

# Paper dels virus respiratoris en la etiologia de la pneumònia adquirida a la comunitat

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Jordi Carratalà

Servei de Malalties Infeccioses

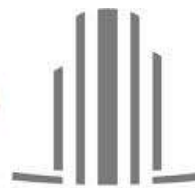
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Bellvitge  
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# CAP: magnitude of the problem

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## UNITED STATES

>4,000,000 people develop CAP every year

>1.3 million hospitalizations

Cost of care for patients with CAP: \$40 billion

Niederman MS. Semin Respir Crit Care Med 2009

## EUROPE

5-10 cases per 1000 inhabitants per year

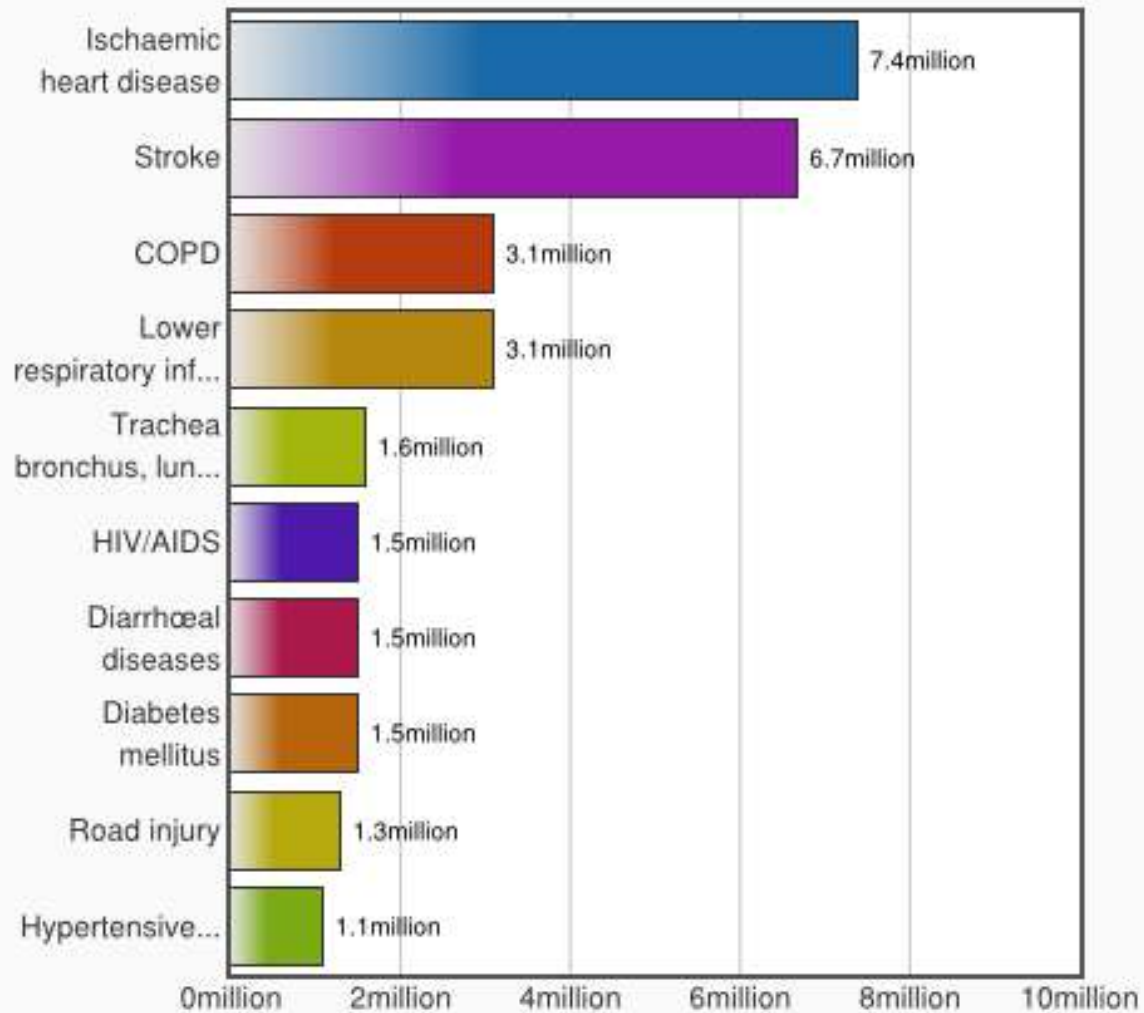
>65 yrs old, >15 cases per 1000 inhabitants per year

