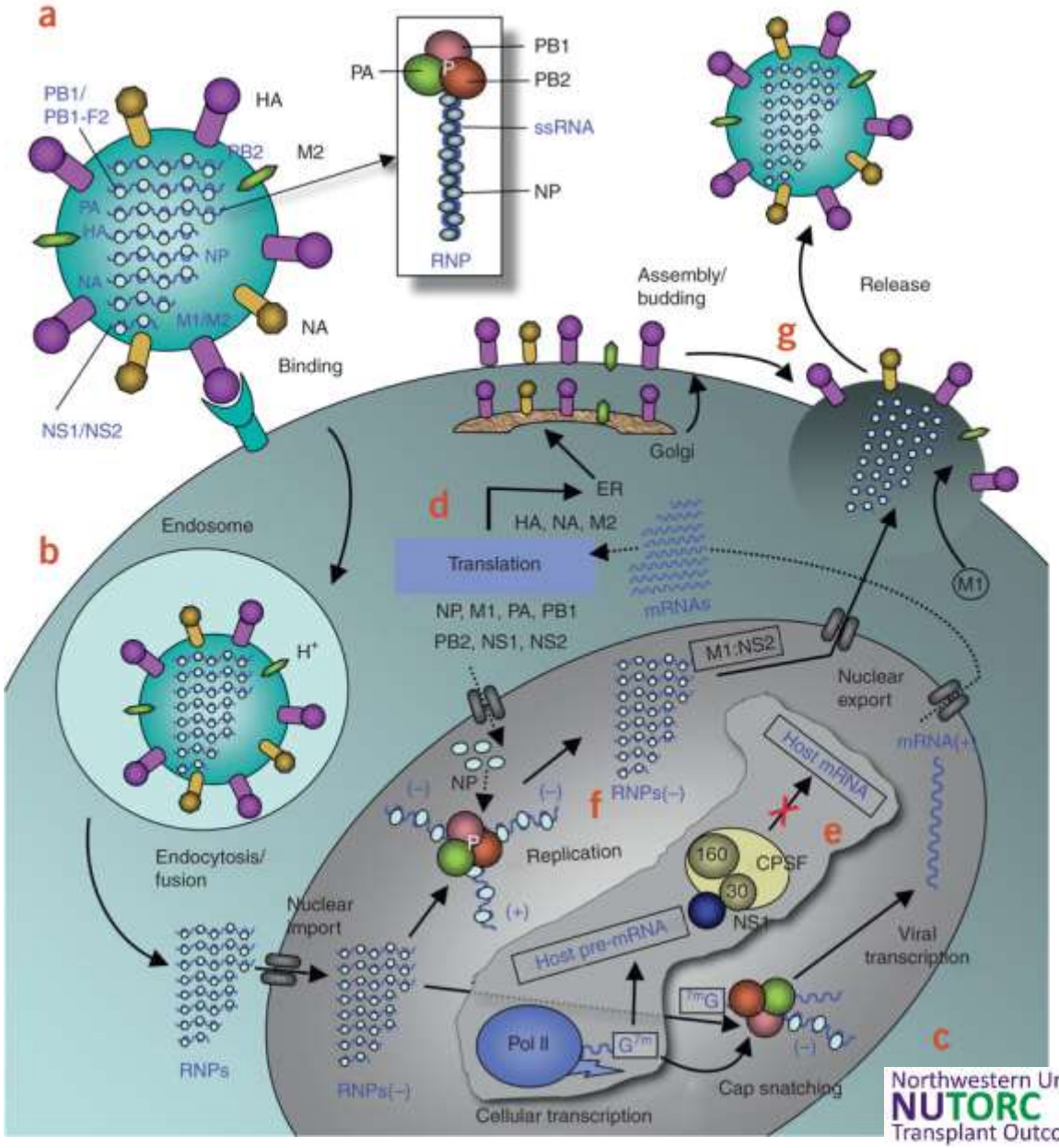
Influenza Virus: *Replication & Antiviral Targets*



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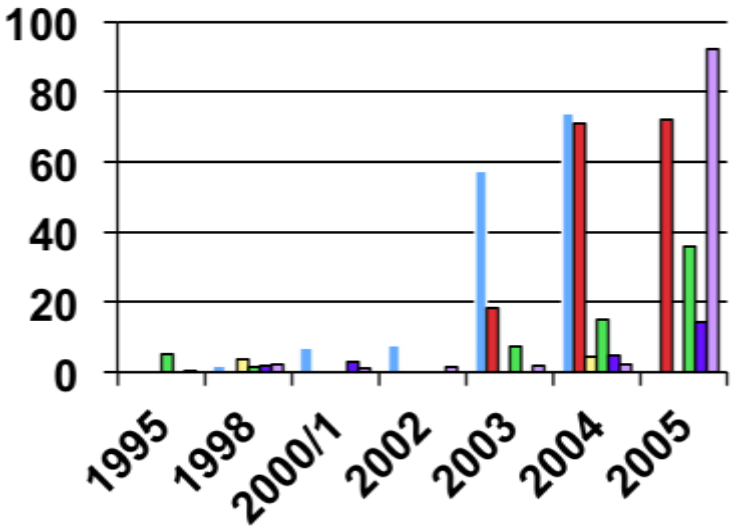
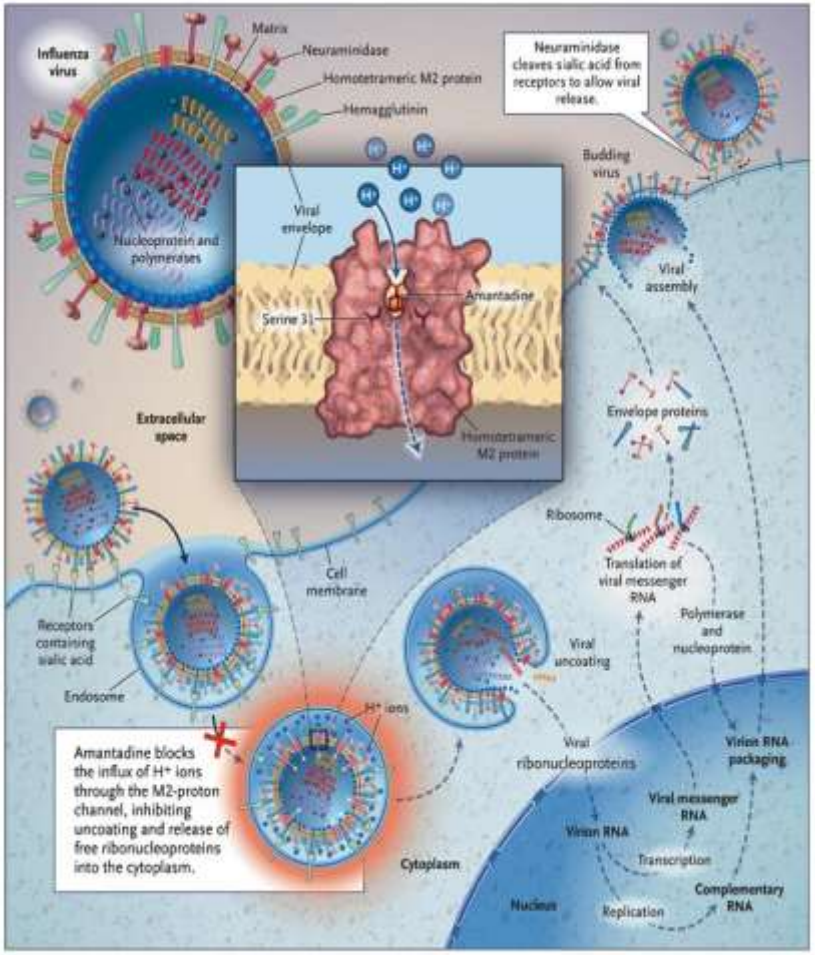
Available Agents: *M2 Inhibitors*

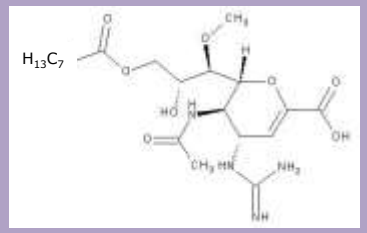
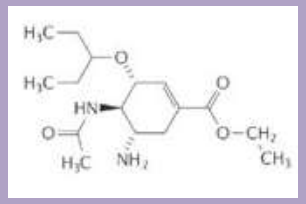
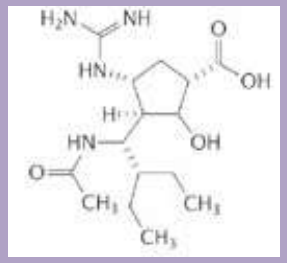
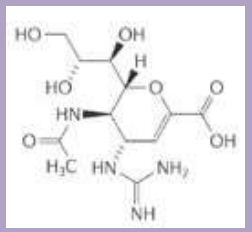
- Due to widespread resistance, M2 Inhibitors are not recommended
  - Amantadine
  - Rimantadine





Hayden. ***N Eng J Med***. 2006; 354:785-788. Bright RA. ***JAMA***. 2006;295:891-895.

Available Neuraminidase Inhibitors

	Laninamivir (Inavir®)	Oseltamivir (Tamiflu®)	Peramivir	Zanamivir (Relenza®)
Structure:				
Dosing frequency	40mg Single dose	75mg BID 5 days	600mg QD 5-10 days	10mg BID 5 days
Route of administration	Inhaled	Oral	Parenteral	Inhaled

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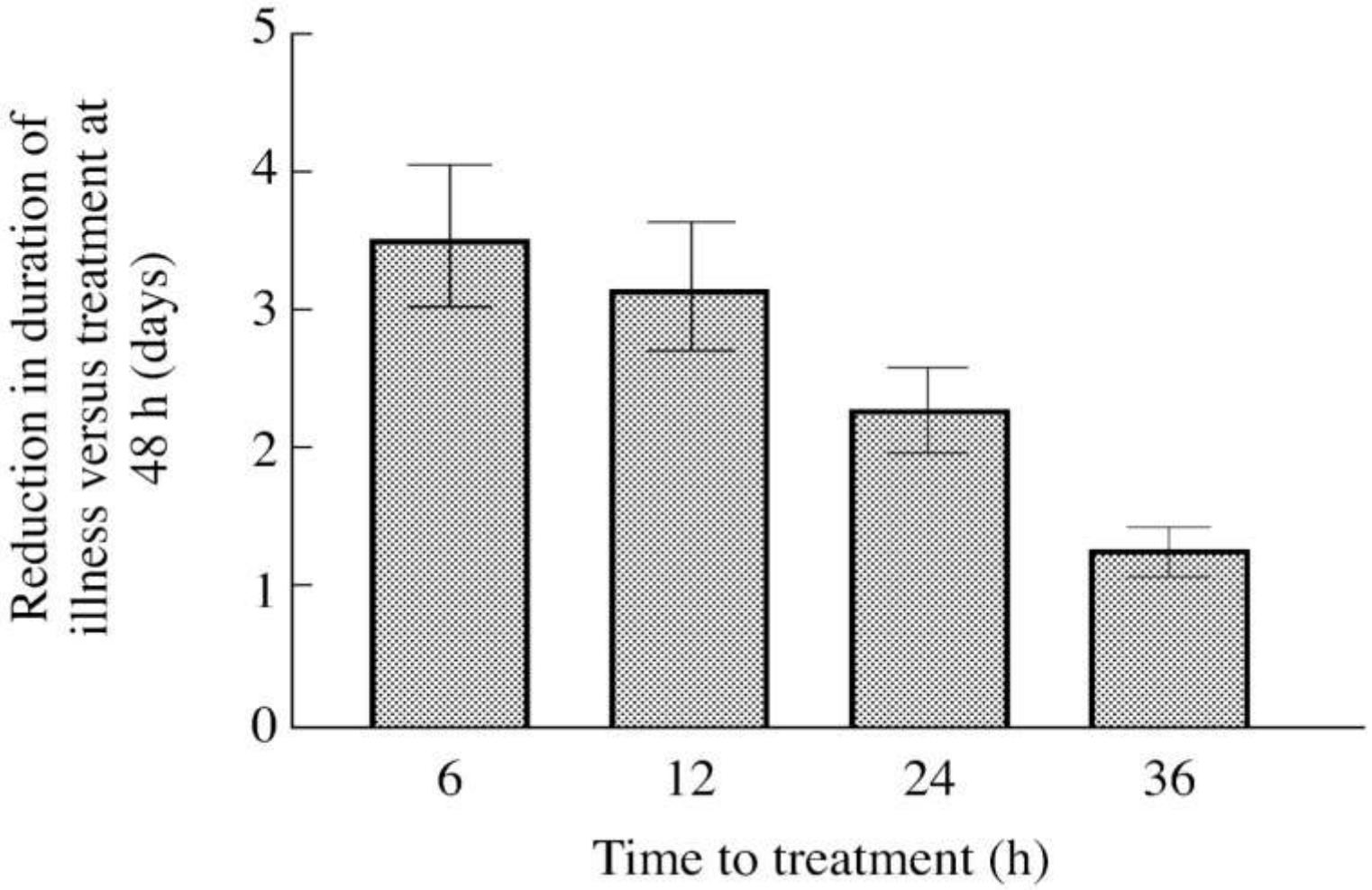
Bantia *et al.* ***Antiviral Res***. 2006; 69: 39-45. Peramivir Investigator Brochure V.4 Jul 2009; oseltamivir, zanamivir & laninamivir package inserts.

