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

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CAP: magnitude of the problem

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

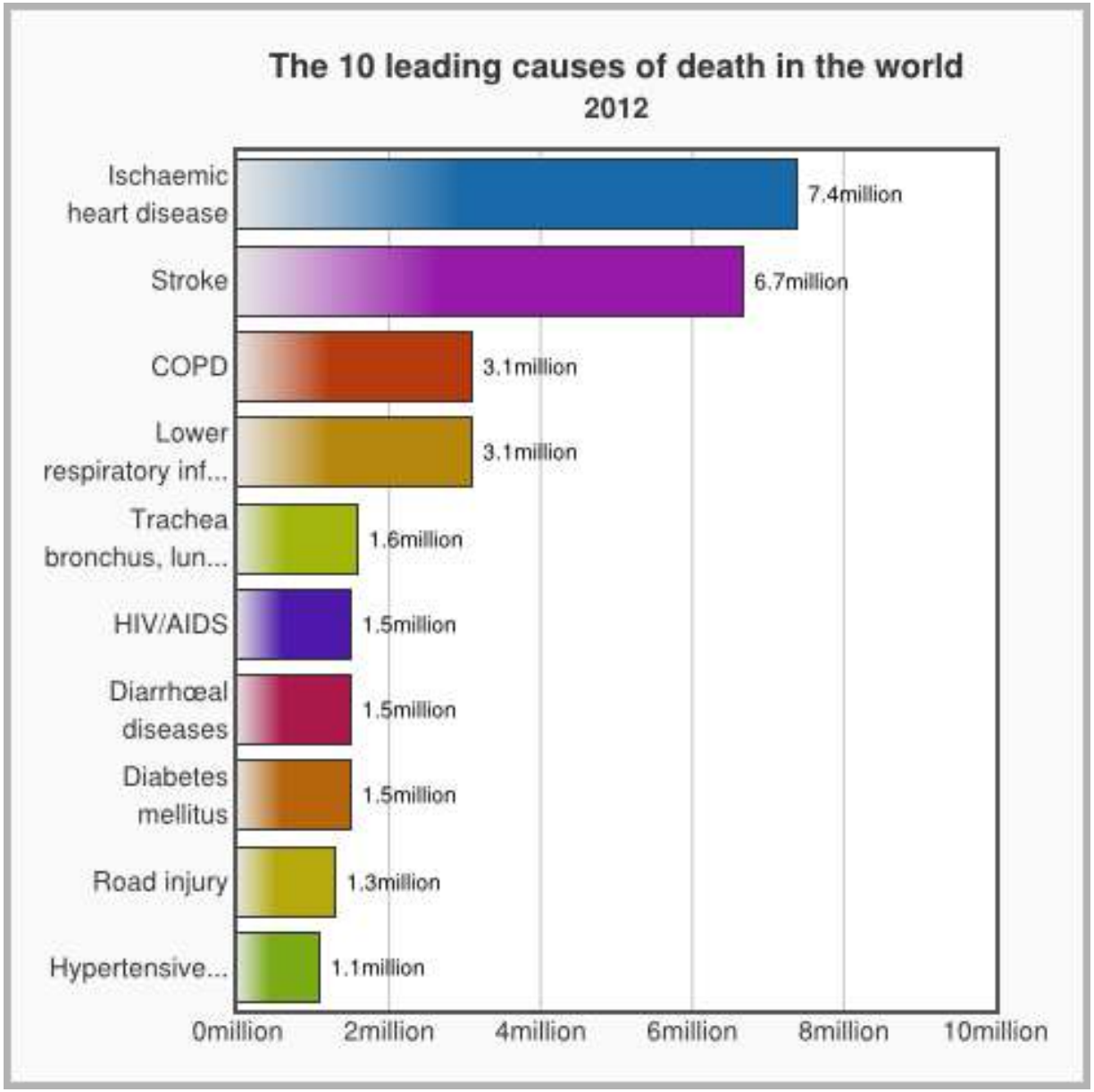
>65 yrs old, >15 cases per 1000 inhabitants per year