CAP results in an annual expenditure of €10.1 billion,  
of this amount inpatient care account for €5.7 billion

ERS. European Lung White Book 2003

Welte T. Thorax 2012

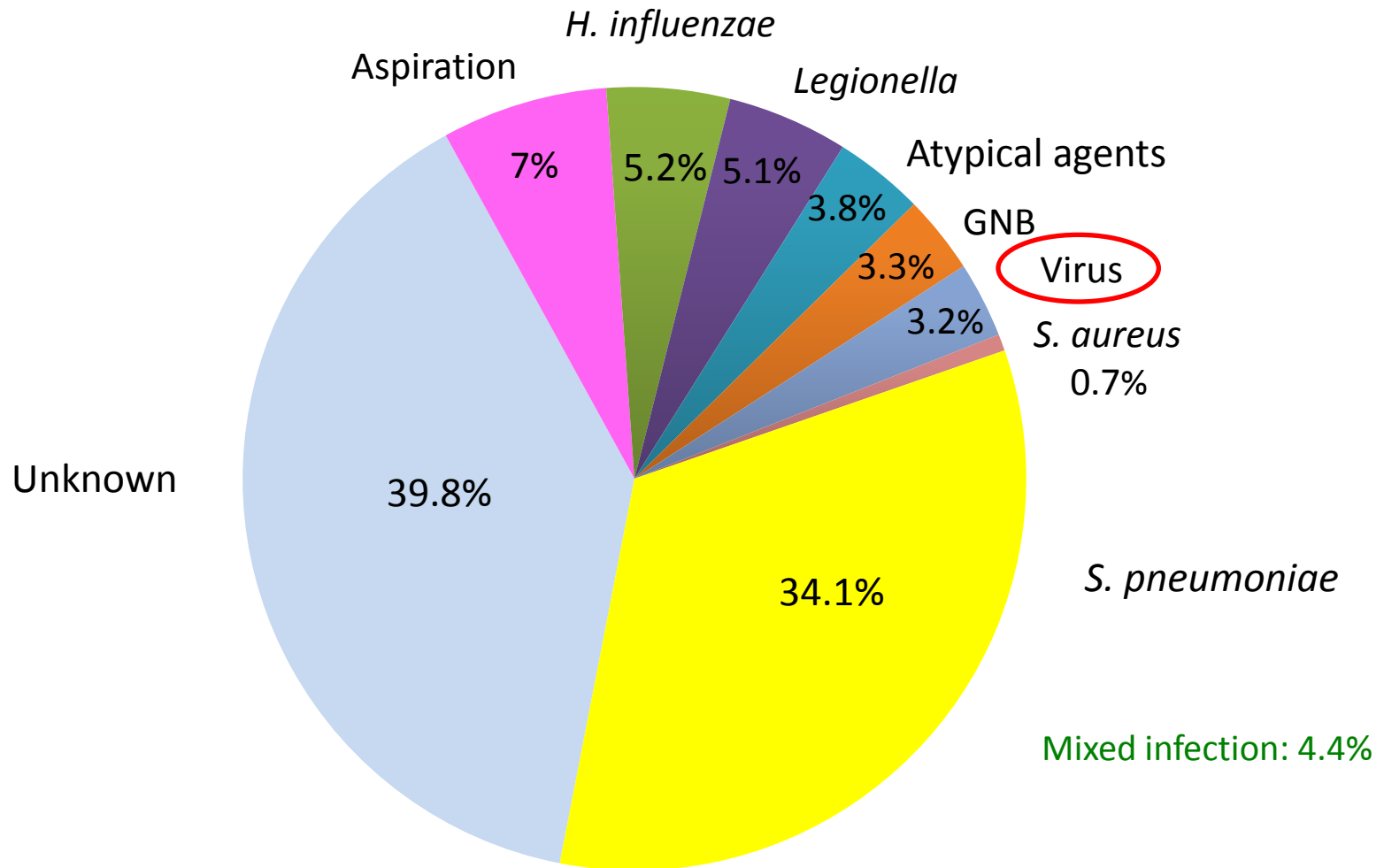
### The 10 leading causes of death in the world 2012



