

Viral Pathogen Identification in CAP

Con



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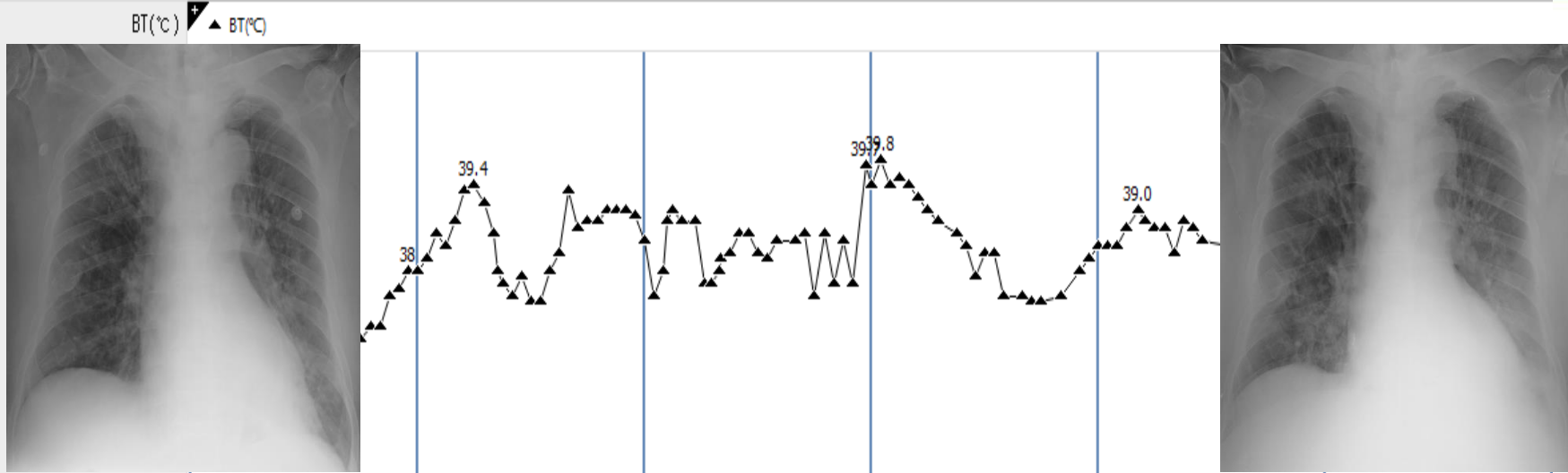
전 경 만



79 YO Male with Fever, Cough



Prolonged Fever



| 그룹명 | 항목명 | 18일 | 12월 09일 | 12월 10일 | 12월 11일 | 12월 12일 | 12월 13일 | 12월 |
|-----|-----|------------------|---------|---------|---------|---------|---------|-----|
| | | 2016-12-07 00:00 | | | | | | |

▲ Vital Sign

| BT | BT(°C) | | 38 | 39.4 | 39.7 | 39.8 | 39 | 37.9 |
|----|--------|--|----|------|------|------|----|------|
| | | | | | | | | |

▲ 검사결과

| | | | | | | | |
|---|--|------|------|-------|------|------|------|
| WBC Count, Blood (x10 ³ /μL) | | 4.92 | 6.35 | 2.80 | 1.64 | 1.20 | 1.53 |
| CRP, Quantitative (High Sensitivity) (mg) | | 9.5 | | 17.55 | | | |
| Procalcitonin, quantitative (ng/mL) | | 4.12 | | 2.37 | | | |

| | | | | | | | |
|----------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Cefepime(q) | | | | | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |
| Levofloxacin(mg) | <input checked="" type="checkbox"/> | | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | | | |
| Meropenem(mg) | | | | | <input checked="" type="checkbox"/> | | |
| Piperacillin/Tazobactam(q) | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | | <input checked="" type="checkbox"/> | | |

No Escalation of Antibiotics



【검체】 Nasopharynx swab(PCR)

- RESULTS

*Target viruses

| Viral species | Results | Detected viruses |
|---------------------------------------|---------|------------------|
| Adenovirus (ADV) | - | |
| Influenza (Flu) A/B | - | |
| Parainfluenza virus (PIV) 1/2/3 | - | |
| Respiratory syncytial virus (RSV) A/B | + | RSV A |

**Additionally detectable viruses

| Viral species | Results | Detected vireses |
|----------------------------|---------|------------------|
| Metapneumovirus (MPV) | - | |
| Rhinovirus | - | |
| Coronavirus 229E/OC43/NL63 | - | |
| Bocavirus | - | |

