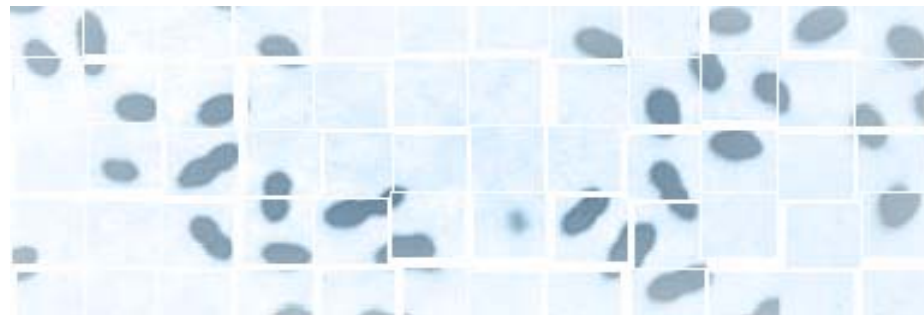
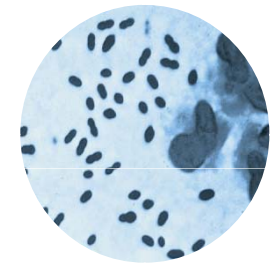


# Antibiotics in low respiratory tract infections

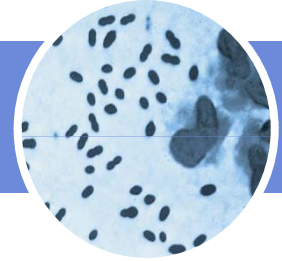
B. Louzir CHU Ia Rabta Tunis -Tunisia



4<sup>TH</sup> Arab Symposium for Antimicrobial Agents  
16<sup>th</sup> National congress of Tunisian society of infectiology

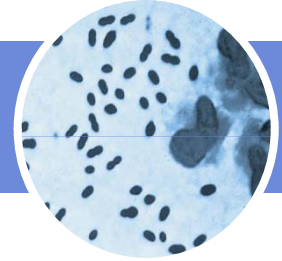
April 2006

# INTRODUCTION



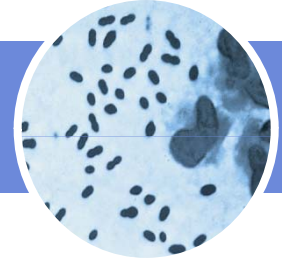
- ❖ Low respiratory tract infections :
  - Most common infections encountered by physicians
  - The leading & essential cause of antibiotic's administration
  - Major cause of death in the world and major cause of death due to infectious diseases
- ❖ In USA : Respiratory tract infections (RTIs) are responsible for 50 million deaths globally each year.

# INTRODUCTION



- ❖ Update topic : Discussed by numerous societies : recommendations
  - ATS (1993,2001),
  - BTS (2001), SPILF(1991, 2001, 2006),
  - AFSSAPS (2003,2005)
- ❖ Low respiratory infection :
  - **CAP** : 5 to 30% mortality
  - **Acute bronchitis** : benign prognosis
  - **COPD exacerbations**

# CONSTRAINT

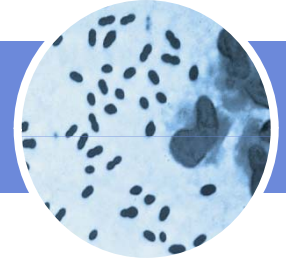


- ❖ Ideally, antibiotic therapy principles depends on :
  - The organism responsible
  - Antibiotic activity

## **BUT**

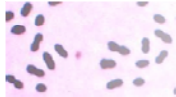
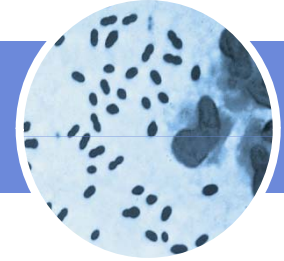
- ❖ No sensitive & rapid microbiological test
- ❖ Lack of specificity and sensitivity of clinical and radiological signs.

# BASIS OF ANTIBIOTHERAPY



- ❖ Empirical treatment are based on
  - Epidemiology :
    - location,
    - season,
    - risk factors,
  - Available antibiotics,
  - Antibiotic resistance

# CAUSATIVE PATHOGENS



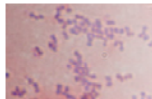
**Streptococcus Pneumoniae**



**Haemophilus influenzae**



**Legionella spp.**



**Staphylococcus aureus**



**Moraxella catarrhalis**



**Gram-negative enteric bacteria**



**Mycoplasma pneumoniae**

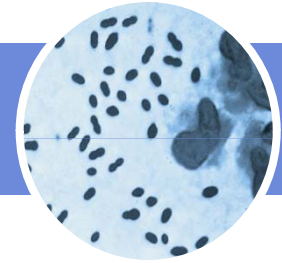


**Chlamydia pneumoniae**



**Viruses**

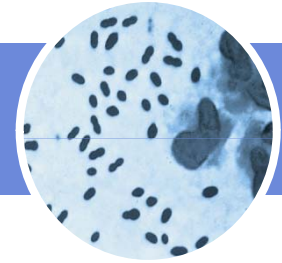
# CAUSATIVE PATHOGENS



Pathogens	% Responsible for CAP in outpatients	% Responsible for CAP in inpatients
<b>Typical pathogens</b>		
<i>Streptococcus pneumoniae</i>	9 - 20	20 - 60
<i>Haemophilus influenzae</i>	3 - 10	3 - 10
<i>Staphylococcus aureus</i>	-	up to 10
<b>Atypical pathogens</b>		
<i>Legionella spp</i>	0,7 - 13	up to 10
<i>Mycoplasma pneumoniae</i>	13 - 37	up to 10
<i>Chlamydophila pneumoniae</i>	17	up to 10

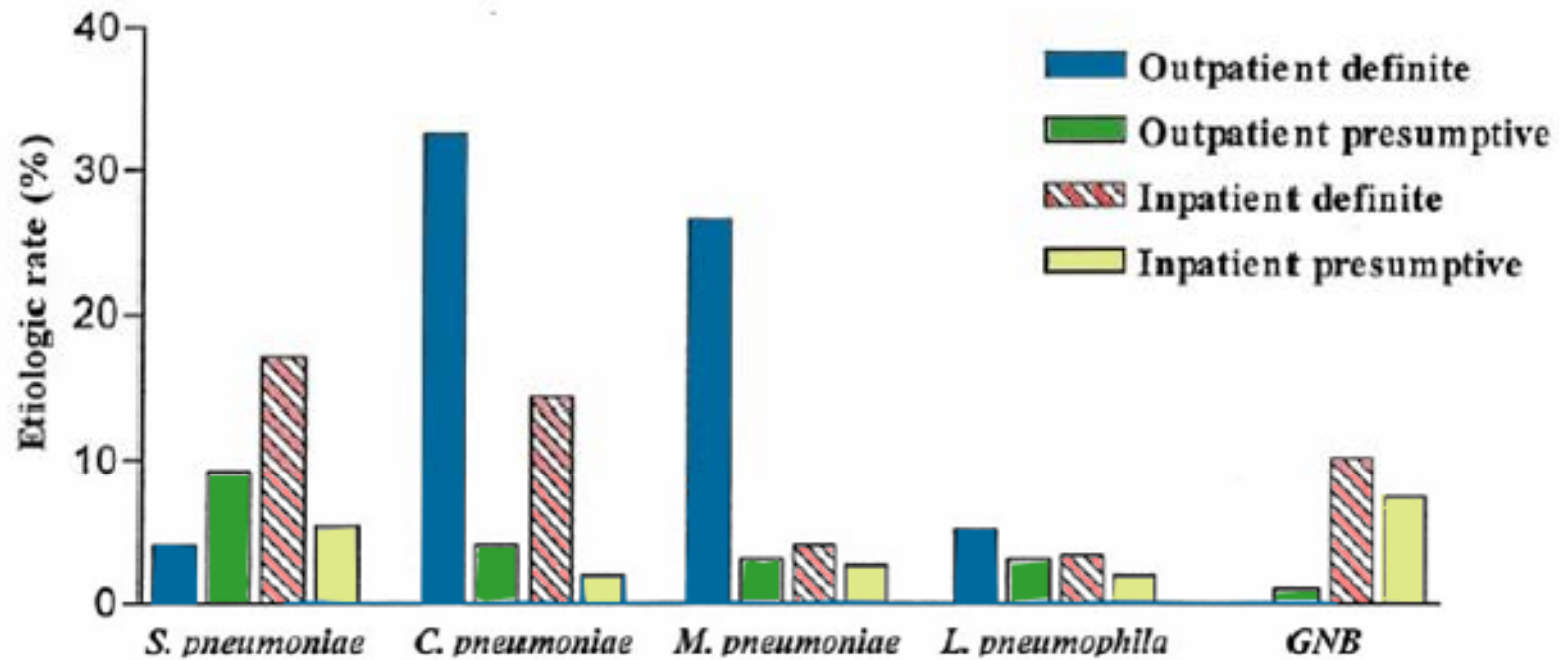
ATS GUIDELINES FOR THE MANAGEMENT OF ADULTS WITH CAP  
 AM J RESPIR CRIT CARE MED 2001