Treatment Efficacy: *Oseltamivir*



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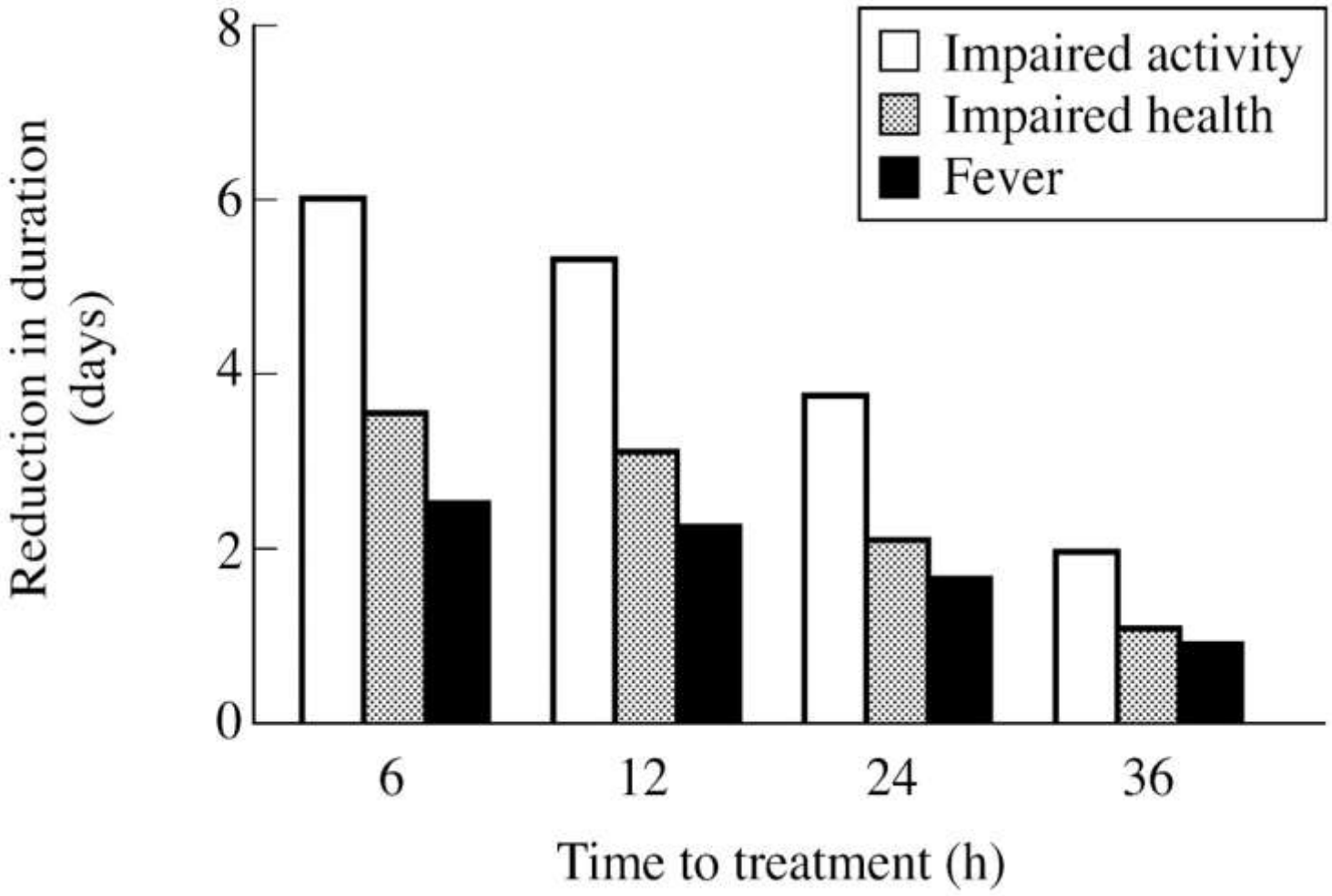
Aoki *et al*. ***J Antimicrob Chemother***. 2003;51:123-129

Treatment Efficacy: *Oseltamivir*



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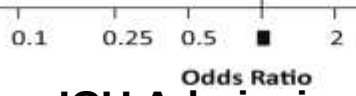
Aoki *et al*. ***J Antimicrob Chemother***. 2003;51:123-129

Antiviral Therapy: *Hospitalized*

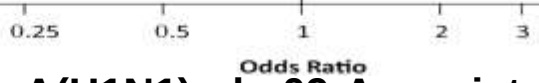
Pooled Analyses from Studies Examining Mortality

Antiviral Exposure	No. of Studies	I^2, %	Pooled OR (95% CI)
NAI vs no NAI treatment	20	49	.72 (.51–1.01)
Early vs late NAI treatment	25	52	.38 (.27–.53)
Early vs no NAI treatment	9	77	.35 (.18–.71)
Preadmission NAI vs no pre-admission NAI	2	0	.59 (.21–1.71)



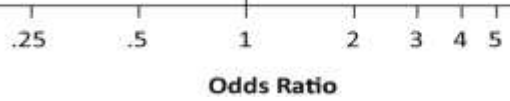
Pooled Analyses from Studies Examining ICU Admission or Death

Antiviral Exposure	No. of Studies	I^2, %	Pooled OR (95% CI)
NAI vs no NAI treatment	23	86	1.76 (1.22–2.54)
Early vs late NAI treatment	24	82	.41 (.30–.56)
Early vs no NAI treatment	11	93	.94 (.50–1.76)
Preadmission NAI vs no preadmission NAI	3	0	.51 (.29–.89)



Pooled Analyses from Studies Examining A(H1N1)pdm09-Associated Pneumonia

Antiviral Exposure	No. of Studies	I^2, %	Pooled OR (95% CI)
NAI vs no NAI treatment	6	26	2.29 (1.16–4.53)
Early vs late NAI treatment	11	50	.35 (.24–.49)
Early vs no NAI treatment	4	48	.73 (.27–2.02)



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Muthuri SG *et al*. ***J Infect Dis***. 2013;207:553-563.

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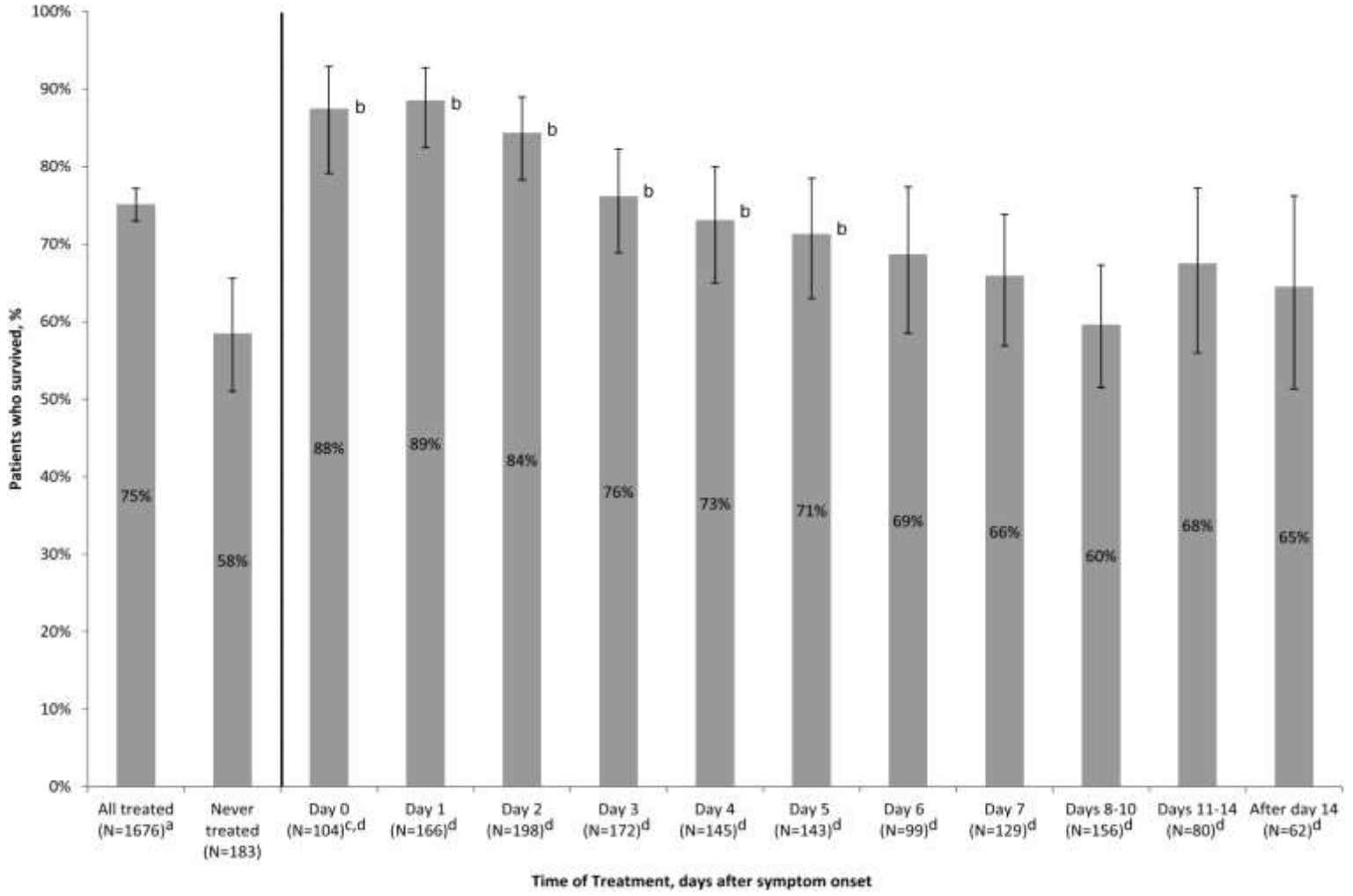
Treatment Effective within 5 days



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Louie *et al*. ***Clin Infect Dis***. 2012; 55: 1198-1204.
Lee & Ison. ***Clin Infect Dis***. 2012; 55: 1205-1208.

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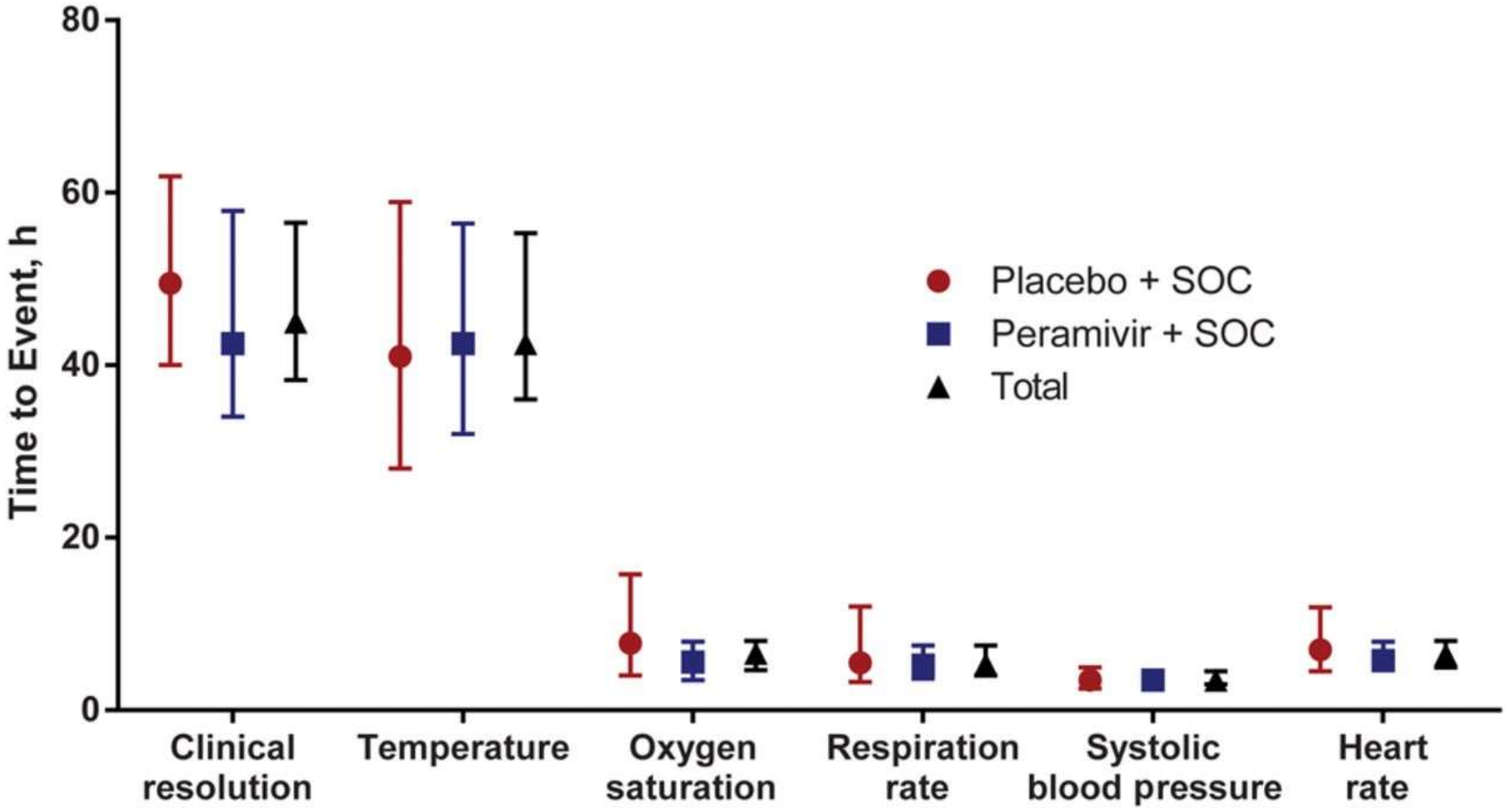
Peramivir: *IV Treatment of Influenza*