Pro and Con Between Comrade



25 YO Military Trainee

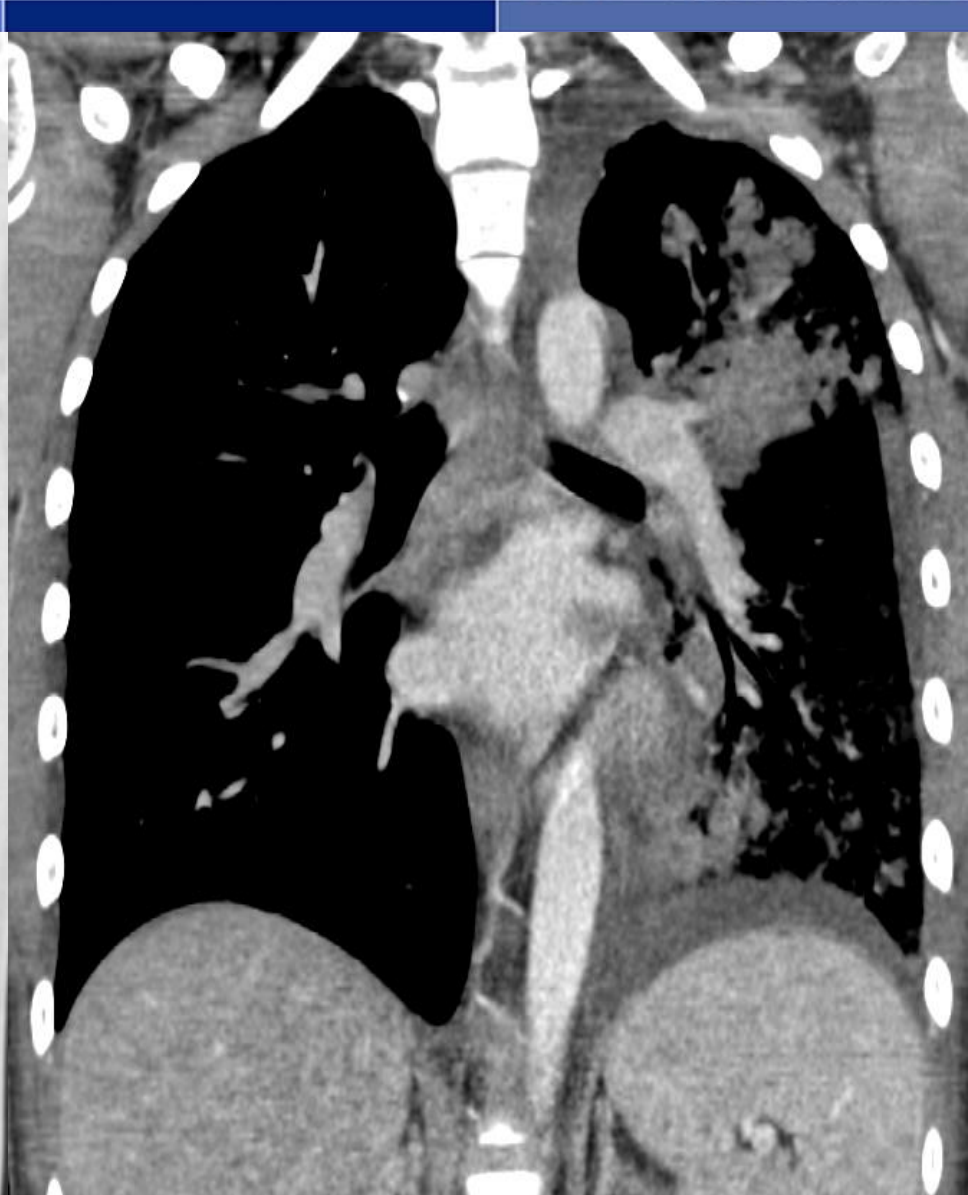


Study Time: 11:
MRN: 3762



Study

Progression of Respiratory Failure



Detected Respiratory Virus



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【검사명】 Gram Stain and Culture, Bacteria [BL4020]
【구분】 응급
【처방일】 2017-03-16 【접수일】 2017-03-16 22:31
【검사일】 2017-03-16 22:31 【보고일】 2017-03-20

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**** 【최종보고】 ****

【검체】 Sputum

■ 결론 및 진단

Gram positive cocci : 6 ~ 30 /HPF
Gram negative cocci : 1 ~ 5 /HPF
WBC : 10 ~ 25 /LPF
Epithelial cell : 10 ~ 25 /LPF

2017-03-18 13:14:43

Throat normal flora.

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【검사명】 Respiratory virus panel, detection
(adenovirus, influenza, parainfluenza, RSV) [Real-time
PCR] [BG5203] 【구분】 응급
【처방일】 2017-03-16 【접수일】 2017-03-16 22:35
【검사일】 2017-03-16 22:35 【보고일】 2017-03-20

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**** 【최종보고】 ****

【검체】 Nasopharynx swab(PCR)

■ 결론 및 진단

*Target viruses

| Viral species | Results | Detected viruses |
|---------------------------------------|---------|------------------|
| Adenovirus (ADV) | + | ADENO |
| Influenza (Flu) A/B | - | |
| Parainfluenza virus (PIV) 1/2/3 | - | |
| Respiratory syncytial virus (RSV) A/B | - | |

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Cost of Respiratory Virus Panel in Korea

Respiratory virus panel, detection (adenovirus, influenza, parainfluenza, RSV) [Real-time PCR]

| 보험 유형 | 고시금액 A. | 종별가산 포함한금액 B. | 선택 진료료 C. | 총 진료비 D=(B+C) |
|-------|------------|------------------|--------------|------------------|
| 보험 | 94,440 | 122,772 | 28,332 | 151,104 |
| 의료급여 | 94,440 | 115,217 | 28,332 | 143,549 |
| 산재 | 94,440 | 136,938 | 28,332 | 165,270 |
| 자보 | 94,440 | 136,938 | 0 | 136,938 |
| 일반 | 191,000 | 191,000 | 0 | 191,000 |
| 국제 | 229,000 | 229,000 | 0 | 229,000 |

High Isolation Rate of Adenovirus Korean Military Recruits with ARD



Table 1 Number of the respiratory viruses isolated from Korean military trainees with acute respiratory illness during four weeks of basic military training

| Virus | No. of isolates (%) |
|-------------------|---------------------|
| Adenovirus | 122 (76.4)* |
| Human coronavirus | 17 (10.6) |
| Human rhinovirus | 16 (9.9) |
| Human bocavirus | 4 (2.5) |
| Influenza A virus | 1 (0.6) |

*One or more other viruses were isolated in 21 military trainees

Inability to Obtain Specimens from Infection Site

- Specimen from the upper and lower airway
 - Nasopharyngeal aspirates or washes
 - Swabs from the nasopharynx, nose, or throat
 - Combined nasopharyngeal and throat swabs
 - Expecterated and induced sputum
 - Tracheal aspirates
 - Bronchoalveolar lavage
 - Lung puncture

Lancet 2011; 377: 1264

► Microbial etiology ?

