Viruses in Severe Respiratory Infections

Canadian Critical Care Forum

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Disclosures

- **Grant funding**
  - US Centers for Disease Control and Prevention (CDC)
  - Massachusetts Department of Public Health

Outline

- Epidemiology & significance
- Diagnosis
- Treatment
- Prevention

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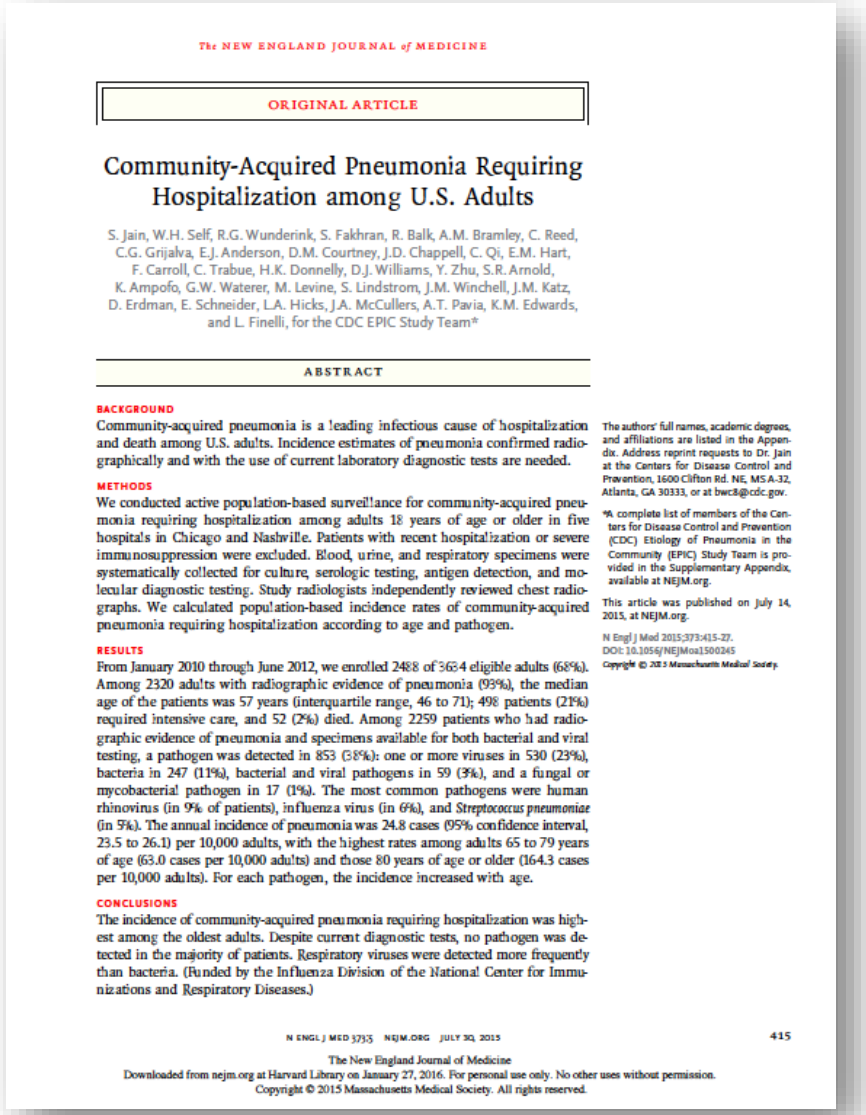
- **Diagnosis**
- **Treatment**
- **Prevention**

Etiology of Community-Acquired Pneumonia



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults

S. Jain, W.H. Self, R.G. Wunderink, S. Fakhran, R. Balk, A.M. Bramley, C. Reed, C.G. Grijalva, E.J. Anderson, D.M. Courtney, J.D. Chappell, C. Qi, E.M. Hart, F. Carroll, C. Trabue, H.K. Donnelly, D.J. Williams, Y. Zhu, S.R. Arnold, K. Ampofo, G.W. Waterer, M. Levine, S. Lindstrom, J.M. Winchell, J.M. Katz, D. Erdman, E. Schneider, L.A. Hicks, J.A. McCullers, A.T. Pavia, K.M. Edwards, and L. Finelli, for the CDC EPIC Study Team*

ABSTRACT

BACKGROUND

Community-acquired pneumonia is a leading infectious cause of hospitalization and death among U.S. adults. Incidence estimates of pneumonia confirmed radiographically and with the use of current laboratory diagnostic tests are needed.

METHODS

We conducted active population-based surveillance for community-acquired pneumonia requiring hospitalization among adults 18 years of age or older in five hospitals in Chicago and Nashville. Patients with recent hospitalization or severe immunosuppression were excluded. Blood, urine, and respiratory specimens were systematically collected for culture, serologic testing, antigen detection, and molecular diagnostic testing. Study radiologists independently reviewed chest radiographs. We calculated population-based incidence rates of community-acquired pneumonia requiring hospitalization according to age and pathogen.

RESULTS

From January 2010 through June 2012, we enrolled 2488 of 3664 eligible adults (68%). Among 2320 adults with radiographic evidence of pneumonia (93%), the median age of the patients was 57 years (interquartile range, 46 to 71); 498 patients (21%) required intensive care, and 52 (2%) died. Among 2259 patients who had radiographic evidence of pneumonia and specimens available for both bacterial and viral testing, a pathogen was detected in 853 (38%): one or more viruses in 530 (23%), bacteria in 247 (11%), bacterial and viral pathogens in 59 (3%), and a fungal or mycobacterial pathogen in 17 (1%). The most common pathogens were human rhinovirus (in 9% of patients), influenza virus (in 6%), and *Streptococcus pneumoniae* (in 5%). The annual incidence of pneumonia was 24.8 cases (95% confidence interval, 23.5 to 26.1) per 10,000 adults, with the highest rates among adults 65 to 79 years of age (63.0 cases per 10,000 adults) and those 80 years of age or older (164.3 cases per 10,000 adults). For each pathogen, the incidence increased with age.

CONCLUSIONS

The incidence of community-acquired pneumonia requiring hospitalization was highest among the oldest adults. Despite current diagnostic tests, no pathogen was detected in the majority of patients. Respiratory viruses were detected more frequently than bacteria. (Funded by the Influenza Division of the National Center for Immunizations and Respiratory Diseases.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jain at the Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, MS A-32, Atlanta, GA 30333, or at bwc8@cdc.gov.

*A complete list of members of the Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) Study Team is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 14, 2015, at NEJM.org.

N Engl J Med 2015;373:415-27.
DOI: 10.1056/NEJMoa1500245

- Prospective evaluation of 2,259 adults admitted to 5 hospitals in Chicago and Nashville with pneumonia
- Extensive evaluation for etiology of pneumonia

Viruses more than twice as common as bacteria!