# EPIDEMIOLOGY



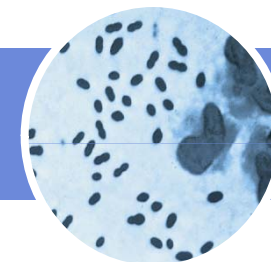
**CAP in Southeast Asia.** Anan W. Chest 2003

**Etiology in 98 outpatients and 147 hospitalized patients with CAP.**





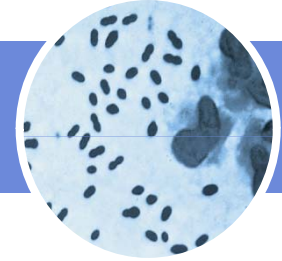
# CAUSATIVE PATHOGENS



## CAP in Europe. Frequency of causative organisms

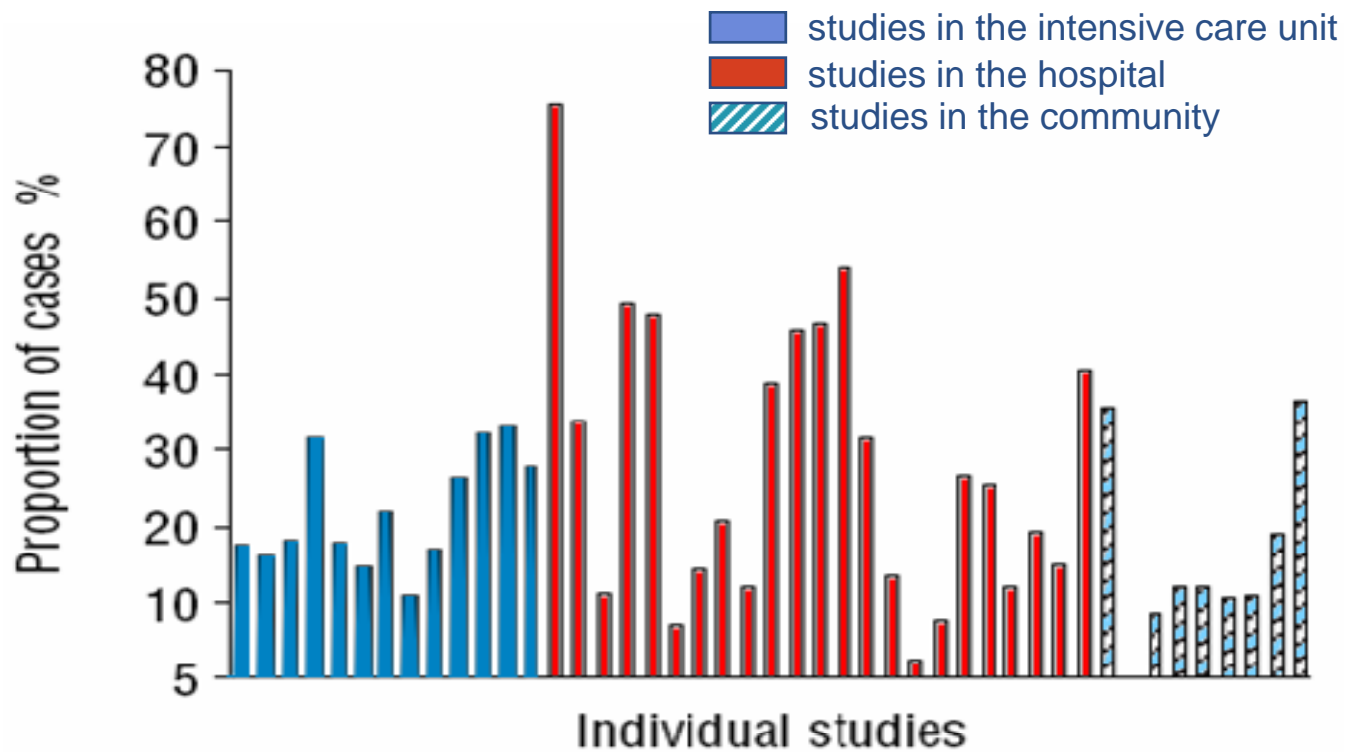
Organism	Community	Hospital	ICU
Studies n <sup>#</sup>	9	23	13
<i>Streptococcus pneumoniae</i>	19.3	25.9	21.7
<i>Haemophilus influenzae</i>	3.3	4.0	5.1
<i>Legionella</i> spp.	1.9	4.9	7.9
<i>Staphylococcus aureus</i>	0.2	1.4	7.6
<i>Moraxella catarrhalis</i>	0.5	2.5	
Gram-negative enteric bacteria	0.4	2.7	7.5
<i>Mycoplasma pneumoniae</i>	11.1	7.5	2
<i>Chlamydia pneumoniae</i>	8	7	
<i>Chlamydia psittaci</i>	1.5	1.9	1.3
<i>Coxiella burnetii</i>	0.9	0.8	0.2
Viruses	11.7	10.9	5.1
Other organisms	1.6	2.2	7.4
No pathogen identified	49.8	43.8	41.5

# EPIDEMIOLOGY

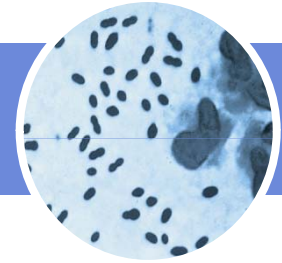


## CAP in Europe. Frequency of identification of *Streptococcus*

*pneumoniae* in prospective studies. M. Woodhead. Eur Respir J 2002; 20: Suppl. 36