CAP results in an annual expenditure of €10.1 billion,

of this amount inpatient care account for €5.7 billion

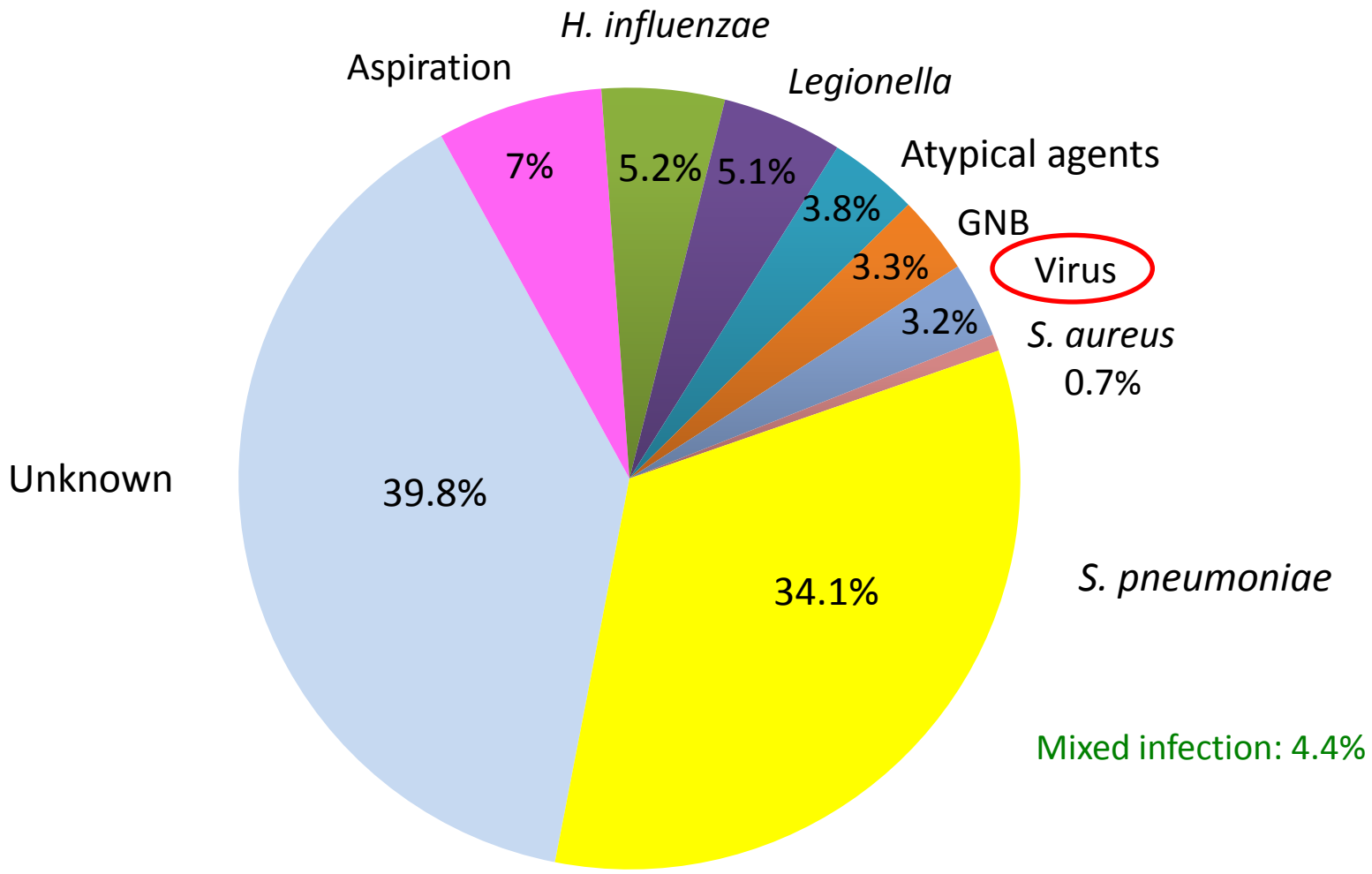
ERS. European Lung White Book 2003

Welte T. Thorax 2012

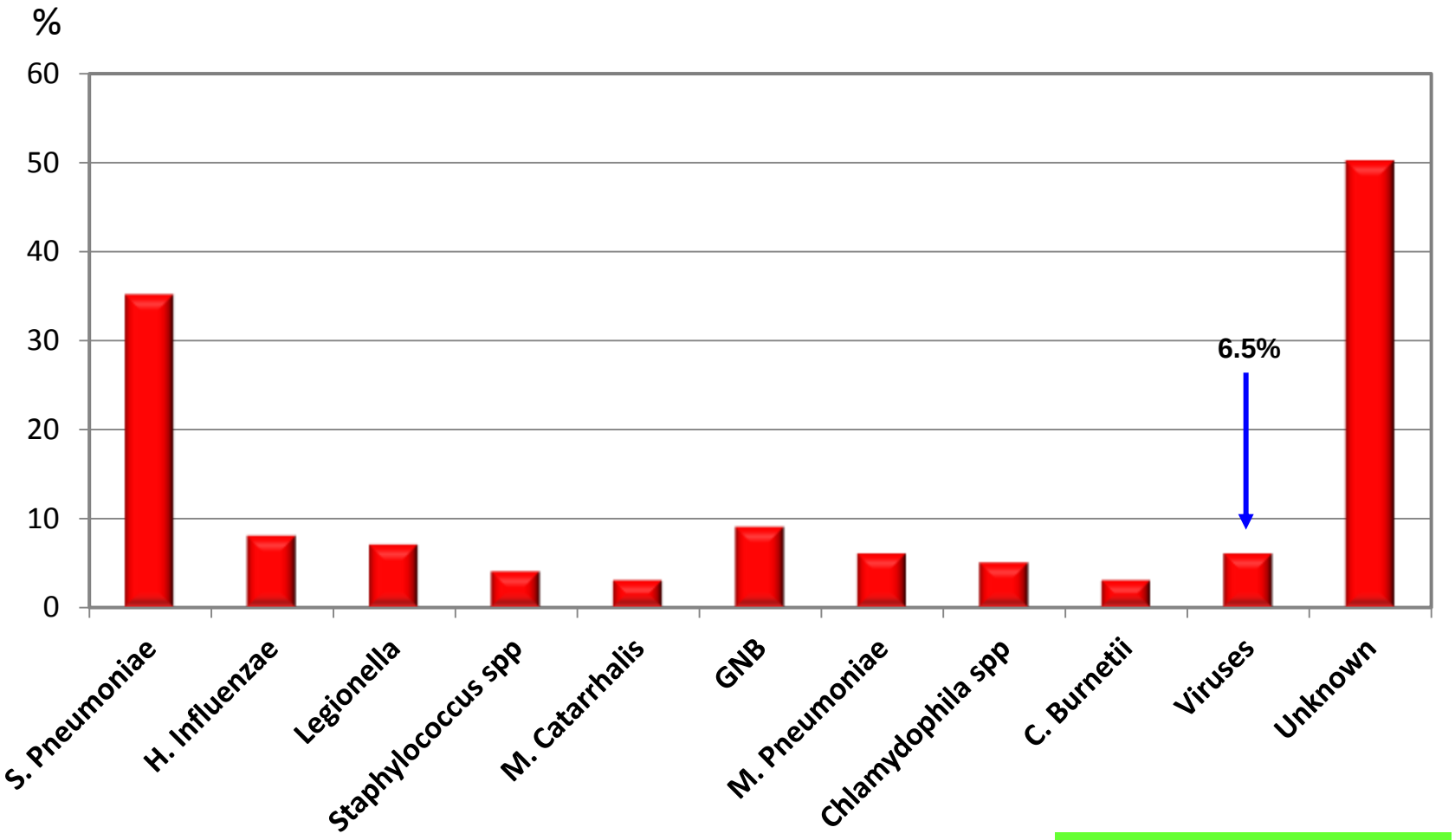


World Health Organization 2012

Etiology of 4707 episodes of CAP in hospitalized adults
Hospital de Bellvitge (1995 – 2013)



Frequency of causative organisms of CAP in Europe
Data from 46 studies (1990 - 2008)



Welte T. Thorax 2012

Etiology of CAP in Europe by treatment setting

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

Welte T. Thorax 2012

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.