# Etiology of 4707 episodes of CAP in hospitalized adults

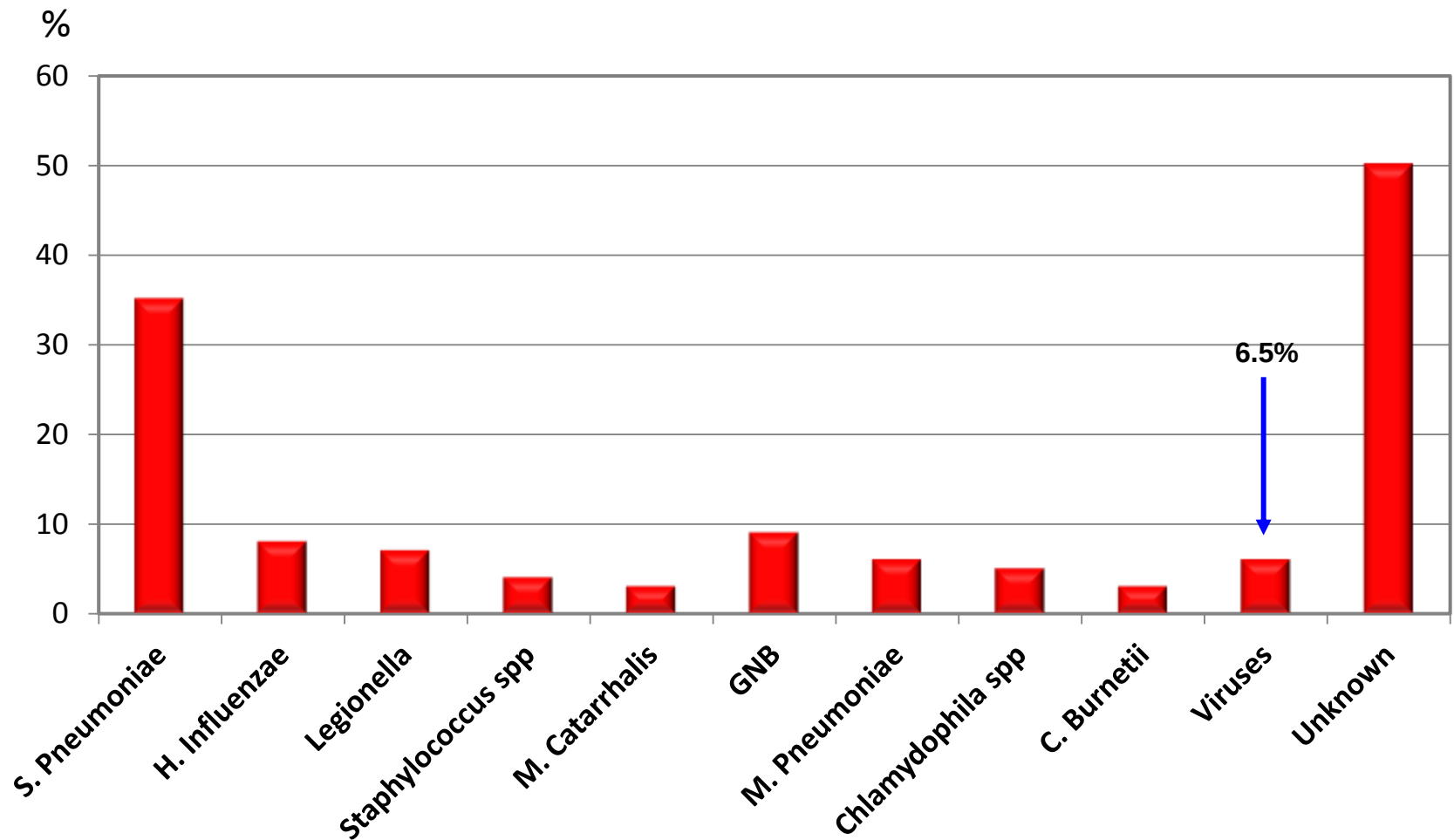
## Hospital de Bellvitge (1995 – 2013)

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# Frequency of causative organisms of CAP in Europe