26% of all pneumonias
60% of pneumonias with an identified pathogen

N Engl J Med 2015;373:415-427

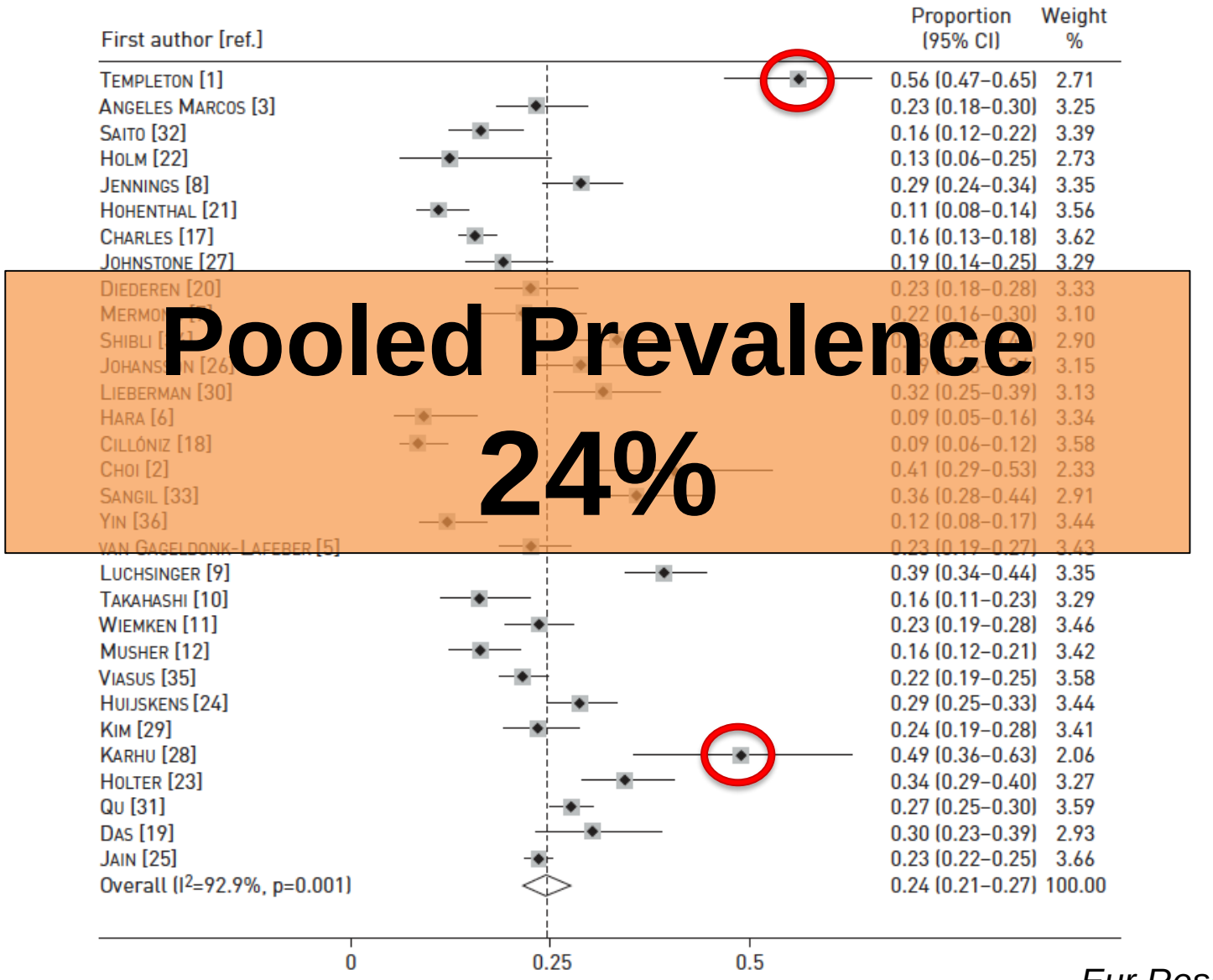
Etiology of Community-Acquired Pneumonia

2,259 adults admitted to 5 hospitals in Chicago and Nashville

Rhinovirus	8.6%
Influenza	5.8%
Strep. pneumoniae	5.1%
Metapneumovirus	3.9%
RSV	3.0%
Parainfluenza	3.0%
Coronavirus	2.3%
Mycoplasma pneumoniae	1.9%
Staph. aureus	1.6%
Adenovirus	1.4%
Legionella pneumophila	1.4%
Enterobacteriaceae	1.4%
Haemophilus influenzae	0.5%
Chlamydia pneumoniae	0.4%
Other	2.3%

N Engl J Med 2015;373:415-427

Prevalence of Viruses in CAP



Pooled Prevalence

24%

Eur Respir Rev 2016;25:178-88

…and so too in hospital-acquired pneumonia

174 Patients with Non-Ventilator HAP
Barnes-Jewish Hospital, St Louis

viruses in

22%

of patients

Respiratory Medicine 2017;122:76-80

99 Patients with HAP Admitted to ICU
Bichat-Claude Bernard Hospital, Paris

viruses in

34%

of patients

18% with virus alone
14% with virus + bacteria

J Clinical Virology 2017;91:52-57

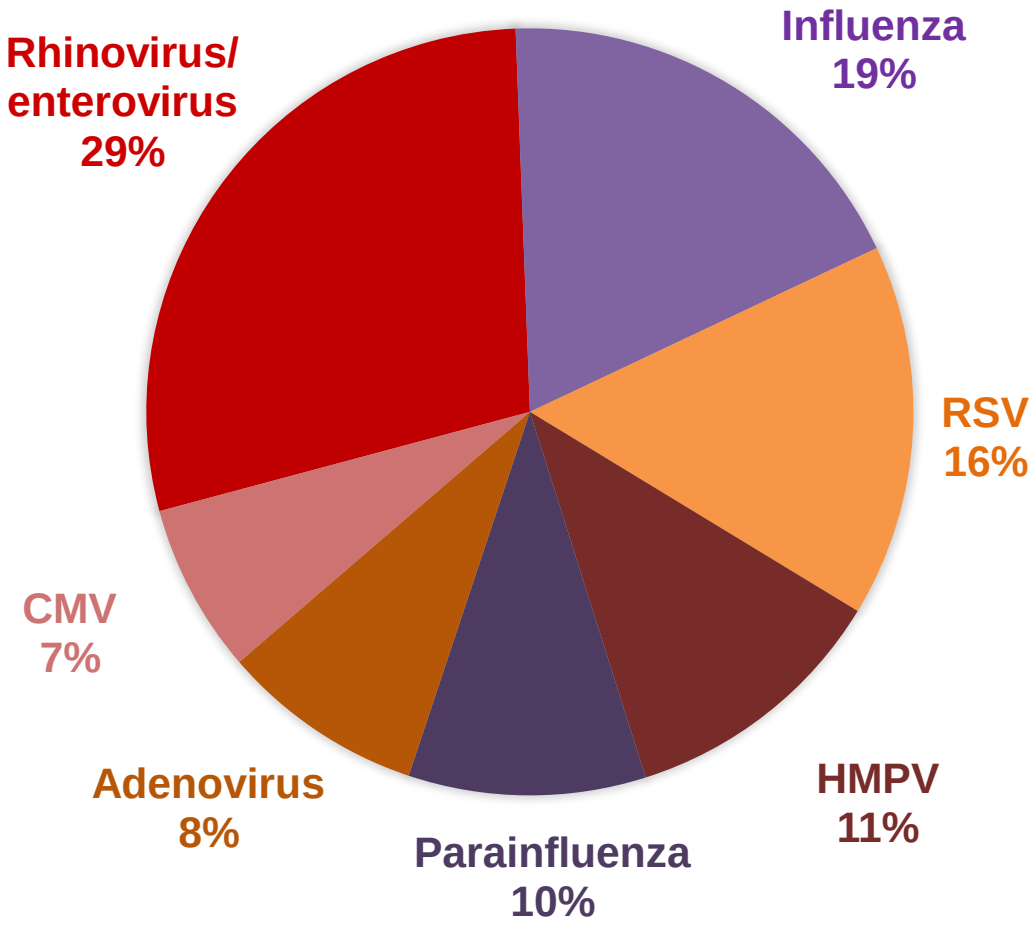
…and so too in severe pneumonias

364 patients with pneumonia (CAP/HAP/VAP) requiring mechanical ventilation, Barnes-Jewish Hospital, St. Louis

viruses in

22%

of patients



Chest 2018; 154:84-90.

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364 patients with pneumonia (CAP/HAP/VAP) requiring mechanical ventilation, Barnes-Jewish Hospital, St. Louis