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de Jong *et al*. ***Clin Infect Dis***. 2014;59:e172-e185

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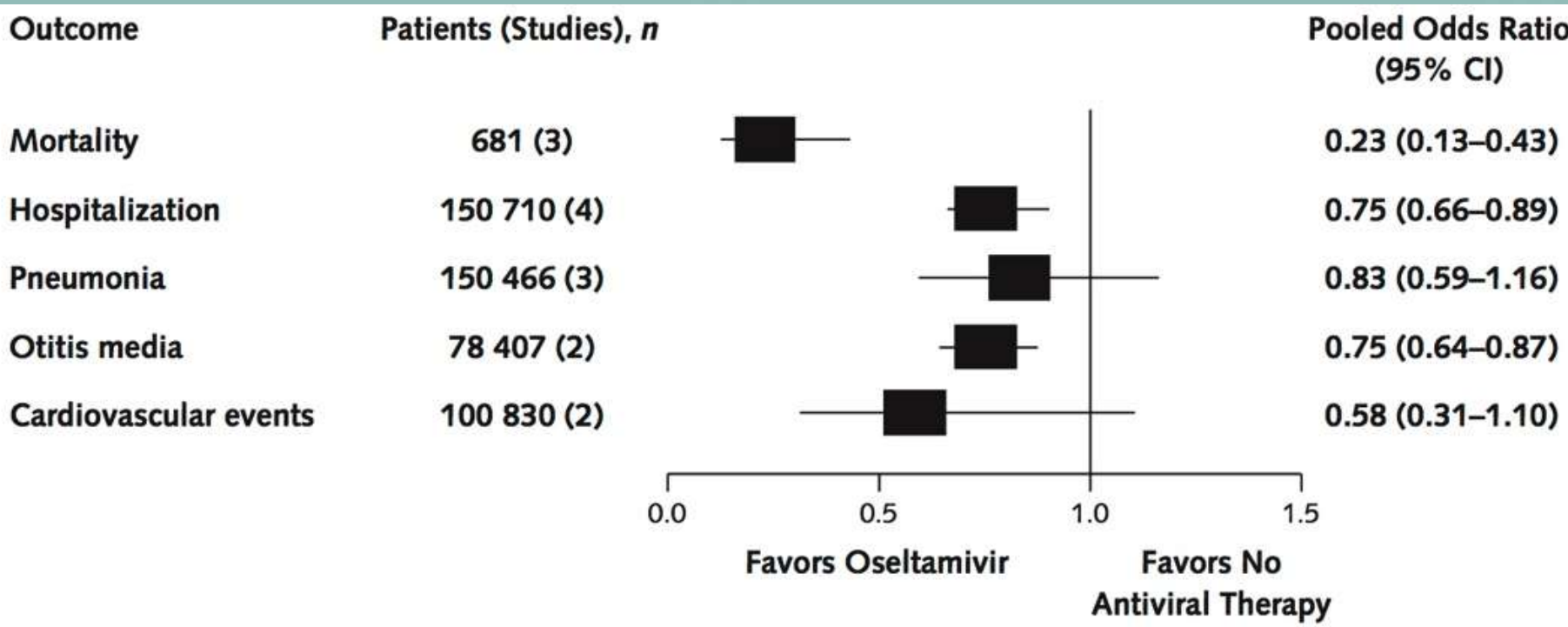
Effect of NAI Therapy on Patient Outcomes

Figure. Random-effects meta-analysis of oral oseltamivir versus no antiviral therapy based on studies that provided adjusted effect measures.



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Hsu *et al*. ***Annals Int Med***. 2012; 156: 512-524.

Treatment of High Risk Adults and Children

- Most current guidelines recommend early treatment
- Do not wait for testing results to start therapy

Table 2. Association Between Neuraminidase Inhibitor Administration and Hospital Admission

	Unadjusted Analysis		Adjusted Analysis[a]	
Population	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 influenza (n = 3376)	0.23 (0.19 to 0.28)	<.001	0.24 (0.20 to 0.30)	<.001
Patients with laboratory-confirmed A(H1N1)pdm09 influenza (n = 3085)	0.23 (0.19 to 0.28)	<.001	0.24 (0.19 to 0.29)	<.001
Adults (aged ≥16 years) (n = 1506)	0.26 (0.19 to 0.35)	<.001	0.26 (0.19 to 0.35)	<.001
Children (aged <16 years) (n = 1747)	0.22 (0.17 to 0.30)	<.001	0.25 (0.18 to 0.34)	<.001
Patients with at least 1 high-risk condition (n = 1019)	0.26 (0.19 to 0.37)	<.001	0.27 (0.19 to 0.38)	<.001
Early neuraminidase inhibitor treatment (≤2 days after onset) vs later (>2 days) in patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 influenza (n = 473)	0.51 (0.28 to 0.93)	.031	0.44 (0.23 to 0.86)	.016

[a]Adjusted for treatment propensity (by quintile) and community-based antibiotic use.

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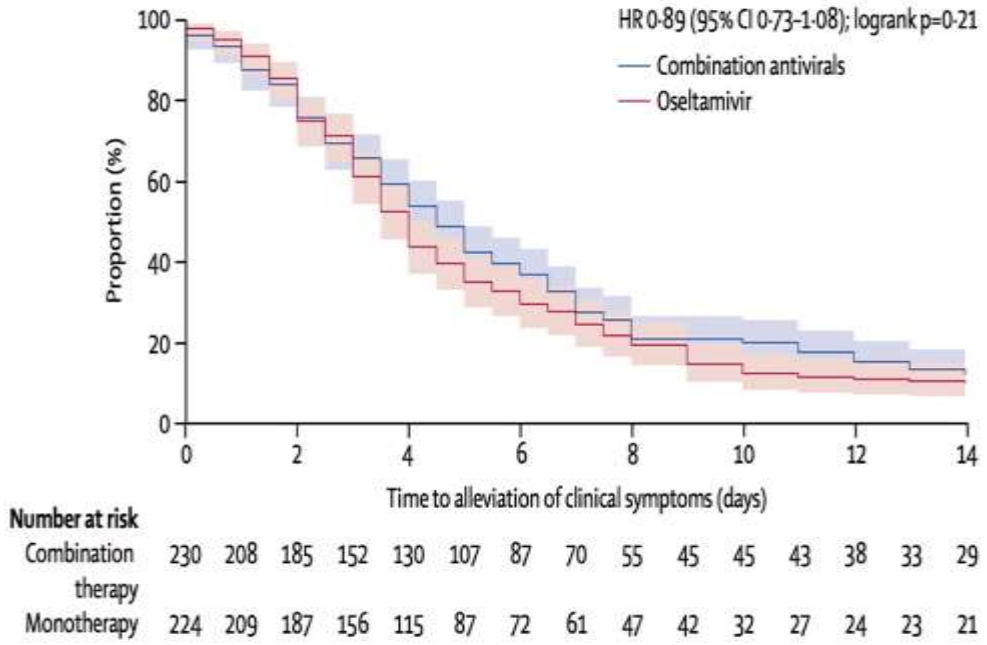
Venkatesan *et al*. ***Clin Infect Dis***. 2017; 64: 1328-1334.

Treatment of High Risk Adults and Children

- One completed prospective, randomized study
  - Patients at high risk of complications
  - Randomized to Triple Combination vs. Oseltamivir BID
  - TCAD: Oseltamivir 75mg, Amantadine 100mg, Ribavirin 600mg



	Combination group (n=230)	Monotherapy group (n=224)	p value
Efficacy population			
Duration of clinical symptoms	4·5 (4·0–5·0)	4·0 (3·5–4·5)	0·21
Duration of fever*	1·0 (1·0–1·5)	1·0 (0·5–1·5)	0·59
Duration of clinical symptoms or fever	5·0 (4·5–6·0)	4·0 (3·5–5·0)	0·10
Duration of time to feel as good as before the onset of influenza	7·5 (7·0–8·0)	6·5 (6·0–7·5)	0·0086
Duration of time to return to pre-influenza function	7·0 (6·0–7·5)	6·0 (5·0–6·5)	0·019
Intention-to-treat population			
Duration of clinical symptoms	4·5 (4·0–5·0)	4·0 (3·5–4·5)	0·44
Duration of fever*	1·0†	1·0 (0·5–1·0)	0·69
Duration of clinical symptoms and fever	4·5 (4·0–5·0)	4·5 (4·0–5·0)	0·30
Duration of time to feel as good as before the onset of influenza	7·5 (7·0–7·5)	6·5 (6·0–7·0)	0·0033
Duration of time to return to pre-influenza function	7·0 (6·0–7·5)	6·0 (5·0–6·5)	0·0086

Data are median duration in days (95% CI). *Data were restricted to patients who reported fever at randomisation. †95% CI was not estimable.

Table 3: **Clinical efficacy by treatment group**

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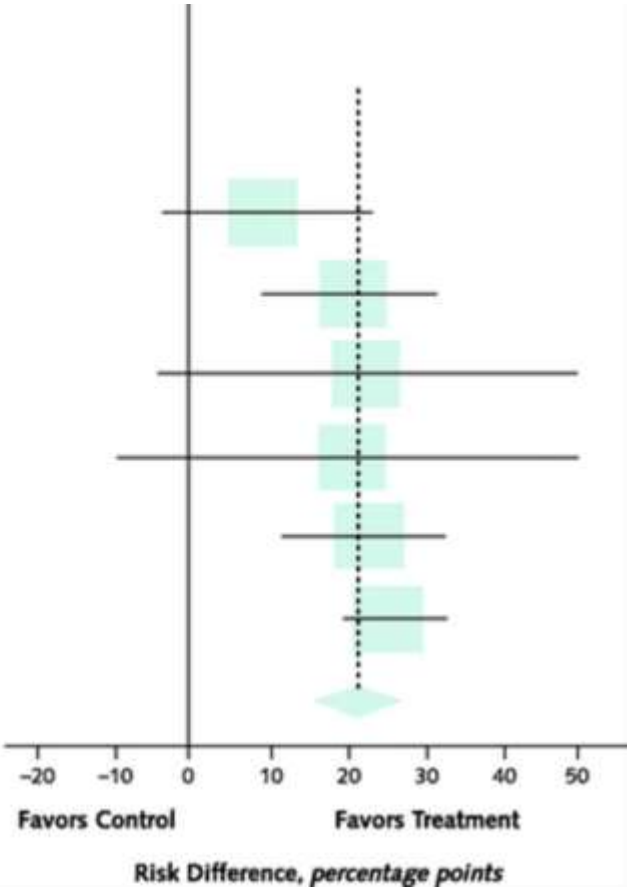
Venkatesan *et al*. ***Clin Infect Dis***. 2017; 64: 1328-1334.

Antiviral Therapy: *Plasma*

Study (Reference)	Mortality Rate, *n/n (%)*		Risk Difference (95% CI), *percentage points*
	Treatment Group	Control Group	
Stoll (17)	25/56 (45)	201/379 (53)	8 (–6 to 22)
O'Malley and Hartman (18)*	3/46 (7)	28/111 (25)	19 (8 to 29)
Ross and Hund (19, 20)	6/28 (21)	9/21 (43)	21 (–5 to 47)
Kahn (21)	12/25 (48)	12/18 (67)	19 (–11 to 48)
Gould (22)	2/30 (7)	82/290 (28)	22 (11 to 32)
McGuire and Redden (23, 24)*	6/151 (4)	120/400 (30)	26 (21 to 31)
Overall	54/336 (16)	452/1219 (37)	21 (15 to 27)



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Luke *et al*. ***Annals Int Med***. 2006; 145(8):599-609.