## Data from 46 studies (1990 - 2008)



# Etiology of CAP in Europe by treatment setting

| Pathogen               | Outpatient (%) | Hospital (%) | ICU (%) |
|------------------------|----------------|--------------|---------|
| <i>S. pneumoniae</i>   | 38             | 27           | 28      |
| <i>M. pneumoniae</i>   | 8              | 5            | 2       |
| <i>H. influenzae</i>   | 13             | 6            | 7       |
| <i>C. pneumoniae</i>   | 21             | 11           | 4       |
| <i>S. aureus</i>       | 1.5            | 3            | 9       |
| Enterobacteriaceae     | 0              | 4            | 9       |
| <i>P. aeruginosa</i>   | 1              | 3            | 4       |
| <i>Legionella</i> spp. | 0              | 5            | 12      |
| <i>C. burnetii</i>     | 1              | 4            | 7       |
| Respiratory viruses    | 17             | 12           | 3       |
| Unclear                | 50             | 41           | 45      |

**Panel: Viruses linked to community-acquired pneumonia in children and adults**

- Respiratory syncytial virus
- Rhinovirus
- Influenza A, B, and C viruses
- Human metapneumovirus
- Parainfluenza viruses types 1, 2, 3, and 4
- Human bocavirus\*
- Coronavirus types 229E, OC43, NL63, HKU1, SARS
- Adenovirus
- Enteroviruses
- Varicella-zoster virus
- Hantavirus
- Parechoviruses
- Epstein-Barr virus
- Human herpesvirus 6 and 7
- Herpes simplex virus
- Mimivirus
- Cytomegalovirus†
- Measles†

\*Mostly in children. †Mostly in developing countries.

# Characteristics of common respiratory viruses

| Virus         | Season                    | Periodicity      | Duration of incubation period | Primary means of transmission |
|---------------|---------------------------|------------------|-------------------------------|-------------------------------|
| Influenza     | Winter                    | Yearly           | 1 - 2 days                    | Small particle aerosols       |
| VSR           | Late fall to early spring | Yearly           | 2 - 8 days                    | Large droplets and fomites    |
| MPVh          | Late winter               | Every other year | 5 - 6 days                    | Large droplets and fomites*   |
| Parainfluenza | Fall through spring       | Every 2-3 years  | 2 - 8 days                    | Large droplets and fomites    |
| Coronavirus   | Winter                    | Every 2-3 years  | 1 - 3 days                    | Large droplets and fomites*   |
| Rhinovirus    | All year/fall             | Yearly           | 8 h a 2 days                  | Fomites                       |

\*Presumptive mode of transmission

Falsey AR. Clin Infect Dis 2006

# Role of viruses in the etiology of CAP in adults

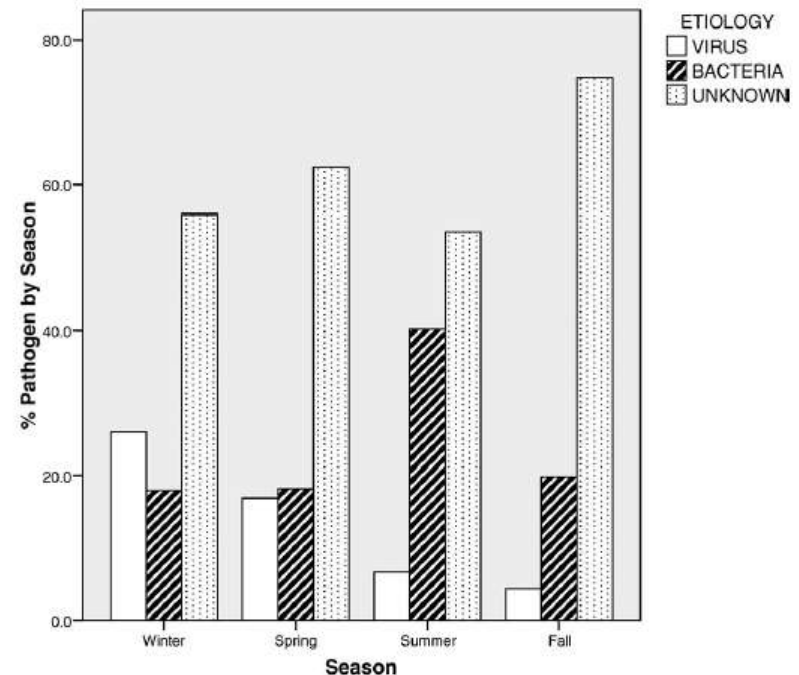
|                        | Johnstone<br>(n= 193) | Jennings<br>(n= 225) | Marcos<br>(n= 198) | Lieberman<br>(n= 183) | Templeton<br>(n= 105) |
|------------------------|-----------------------|----------------------|--------------------|-----------------------|-----------------------|
| Any virus              | 15%                   | 34%                  | 23%                | 32%                   | 54%                   |
| Co-infection           | 4%                    | 30%                  | 10%                | 30%                   | 27%                   |
| Influenza              | 4%                    | 12%                  | 8%                 | 12%                   | 10%                   |
| VSR                    | 3%                    | 4%                   | 2.5%               | 4%                    | 3%                    |
| MPVh                   | 4%                    | 0                    | 0                  | 0                     | 0                     |
| Adenovirus             | 1%                    | 4%                   | 4%                 | 4%                    | 4%                    |
| Parainfluenza          | 2%                    | 1%                   | 2.5%               | 1%                    | 8%                    |
| Rhinovirus/enterovirus | 2%                    | 13%                  | 4.5%               | 13%                   | 17%                   |
| Coronavirus            | 2%                    | 2%                   | 2.5%               | 2%                    | 13%                   |