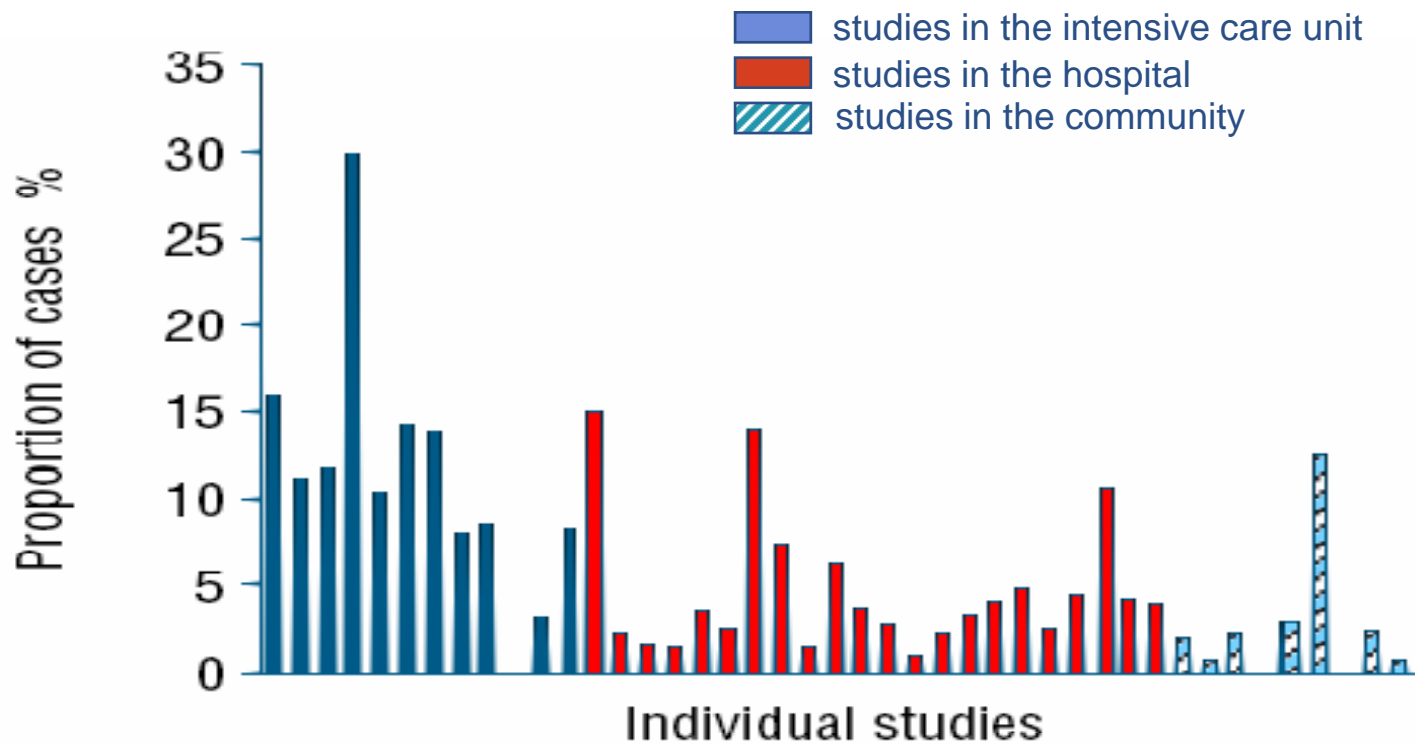


# EPIDEMIOLOGY

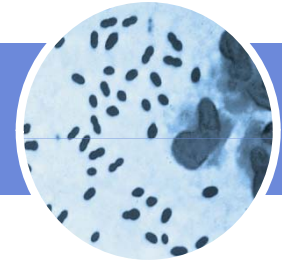


## CAP in Europe. Frequency of identification of *Legionella*

**bacteria in prospective studies.** M. Woodhead. Eur Respir J 2002; 20: Suppl. 36

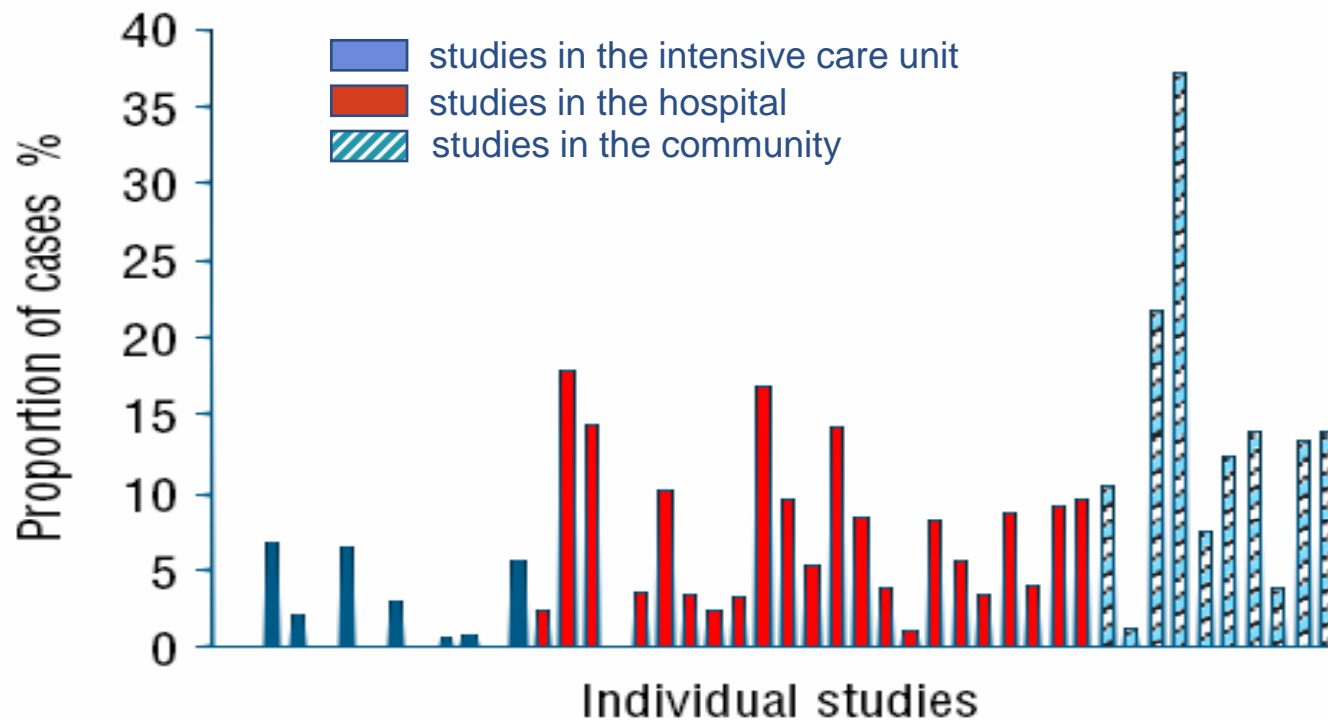


# EPIDEMIOLOGY

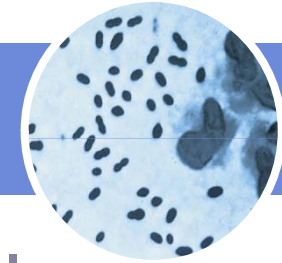


## CAP in Europe. Frequency of identification of *Mycoplasma*

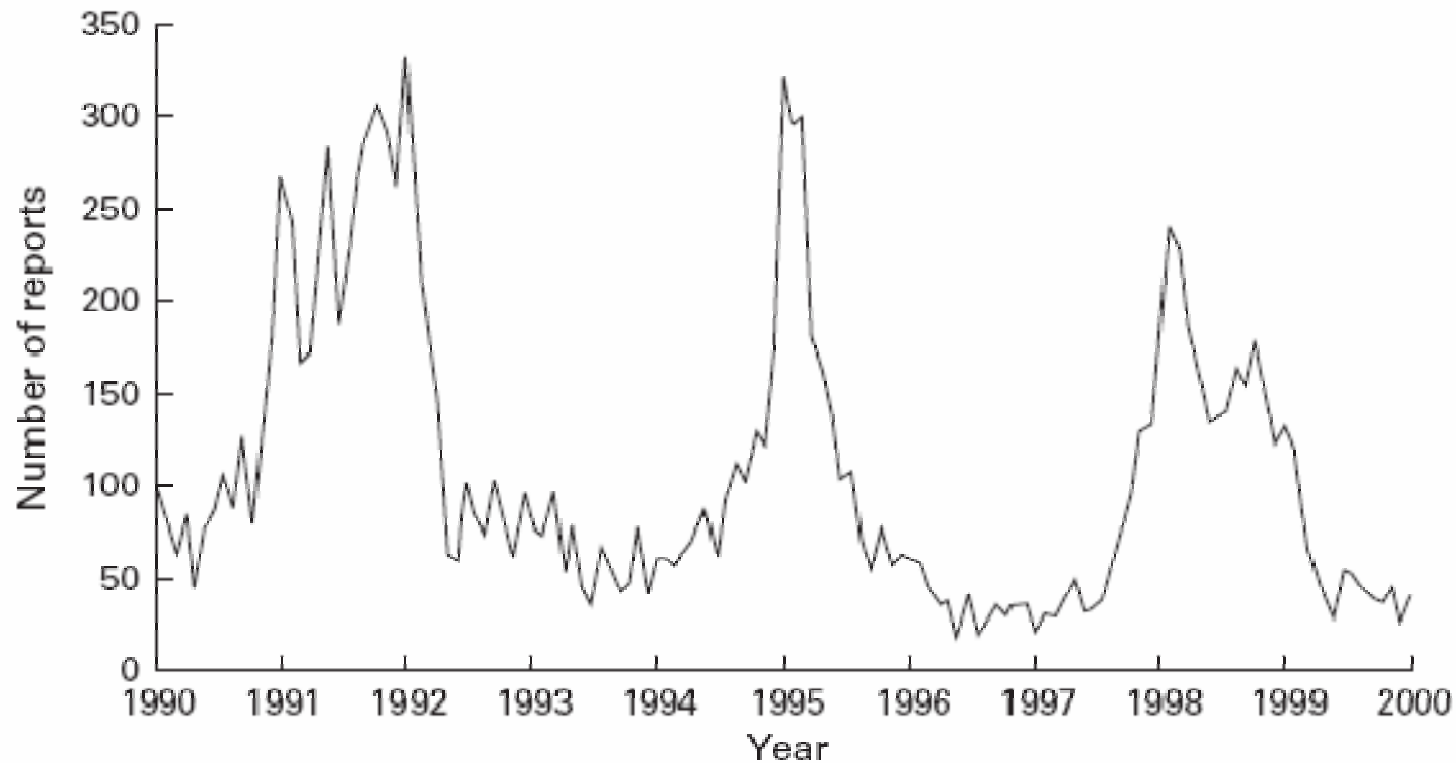
*pneumoniae* in prospective studies. M. Woodhead. Eur Respir J 2002; 20: Suppl. 36



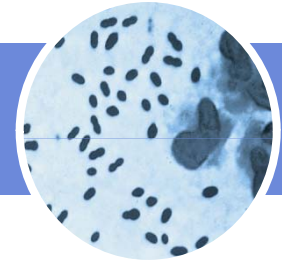
# EPIDEMIOLOGY



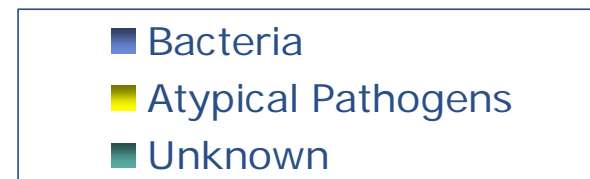
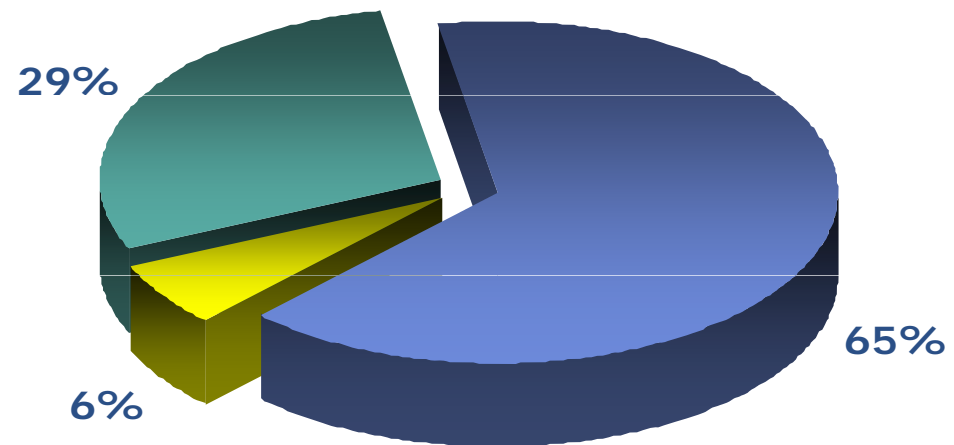
## Laboratory reports of Mycoplasma infections to the Communicable Disease Surveillance Centre, England and Wales, 1990–2000



# CAUSATIVE PATHOGENS



- ❖ 221 cases of community acquired pneumonia : (January 2002- June 2004)
- ❖ 150 men et 71 women,
- ❖ Average age : 42.7 years,
- ❖ 117 patients from the Pneumology departments and 104 from the ICU.

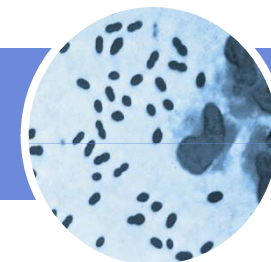


**W. Mahjoubi, E. Mhiri Zghal, L. Slim Saidi**

Microbiology Laboratory - Ariana Hospital

Congress of the Tunisian Society of Respiratory Disease December 2004