viruses in

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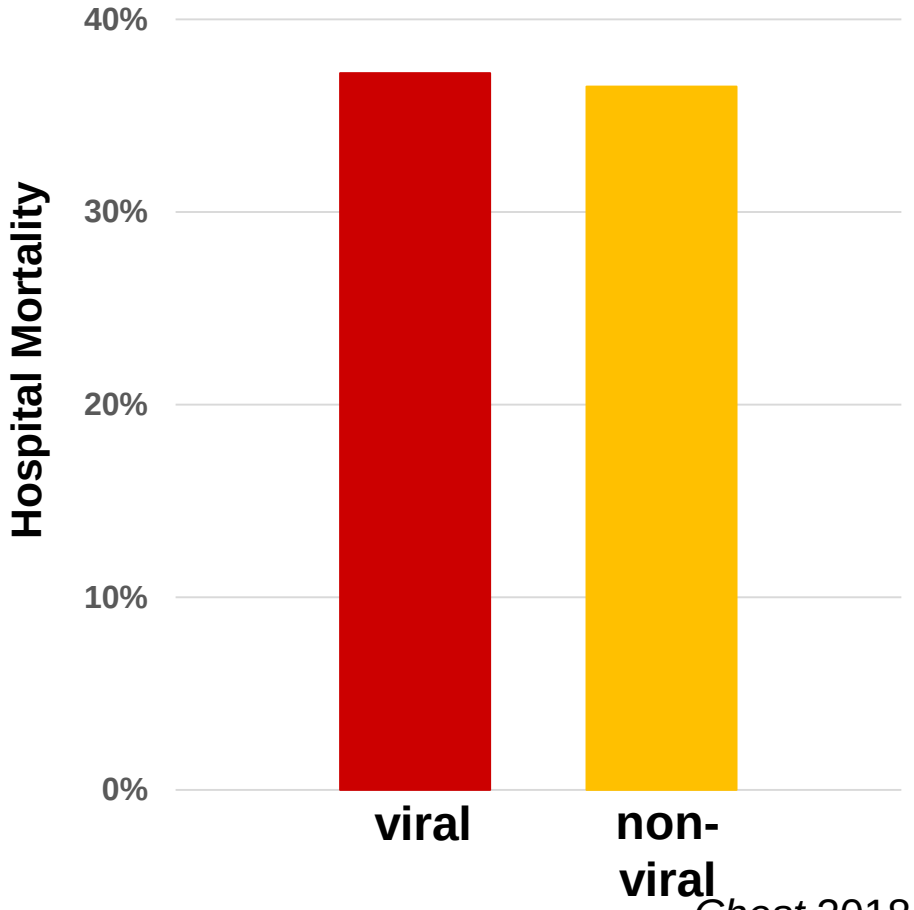
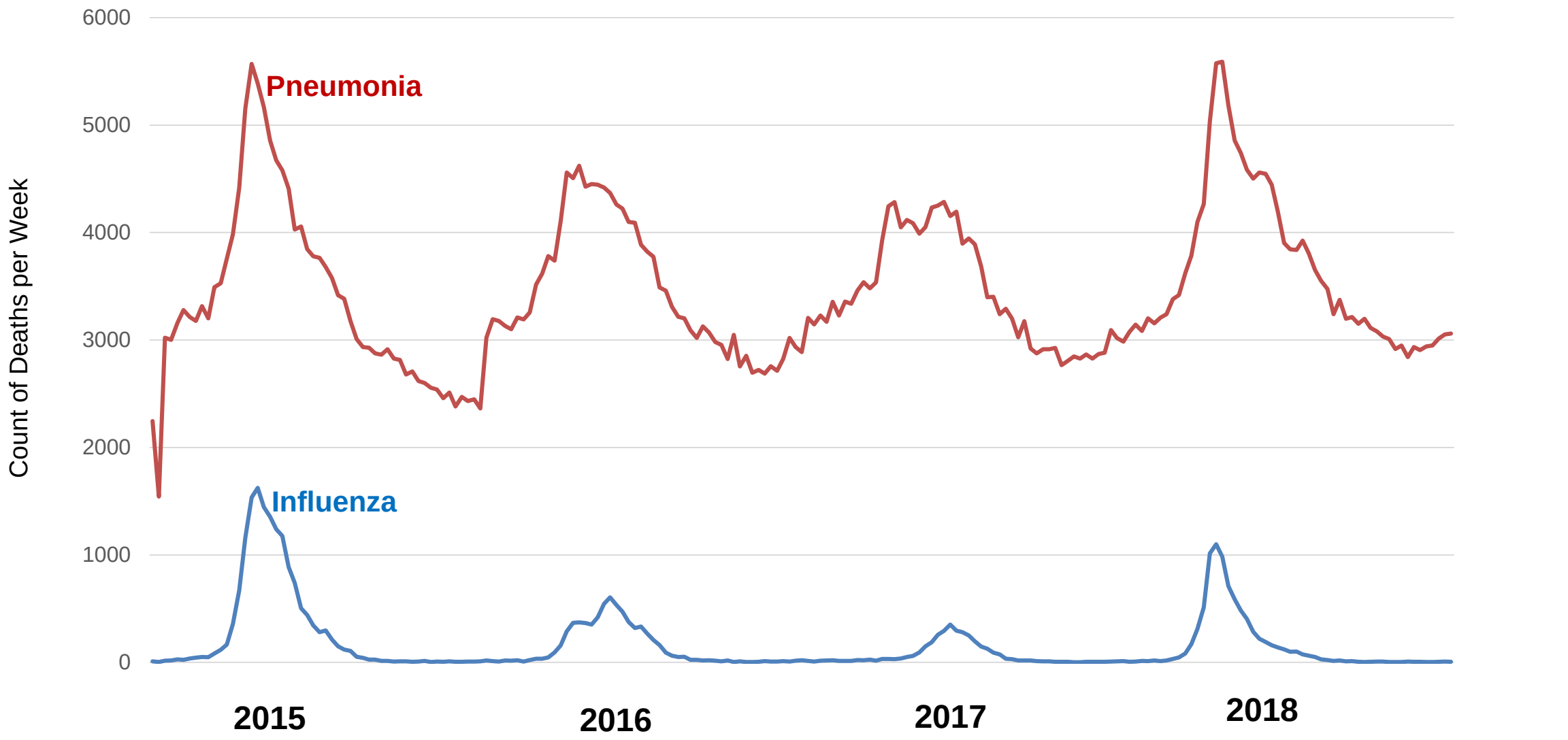
Mortality Rates High and Similar for Viral and Non-Viral Pneumonias



Chest 2018; 154:84-90.