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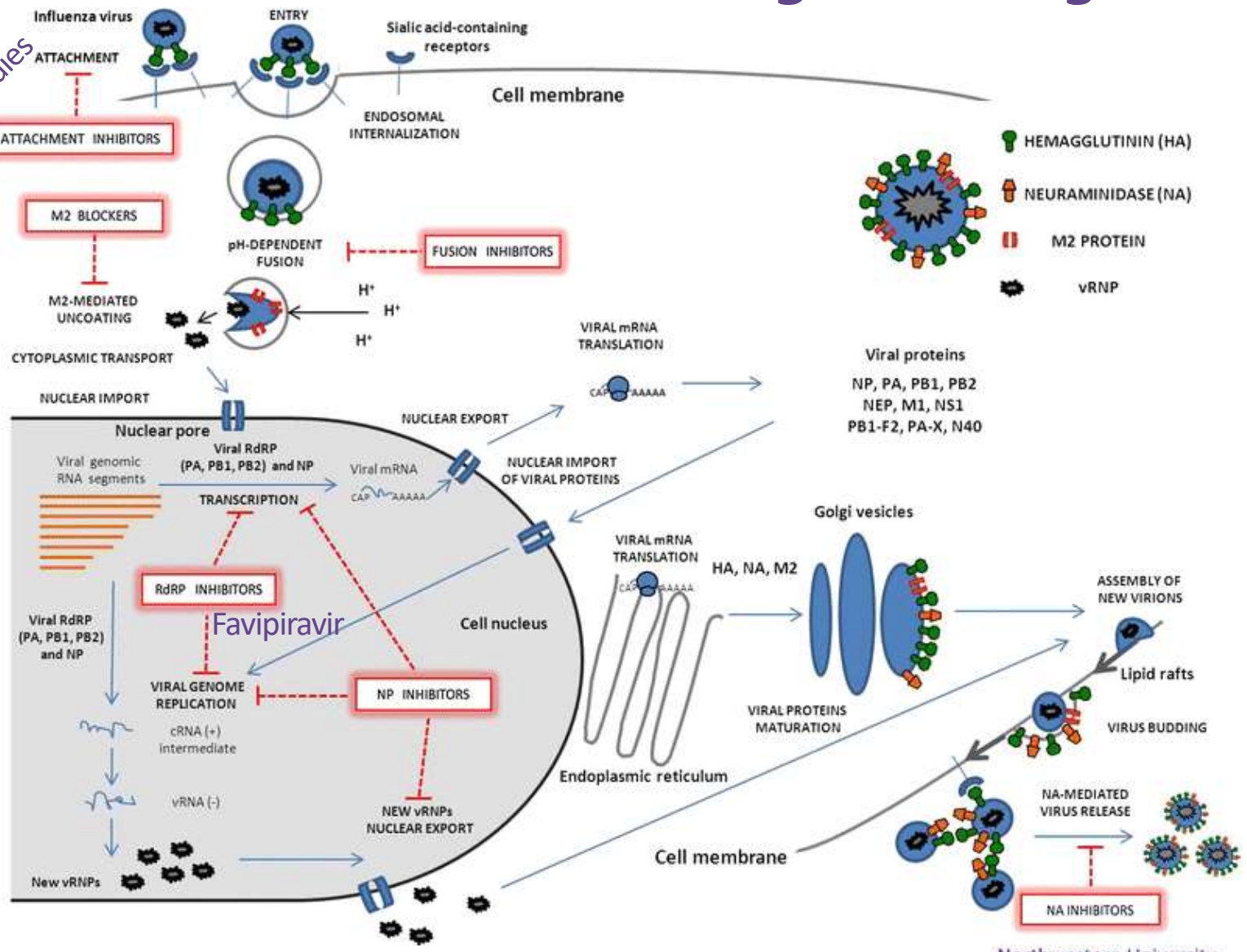
Influenza Antivirals: *Investigational Agents*

HA Antibodies

M2:
New antibodies
New small molecule



Loregian *et al*. ***Cell Mol Life Sci***. 2014; 71:3659-3683.

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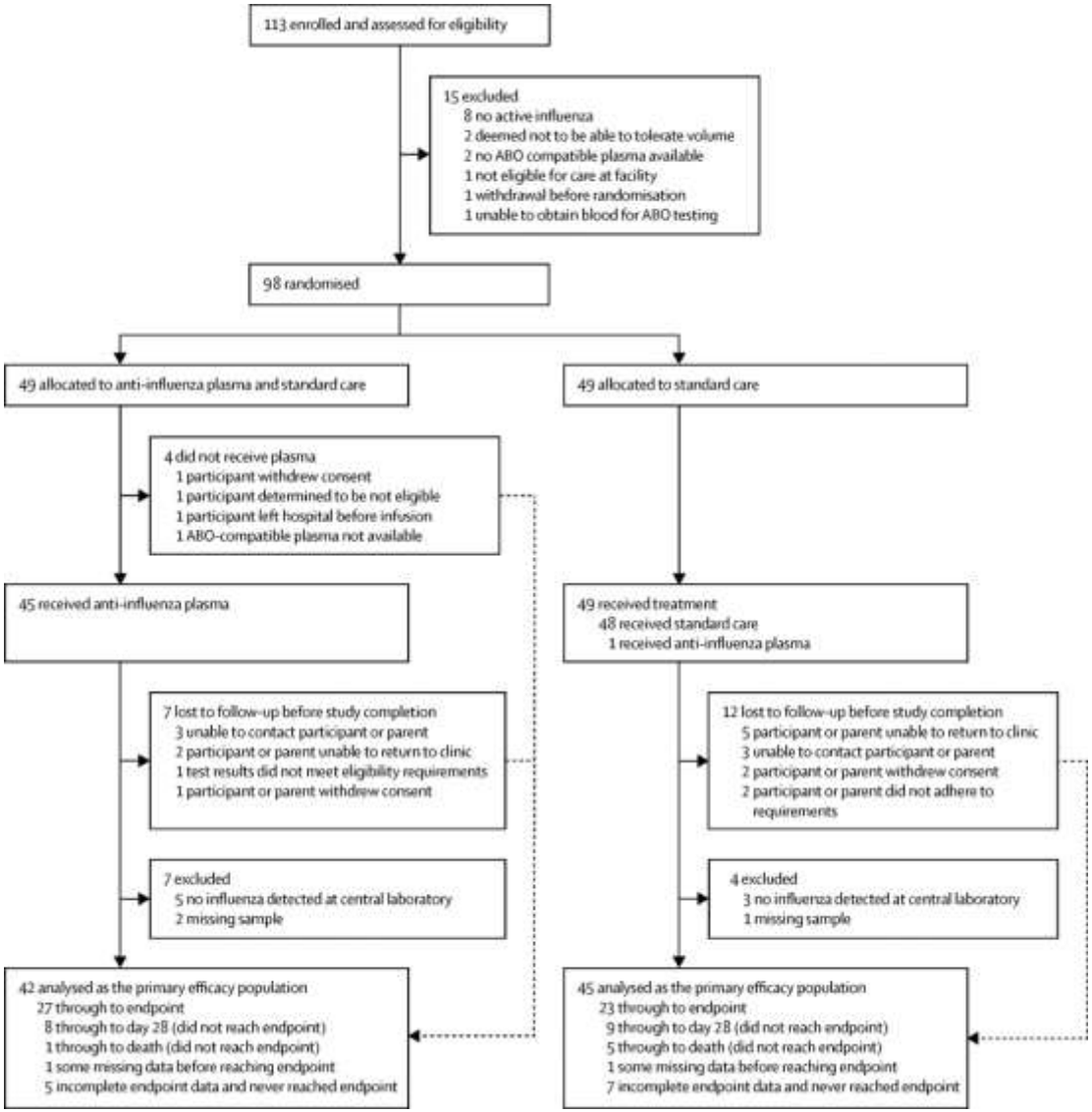
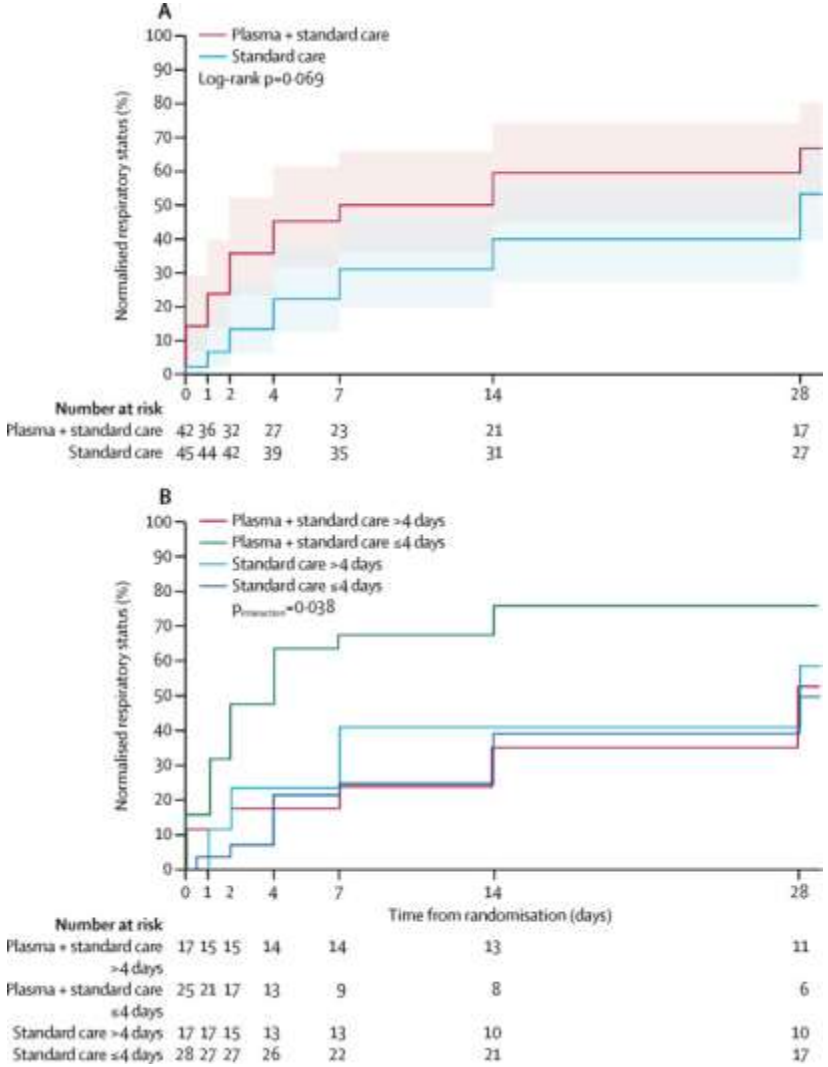
Treatment: *High Dose Influenza-Specific Plasma*



Beigel *et al*. ***Lancet Resp Med***. 2017. 5: 500-511.

Treatment: *High Dose Influenza-Specific Plasma*



Kaplan-Meier curves of normalised respiratory status over time with intention-to-treat analyses in the primary efficacy population
Normalised respiratory status over time, by randomised treatment (A) and by randomised treatment and days from symptoms onset to randomisation.

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Beigel *et al*. ***Lancet Resp Med***. 2017. 5: 500-511.

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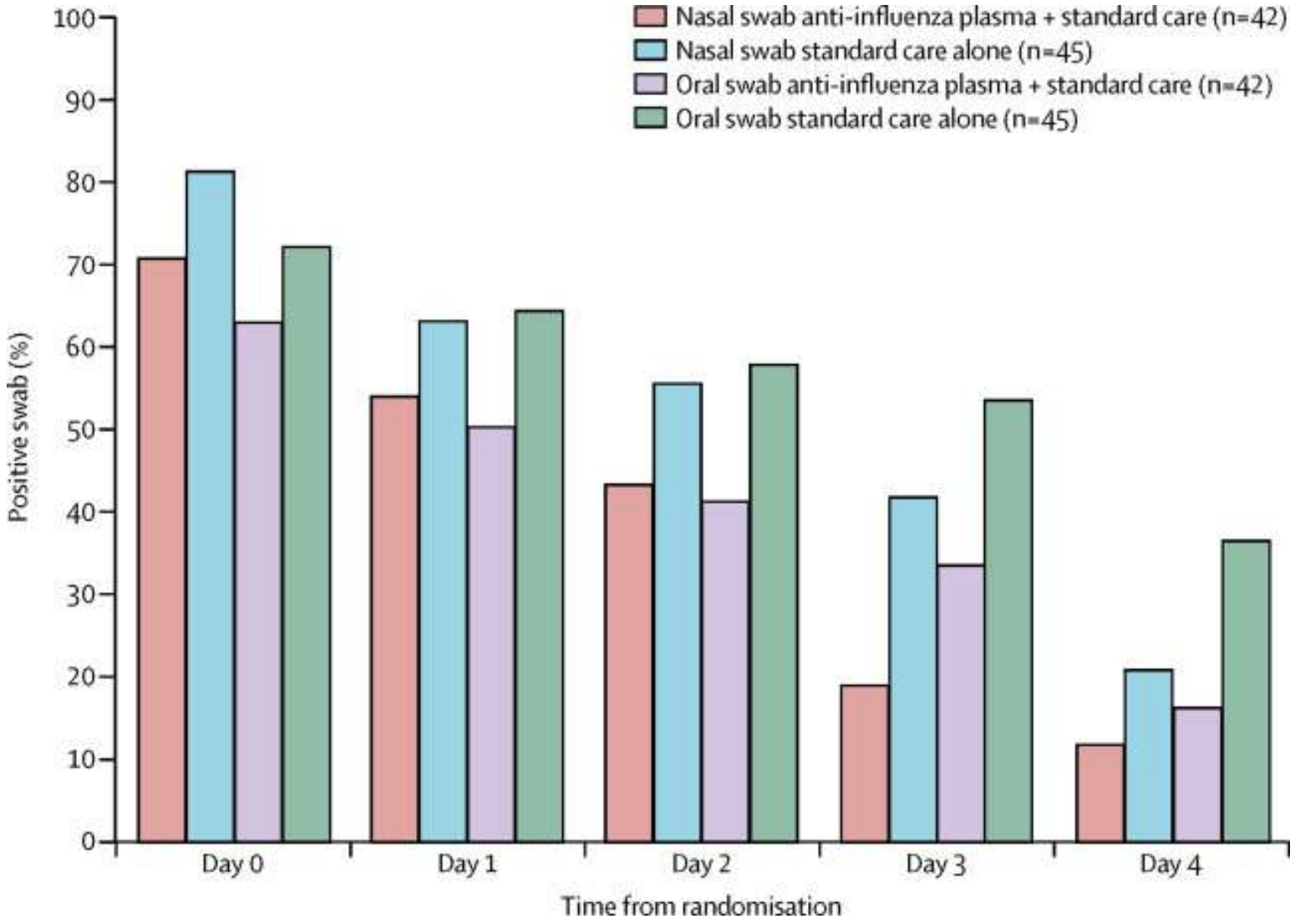
Treatment: *High Dose Influenza-Specific Plasma*



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Beigel *et al*. ***Lancet Resp Med***. 2017. 5: 500-511.