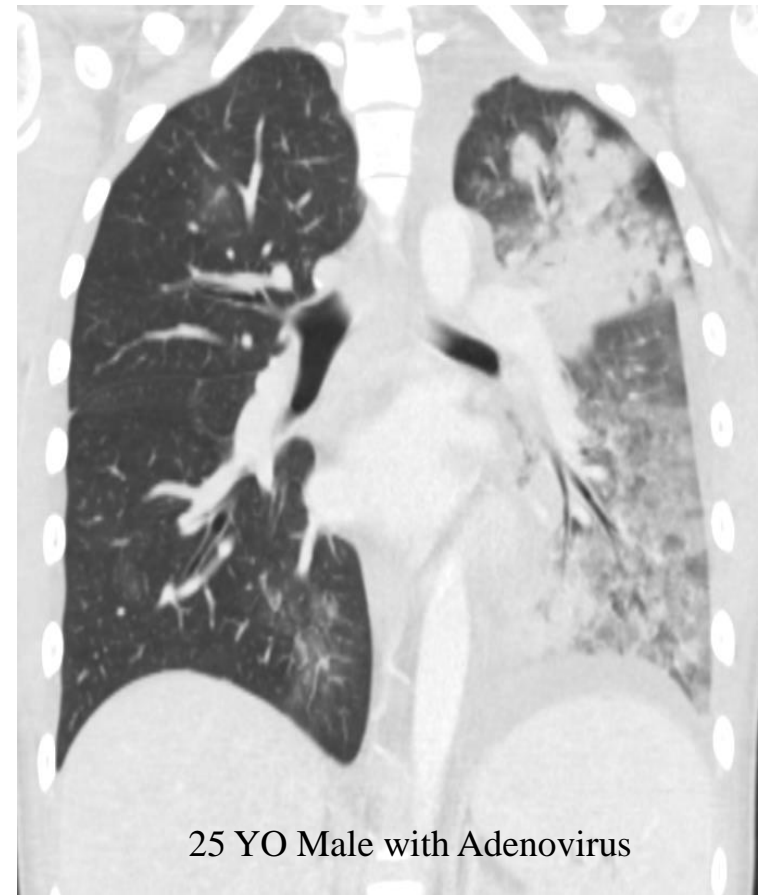
: detection of known pathogens in good-quality specimens **collected directly from the site of infection**

Difficulties Establishing Pneumonia Causation

Cause of pneumonia



Co-incidental findings following URI



Major Challenge

Uncertainty in Causality



- All the major viruses that cause pneumonia are more usually associated with nonpneumonic respiratory illnesses (URIs)
 - Ex. Typically experience >4 URIs annually
 - ▶ Typically detected for at least 7 days during illness
 - ▶ May test positive for a respiratory virus for at least 1 month of every year

May be causal (either directly or by leading to secondary bacterial pneumonia)

May be incidental

J Clin Microbiol 2009; 47: 3405

Virus Detection in Asymptomatic Subjects

Identification of Respiratory Viruses in Asymptomatic Subjects

Asymptomatic Respiratory Viral Infections

Tuomas Jartti, MD, Laura Jartti, MD,† Ville Peltola, MD,* Matti Waris, PhD,‡
and Olli Ruuskanen, MD**

Abstract: The medical literature of the past 4 decades was searched regarding respiratory virus detection by polymerase chain reaction and conventional methods (culture, antigen detection, serology) in asymptomatic subjects in an attempt to determine the prevalence and clinical significance of such viruses in normal persons.

Key Words: asymptomatic, respiratory virus, rhinovirus, infection
(*Pediatr Infect Dis J* 2008;27: 1103–1107)

CONCLUSIONS

Many studies in asymptomatic subjects have shown markedly higher respiratory virus detection rates with PCR than with conventional methods. No clear conclusion, however, can be drawn on the significance of PCR positive findings in asymptomatic subjects because of limited number of prospective studies with repeated sampling and lack of concomitant serologic studies. The available reports, however, suggest that the persistence of PCR-positive respiratory viral findings is rather short lasting (few weeks) and infrequent ($\leq 5\%$) overall. Furthermore, recurrent infections with the same virus strain appear also to be rare even in children with frequent respiratory illnesses. These findings suggest that PCR is likely to detect true respiratory infections with or without symptoms and is in agreement with the definition suggested by Casadevall and Pirofski⁹³: “infection is defined as acquisition of microbe by host.” Causality between viral findings and symptoms, however, remains uncertain, especially when low copy numbers and multiple viruses are detected. Quantitative PCR and careful serologic studies may be feasible tools for some viruses in this respect, but more data are needed.

Virus Detection in Asymptomatic Subjects

Adults Only Data

Using Conventional Diagnostics

| Author, year | n | Age, years | Chronic condition | Methods | | | Viral findings, % | | | | | | | | | |
|-----------------|-----|------------|-------------------|---------|----|-----------------|-------------------|----|----------|-----|--------|--------|--------|--------|-------------------------|--|
| | | | | Cu | Ag | Se ¹ | HRV | EV | Picornia | RSV | PIV | Flu | AdV | CoV | ≥1 viruses ¹ | |
| Falsey 2006 | 112 | ≥40 | COPD | | | X | | | | | 2 (2%) | | | | | |
| Russell 2006 | 254 | adults | No | X | X | X | | | | | | | 4 (2%) | | | |
| Falsey 2005 | 608 | adults | No | | | X | | | | | 5 (%) | | | | | |
| Echavarria 2003 | 42 | adults | No | X | | | | | | | | | 0 (0%) | | | |
| Graat 2003 | 91 | ≥60 | No | | | X | | | | | | 0 (0%) | 0 (0%) | 0 (0%) | | |