Weekly Pneumonia & Influenza Deaths, USA, 2014-2018

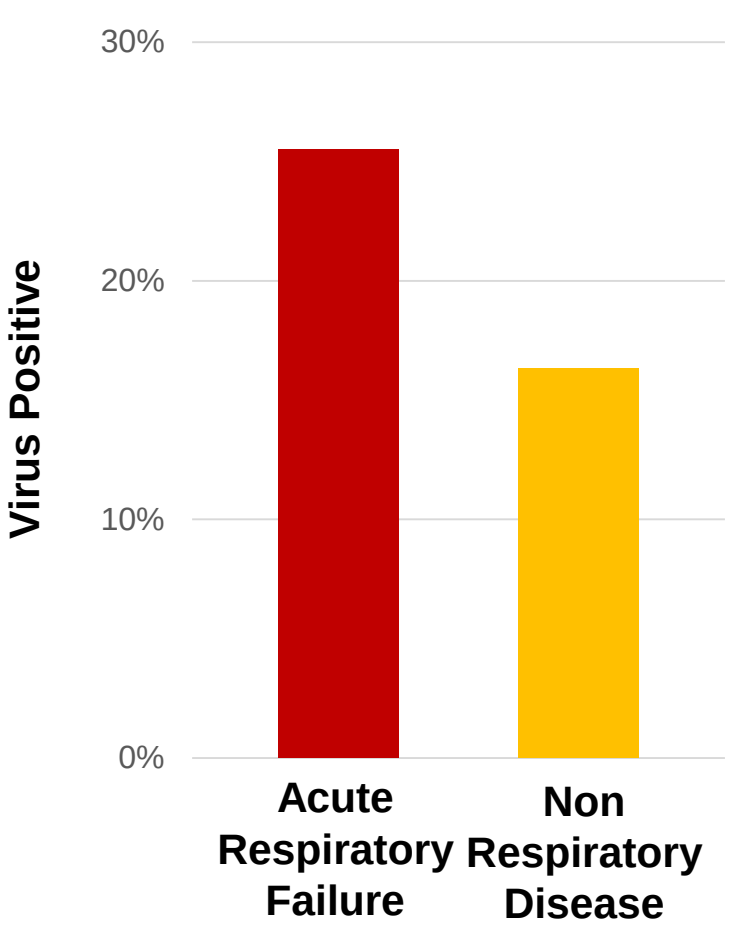


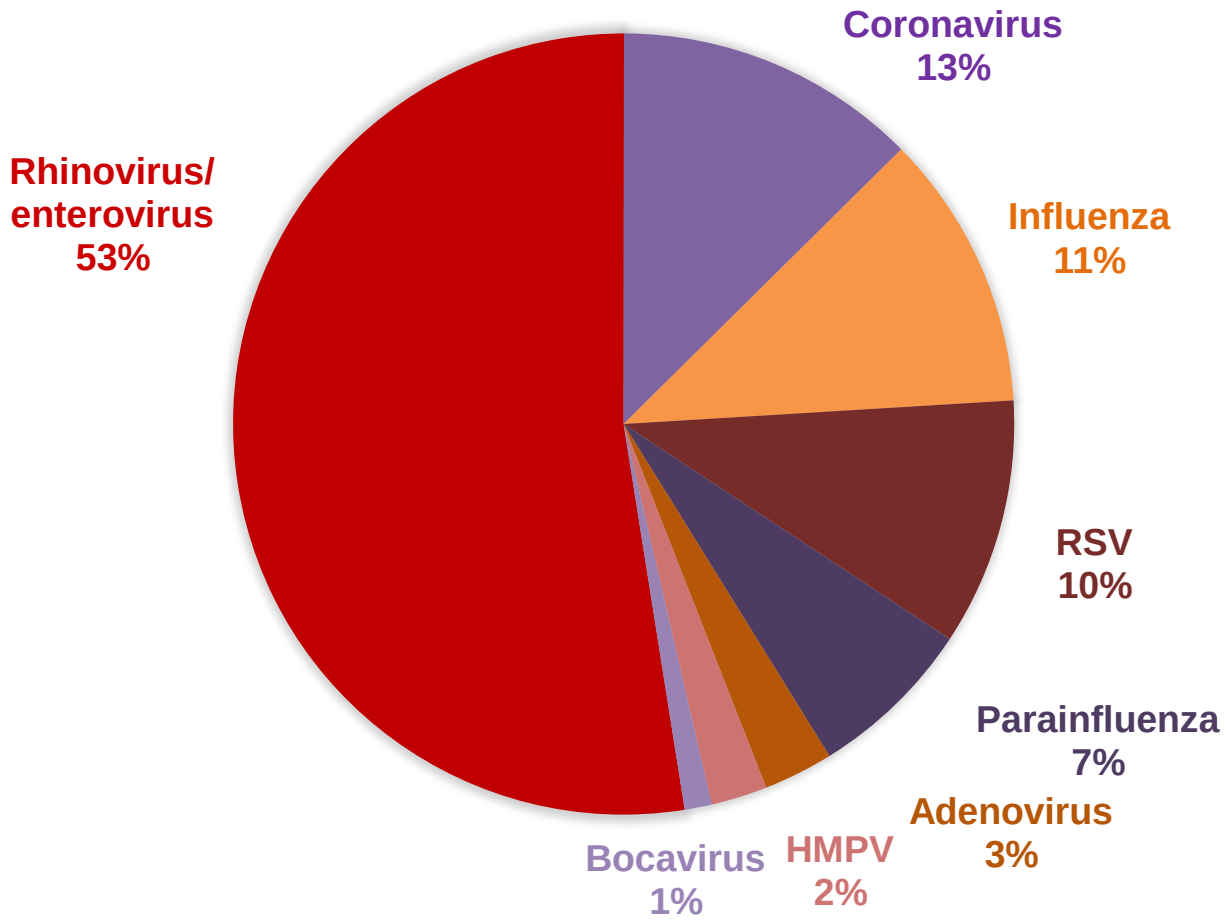
US Centers for Disease Control & Prevention

Significance of Viruses

Multiplex PCRs on 747 patients with hematologic malignancies admitted to 17 ICUs in France

60% with acute respiratory failure, 35% on mechanical ventilation





AJRCCM 2018;ePub (10.1164/rccm.201804-0681OC)

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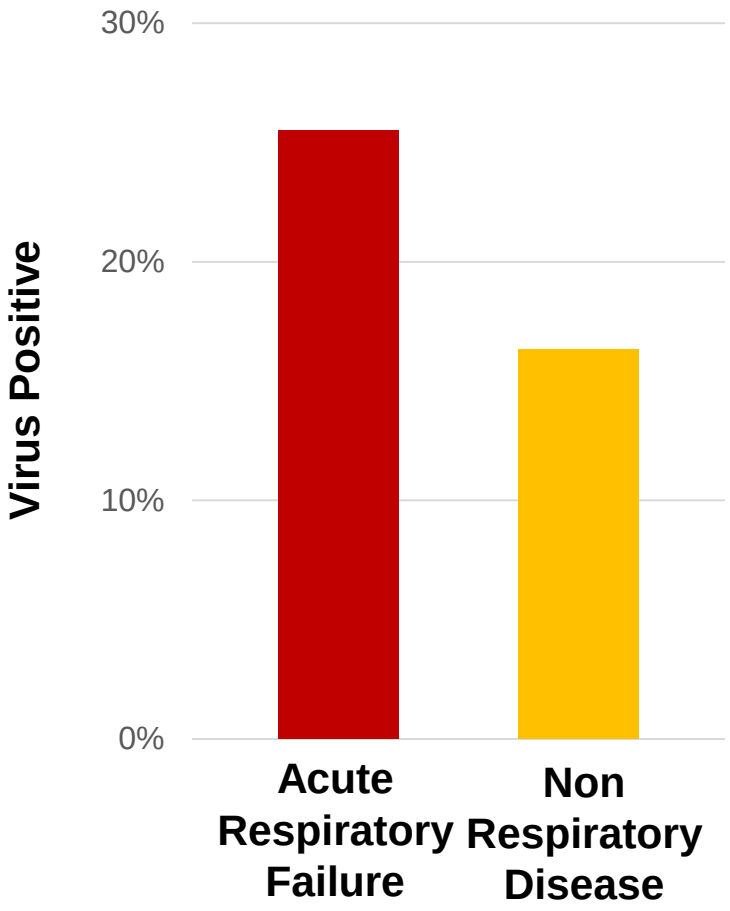
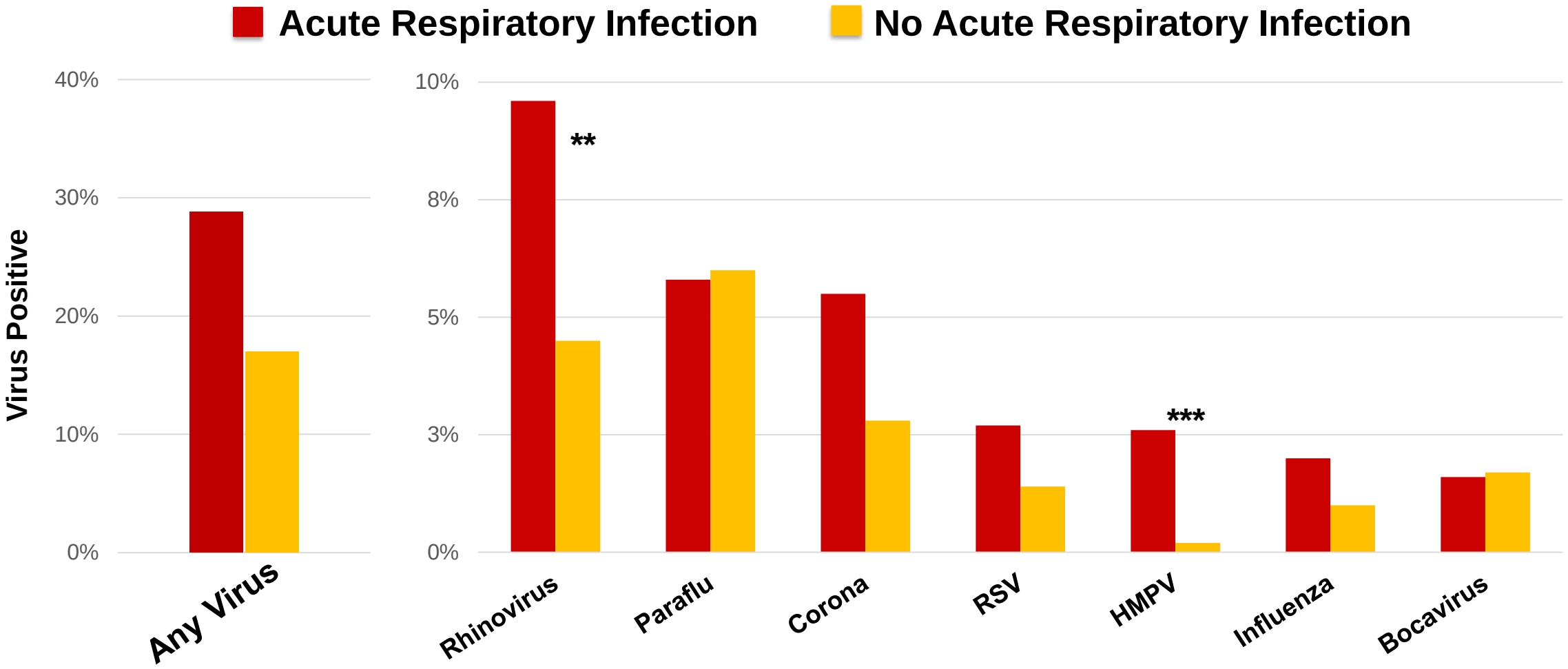