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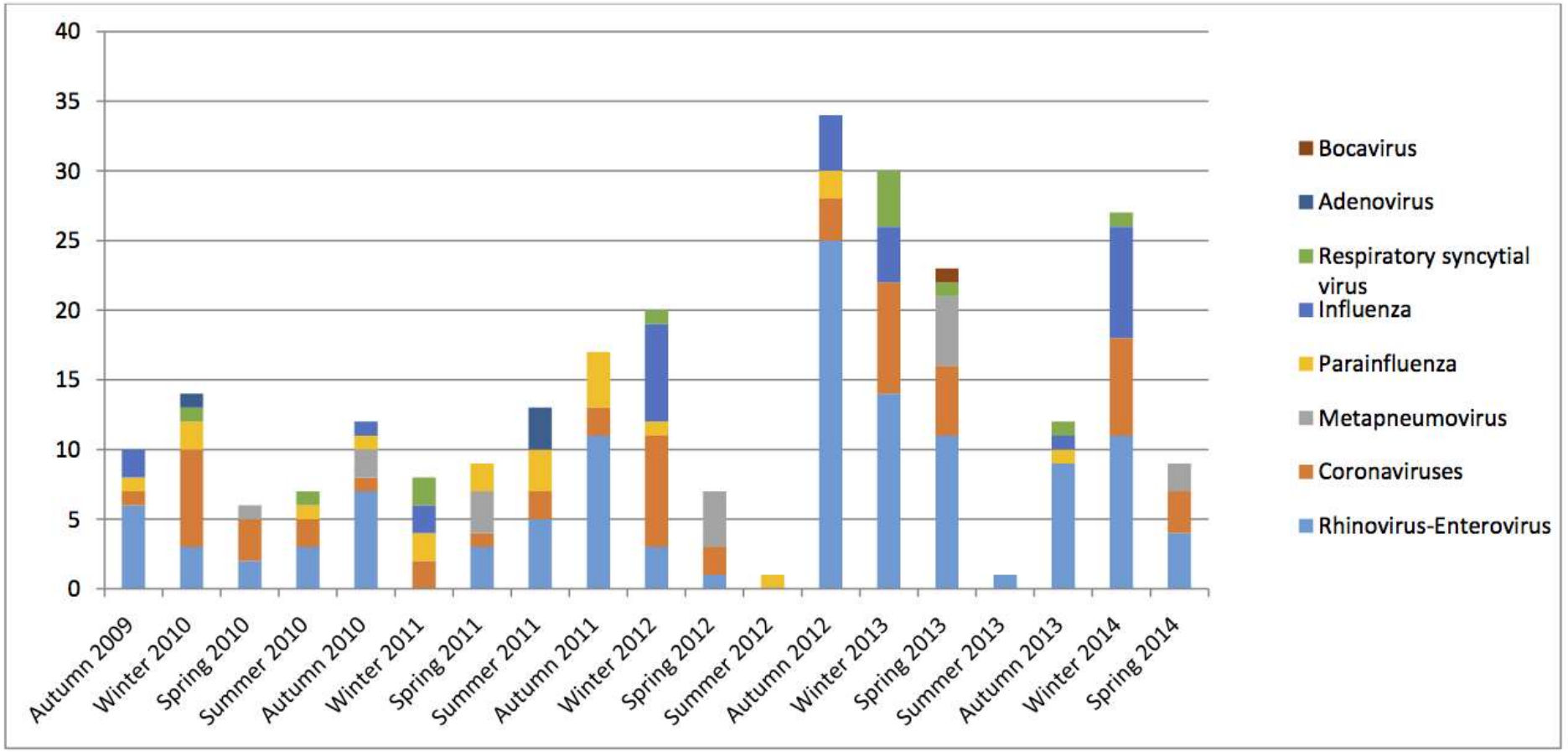
Influenza: *Immunocompromised*

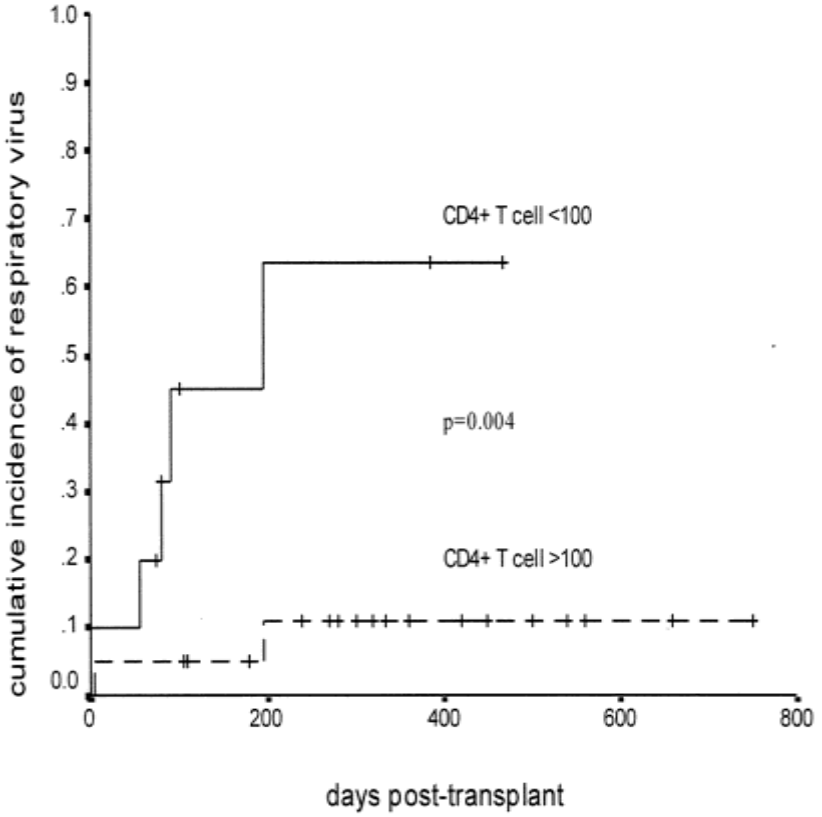
Epidemiology of RVIs: *Lung Transplantation*



Peghin *et al*. ***Am J Transplt***. 2016. ePub Ahead of Print.

Epidemiology of RVI: *Risk Factors*

- Solid Organ Transplant
  - Early onset post Tx (<3 m)
  - Steroid boluses, OKT3
  - Young children (<1 year)
  - Lung Transplantation
- Stem Cell Transplant
  - Early onset post-Tx
  - Chronic GVHD
  - Lymphopenia
  - Allogeneic HSCT (OR 5.26, 95%CI 1.05-27.5)



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Chakrabarti *et al*. ***Transplantation.*** 2001**.**
Ljungman *et al***.** ***BMT***. 2001;28:479-484.

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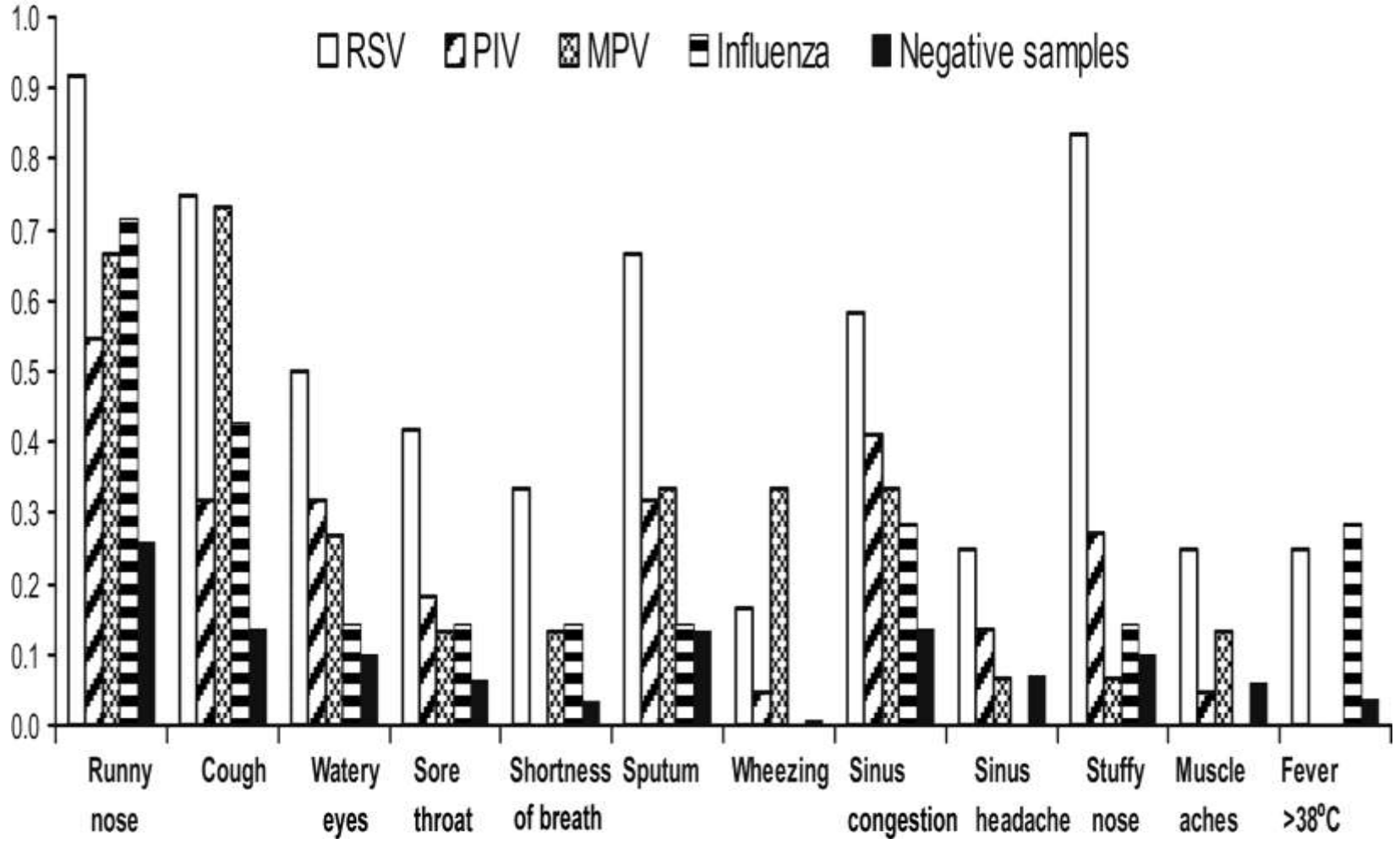
Epidemiology of RVI: *Clinical Presentation in HSCT*



Peck *et al*. ***Blood.*** 2007;110:1681-1688.

Epidemiology of RVI: *Clinical Presentation in SOT*

	Adults	Children	p value*
Fever >38°C	115/144 (80%)	78/82 (95%)	0·003
Cough	132/145 (91%)	67/73 (92%)	1·000
Sore throat	50/134 (37%)	30/51 (59%)	0·013
Rhinorrhoea	40/134 (30%)	42/59 (71%)	<0·001
Headache	33/136 (24%)	26/50 (52%)	0·001
Myalgias	70/135 (52%)	21/43 (49%)	0·866
Gastrointestinal symptoms	66/154 (43%)	39/83 (47%)	0·636
Pneumonia on chest radiograph or CT scan	60/149 (40%)	13/81 (16%)	<0·001
Admission to hospital	112/154 (73%)	55/83 (66%)	0·373
Admission to the intensive care unit	27/154 (17·5%)	10/83 (12·0%)	0·357
Mechanical ventilation	18/153 (12%)	3/83 (4%)	0·063
Antiviral treatment within 48 h	43/138 (31%)	47/77 (61%)	<0·001
Antiviral treatment after 48 h	95/138 (69%)	30/77 (39%)	<0·001
Death	10/154 (7%)	0/83 (0%)	0·016

*Statistical differences are by χ^2 test.

Table 2: **Clinical presentation and complications of influenza A in adult and paediatric recipients of solid-organ transplants**

Kumar *et al*. ***Lancet Infect Dis***. 2010; 10: 521-526.

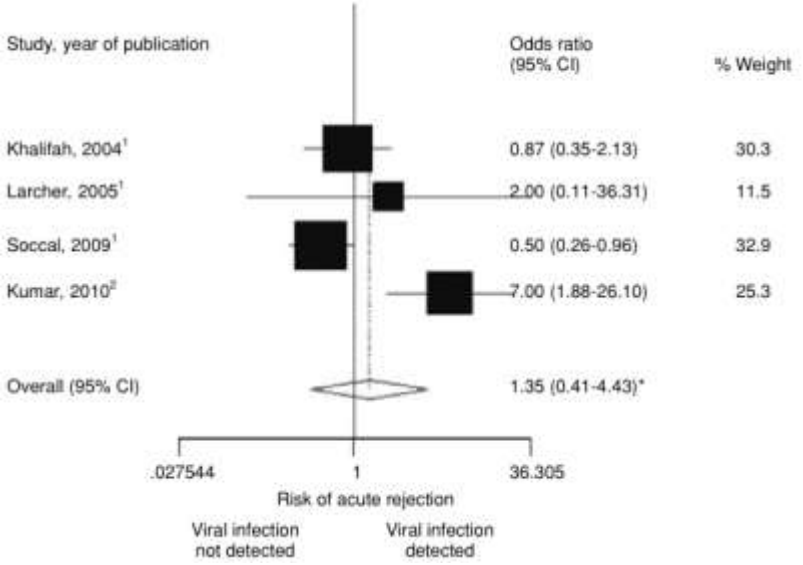
Epidemiology of RVI: *Long Term Complications*

Multivariable survival model

Variable	Multivariable survival model with time-dependent events: Hazard ratio (95% CI)	*P*-value
RVI	2.6 (1.6, 4.4)	<0.001
A2 rejection	0.46 (0.29, 0.74)	<0.001
Lung fungal	2.4 (1.5, 3.9)	<0.001
BOS	7.4 (4.0, 13.4)	<0.001
Tx type: single versus bilateral/other	1.03 (0.32, 3.3)	0.96
Tx type: heart/lung versus bilateral/other	1.7 (1.1, 2.6)	0.014
Tx type: living donor versus bilateral/other	3.6 (1.8, 7.3)	<0.001

CI, confidence interval; RVI, respiratory viral infection; A2, grade of rejection; BOS, bronchiolitis obliterans syndrome; Tx, transplant.