# CAUSATIVE PATHOGENS



- ❖ 221 cases of community acquired pneumonia : (January 2002- June 2004)
- ❖ 150 men et 71 women,
- ❖ Average age : 42.7 years,
- ❖ 117 patients from the Pneumology departments and 104 from the ICU.

Causative Pathogens	%
<i>Streptococcus Pneumoniae</i>	38,5
<i>Haemophilus Influenzae</i>	15
<i>Staphylococcus Aureus</i>	4,5
<i>Klebsiella Pneumoniae</i>	4,5
<i>Moraxela Catarrhalis</i>	2,5
<i>Legionela Pneumophila</i>	2
<i>Mycoplasma Pneumoniae</i>	8,5
<i>Chlamydiae Pneumoniae</i>	3,5
<i>Coxiella burnetti</i>	1

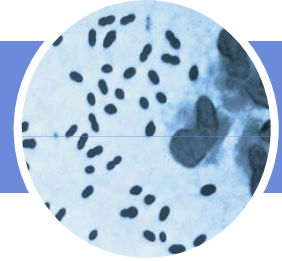
94 patients

**W. Mahjoubi, E. Mhiri Zghal, L. Slim Saidi**

Microbiology Laboratory - A. Mami Hospital - Ariana

Congress of the Tunisian Society of Respiratory Disease December 2004

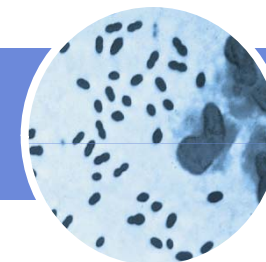
# ETIOLOGY OF CAP



- ❖ No two studies of the etiology of CAP are the same.
- ❖ Results depend on :
  - Age, comorbid diseases, severity of CAP,
  - microbiological tests,
  - Geographical areas.
- ❖ Epidemiology of outpatients CAP : few data
  - Predominance of *S. Pneumoniae*
  - Emergence of atypical pathogens,
  - H. influenzae, Staphylococcus ... host dependant