- 14% of patients with positive viral assays did not have any respiratory symptoms
- 27% of patients with positive viral assays and acute respiratory failure had clinically or microbiologically suspected bacterial coinfection
- 10% of patients with positive viral assays were diagnosed with invasive pulmonary aspergillosis (vs 4% of virus negative patients)
- +viral assay associated with adjusted OR for ICU death 2.1 (95% CI 1.2-3.5) in pts w. acute respiratory failure

AJRCCM 2018;ePub (10.1164/rccm.201804-0681OC)

Significance of Viruses 2

1,407 patients requiring mechanical ventilation admitted to 5 Dutch ICUs. Nasopharyngeal swabs and tracheal aspirates sent for respiratory virus PCRs in all patients, regardless of reason for admission



Crit Care Med 2018;46:29-36

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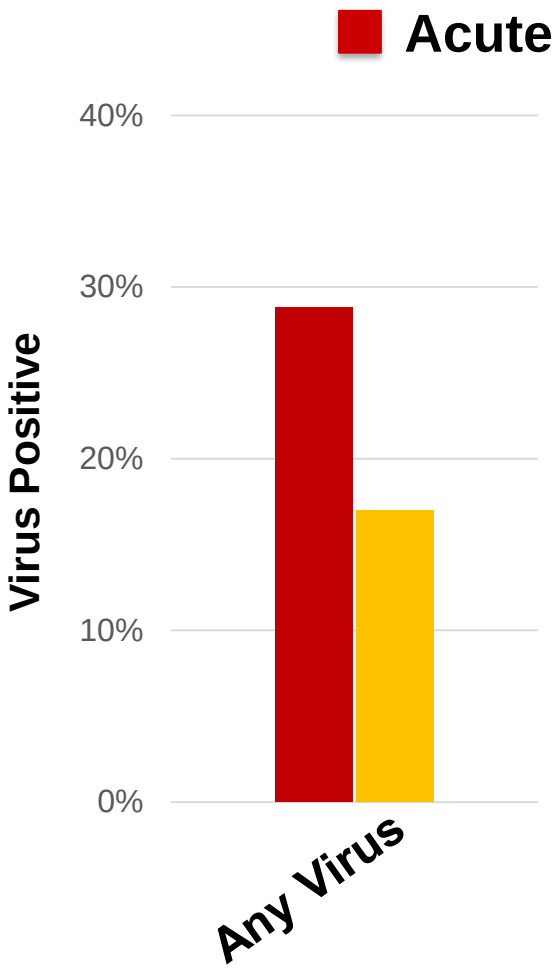

Category included:

- Sepsis (19% with viruses)
- Cardiac arrest (16% with viruses)
- Congestive heart failure (28% with viruses)
- Cardiogenic shock (25% with viruses)
- Rhythm disturbance (11% with viruses)
- COPD exacerbation (64% with viruses)

Crit Care Med 2018;46:29-36

Flu Increases Risk of MI 6-fold!

Self-controlled case series in 364 adults with MI and lab-confirmed flu within 1 year of each other. Assessed MI risk in the week following flu vs weekly risk in the preceding and following year

Count of MIs in the week following lab-confirmed flu: **20**

Weekly count of MIs in the year before and after confirmed flu: **3.3**

Odds Ratio

for MI with Flu Infection

6.1

(95% CI 3.9-9.5)

Odds Ratio 3.5 for RSV, 2.8 for other respiratory viruses

N Engl J Med 2018;378:345-353

Outline

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- **Diagnosis**
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Rapid Viral PCR Panels

Articles

Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial

Nathan J Brendish, Ahalya K Malachira, Lawrence Armstrong, Rebecca Houghton, Sandra Aitken, Esther Nyimbili, Sean Ewings, Patrick J Lillie, Tristan W Clark

Summary

Background Respiratory virus infection is a common cause of hospitalisation in adults. Rapid point-of-care testing (POCT) for respiratory viruses might improve clinical care by reducing unnecessary antibiotic use, shortening length of hospital stay, improving influenza detection and treatment, and rationalising isolation facility use; however, insufficient evidence exists to support its use over standard clinical care. We aimed to assess the effect of routine POCT on a broad range of clinical outcomes including antibiotic use.

Methods In this pragmatic, parallel-group, open-label, randomised controlled trial, we enrolled adults (aged ≥18 years) within 24 h of presenting to the emergency department or acute medical unit of a large UK hospital with acute respiratory illness or fever higher than 37·5°C (≤7 days duration), or both, over two winter seasons. Patients were randomly assigned (1:1), via an internet-based allocation sequence with random permuted blocks, to have a molecular POC test for respiratory viruses or routine clinical care. The primary outcome was the proportion of patients who received antibiotics while hospitalised (up to 30 days). Secondary outcomes included duration of antibiotics, proportion of patients receiving single doses or brief courses of antibiotics, length of stay, antiviral use, isolation facility use, and safety. Analysis was by modified intention to treat, excluding patients who declined intervention or were withdrawn for protocol violations. This study is registered with ISRCTN, number 90211642, and has been completed.

Findings Between Jan 15, 2015, and April 30, 2015, and between Oct 1, 2015, and April 30, 2016, we enrolled 720 patients (362 assigned to POCT and 358 to routine care). Six patients withdrew or had protocol violations. 301 (84%) of 360 patients in the POCT group received antibiotics compared with 294 (83%) of 354 controls (difference 0·6%, 95% CI −4·9 to 6·0; p=0·84). Mean duration of antibiotics did not differ between groups (7·2 days [SD 5·1] in the POCT group *vs* 7·7 days [4·9] in the control group; difference −0·4, 95% CI −1·2 to 0·4; p=0·32). 50 (17%) of 301 patients treated with antibiotics in the POCT group received single doses or brief courses of antibiotics (<48 h) compared with 26 (9%) of 294 patients in the control group (difference 7·8%, 95% CI 2·5 to 13·1; p=0·0047; number needed to test=13). Mean length of stay was shorter in the POCT group (5·7 days [SD 6·3]) than in the control group (6·8 days [7·7]; difference −1·1, 95% CI −2·2 to −0·3; p=0·0443). Appropriate antiviral treatment of influenza-positive patients was more common in the POCT group (52 [91%] of 57 patients) than in the control group (24 [65%] of 37 patients; difference 26·4%, 95% CI 9·6 to 43·2; p=0·0026; number needed to test=4). We found no differences in adverse outcomes between the groups (77 [21%] of 360 patients in the POCT group *vs* 88 [25%] of 354 patients in the control group; −3·5%, −9·7 to 2·7; p=0·29).

Interpretation Routine use of molecular POCT for respiratory viruses did not reduce the proportion of patients treated with antibiotics. However, the primary outcome measure failed to capture differences in antibiotic use because many patients were started on antibiotics before the results of POCT could be made available. Although POCT was not associated with a reduction in the duration of antibiotics overall, more patients in the POCT group received single doses or brief courses of antibiotics than did patients in the control group. POCT was also associated with a reduced length of stay and improved influenza detection and antiviral use, and appeared to be safe.

Funding University of Southampton.