Using PCR Diagnostics

| Author, year | n | Age, years | Chronic condition | | Viral findings, n (%) | | | | | | | | | | | |
|-----------------|-----|------------|-------------------|------|-----------------------|--------|----------|--------|----------|--------|--------|-----|--------|--------|------------|----------|
| | | | No | Pulm | HRV | EV | Picornia | RSV | PIV | Flu | AdV | CoV | HMPV | HBoV | ≥1 viruses | |
| Falsey 2006 | 112 | ≥40 | | X | | | | | 3 (3%) | | | | | | | |
| Russell 2006 | 254 | adults | | | | | | | | | 4 (2%) | | | | | |
| Falsey 2006 | 158 | 19-87 | X | | | | | | 1 (1%) | | | | | 0 (0%) | | |
| Jarti 2004 | 79 | 0.3-14 | X | | 6 (8%) | | | 7 (9%) | | | | | | | | |
| Williams 2004 | 86 | ≥60 | | | | | | | | | | | | 1 (1%) | | |
| Borg 2003 | 46 | elderly | | X | | | | | 13 (28%) | | | | | | | |
| Falsey 2003 | 146 | adults | X | | | | | | | | | | | 8 (5%) | | |
| Echavarria 2003 | 42 | adults | X | | | | | | | | 0 (0%) | | | | | |
| Graat 2003 | 91 | ≥60 | X | | 2 (2%) | 0 (0%) | 2 (2%) | 0 (0%) | | | | | 2 (2%) | | | 4 (4%) |
| Seemungal 2001 | 68 | 68 | | X | 5 (7%) | | | | | 1 (1%) | | | 4 (6%) | | | 10 (15%) |
| Johnston 1993 | 53 | adults | X | | | | | 2 (3%) | | | | | | | | |

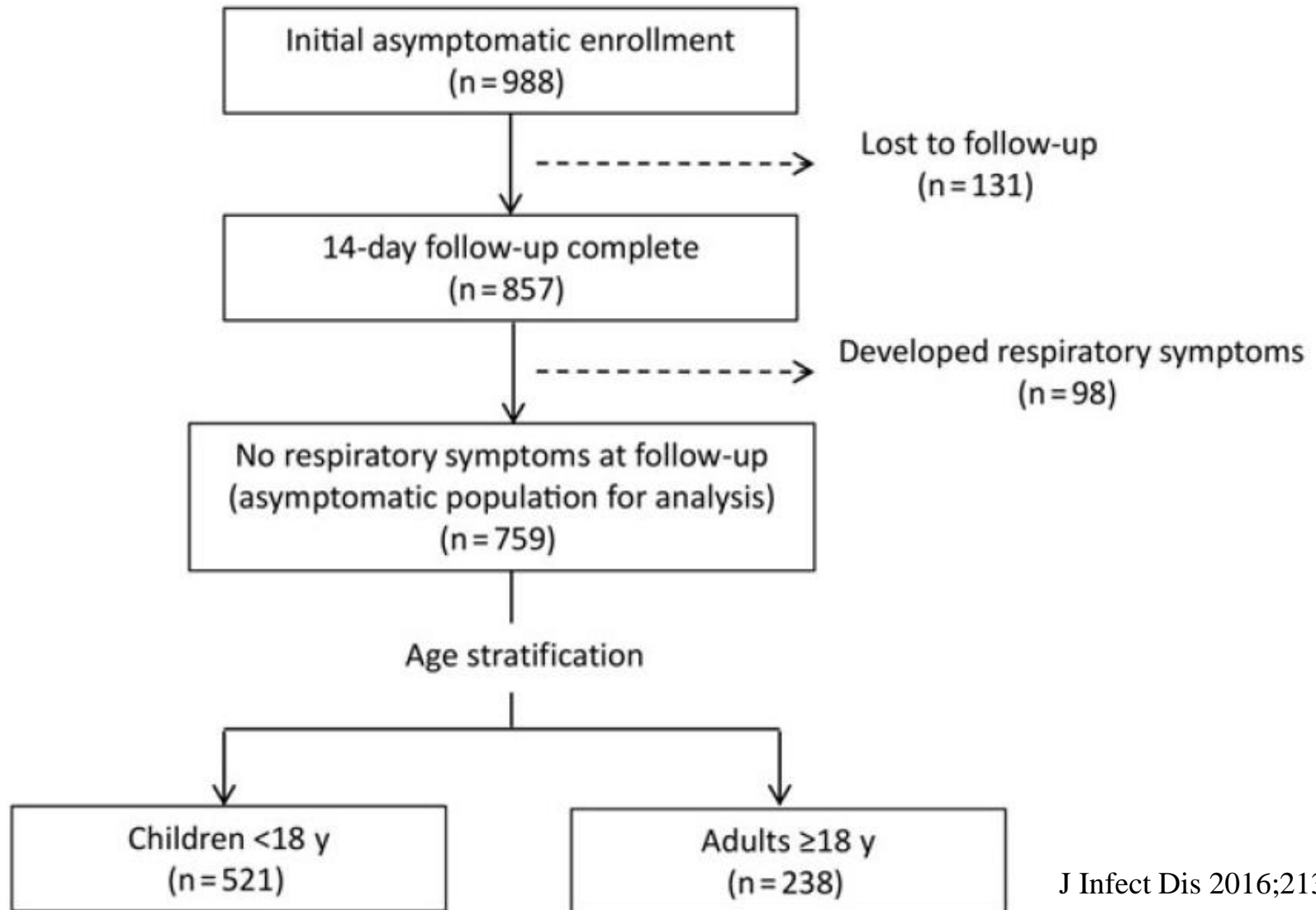
Analytical Sensitivity vs. Clinical Sensitivity

Nucleic Acid Amplification Tests (NAATs)