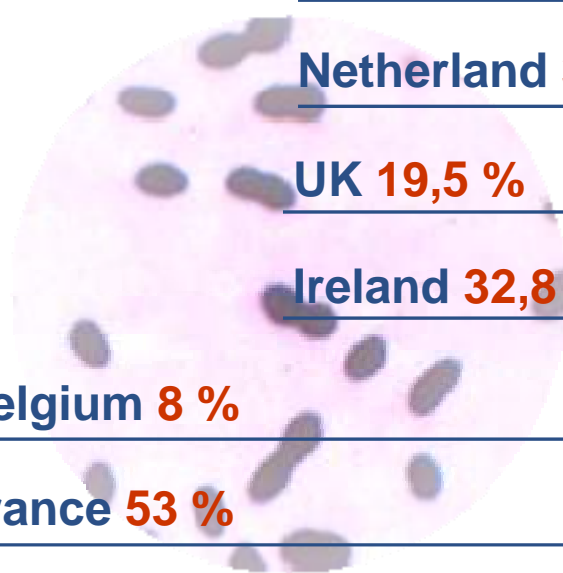
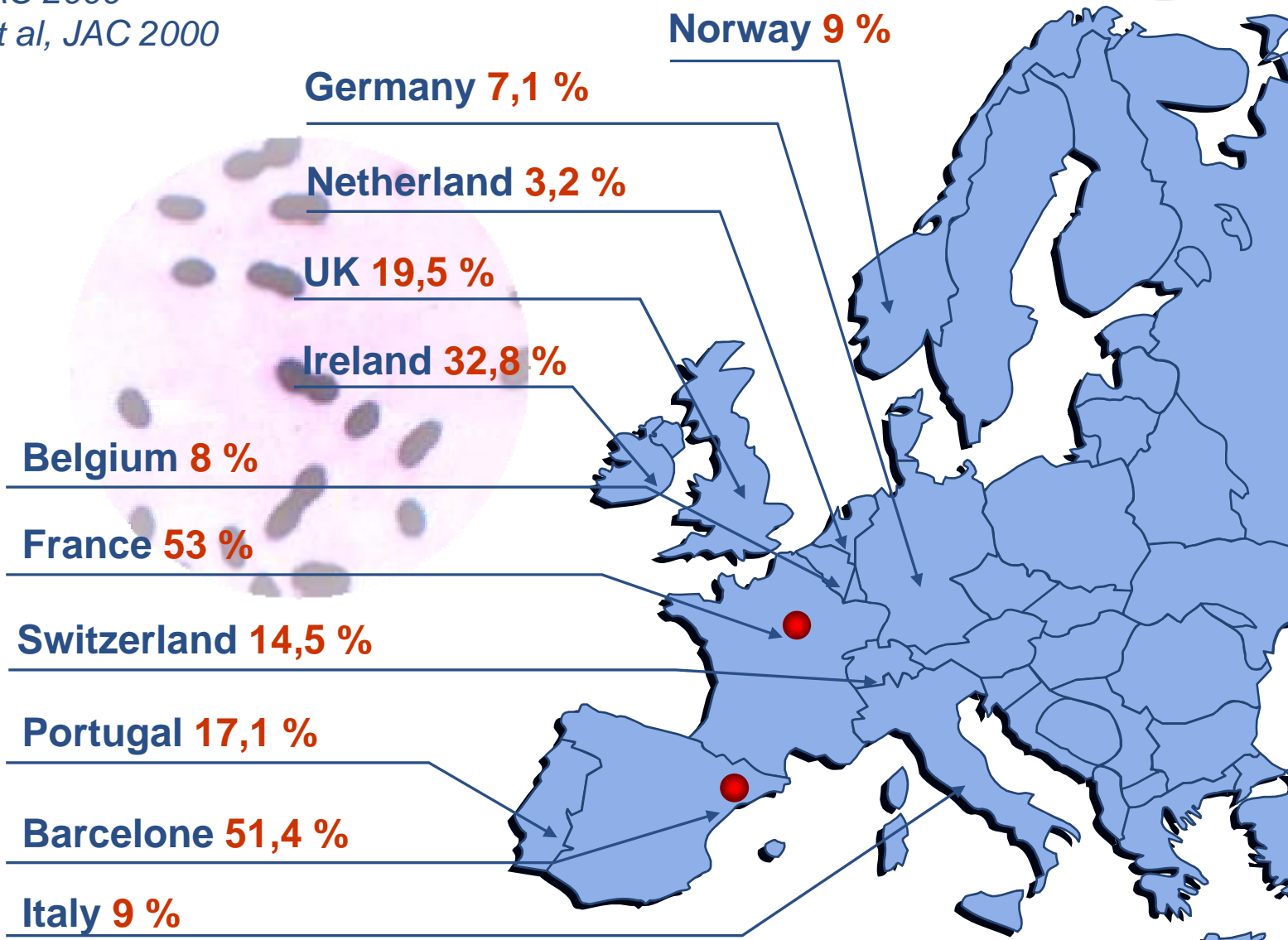


# Resistance to Penicillin Among *S. pneumoniae* isolates in Europe (1997 – 1998)

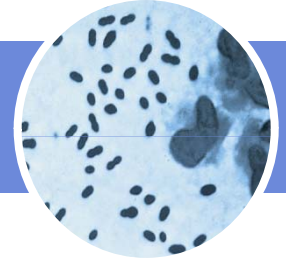


Schito et al, JAC 2000

Felmingham et al, JAC 2000



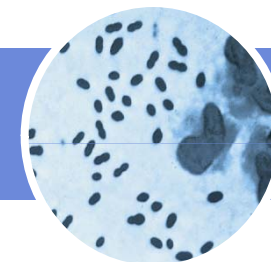
# RESISTANCE OF S. PNEUMONIAE



## Macrolides :

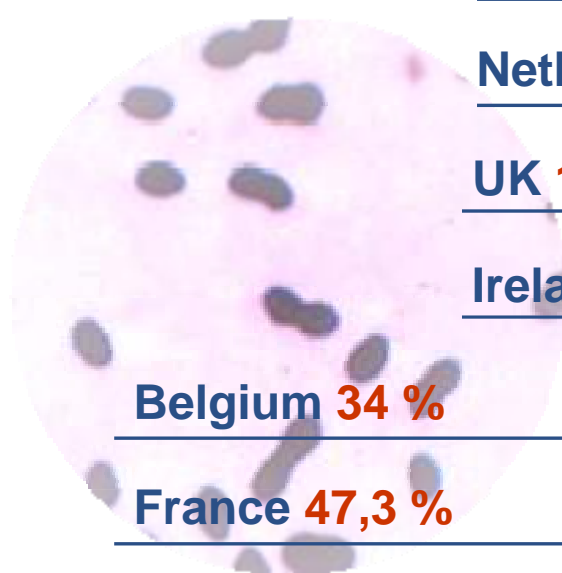
- ❖ Resistance to erythromycin is the result of genetic mutations
- ❖ 52% to 93%
- ❖ Penicillin and macrolide resistance are frequently linked (95%)