Introduction

Acute respiratory tract infections are responsible for a huge burden of disease and are the third most common cause of death worldwide.[1,2] Although bacteria were previously considered to be the principal aetiological agents of severe respiratory tract infections, the global importance of respiratory viruses in this group has been increasingly recognised in recent years.[3–6]

Around 700 000 emergency hospital admissions with acute respiratory infection (including exacerbations of chronic lung disease) occurred in England in 2014–15, with approximately 50 000 deaths.[7] Recent, large studies using modern molecular diagnostic tests have shown that respiratory viruses are detectable in around 40–50% of hospitalised adults with acute respiratory illness.[3,8]

Lancet Respir Med 2017; 5: 401–11
Published Online April 5, 2017 http://dx.doi.org/10.1016/S2213-2600(17)30120-0
See Comment page 364

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Correspondence to: Dr Tristan William Clark, Southampton General Hospital, Southampton, SO16 6YD, UK TW.Clark@soton.ac.uk

Randomized Controlled Trial

- 720 patients with acute respiratory illness, fever >37.5ºC, or both presenting to an emergency department in England in the winter
- Randomized to rapid respiratory virus PCR panel vs usual care
- Outcomes
  - antibiotic starts
  - antibiotic days
  - length-of-stay

Lancet Repir Med 2017;5:401-11

Rapid Viral PCR Panels

720 patients randomized to rapid viral PCR panels vs usual care

- No difference in antibiotic starts
- No difference in mean duration of antibiotics

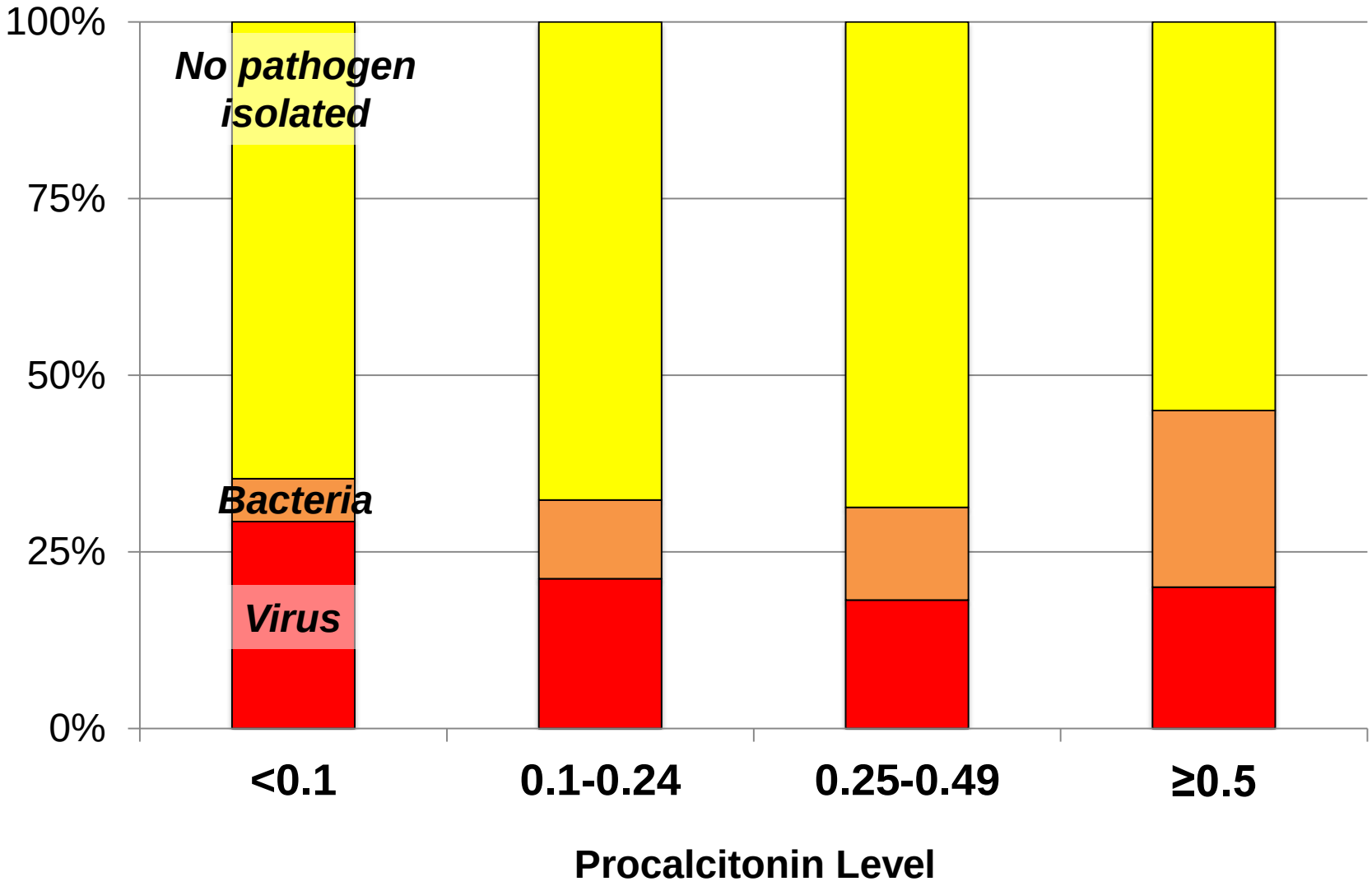
But…

- More patients in the viral PCR group received very brief (<48h) courses of antibiotics (17% vs 9%)
- Length-of-stay shorter in the PCR group (mean 5.7 vs 6.8 days)
- Appropriate antiviral treatment for flu was more common in the PCR group (91% vs 65%)

Lancet Repir Med 2017;5:401-11

Procalcitonin and Pneumonia Etiology

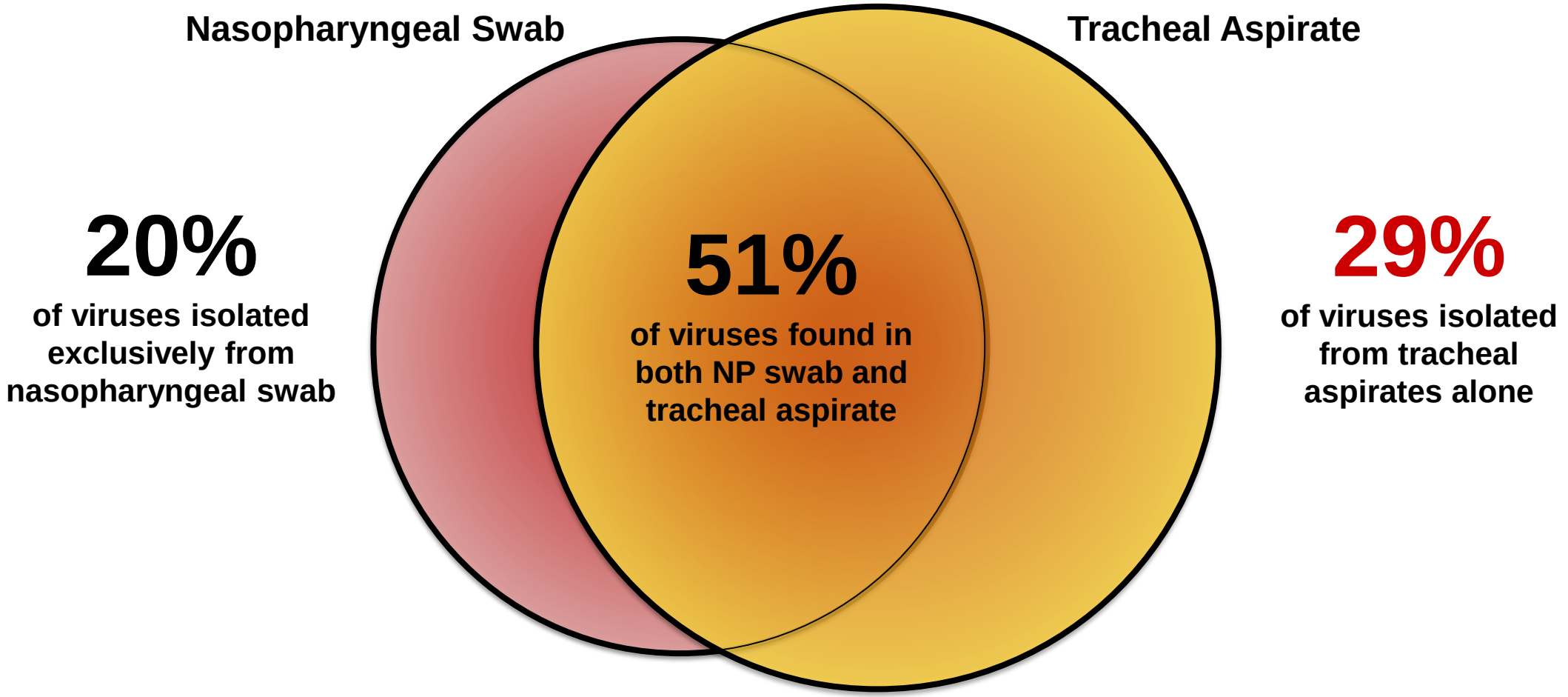
1,735 adults admitted to 5 U.S. hospitals with pneumonia