# Viral infection in adults hospitalized with CAP

- Prospective, multicenter study carried out in Canada (2004-2006).
- A total of 193 pts were included (47% had severe CAP).
- Nasal swabs: NATs and DFA testing.

**Table 1—Distribution of Viral and Bacterial Respiratory Pathogens**

| Pathogens                            | No. |
|--------------------------------------|-----|
| Viral pathogens* (n = 29) <b>15%</b> |     |
| Influenza A                          | 3   |
| Influenza B                          | 4   |
| hMPV                                 | 7   |
| RSV                                  | 5   |
| Parainfluenza 1-4                    | 3   |
| Rhinovirus                           | 4   |
| Coronavirus OC43                     | 4   |
| Coronavirus 229E                     | 0   |
| Coronavirus NL63                     | 0   |
| Adenovirus                           | 2   |
| Bacterial pathogens† (n = 38)        |     |



Compared with bacterial infections, pts with viral infection were older (76 vs 64 yrs), were more likely to have cardiac disease (66% vs 32%) and were more frail (48% vs 21%).

# Respiratory viruses in adults with CAP

- Study population: 183 adults with CAP, 450 control subjects, and 201 with NPLRTI.
- Oropharyngeal swab, nasopharyngeal swab, and nasopharyngeal washing; samples were tested for detection of 12 RVs by RT-PCR.

*Table 2—Frequency Distribution of the 12 Viruses Identified in the Three Study Groups<sup>a</sup>*

| Virus                          | CAP (n = 183) | Controls (n = 450) | NPLRTI (n = 201) | P Value, CAP vs Controls | P Value, CAP vs NPLRTI |
|--------------------------------|---------------|--------------------|------------------|--------------------------|------------------------|
| Coronaviruses                  | 24 (13.1)     | 17 (3.8)           | 21 (10.4)        | <.01                     | .513                   |
| NL63                           | 3 (1.6)       | 6 (1.3)            | 2 (1.0)          | ...                      | ...                    |
| 229E                           | 5 (2.7)       | 2 (0.4)            | 4 (2.0)          | ...                      | ...                    |
| OC43                           | 13 (7.1)      | 8 (1.8)            | 14 (7.0)         | ...                      | ...                    |
| HKU                            | 3 (1.6)       | 1 (0.2)            | 1 (0.5)          | ...                      | ...                    |
| Respiratory syncytial virus    | 13 (7.1)      | 4 (0.9)            | 7 (3.5)          | <.01                     | .172                   |
| Rhinovirus                     | 9 (4.9)       | 9 (2.0)            | 15 (7.5)         | .080                     | .413                   |
| Influenza viruses              | 8 (4.4)       | 2 (0.4)            | 63 (31.3)        | <.01                     | <.01                   |
| Influenza A                    | 8 (4.4)       | 2 (0.4)            | 62 (30.8)        | ...                      | ...                    |
| Influenza B                    | 0             | 0                  | 1 (0.5)          | ...                      | ...                    |
| Adenovirus                     | 3 (1.6)       | 0                  | 0                | ...                      | ...                    |
| Human metapneumovirus          | 2 (1.1)       | 0                  | 0                | ...                      | ...                    |
| Parainfluenza 3 virus          | 0             | 0                  | 3 (1.5)          | ...                      | ...                    |
| Parainfluenza 2 virus          | 0             | 0                  | 0                | ...                      | ...                    |
| Total                          |               |                    |                  |                          |                        |
| Viruses                        | 59 (32.2)     | 32 (7.1)           | 110 (54.7)       | <.01                     | <.01                   |
| Positive subjects <sup>b</sup> | 58 (31.7)     | 32 (7.1)           | 104 (51.7)       | <.01                     | <.01                   |