- Analytical sensitivity is frequently confused with clinical (diagnostic) sensitivity
 - Analytical sensitivity (lower limit of detection)
 - Smallest amount of target that can be accurately detected by the assay
 - Clinical sensitivity: comparing with a “gold standard” test
 - Proportion of true-positive patient samples that are correctly identified by the assay
 - High analytical sensitivity **does not guarantee high clinical sensitivity**
- ▶ So sensitive assay detects asymptomatic infection **may lead to difficulties in attributing etiology** to a pathogen.
- ▶ Most studies of viral pneumonia have **not used control groups** and have **not questioned the implication that a positive test from a nasopharyngeal specimen indicates causation.**

Respiratory Virus Detection

Comparing Asymptomatic Controls with CAP Patients (EPIC)



Respiratory Virus Detection

Calculating Attributable Fraction (AF)



Table 2. Prevalence of Respiratory Virus Detection With rRT-PCR in Asymptomatic Controls and Patients With CAP <18 Years Old

| Virus | Asymptomatic Children, No. (%) (n = 521) | Children With CAP, No. (%) (n = 832) | P Value ^a | aOR (95% CI) ^b | AF (95% CI) |
|------------------------------|---|---|----------------------|---------------------------|--------------------|
| Any virus ^c | 127 (24.4) | 572 (68.8) | <.01 | NC ^d | NC |
| hRV | 90 (17.3) | 182 (21.9) | .04 | 1.13 (.84–1.51) | 0.12 (–.18–.34) |
| RSV | 10 (1.9) | 221 (26.6) | <.01 | 15.2 (7.92–29.2) | 0.93 (.87–.97) |
| hMPV | 8 (1.5) | 126 (15.1) | <.01 | 10.4 (5.02–21.6) | 0.90 (.80–.95) |
| AdV | 16 (3.1) | 53 (6.4) | <.01 | 1.77 (.99–3.17) | 0.44 (–.01 to .68) |
| Influenza (A and B) | 0 | 28 (3.4) | <.01 | NC | NC |
| PIV (types 1–3) | 10 (1.9) | 39 (4.7) | .01 | 2.29 (1.11–4.69) | 0.56 (.10–.79) |
| CoV (229E, HKU1, NL63, OC43) | 8 (1.5) | 37 (4.5) | <.01 | 3.17 (1.44–6.99) | 0.68 (.31–.86) |

Table 3. Prevalence of Respiratory Virus Detection With rRT-PCR in Asymptomatic Controls and Patients With CAP ≥18 Years Old

| Virus | Asymptomatic Adults, No. (%) (n = 238) | Adults With CAP, n (%) (n = 192) | P Value ^a | aOR (95% CI) ^b | AF (95% CI) |
|------------------------------|---|-------------------------------------|----------------------|---------------------------|--------------------|
| Any virus ^c | 5 (2.1) | 47 (24.5) | <.01 | NC ^d | NC ^d |
| hRV | 2 (0.8) | 21 (10.9) | <.01 | 13.4 (3.04–59.1) | 0.93 (.67–.98) |
| RSV | 0 | 3 (1.6) | .09 | NC ^d | NC |
| hMPV | 1 (0.4) | 8 (4.2) | .01 | 13.5 (1.65–110) | 0.93 (.39–.99) |
| AdV | 0 | 3 (1.6) | .09 | NC | NC |
| Influenza (A and B) | 0 | 5 (2.6) | .02 | NC | NC |
| PIV (types 1–3) | 0 | 3 (1.6) | .09 | NC | NC |
| CoV (229E, HKU1, NL63, OC43) | 2 (0.8) | 6 (3.1) | .14 | 3.19 (.59–17.1) | 0.69 (–.69 to .94) |

► Detections of influenza, RSV, and hMPV among patients with CAP of all ages probably indicate an etiologic role, whereas detections of PIV, CoV, rhinovirus, and adenovirus, especially in children, require further scrutiny.

Clinical Relevance of Virus in CAP

Ongoing Systematic Review



PROSPERO International prospective register of systematic reviews

The role of respiratory viruses in community acquired pneumonia: a systematic review and meta-analysis

Yewande Alimi, Jonathan Van-Tam, Wei Shen Lim, Jo Leonardi-Bee, Louise Lansbury

Citation

Yewande Alimi, Jonathan Van-Tam, Wei Shen Lim, Jo Leonardi-Bee, Louise Lansbury. The role of respiratory viruses in community acquired pneumonia: a systematic review and meta-analysis. PROSPERO 2016:CRD42016037233 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037233

Review question(s)

What is the relative contribution of respiratory viruses (overall, compared to bacteria, and individually compared to each other) in the aetiology of community acquired pneumonia in adults in Europe.

Searches

Electronic databases and grey literature will be searched for relevant studies. The bibliography of selected (included) papers will be searched for relevant papers. The bibliography of non-selected papers (non-included) will also be searched.

Literature sources

- a. EMBASE
- b. MEDLINE
- c. CINAHL
- d. WHOLIS
- e. COCHRANE LIBRARY

Types of study to be included

Observational study designs; cohort studies and case-series performed in European countries. All other study designs will be excluded from this review.

Antiviral Treatment and Prevention



| | Treatment | Prevention |
|-----------------------------|--|--|
| Influenza A and B viruses | Oseltamivir (oral); zanamivir (inhalation, intravenous); peramivir (intravenous) | Vaccines (inactivated, live); oseltamivir; zanamivir |
| Influenza A virus | Amantadine (oral); rimantadine (oral) | .. |
| Respiratory syncytial virus | Ribavirin (inhalation, intravenous) | Palivizumab (intramuscular) |
| Adenovirus | Cidofovir (intravenous) | Vaccine for types 4 and 7* |
| Rhinovirus | Pleconaril† | Alfa interferon (intranasal) |
| Enteroviruses | Pleconaril† | .. |
| Human metapneumovirus | Ribavirin (intravenous) | .. |
| Hantavirus | Ribavirin (intravenous) | .. |
| Varicella-zoster virus | Aciclovir (intravenous) | Vaccine |