# Resistance to Macrolide Among *S. pneumoniae* isolates in Europe (1997 – 1998)



Schito et al, JAC 2000

Felmingham et al, JAC 2000



Belgium 34 %

France 47,3 %

Switzerland 18,8 %

Portugal 19,3 %

Barcelone 32,6 %

Italy 42 %

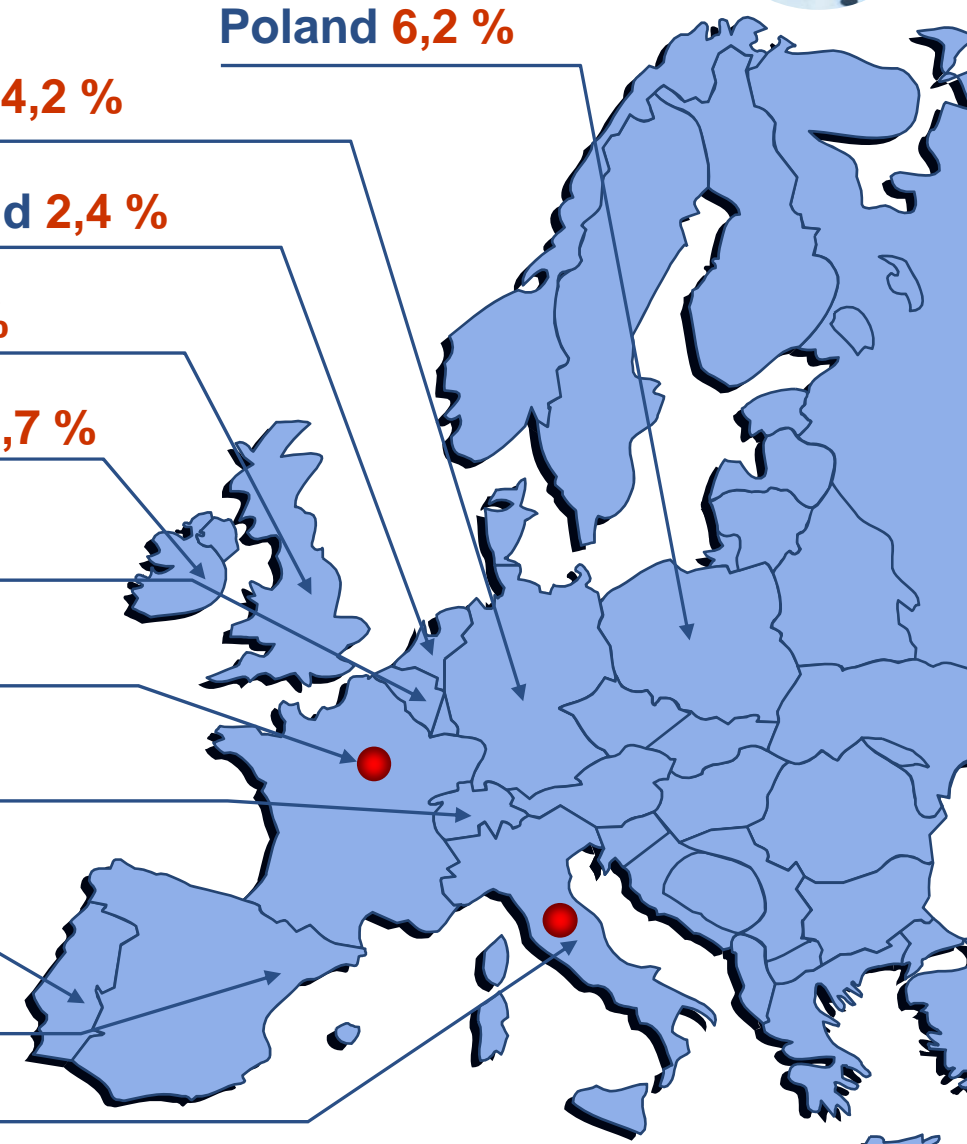
Germany 4,2 %

Netherland 2,4 %

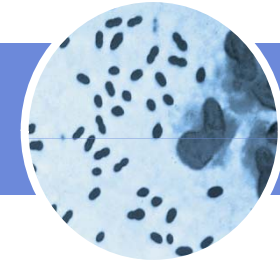
UK 18,4 %

Ireland 12,7 %

Poland 6,2 %

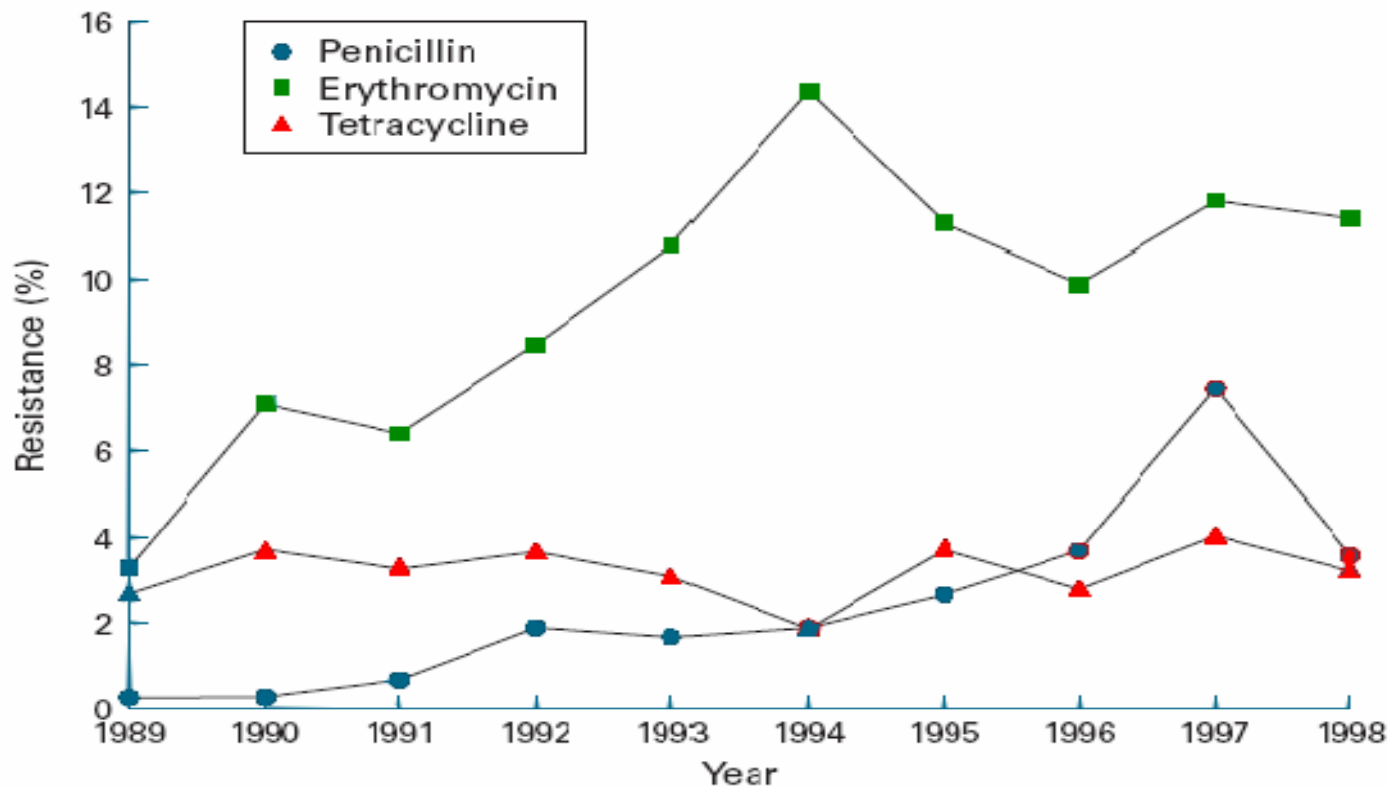


# RESISTANCE OF *S. PNEUMONIAE*

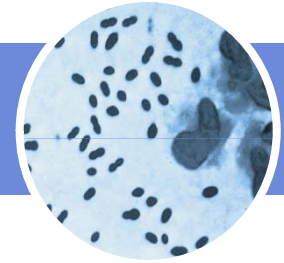


Resistance (%) to penicillin, erythromycin and tetracycline among selected *S pneumoniae* isolates (UK).