Two winter periods: Nov 2004 - March 2005; Nov 2005 – March 2006

Lieberman D. Chest 2010

# The role of viruses in the etiology of CAP

- 198 of 340 adult pts diagnosed with CAP (Jan 2003 – March 2004)
- Nasal swabs: immunofluorescence, cell culture, and RT-PCR
- *S. pneumoniae* was the most frequent causative agent (58 pts, 29%), followed by respiratory viruses (46 pts, 23%).
- 48 viruses were identified:
  - Influenza A (16)
  - VSR (5)
  - Adenovirus (8)
  - Enterovirus (1)
  - Rhinovirus (8)
  - Coronavirus (5)
  - Parainfluenza (5)

Only virus 26 (13%); only bacteria 66 (33%); virus & bacteria 20 (10%)  
Serology (6 viruses), immunofluorescence (8), culture (12), PCR (45)

The only characteristic that significantly distinguished viral from bacterial etiology was a lower number of leukocytes

# Etiology of CAP in a population-based study

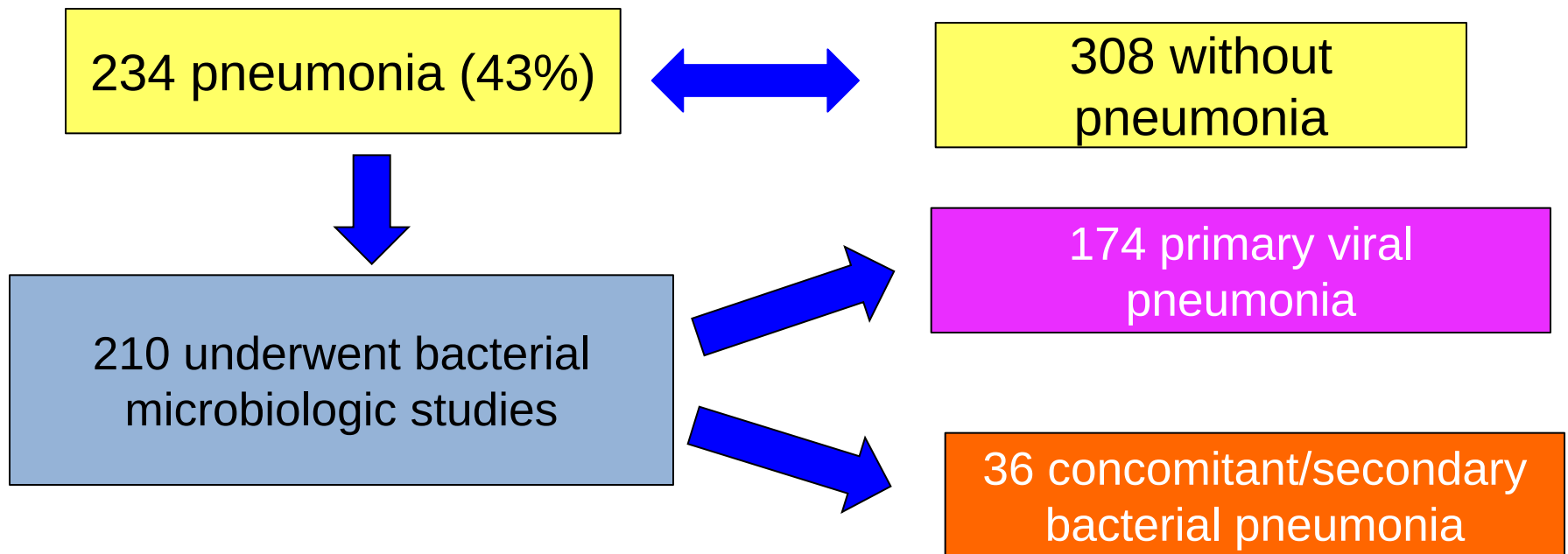
|                                              | Inpatients<br>(N = 276) | Outpatients<br>(N = 424) |
|----------------------------------------------|-------------------------|--------------------------|
| Any pathogen identified                      | 196 (71)                | 194 (45.7)               |
| Conventional bacteria <sup>†</sup>           | 136 (69.4)              | 43 (22.2)                |
| <i>Streptococcus pneumoniae</i> <sup>†</sup> | 127 (64.8)              | 43 (22.2)                |
| Others bacteria                              | 9 (4.6)                 | 0 (0)                    |
| Atypical pathogen <sup>†</sup>               | 60 (30.6)               | 130 (67)                 |
| <i>Coxiella burnetii</i> <sup>†</sup>        | 15 (7.7)                | 57 (29.4)                |
| <i>Mycoplasma pneumoniae</i>                 | 22 (11.2)               | 40 (20.6)                |
| <i>Chlamydia pneumoniae</i>                  | 11 (5.6)                | 26 (13.4)                |
| <i>Chlamydia psittaci</i>                    | 1 (0.5)                 | 1 (0.5)                  |
| <i>Legionella pneumophila</i> <sup>†</sup>   | 11 (5.6)                | 6 (3.1)                  |
| Virus                                        | 21 (10.7)               | 35 (18)                  |
| <i>Influenza virus</i>                       | 6 (3.1)                 | 18 (9.3)                 |
| <i>Parainfluenza virus</i>                   | 15 (7.7)                | 17 (8.8)                 |
| Total, mixed infection                       | 21 (10.7)               | 14 (7.2)                 |