Ruuskanen O. Lancet 2011

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

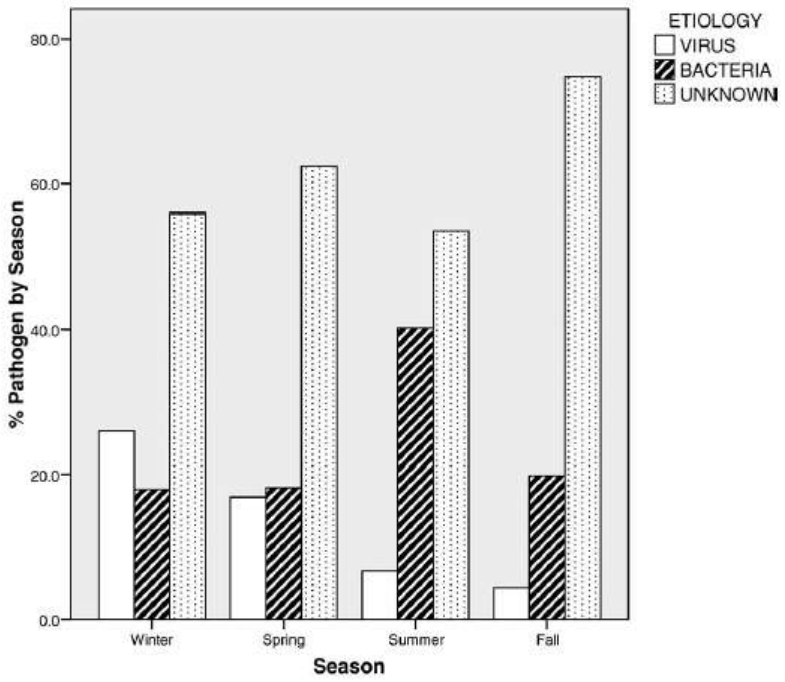
	Johnstone (n= 193)	Jennings (n= 225)	Marcos (n= 198)	Lieberman (n= 183)	Templeton (n= 105)
Any virus	15%	34%	23%	32%	54%
Co-infection	4%	30%	10%	30%	27%
Influenza	4%	12%	8%	12%	10%
VSR	3%	4%	2.5%	4%	3%
MPVh	4%	0	0	0	0
Adenovirus	1%	4%	4%	4%	4%
Parainfluenza	2%	1%	2.5%	1%	8%
Rhinovirus/enterovirus	2%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

Johnstone J. Chest 2008

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*[a]

Virus	CAP (n = 183)	Controls (n = 450)	NPLRTI (n = 201)	*P* Value, CAP vs Controls	*P* Value, CAP vs NPRTLI
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[b]	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)	- Rhinovirus (8)
- VSR (5)	- Coronavirus (5)
- Adenovirus (8)	- Parainfluenza (5)
- Enterovirus (1)	

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

Marcos MA. Antivir Ther 2006

Etiology of CAP in a population-based study

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

The Comarca Interior region, Basque Country (2006-2007)