Table 5



Liu *et al*. ***Transplant Infect Dis***. 2009; 11:304-312.
Vu *et al*. ***Am J Transplant***. 2011; 11:1071-1078.

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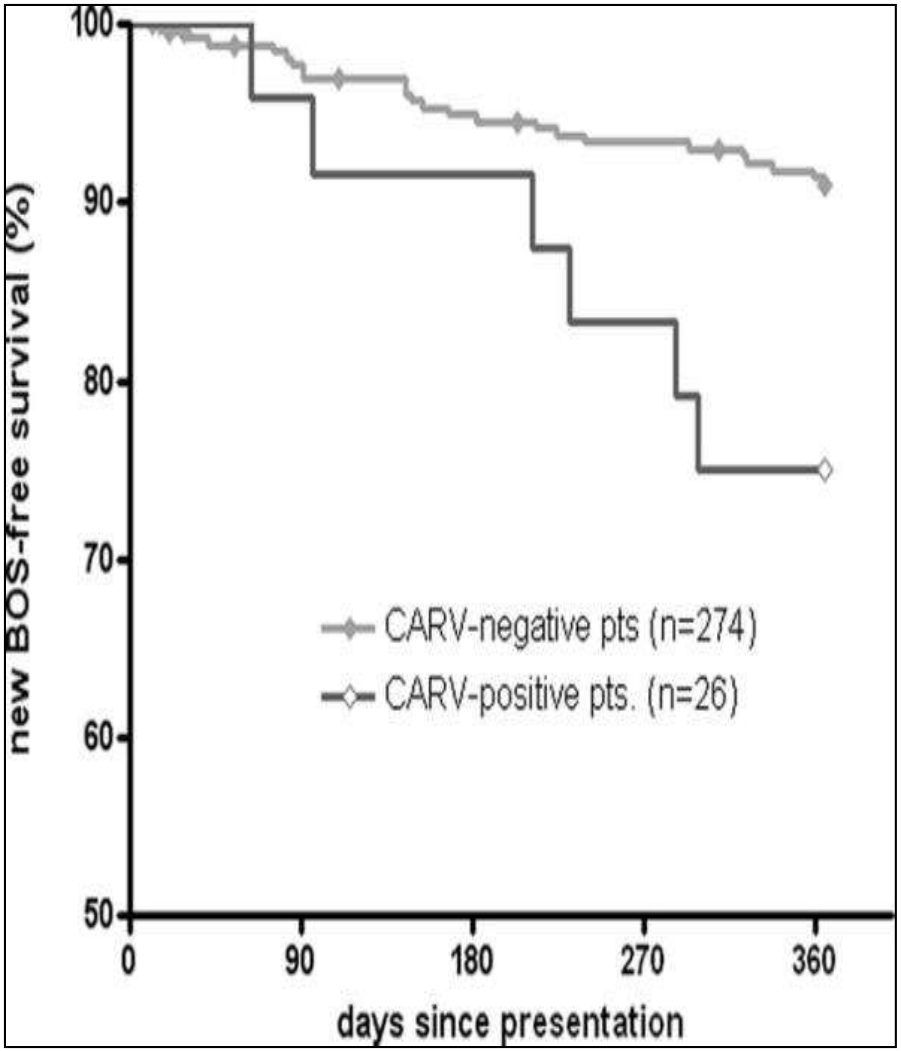
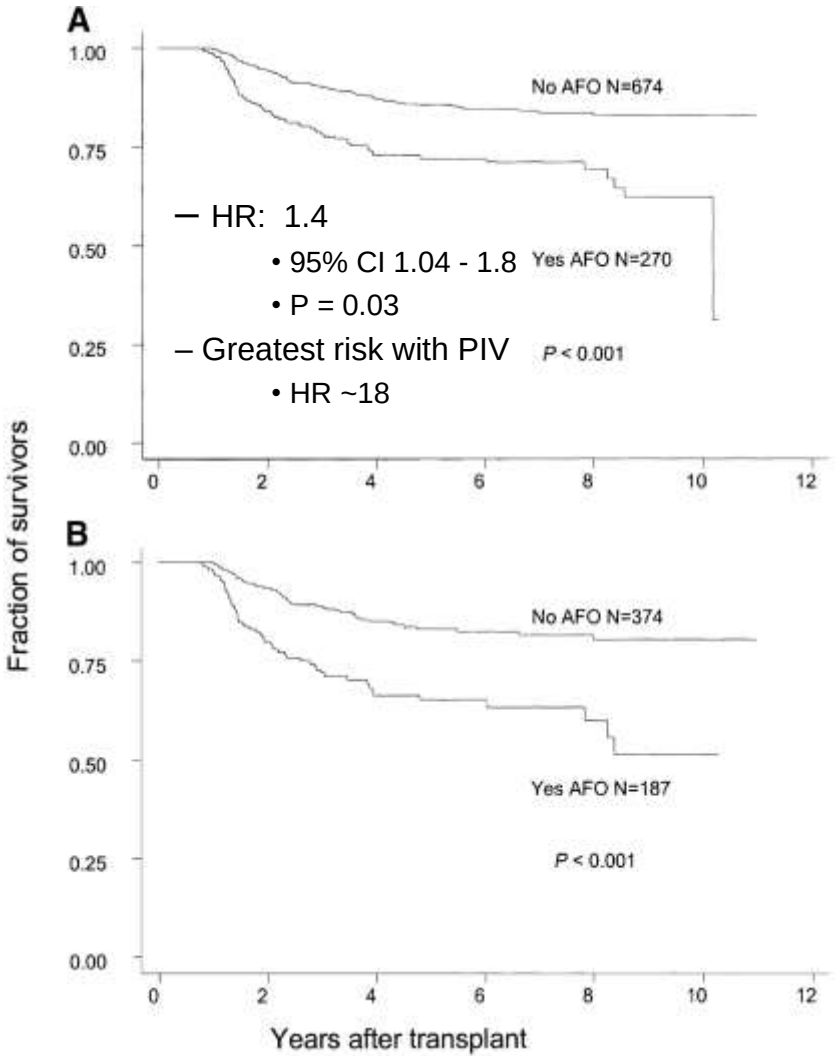
Epidemiology of RVI: *Long Term Complications*





Gottlieb *et al*. ***Transplantation***. 2009. 87: 1530-537.
Chien *et al*. ***AJRCCM***. 2003;168:208-214.
Erard *et al*. ***J Infect Dis***. 2006; 193: 1619-1625.

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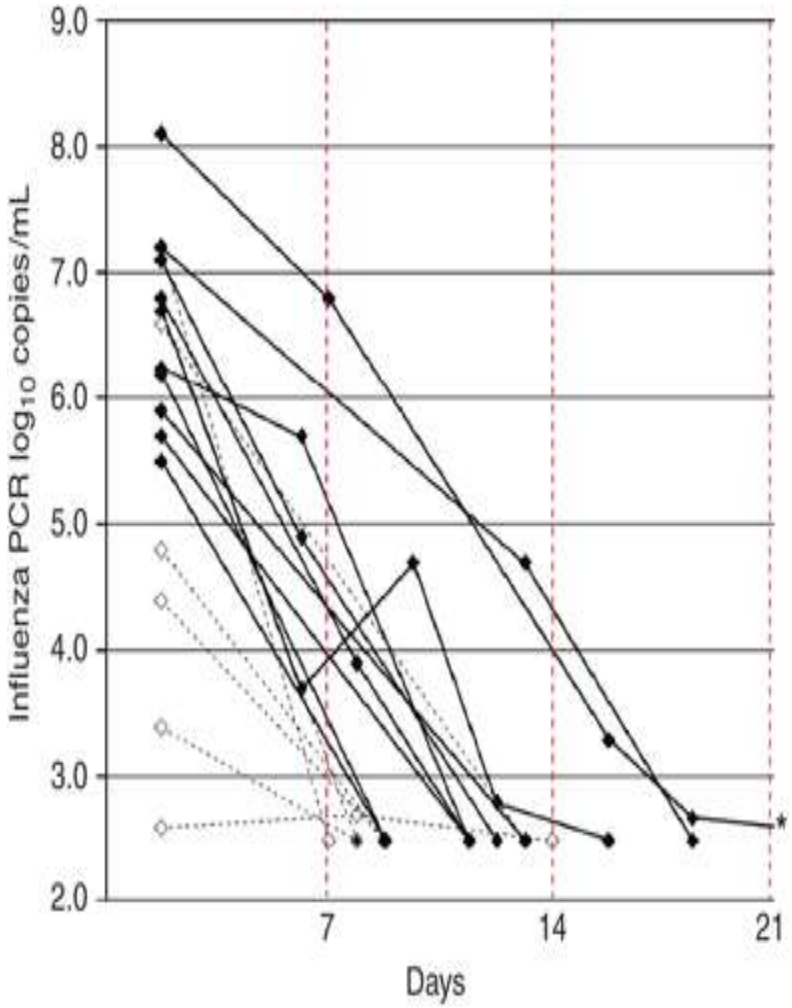
Treatment of Influenza

- Antiviral Therapy and Outcomes
  - No prospectively collected data
  - Most data with NAIs > M2 Inhibitors
  - Reduced mortality
    - M2 Inhibitors: 60% vs. 70%
    - NAI: Few deaths reported with use
  - Reduced viral shedding at day 10
    - M2 Inhibitors 20% vs. 50%
  - Lower rate of pneumonia
    - M2 inhibitors: 11% vs. 21%
    - NAI: 0-5% vs. 21%
  - Reduced risk of BOS
  - Risk of resistance emergence



Ison MG. ***Antiviral Therapy***. 2007; 12:627-638.
Ison MG *et al*. ***J Heart Lung Transplant***. 2008; 27: 282-288.
Khanna *et al*. ***Transpl Infect Dis***. 2009; 11:100-105.

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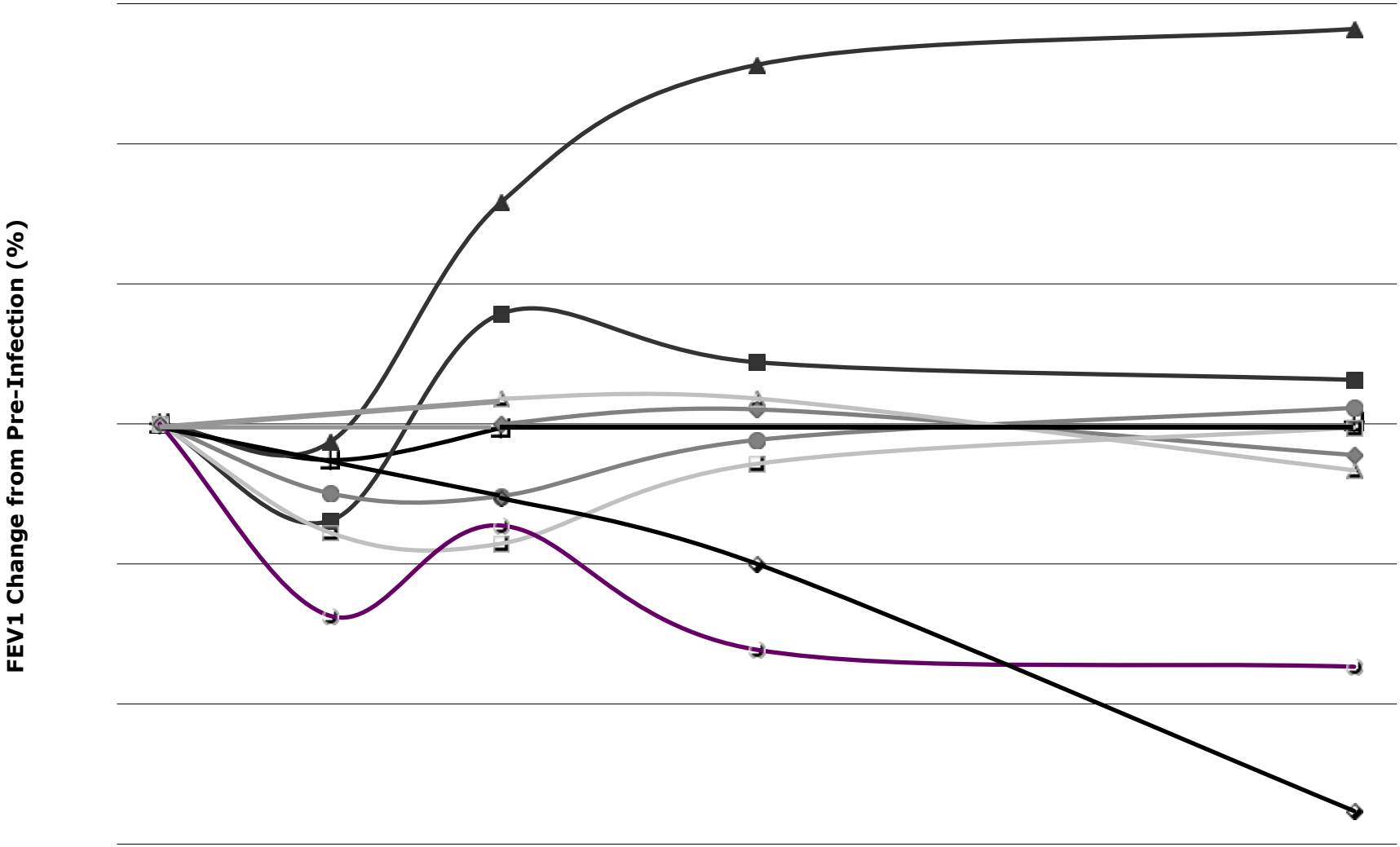
Treatment of Influenza



Ison *et al*. ***J Heart Lung Transplant***. 2008; 27: 282-288.