| Clinical evolution and outcomes  | Conventional Bacteria (N = 163) | Atypical Agents (N = 151) | Virus (N = 41) |
|----------------------------------|---------------------------------|---------------------------|----------------|
| <b>Clinical evolution</b>        |                                 |                           |                |
| Treatment failure                | 15 (9.2)                        | 8 (5.3)                   | 0 (0)          |
| Severe sepsis                    | 71 (43.8)                       | 22 (14.6)                 | 6 (14.6)       |
| Septic shock                     | 8 (4.9)                         | 1 (0.7)                   | 0 (0)          |
| Hospitalized                     | 123 (75.5)                      | 39 (25.8)                 | 13 (31.7)      |
| Admission to intensive care unit | 14 (8.6)                        | 1 (0.7)                   | 0 (0)          |
| Use of mechanical ventilation    | 2 (1.2)                         | 1 (0.7)                   | 0 (0)          |
| <b>Outcomes</b>                  |                                 |                           |                |
| Mortality within 30 days         | 7 (4.3)                         | 2 (1.3)                   | 0 (0)          |
| In-hospital mortality*           | 5 (4.1)                         | 2 (5.1)                   | 0 (0)          |
| Readmission within 30 days*      | 10 (8.1)                        | 2 (5.1)                   | 0 (0)          |
| Length of hospital stay** (days) |                                 |                           |                |
| Mean (SD)                        | 3.9 (3.1)                       | 3 (2.7)                   | 2.9 (2)        |

# Pneumonia complicating pandemic (H1N1) 2009

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Chest radiography was obtained in 542 of 585 cases



|                                             | <b>Patients With<br/>Pneumonia<br/>(n = 234)<br/>No. (%)</b> | <b>Patients<br/>Without<br/>Pneumonia<br/>(n = 308)<br/>No. (%)</b> | <b>P</b> |
|---------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------------------|----------|
| Length of hospital stay,<br>median (IQR), d | 7 (5–11)                                                     | 5 (3–7)                                                             | <0.001   |
| Shock at any time during<br>admission       | 23 (9.8)                                                     | 3 (1)                                                               | <0.001   |
| Nosocomial infection*                       | 14 (6)                                                       | 2 (0.6)                                                             | <0.001   |
| Heart complications†                        | 10 (4.3)                                                     | 2 (0.6)                                                             | <0.001   |
| ICU admission                               | 53 (22.6)                                                    | 18 (5.8)                                                            | <0.001   |
| Need for mechanical<br>ventilation          | 42 (17.9)                                                    | 10 (3.2)                                                            | <0.001   |
| Inhospital mortality                        | 12 (5.2)                                                     | 0 (0)                                                               | <0.001   |