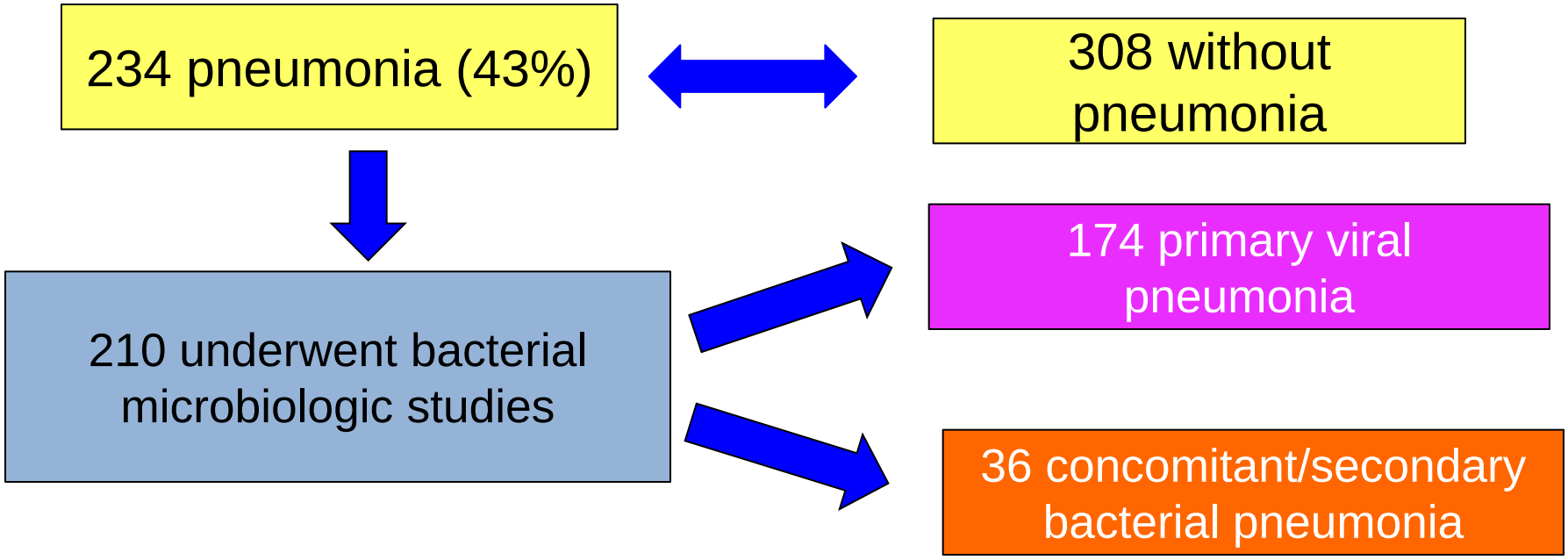
Capelastegui A. BMC Infect Dis 2012

Clinical evolution and outcomes	Conventional Bacteria (N = 163)	Atypical Agents (N = 151)	Virus (N = 41)
Clinical evolution			
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)
Outcomes			
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)

Capelastegui A. BMC Infect Dis 2012

Pneumonia complicating pandemic (H1N1) 2009

Chest radiography was obtained in 542 of 585 cases



Viasus D. Medicine (Baltimore) 2011

	Patients With Pneumonia (n = 234) No. (%)	Patients Without Pneumonia (n = 308) No. (%)	P
Length of hospital stay, median (IQR), d	7 (5–11)	5 (3–7)	<0.001
Shock at any time during 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 ventilation	42 (17.9)	10 (3.2)	<0.001
Inhospital mortality	12 (5.2)	0 (0)	<0.001

Viasus D. Medicine (Baltimore) 2011

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).[a]

	N = 747 *n* (%)
Bacterial	154 (21.9)[b]
Streptococcus pneumoniae	98 (13.1)
Haemophilus influenzae	13 (1.7)
Staphylococcus aureus[c]	11 (1.5)
Pseudomonas aeruginosa	9 (1.2)
Legionella pneumophila	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 + *S. Pneumoniae*	11 (1.5)
Rhinovirus + *S. pneumoniae*	3 (0.4)
Influenza B + *S. pneumoniae*	3 (0.4)
RSV + *S. pneumoniae*	3 (0.4)
Others	16 (2.1)
Unknown aetiology	432 (57.2)

Viasus D. J Infect 2013

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

Characteristic	All cases $N = 747$	Bacterial $n = 154$	Viral $n = 125$	Mixed $n = 36$	Unknown $n = 432$
In-hospital complications					
Acute cardiac events[a]	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[b]	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)

Viasus D. J Infect 2013

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.

Ruuskanen O. Lancet 2011

Comments

- 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

- 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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