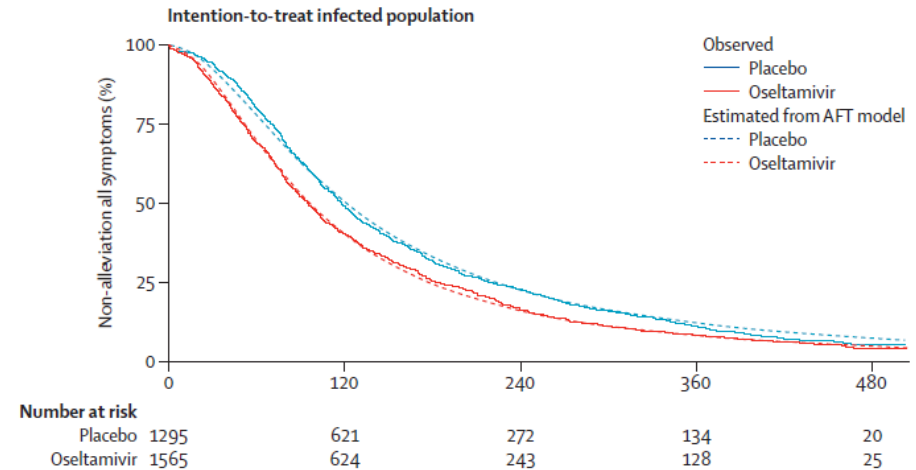
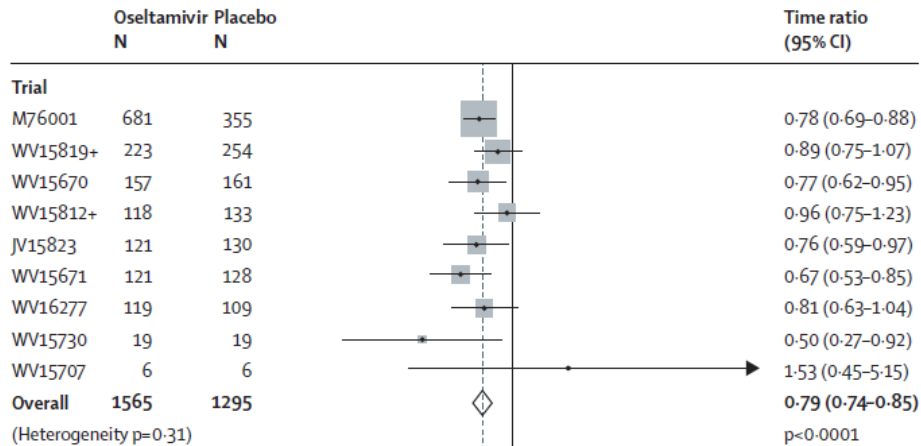
Lancet 2011; 377: 1264

Oseltamivir Treatment for Influenza

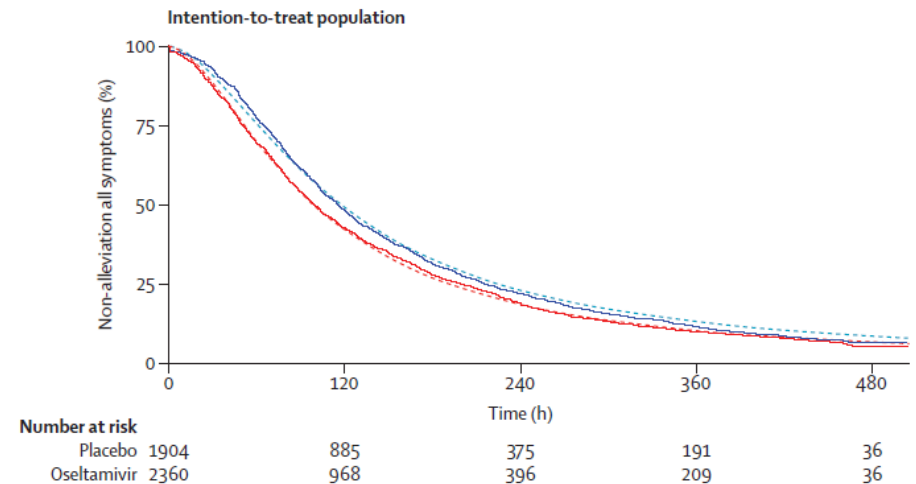
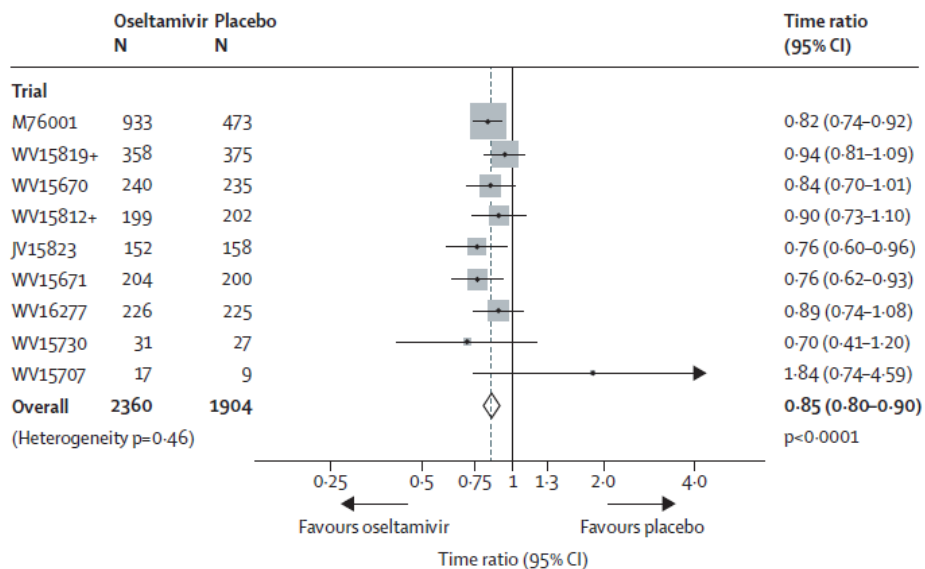
Meta-analysis of Randomized Controlled Trials