Clin Infect Dis 2017;65:183-90

Lower Tract Specimens Increase Diagnostic Yield

1,407 patients requiring mechanical ventilation admitted to 5 Dutch ICUs. Nasopharyngeal swabs and tracheal aspirates sent for respiratory virus PCRs in all patients, regardless of reason for admission



Crit Care Med 2018;46:29-36

Outline

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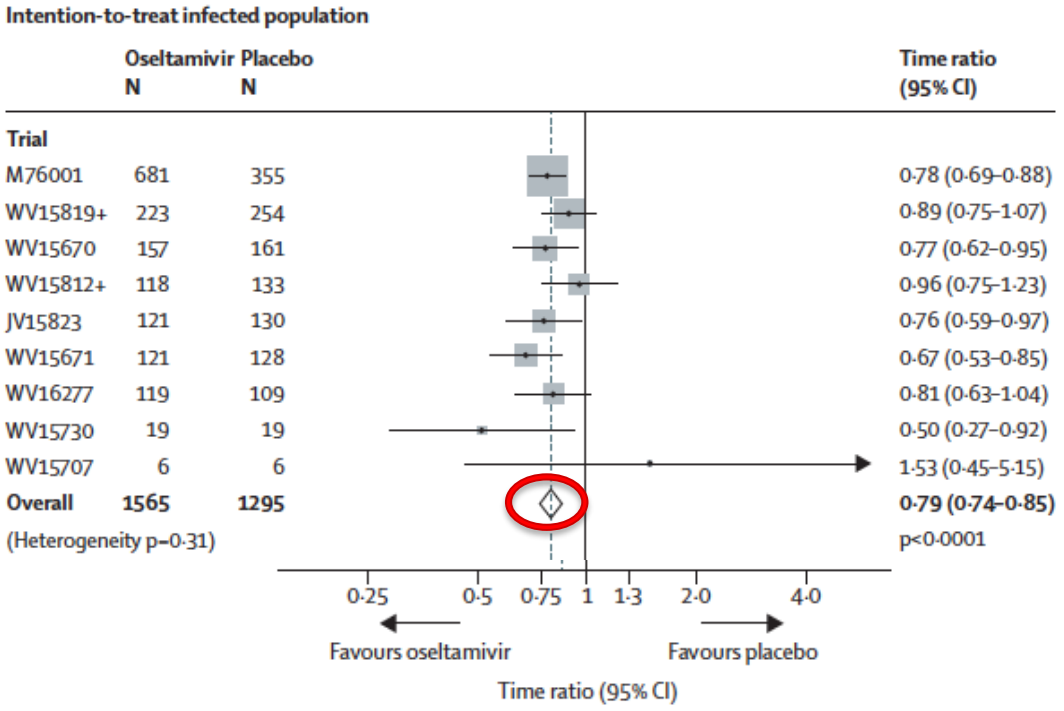
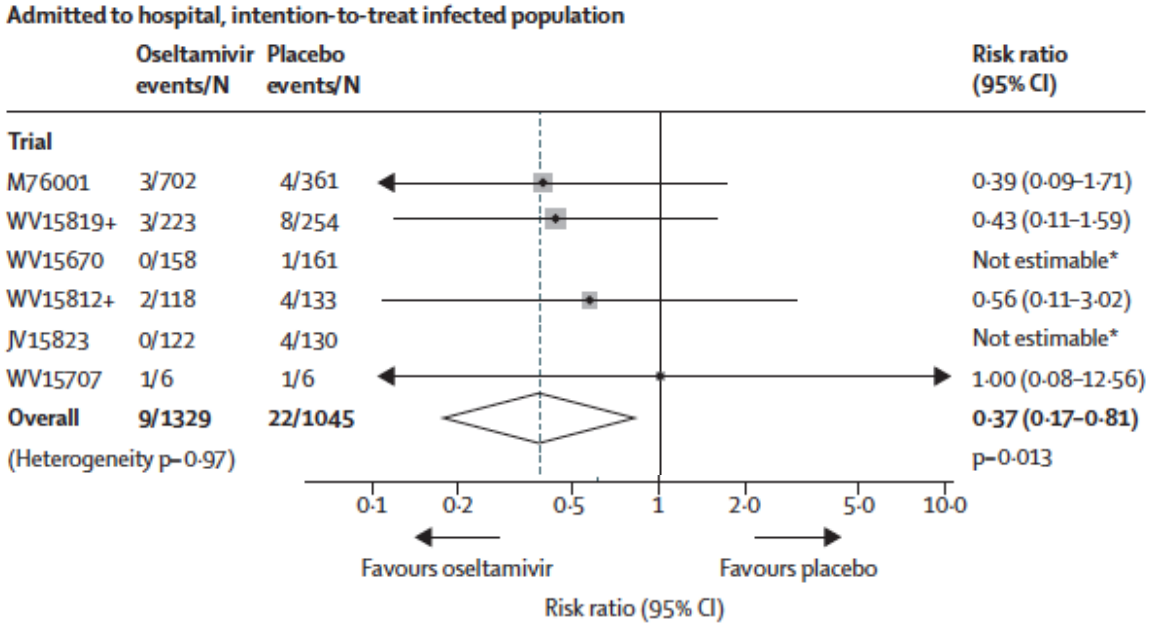
Oseltamivir in Outpatients

Time to Resolution of Symptoms



Symptom resolution about 25 hours sooner with oseltamivir

Hospital Admissions

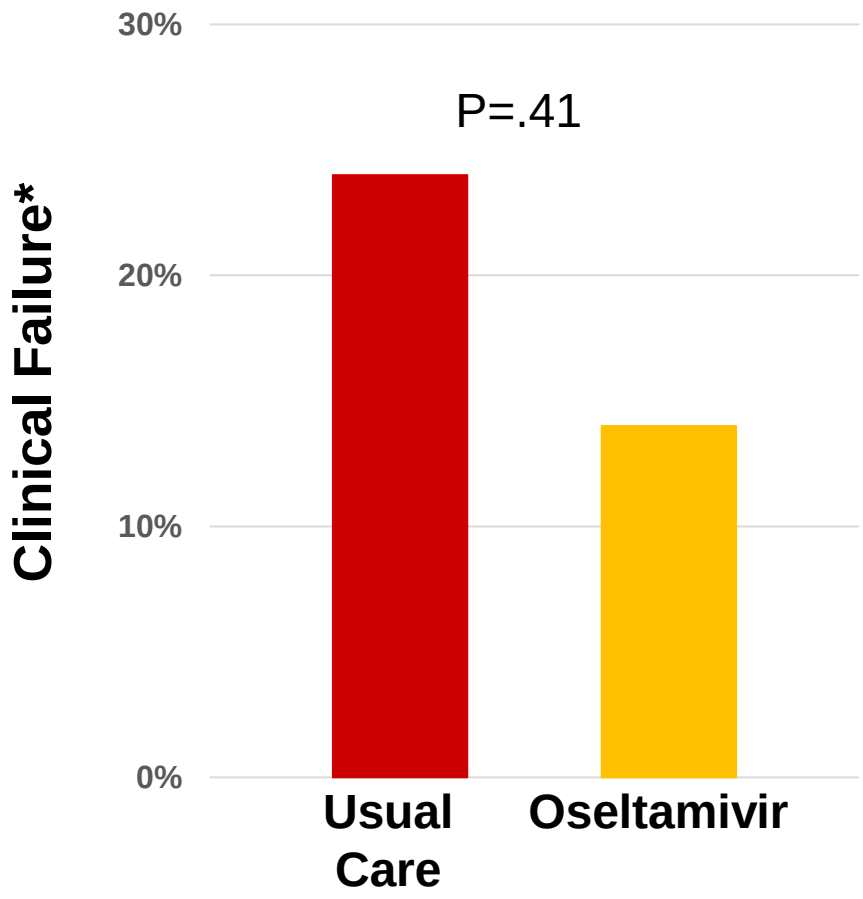


Hospital admissions ~60% less common with oseltamivir

Lancet 2015;385: 1729–37

Oseltamivir in Hospitalized Patients

Randomized trial of usual care vs oseltamivir in 74 patients with confirmed influenza.
Median 5 days of symptoms before admission to hospital.