BTS Guidelines for the management of CAP in adults. Thorax 2001;56;1-64



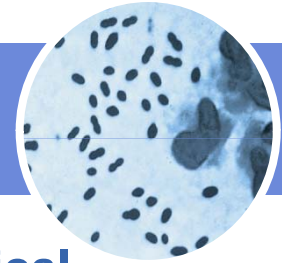
# RESISTANCE OF *S. PNEUMONIAE*



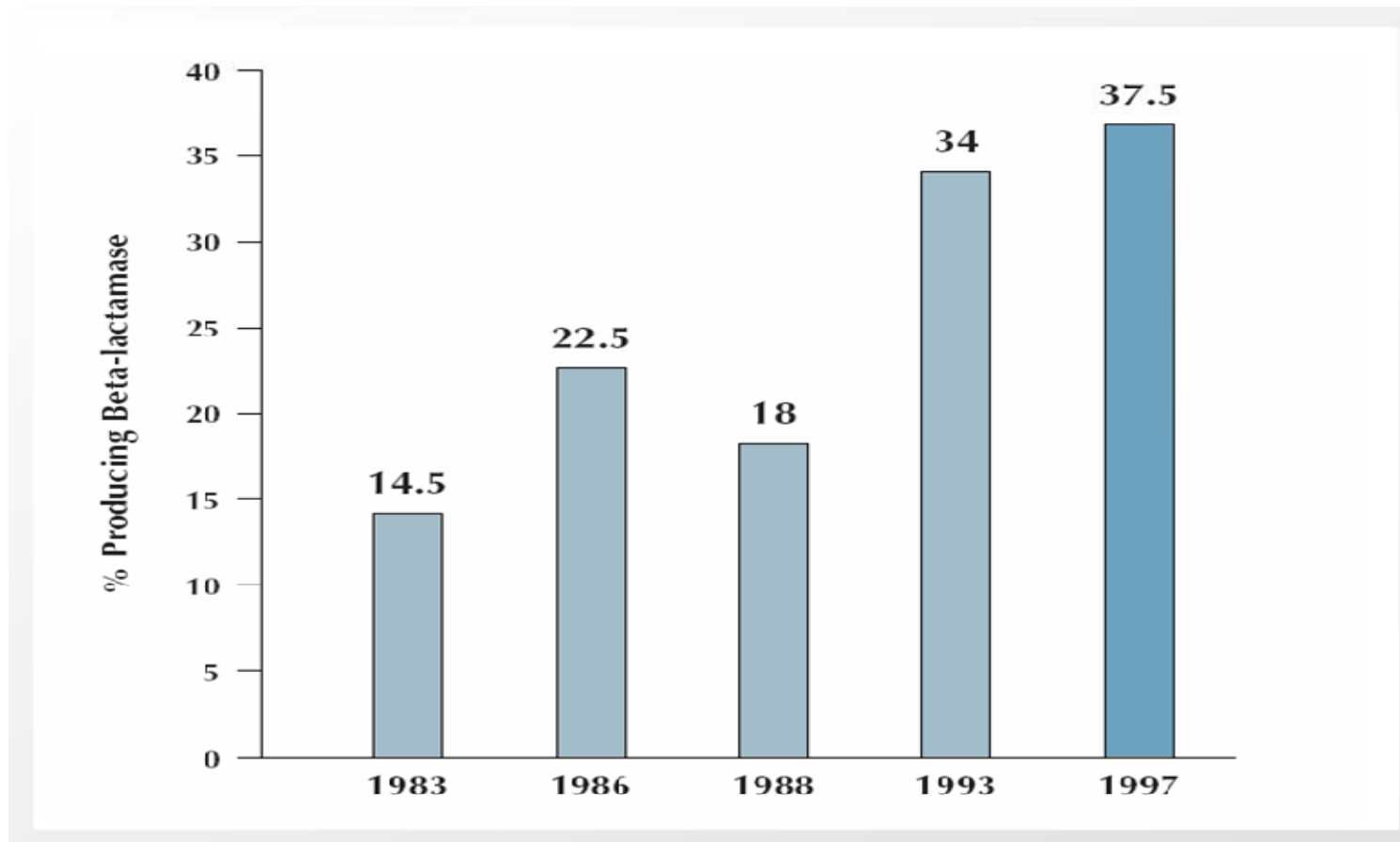
## Other antibiotics

- ❖ Reduced susceptibility of *S pneumoniae* to fluoroquinolones is beginning to be reported
- ❖ Tetracyclines are not widely used in the treatment of CAP and resistance among *S pneumoniae* is not very high.

# RESISTANCE OF H. INFLUENZAE

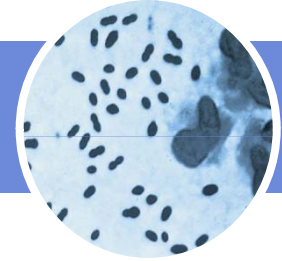


Prevalence of Beta-Lactamase–Mediated Resistance Among Clinical Isolates of *H influenzae* in USA. SENTRY Surveillance Program, 1983-1997

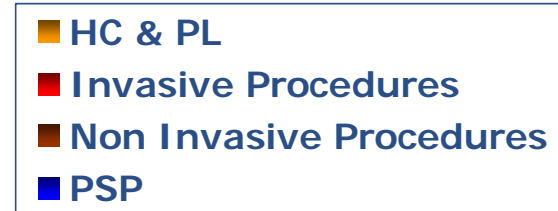
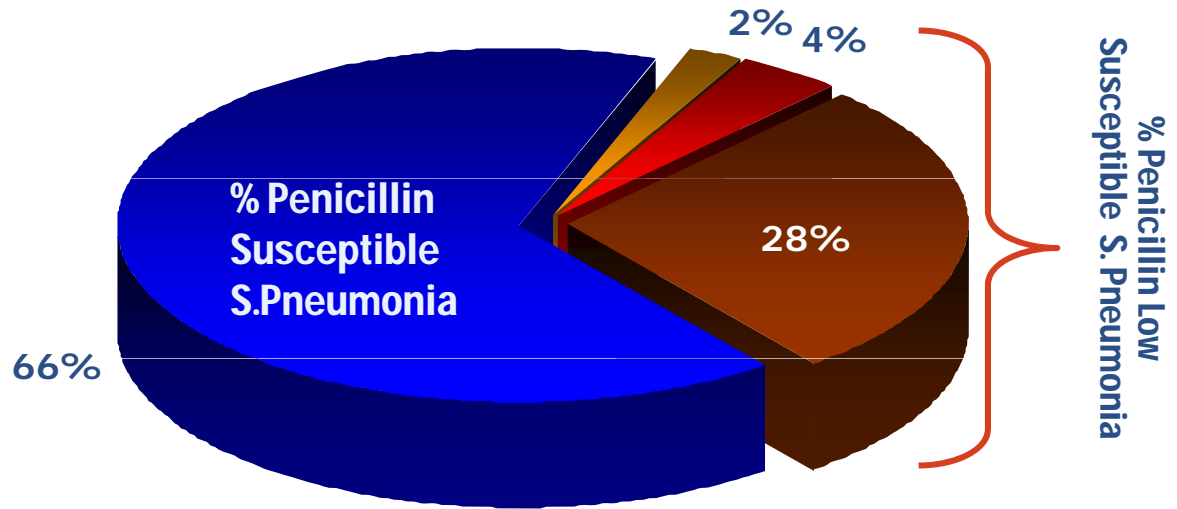


*Antimicrob Agents Chemother* 1999

# RESISTANCE TO PENICILLIN AMONG *S.PNEUMONIAE* ISOLATES IN TUNISIA

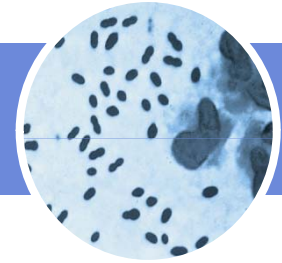


- ❖ 964 samples.
- ❖ Study period : 2000 – 2004.
- ❖ Respiratory tract infections.



**W. Mahjoubi, E. Mhiri Zghal, L. Slim Saidi**  
Microbiology Laboratory Ariana Hospital  
RICAI 2005

# ANTIBIOTIC RESISTANCE

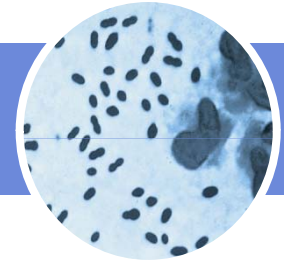


<b>Streptococcus Pneumoniae</b>	<b>%</b>
<i>Penicillin Resistance S. Pneumoniae</i>	35
<i>Amoxicillin Resistance S. Pneumoniae</i>	24,5
<i>High level</i>	3,6
<i>Intermediate level</i>	18,9
<i>Cefotaxim Resistance S. Pneumoniae</i>	14
<i>High level</i>	4
<i>Intermediate level</i>	10
<i>Erythromycin Resistance S. Pneumoniae</i>	28
<i>Cyclin Resistance S. Pneumoniae</i>	23
<i>Cotrimoxazole Resistance S. Pneumoniae</i>	28

BEN REJEB S., BEN HASSEN A, HAMMAMI A, KECHRID A.