# CAP during the first post-pandemic season: A prospective, multicenter cohort study

**Table 1** Causative organisms in hospitalized patients with CAP during the first post-pandemic influenza season (2010–2011).<sup>a</sup>

|                                                   | <i>N</i> = 747 <i>n</i> (%) |
|---------------------------------------------------|-----------------------------|
| Bacterial                                         | 154 (21.9) <sup>b</sup>     |
| <i>Streptococcus pneumoniae</i>                   | 98 (13.1)                   |
| <i>Haemophilus influenzae</i>                     | 13 (1.7)                    |
| <i>Staphylococcus aureus</i> <sup>c</sup>         | 11 (1.5)                    |
| <i>Pseudomonas aeruginosa</i>                     | 9 (1.2)                     |
| <i>Legionella pneumophila</i>                     | 6 (0.8)                     |
| Others                                            | 17 (2.2)                    |
| Viral                                             | 125 (16.7)                  |
| Influenza A (H1N1)pdm09                           | 96 (12.8)                   |
| Rhinovirus                                        | 16 (2.1)                    |
| Influenza B                                       | 5 (0.6)                     |
| Parainfluenza                                     | 4 (0.5)                     |
| Others                                            | 4 (0.5)                     |
| Mixed                                             | 36 (4.8)                    |
| Influenza A (H1N1)pdm09<br>+ <i>S. pneumoniae</i> | 11 (1.5)                    |
| Rhinovirus + <i>S. pneumoniae</i>                 | 3 (0.4)                     |
| Influenza B + <i>S. pneumoniae</i>                | 3 (0.4)                     |
| RSV + <i>S. pneumoniae</i>                        | 3 (0.4)                     |
| Others                                            | 16 (2.1)                    |
| Unknown aetiology                                 | 432 (57.2)                  |

**Table 3** Clinical outcomes of hospitalized patients with CAP during the first post-pandemic influenza season (2010–2011).

| Characteristic                                 | All cases<br><i>N</i> = 747 | Bacterial<br><i>n</i> = 154 | Viral<br><i>n</i> = 125 | Mixed<br><i>n</i> = 36 | Unknown<br><i>n</i> = 432 |
|------------------------------------------------|-----------------------------|-----------------------------|-------------------------|------------------------|---------------------------|
| In-hospital complications                      |                             |                             |                         |                        |                           |
| Acute cardiac events <sup>a</sup>              | 79 (10.6)                   | 14 (9.1)                    | 18 (14.4)               | 1 (2.8)                | 46 (10.6)                 |
| Nosocomial infections                          | 31 (4.1)                    | 5 (3.2)                     | 13 (10.4)               | 1 (2.8)                | 12 (2.8)                  |
| ICU admission <sup>b</sup>                     | 94 (12.6)                   | 18 (11.7)                   | 41 (32.8)               | 11 (30.6)              | 24 (5.6)                  |
| Need for mechanical ventilation (intubation)   | 59 (7.9)                    | 9 (5.8)                     | 30 (24.4)               | 8 (22.2)               | 12 (2.8)                  |
| ARDS                                           | 58 (7.8)                    | 11 (7.1)                    | 27 (21.6)               | 9 (25)                 | 11 (2.5)                  |
| Time to clinical stability, median (IQR), days | 2 (1–4)                     | 2 (1–5)                     | 3 (1–7)                 | 4 (2–7)                | 2 (1–3)                   |
| Length of hospital stay, median (IQR), days    | 8 (5–13)                    | 9 (6–14)                    | 9 (6–15)                | 8 (6.5–16.5)           | 8 (5–11)                  |
| In-hospital mortality                          | 61 (8.2)                    | 11 (7.1)                    | 22 (17.6)               | 6 (16.7)               | 22 (5.1)                  |

# Possibilities for antiviral treatment and prevention of severe pneumonia

|                             | 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                                              |

\*Long successful use in US military conscripts, no production now. †Has been used for compassionate cases.

# Comments

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- Respiratory viruses, particularly influenza, are a common cause of CAP.
- Respiratory viruses are detected in 15%-54% of adult patients hospitalized with CAP, when extensive test for virus are used.
- Co-infection with viruses and bacteria are common, occurring in 4-30% of cases.
- Differentiating viral CAP from mixed infection and bacterial CAP remains challenging.

# Comments

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- Pneumonia is a frequent complication among hospitalized patients with influenza and causes significant morbidity and mortality.
- With the exception of antiinfluenza agents, there is a lack of licensed antiviral drugs against the large variety of clinically important respiratory viruses.

Gràcies per la vostra atenció!

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