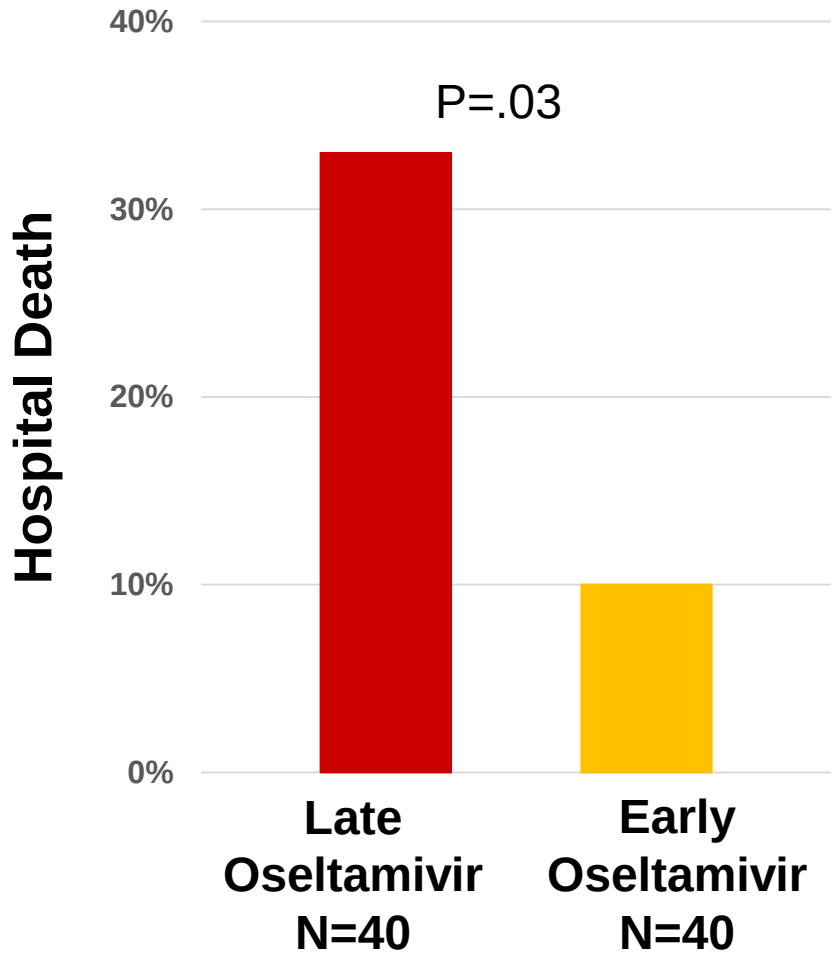
"Trend" towards less clinical failure with oseltamivir but study grossly underpowered (n=74)!

*No improvement by day 7, transfer to ICU, death or rehospitalization within 30 days.

Clin Infect Dis 2018;67:736-42

Oseltamivir in ICU Patients

Propensity matched analysis of 40 ICU patients treated for influenza with oseltamivir within 48 hours of admission vs 40 patients treated with oseltamivir >48 hours after admission



Lower mortality rate with <u>early</u> oseltamivir but possible residual confounding

Intensive Care Med 2018;44:257–260

Peramivir IV vs Oseltamivir PO

Peramivir 600mg IV x 1 vs oseltamivir 75mg PO bid x 5d

Time to Resolution of Symptoms in Outpatients Randomized Trial, N=727

81 vs 82 hours

Antimicrob Agents Chemother 2011;55:5267–5276

28-day Mortality In ICU Patients Retrospective Cohort Study, N=60

35% vs 35%

J Medical Virology 2015;87:1649–1655

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Preventing Nosocomial Respiratory Virus Infections

- **If 20-30% of pneumonias are due to viruses what more could we be doing to prevent transmission?**
  - Active patient screening on admission
  - Active visitor screening & exclusion
  - Daily patient screening for flu-like symptoms
  - Broader and more active viral testing of symptomatic patients
  - Contact + Droplet precautions for **all** patients with suspected or confirmed viral infections
  - Vaccinate all healthcare workers against flu
  - Eye protection for healthcare workers?

Many single center, before-after studies have described success aborting outbreaks or reducing respiratory virus infection rates using some or all of these options.

Impact of Active Surveillance for Influenza in Hospitalized Patients

Descriptive study of active influenza screening of all patients on admission and daily thereafter during flu season, North York General Hospital, 2012-2015

10% of hospitalized patients tested for flu
(661 lab-confirmed cases)

85%
detected
on admission

- Many with vague symptoms
- Consider viruses in patients with exacerbations of chronic cardiac & pulmonary disease

- 7% of flu cases nosocomial!
- Higher secondary attack rate (patients are most infectious early in the course of illness)

15%
detected
after admission

55%
community-onset
with delayed detection

86 roommates exposed
21 tested
0 secondary cases

45%
nosocomial onset

57 roommates exposed
16 tested
2 secondary cases

ICHE 2017;38:387-392

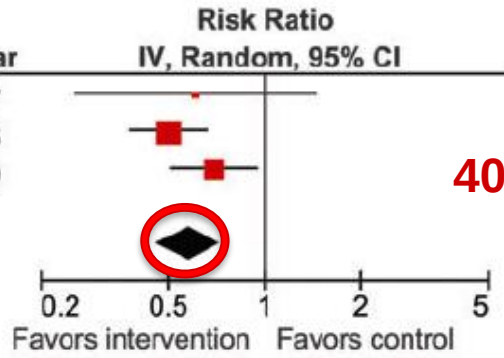
Impact of Vaccinating Health Care Workers on Patient Outcomes

Influenza-like Illness

Study or Subgroup	log[Risk Ratio]	SE	Intervention Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Potter 1997	-0.4972	0.4432	490	569	6.6%	0.61 [.26, 1.45]	1997
Hayward 2006	-0.6904	0.1424	1249	1323	51.2%	0.50 [.38, .66]	2006
Lemaitre 2009	-0.366	0.1606	1722	1678	42.2%	0.69 [.51, .95]	2009
Total (95% CI)			**3461**	**3570**	**100.0%**	**0.58 [.46, .73]**	

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 2.30$, df = 2 ($P = .32$); $I^2 = 13\%$

Test for overall effect: $Z = 4.68$ ($P < .00001$)



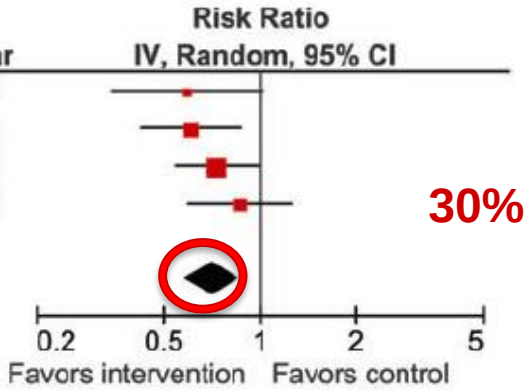
40% decrease!

All cause mortality

Study or Subgroup	log[Risk Ratio]	SE	Intervention Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Potter 1997	-0.5235	0.2815	490	569	11.6%	0.59 [.34, 1.03]	1997
Carman 2000	-0.4969	0.1874	749	688	26.2%	0.61 [.42, .88]	2000
Hayward 2006	-0.314	0.1554	1249	1323	38.1%	0.73 [.54, .99]	2006
Lemaitre 2009	-0.1424	0.1952	1722	1678	24.1%	0.87 [.59, 1.27]	2009
Total (95% CI)			**4210**	**4258**	**100.0%**	**0.71 [.59, .85]**	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.18$, df = 3 ($P = .54$); $I^2 = 0\%$

Test for overall effect: $Z = 3.60$ ($P = .0003$)



30% decrease!

Clin Infect Dis 2014;58:50-57

Summary

- Viruses are common in CAP and HAP, including severe cases requiring ICU admission
  - Often also present in patients without overt respiratory disease
- Prognosis for viral pneumonia similar to bacterial pneumonia
- Test for viruses. Think beyond flu alone.
  - Positive results can inform prognosis and treatment (oseltamivir), trigger infection control measures, and allay diagnostic uncertainty
- Bacterial coinfection is common so keep an open mind
- Negative procalcitonin suggestive but not definitive
- Protect the critically ill from viral infections in the hospital

Thank You!

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