Treatment of Influenza

	Not admitted to the ICU	Admitted to the ICU	p value*
Early antiviral therapy (within 48 h)	83/180 (46%)	7/35 (20%)	0·007
Delayed antiviral therapy (after 48 h)	97/180 (54%)	28/35 (80%)	0·007
Diabetes mellitus	56/199 (28%)	19/37 (52%)	0·01
Antilymphocyte globulin use in the previous 6 months	12/200 (6%)	6/37 (16%)	0·043
Abnormal chest imaging at presentation	46/193 (24%)	27/37 (73%)	<0·001
Lymphopenia at time of presentation	94/162 (58%)	22/28 (79%)	0·064

*Statistical differences are by χ^2 test.

Table 3: **Univariate analysis of factors associated with admission to the intensive care unit (ICU)**

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Kumar *et al*. ***Lancet Infect Dis***. 2010; 10: 521-526.

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Risk Score for Influenza: *HSCT*

	Criteria	Patients 237 (N, %)	Progression to LRTI 37 (n, %)	Adjusted Hazard Ratio (95% CI)	Weighing criteria	Assigned weights (score)
1	ANC <500/μL	11 (5)	7 (64)	4.1 (1.4-11.6)	>2.5	3
2	ALC <200/μL	35 (15)	11 (31)	2.6 (1.02-6.4)	>2.5	3
3	Age ≥40 years	154 (65)	28 (18)	2.5 (1.1-5.6)	2.0-2.5	2
4	Myeloablative conditioning regimen	98 (41)	17 (17)	1.2 (0.6-2.3)	<2.0	1
5	GVHD (acute or chronic)	149 (63)	19 (13)	1.0 (0.5-2.2)	<2.0	1
6	Corticosteroids†	117 (49)	17 (15)	0.89 (0.4-1.8)	<2.0	1
7	Recent† or pre-engraftment allo-HSCT	21 (9)	5 (24)	0.68 (0.2-2.3)	<2.0	1

†Within 30 days of assessment

Low Risk: 0-2; Moderate Risk: 3-6; High Risk 7-12

Kmeid *et al*. ***Bio Blood Marrow Transplant***. 2016; 22: 542-548.

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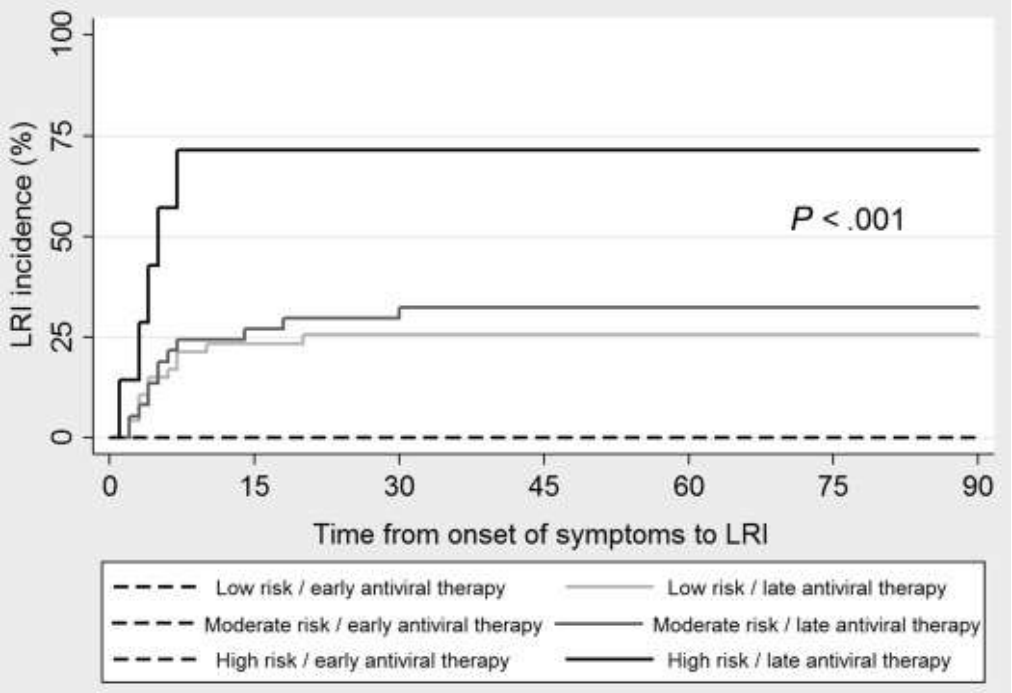
Risk Score for Influenza: *HSCT*

Table 3
Incidence of LRI and Influenza-Associated Death Stratified by ISI Risk Groups and Antiviral Therapy (N = 142)

Risk Groups as Defined by the ISI	Total			Antiviral Therapy				
				Early (within 48 hours of symptom onset)		Late (after 48 hours of symptom onset)		
	n	LRI	Influenza-Related Death	n	LRI/Death	n	LRI	Death
Low-risk (ISI of 0 to 2)	78	13 (17)	2 (3)	13	0	48	13 (27)	2 (4)
Moderate-risk (ISI of 3 to 6)	53	15 (28)	2 (4)	9	0	38	13 (34)	2 (5)
High-risk (ISI of 7 to 12)	11	5 (45)	2 (18)	3	0	7	5 (71)	2 (29)

Note: Data required for generating ISI were missing in 4 patients.



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Kmeid *et al*. ***Bio Blood Marrow Transplant***. 2016; 22: 542-548.

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Treatment of Influenza: *Unanswered Questions*

- Optimal Duration of Antiviral Therapy
  - Patients have prolonged shedding
  - Premature interruption of therapy could result in resistance and clinical decline
  - Many experts recommend a duration > 5 days
    - Many recommend that duration is guided by duration of shedding

- Optimal Dose of Therapy
  - Studies have failed to document improved outcome with high dose oseltamivir
  - 2 of the 3 studies demonstrated a lower rate of resistance with the higher dose

- Role of IV Therapy, Antibodies and Combination

- Management of Resistant Influenza

Influenza Resistance Testing: *Genotypic & Phenotypic*

Classification	Abbreviations	Influenza A	Influenza B
Normal Inhibition	NI	<10-fold above normal inhibition	<5-fold above normal inhibition
Reduced Inhibition	RI	10 to 100-fold above normal inhibition	5 to 50-fold above normal inhibition
Highly Reduced Inhibition	HRI	>100-fold above normal inhibition	>50-fold above normal inhibition

Drug	N1	N2	N9	B
Oseltamivir	H275Y N295S	E119V R292K	R292K	H273Y
Zanamivir	Q136K			
Peramivir	H275Y	E119V R292K		H273Y

http://www.who.int/influenza/gisrs_laboratory/antiviral_susceptibility/nai_overview/en/

Questions?

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Challenges of Clinical Trials in Hospitalized

- Significant variation in indication for admission
- Poor Recognition of influenza among hospitalized patients
- Recruitment hurdles
  - Small numbers spread with significant geographic and seasonal dispersion
  - Difficulty getting consent: late results, need for urgent therapy
- Significant variation in clinical disease present in the admitted patients
- Disease pathogenesis, clinical course, and prognosis are effected by:
  - Age of the patient, Co-morbidities
  - Time to presentation for care
  - Type/subtype of virus, Antiviral susceptibility
  - Immunocompentence of patients
- Inability for some hospitalized patients to provide assessment of current symptoms (intubated, short of breath, communications challenges)
- More challenging to control confounding medications
- Most would consider a placebo controlled study unethical

Ison *et al*. ***J Infect Dis***. 2010; 201: 1654-1652.

Endpoints Used in Clinical Studies: *Completed Studies*

- IV Peramivir (Hospitalized)
  - Primary Outcome: Time to Clinical Resolution (Kaplan-Meier Estimate day 10)
    - Normalization of at least 4 of the 5 signs within the respective normalization criteria, maintained for at least 24-hours: normal temperature (≤37.2° C), oxygen saturation ≥ 92%, respiratory rate ≤ 24/min, heart rate ≤ 100 bpm, and systolic blood pressure ≥ 90 mmHg
- IV Zanamivir (Hospitalized)
  - Primary Outcome: a composite of vital sign stabilisation and hospital discharge—in the influenza-positive population
- IRC002/High Titer Influenza Plasma
  - NCT1052480
  - Primary Outcome: Time to normalization of respiratory status (defined as room air saturation of oxygen [SaO2] greater than or equal to 93% AND respiratory rate within normal ranges)

Panel: Time to clinical response criteria

Temperature*
- ≤36·6°C (≤97·9°F)—axilla, or
- ≤37·2°C (≤99°F)—oral, or
- ≤37·7°C (≤99·9°F)—rectal, core, or tympanic

AND

Oxygen saturation†‡
- ≥95% (without supplemental oxygen)

AND two of the following three:

Respiratory status
- Return to pre-morbid oxygen requirement (patients with chronic oxygen use), OR
- Need for supplemental oxygen (given in any way-ventilator, non-invasive ventilation, facemask, face-tent, or nasal cannula) to no need for supplemental oxygen, OR
- Respiratory rate ≤24 per min (without supplemental oxygen)

Heart rate
- ≤100 beats per min

Systolic blood pressure§
- ≥90 mmHg

OR

Hospital discharge
- Patients who were discharged from hospital alive were deemed to have met the clinical response endpoint at the time of hospital discharge and did not need to have documented resolution of at least four response criteria (ie, achieved treatment success at the time of discharge if not recorded before it).

*Without the use of antipyretics within 8 h. †A patient with a history of chronic hypoxia (without supplemental oxygen) satisfied normalisation criteria for oxygen saturation if the value (without supplemental oxygen) was ≤2% from patient's historical oxygen saturation baseline as recorded within 12 months before enrolment as documented in the patient's medical records. ‡This requirement was waived for patients with a history of chronic supplemental oxygen requirement who had a baseline oxygen saturation <95% with supplemental oxygen, within 12 months of enrolment as documented in the patient's medical records. §Without inotropic support given within 2 h of assessment. For patients who achieved four of the five vital sign resolution criteria above, maintained for at least 24 h, it was mandatory that both the temperature and oxygen saturation response criteria were achieved for the clinical response endpoint to be met.

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de Jong *et al*. ***Clin Infect Dis***. 2014; 59:e172-e185.

Marty *et al*. ***Lancet Resp Med***. 2017; epub ahead of print.

Endpoints Used in Clinical Studies: *Ongoing Studies*

- Danirixin (CXCR-2 Inhibitor) ± Oseltamivir: NCT02927431
  - Primary Endpoint: Time to Clinical Response: Discharged from hospital or if normalization of the following parameters are maintained for 24 hours: temperature; oxygen saturation; and 2 out of the following 3 parameters, respiratory status/heart rate/systolic blood pressure (SBP). Subjects will be assessed daily during treatment and post treatment inpatient days up to discharge or Day 45. For subjects who are discharged before Day 45, outpatient assessments will also be done on post treatment Day 3 and study Day 45.
- MHAA4549A ± Oseltamivir: NCT02293863
  - Primary Outcome Measures: % with AE, % with anti-MHAA4549A Antibodies, Time to cessation of O_2 support by pulse oximetry
- IRC005/High Titer Anti-Influenza Plasma: NCT02572817
  - Primary Endpoint: 6-Point Ordinal Scale measured at day 7
- INSIGHT Anti-Influenza Hyperimmune Immunoglobulin: NCT02287467
  - Primary Outcome Measure: % of participants at day 7 who died, in ICU, non-ICU with O2 supplementation, non-ICU without O2 supplementation, discharged but not resumed normal activity, discharged and resumed normal activity
- MEDI8852 ± Standard of Care: NCT03028909
  - Primary Outcomes: Time to normalization of respiratory function by day 14 and AE, SAE, AE of Special Interest

Endpoints Used in Clinical Studies: *Ordinal Scale*

- Five mutually exclusive clinical outcomes are recorded daily for each patient on Days 0 (baseline) and Days 1 – 14
- Outcomes are included as the components of an ordinal endpoint, ranged from most to least severe:
  - Death
  - ICU with Ventilation
  - ICU w/o Ventilation
  - Hospitalized with supplemental O_2
  - Hospitalized without supplemental O_2
  - Discharged from Hospital with abnormal function
  - Discharge from Hospital with normal function
- The relative frequency distribution and mean score of ordinal components (assuming a unit decrease from 5 for death to 1 for discharge) are plotted daily
- Range of analysis plans under study