Intention-to-treat infected population



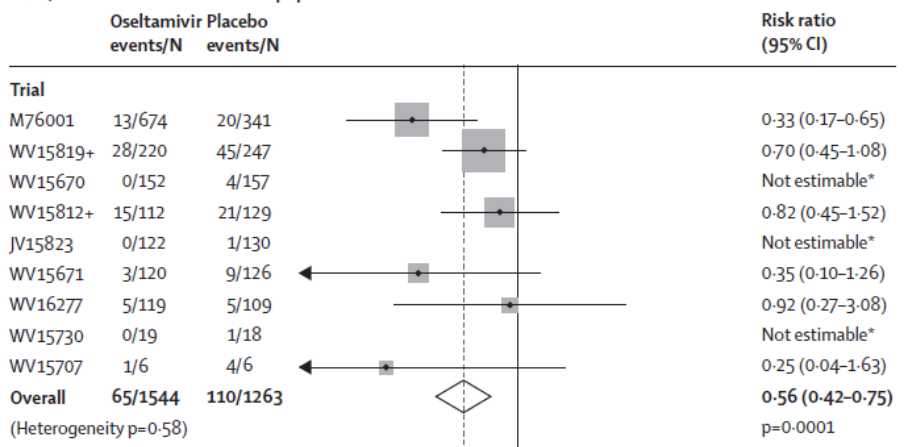
Intention-to-treat population



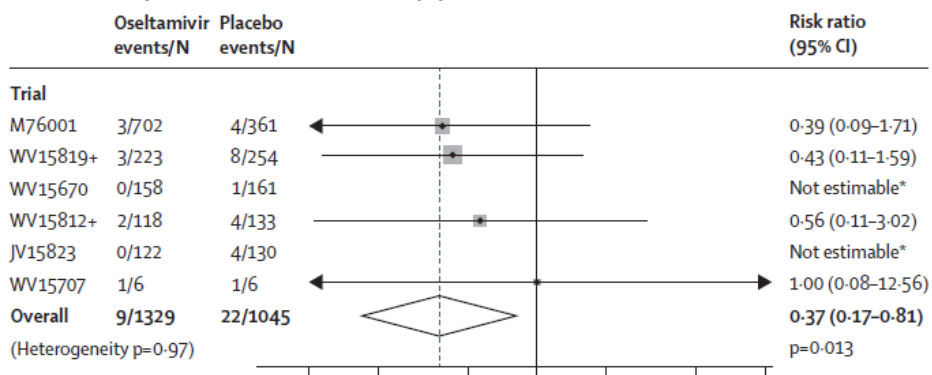


Oseltamivir for Prevention of LRTI, Hospitalization Meta-analysis of Randomized Controlled Trials

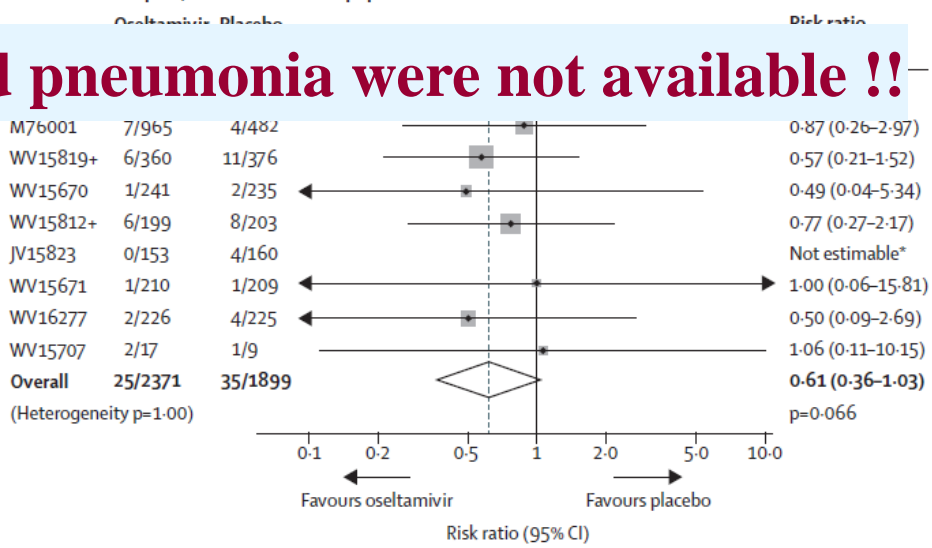
LRTC, intention-to-treat infected population



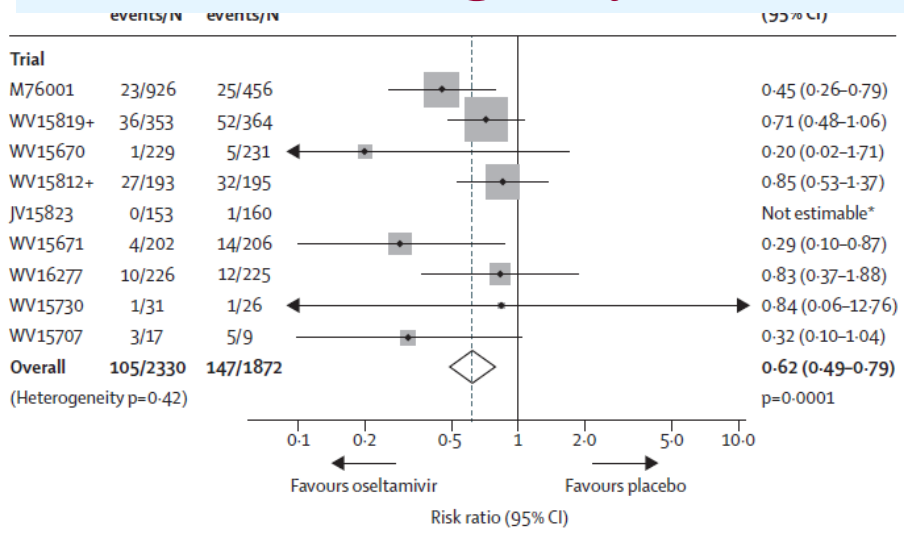
Admitted to hospital, intention-to-treat infected population



Admitted to hospital, intention-to-treat population



Data on radiologically confirmed pneumonia were not available !!