Admission Risk Stratification: *NEWS*

- National Early Warning Scores
  - Use clinically available data to inform need for escalated clinical assessment
  - Early Warning Scores have been developed to facilitate early detection of deterioration by categorising a patient's severity of illness and prompting nursing staff to request a medical review at specific trigger points utilising a structured communication tool while following a definitive escalation plan
  - Adopting a National Early Warning Score (NEWS) is beneficial for standardising the assessment of acute illness severity, enabling a more timely response using a common language across acute hospitals nationally [in the United Kingdom]
  - Utilized by the National Pandemic Flu Service to triage patients
  - Now proposed as a way to stratify patients for enrollment

http://health.gov.ie/wp-content/uploads/2015/01/NEWSFull-ReportAugust2014.pdf

Admission Risk Stratification: *NEWS*

- Use of NEWS to categorize patients on admission
  - Score on presentation: respiratory rate, O2 saturation, use of supplemental O2, temperature, systolic BP, heart rate and level of consciousness

Parameter	3	2	1	0	1	2	3
Resp Rate	≤8		9-11	12-20		21-24	≥25
O_2 Sat	≤91	92-93	94-95	≥96			
Any Supp O_2?		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 -38.0	38.1 -39.0	≥39.1	
Systolic BP	≤90	91-100	101-110	111-219			≥220
Heart Rate	≤40		41-50	51-90	91-110	111-130	≥131
Level of Consciousness				A			V, P, or U

http://health.gov.ie/wp-content/uploads/2015/01/NEWSFull-ReportAugust2014.pdf

Potential Endpoints: *Clinical*

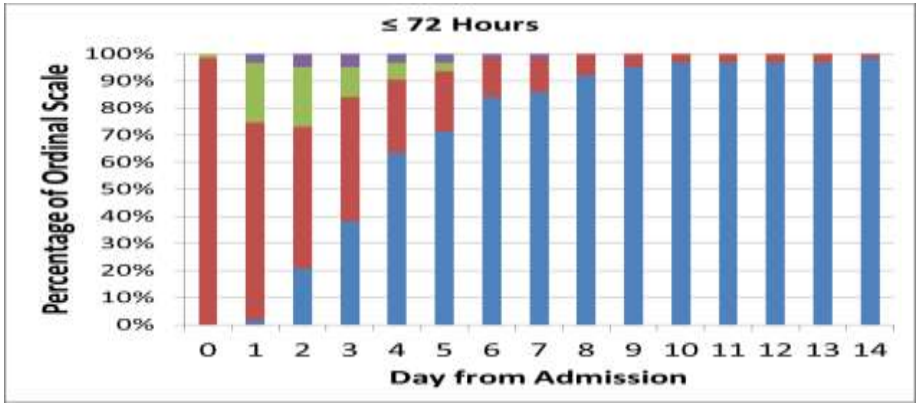
- Use of NEWS to categorize patients on admission – NU Data

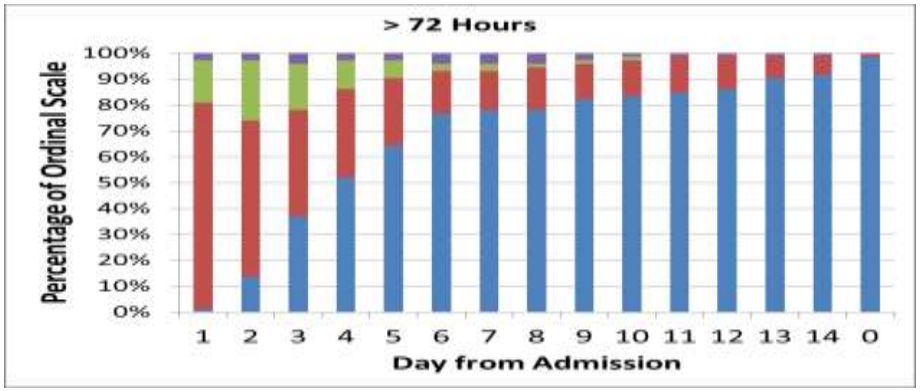
Variable	NEWS 1-3		NEWS 4-6		NEWS > 6	
	≤ 72 (N=43)	> 72 Hours (N=57)	≤ 72 Hours (N=63)	> 72 Hours (N=73)	≤ 72 Hours (N=31)	> 72 Hours (N=48)
Age (Years)						
Mean (SD)	50.1 (21.0)	54.6 (18.4)	53.2 (20.4)	54.7 (19.3)	51.4 (16.7)	56.9 (19.4)
Min, Max	20, 93	22, 92	22, 100	21, 89	20, 80	18, 93
N (%)						
< 50	21 (48.8)	24 (42.1)	27 (42.9)	30 (41.1)	12 (38.7)	15 (31.2)
50-65	11 (25.6)	17 (29.8)	17 (27.0)	21 (28.8)	12 (38.7)	20 (41.7)
> 65	11 (25.6)	16 (28.1)	19 (30.1)	22 (30.1)	7 (22.6)	13 (27.1)
Sex, N (%)						
Female	24 (55.8)	25 (43.9)	44 (69.8)	47 (64.4)	18 (58.1)	23 (47.9)
NEWS Score						
Mean (SD)	2.2 (0.8)	2.1 (0.8)	4.9 (0.8)	4.9 (0.8)	8.6 (1.7)	8.3 (1.4)
Min, Max	1, 3	1, 3	4, 6	4, 6	7, 13	7, 11

Potential Endpoints: *Clinical – NEWS Directed Ordinal*

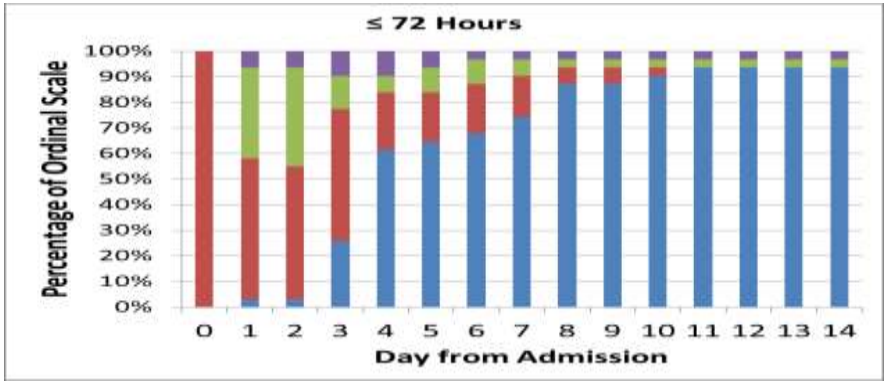
- Use of NEWS to categorize patients on admission

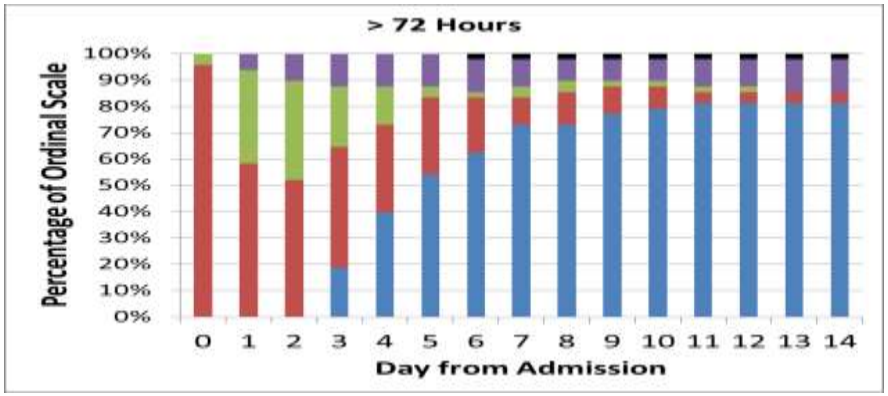
NEWS 4-6





NEWS > 6





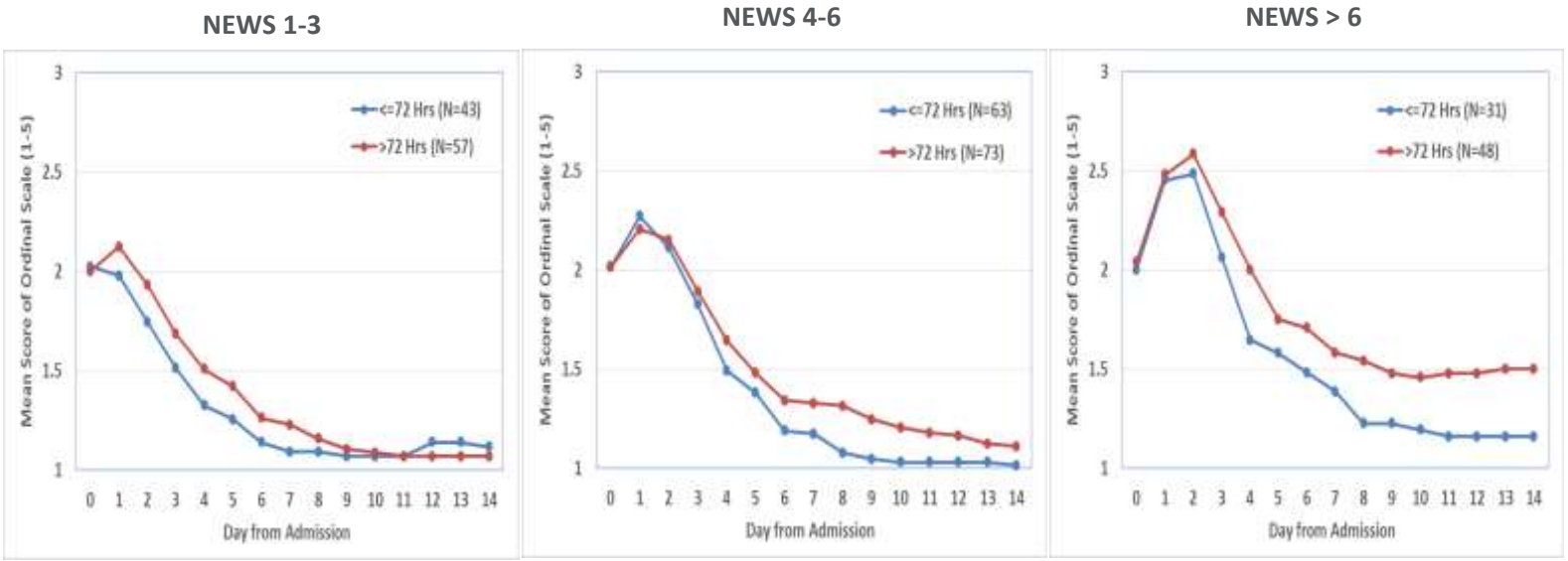
Discharged Hospitalized ICU Ventilator Death

Ison *et al*. Options IX, Chicago. Abstract LBP-17.

Potential Endpoints: *Clinical*

- Use of NEWS to categorize patients on admission

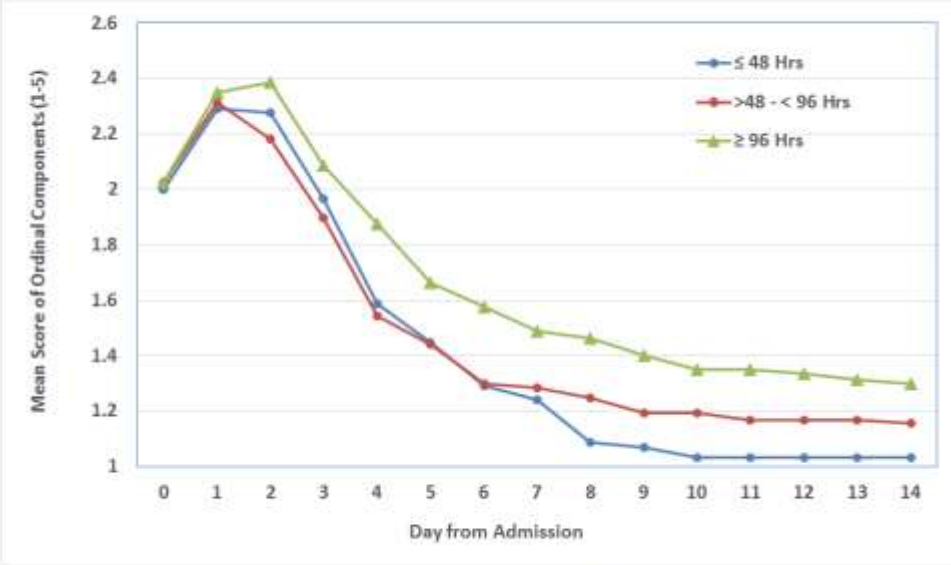
Figure 2: Mean Score of Ordinal Scale Endpoints



Ison *et al*. Options IX, Chicago. Abstract LBP-17.

Potential Endpoints: *Clinical – Time Directed Ordinal*

Figure 2: Mean score of ordinal components by days from admission



Score: 1 = Discharged, 2 = Hospitalized, 3 = ICU, 4 = Ventilator, 5 = Death

Table 2: Ordinal logistic model comparing two treatment groups (≤ 48 hrs vs ≥ 96 hrs)

Days	P value	Odds Ratio	Lower 95% CL	Upper 95% CL
Day 1	0.6607	1.2	0.6	2.4
Day 2	0.3654	1.4	0.7	2.6
Day 3	0.4429	1.3	0.7	2.4
Day 4	**0.0481**	**1.9**	**1.0**	**3.7**
Day 5	0.1296	1.7	0.9	3.4
Day 6	0.2032	1.6	0.8	3.5
Day 7	0.3034	1.5	0.7	3.5
Day 8	**0.0141**	**3.7**	**1.3**	**10.7**
Day 9	**0.0161**	**4.1**	**1.3**	**12.9**

Longitudinal analysis of ordinal endpoint across all 9 days showed an overall odds ratio of 2.1 (95%CI: 1.1 - 3.8) with p-value of 0.0173.