Impact of NIs on Influenza H1N1 Pneumonia

Individual Participant Data Meta-analysis, PRIDE Study

| Clinical outcomes/exposures studied | Influenza-related pneumonia (IRP) | | Any pneumonia [†] | |
|--|-----------------------------------|------------------------------------|----------------------------|------------------------------------|
| | Crude OR (95% CI) | Adjusted ^{††} OR (95% CI) | Crude OR (95% CI) | Adjusted ^{††} OR (95% CI) |
| Admission to an intensive care unit | | | | |
| Early versus no NAI ($n_1 = 1480$; $n_2 = 1855$) | 1.51 (1.01–2.25)* | 1.44 (0.94–2.18) | 2.02 (1.44–2.83)*** | 1.81 (1.27–2.58)** |
| Early versus later NAI ($n_1 = 3905$; $n_2 = 4709$) | 1.15 (0.94–1.39) | 0.89 (0.71–1.11) | 1.09 (0.92–1.29) | 0.95 (0.79–1.14) |
| Later versus no NAI ($n_1 = 3255$; $n_2 = 3864$) | 2.59 (1.85–3.61)*** | 2.43 (1.71–3.45)*** | 2.91 (2.16–3.91)*** | 2.66 (1.95–3.62)*** |
| NAI versus no NAI ($n_1 = 5962$; $n_2 = 6976$) | 1.69 (1.30–2.19)*** | 1.59 (1.21–2.09)** | 1.96 (1.55–2.50)*** | 1.78 (1.38–2.28)*** |
| Ventilation support | | | | |
| Early versus no NAI ($n_1 = 1131$; $n_2 = 1287$) | 1.12 (0.70–1.79) | 1.17 (0.71–1.92) | 1.24 (0.82–1.87) | 1.13 (0.73–1.75) |
| Early versus later NAI ($n_1 = 3084$; $n_2 = 3459$) | 0.69 (0.56–0.86)** | 0.68 (0.54–0.85)** | 0.74 (0.60–0.90)** | 0.75 (0.61–0.93)** |
| Later versus no NAI ($n_1 = 2489$; $n_2 = 2760$) | 2.31 (1.50–3.55)*** | 2.48 (1.57–3.92)*** | 2.18 (1.48–3.21)*** | 2.21 (1.47–3.32)*** |
| NAI versus no NAI ($n_1 = 4739$; $n_2 = 5182$) | 1.70 (1.25–2.30)** | 1.67 (1.22–2.29)** | 1.69 (1.27–2.25)*** | 1.59 (1.19–2.13)** |
| Acute respiratory distress syndrome | | | | |
| Early versus no NAI ($n_1 = 454$; $n_2 = 546$) | 1.14 (0.32–4.07) | 1.98 (0.46–8.54) | 2.26 (0.76–6.67) | 2.98 (0.77–11.60) |
| Early versus later NAI ($n_1 = 1234$; $n_2 = 1434$) | 0.54 (0.33–0.90)* | 0.65 (0.38–1.11) | 0.55 (0.37–0.83)** | 0.61 (0.40–0.94)* |
| Later versus no NAI ($n_1 = 1032$; $n_2 = 1178$) | 2.34 (0.98–5.55) | 2.23 (0.90–5.54) | 3.42 (1.50–7.82)** | 3.21 (1.36–7.58)** |
| NAI versus no NAI ($n_1 = 1549$; $n_2 = 1836$) | 1.99 (0.84–4.70) | 2.13 (0.87–5.21) | 3.06 (1.35–6.94)** | 3.14 (1.37–7.29)** |
| Mortality | | | | |
| Early versus no NAI ($n_1 = 1490$; $n_2 = 1866$) | 0.61 (0.38–0.96)* | 0.72 (0.44–1.17) | 0.59 (0.39–0.89)* | 0.62 (0.40–0.96)* |
| Early versus later NAI ($n_1 = 3906$; $n_2 = 4711$) | 0.84 (0.67–1.04) | 0.70 (0.55–0.88)** | 0.77 (0.63–0.95)* | 0.69 (0.56–0.86)** |
| Later versus no NAI ($n_1 = 3266$; $n_2 = 3875$) | 1.05 (0.73–1.52) | 1.18 (0.81–1.74) | 1.06 (0.76–1.49) | 1.13 (0.80–1.61) |
| NAI versus no NAI ($n_1 = 5974$; $n_2 = 7050$) | 0.88 (0.66–1.18) | 0.90 (0.67–1.22) | 0.89 (0.69–1.17) | 0.89 (0.67–1.17) |

Viral Pathogen Identification in CAP: **Con**

Summary



- **Problems on the diagnosis of viral pneumonia**
 - Inability to obtain specimens from the site of infection
 - Difficulties establishing pneumonia causation

 - **Uncertain clinical relevance of respiratory viruses in CAP**
 - Virus detection in asymptomatic subjects
 - May be a bystander, but not pathogenic

 - **Extremely limited treatment options**
 - Limited data on neuraminidase inhibitors even in influenza related pneumonia
 - Need a lot of time to use new antiviral agents in clinics
- ▶ Don't agree that viral identification tests should be conducted in non-selected patients with community-acquired pneumonia**