# ANTIBIOTIC RESISTANCE



## Haemophilus Influenzae

%

*Amoxicillin Resistance H. Influenzae*

24,5

*Erythromycin Resistance H. Influenzae*

67

*Cyclin Resistance H. Influenzae*

17

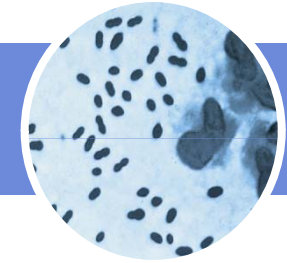
*Cefotaxim Resistance H. Influenzae*

0

*Amoxicillin/Clavulanate Resistance H. Influenzae*

0

# CAP : **ATS** GUIDELINES



## **GROUP I** : OUTPATIENTS, NO CARDIOPULMONARY DISEASE, NO MODIFYING FACTORS

---

### Organisms

---

### Therapy

---

*Streptococcus pneumoniae*

*Mycoplasma pneumoniae*

*Chlamydia pneumoniae* (alone or  
as mixed infection)

*Hemophilus influenzae*

Respiratory viruses

Miscellaneous

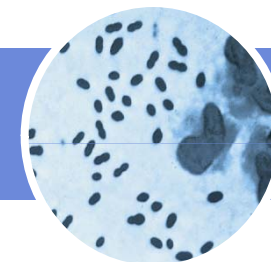
*Legionella* spp.

*Mycobacterium tuberculosis*

Endemic fungi

Advanced generation macrolide:  
azithromycin or clarithromycin<sup>‡</sup>  
or  
Doxycycline<sup>§</sup>

# CAP : **ATS** GUIDELINES



## **GROUP II : OUTPATIENTS, WITH CARDIOPULMONARY DISEASE, AND/OR OTHER MODIFYING FACTORS**

Am J Respir Crit Care Med 2001

---

### Organisms

---

### Therapy

---

*Streptococcus pneumoniae* (including DRSP)

*Mycoplasma pneumoniae*

*Chlamydia pneumoniae*

Mixed infection (bacteria plus atypical pathogen or virus)

*Hemophilus influenzae*

Enteric gram-negatives

Respiratory viruses

Miscellaneous

*Moraxella catarrhalis*, *Legionella* spp., aspiration (anaerobes), *Mycobacterium tuberculosis*, endemic fungi

---

$\beta$ -Lactam (oral cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin/clavulanate; or parenteral ceftriaxone followed by oral cefpodoxime)

plus

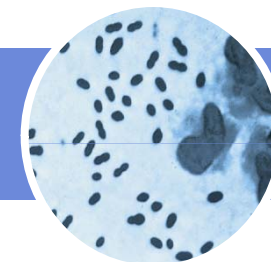
Macrolide or doxycycline

or

Antipneumococcal fluoroquinolone (used alone)

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# CAP : **ATS** GUIDELINES



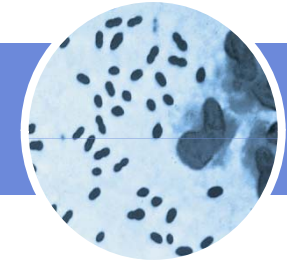
## GROUP III : OUTPATIENTS, INPATIENTS, NOT IN ICU

### a) Cardiopulmonary Disease and/or Modifying Factors

Organisms	Therapy
<i>Streptococcus pneumoniae</i> (Including DRSP) <i>Hemophilus influenzae</i> <i>Mycoplasma pneumoniae</i> <i>Chlamdia pneumoniae</i> Mixed infection (bacteria plus atypical pathogen)	Intravenous $\beta$ -lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin) <i>plus</i> Intravenous or oral macrolide or doxycycline
Enteric gram-negatives Aspiration (anaerobes)	<i>or</i> Intravenous antipneumococcal fluoroquinolone alone
Viruses <i>Legionella</i> spp. Miscellaneous <i>Mycobacterium tuberculosis</i> , endemic fungi, <i>Pneumocystis carinii</i>	

Am J Respir Crit Care Med 2001

# CAP : **ATS** GUIDELINES



## **GROUP III** : OUTPATIENTS, INPATIENTS, NOT IN ICU

**b)** No cardiopulmonary Disease and/or Modifying Factors

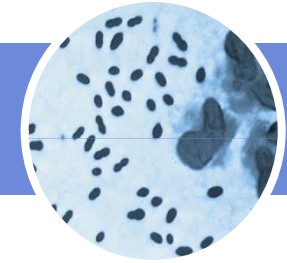
---

Organisms	Therapy <sup>‡</sup>
<i>S. pneumoniae</i>	Intravenous azithromycin alone
<i>H. influenzae</i>	If macrolide allergic
<i>M. pneumoniae</i>	or intolerant:
<i>C. pneumoniae</i>	Doxycycline
Mixed infection (bacteria plus atypical pathogen)	and a $\beta$ -lactam or
Viruses	Monotherapy with an antipneumococcal
<i>Legionella</i> spp.	fluoroquinolone
Miscellaneous	
<i>M. tuberculosis</i> , endemic fungi, <i>P. carinii</i>	

---

Am J Respir Crit Care Med 2001

# CAP : **BTS** GUIDELINES



## Preferred and alternative initial empirical treatment regimens for adults with CAP managed in the community

---

### *Preferred*

#### **Home treated, not severe**

- Amoxicillin 500 mg-1.0 g tds po

---

### *Alternative\**

- Erythromycin 500 mg qds po *or* clarithromycin 500 mg bd† po

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bd = twice daily; tds = 3 times/day; qds = 4 times/day; po = oral.

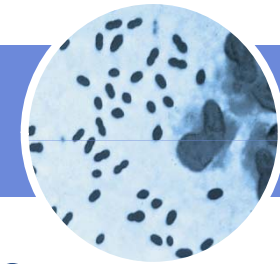
\*An alternative regimen is provided for those intolerant of or hypersensitive to the preferred regimen.

†Clarithromycin may be substituted for those with gastrointestinal intolerance to oral erythromycin and also has the benefit of twice daily dosage.

BTS Guidelines for the Management of Community Acquired Pneumonia in Adults

Thorax 2001;56;1-64

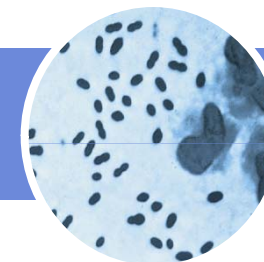
# CAP : **BTS** GUIDELINES



## Preferred and alternative initial empirical treatment regimens for adults with CAP seen and managed in hospital. Thorax 2001;56;1-64

<i>Preferred</i>	<i>Alternative*</i>
<b>Hospital treated, not severe</b> (admitted for non-clinical reasons or previously untreated in the community) <ul style="list-style-type: none"><li>● Amoxicillin 500 mg–1.0 g tds po</li></ul>	<ul style="list-style-type: none"><li>● Erythromycin 500 mg qds po <i>or</i> clarithromycin 500 mg bd† po</li></ul>
<b>Hospital treated, not severe</b> Oral: <ul style="list-style-type: none"><li>● Amoxicillin 500 mg–1.0 g tds po <i>plus</i> erythromycin 500 mg qds po <i>or</i> clarithromycin 500 mg bd po</li></ul> If intravenous treatment needed: <ul style="list-style-type: none"><li>● Ampicillin 500 mg qds iv <i>or</i> benzylpenicillin 1.2 g qds iv <i>plus</i> erythromycin 500 mg qds iv <i>or</i> clarithromycin 500 mg bd iv</li></ul>	<ul style="list-style-type: none"><li>● Fluoroquinolone with some enhanced pneumococcal activity, e.g. levofloxacin 500 mg od po‡ (the only such licensed agent in the UK at the time of writing)</li><li>● Levofloxacin 500 mg od iv‡</li></ul>
<b>Hospital treated, severe</b> <ul style="list-style-type: none"><li>● Co-amoxiclav 1.2 g tds <i>or</i> cefuroxime 1.5 g tds <i>or</i> cefotaxime 1 g tds <i>or</i> ceftriaxone 2 g od (all iv) <i>plus</i> erythromycin 500 mg qds iv <i>or</i> clarithromycin 500 mg bd iv (with or without rifampicin 600 mg od <i>or</i> bd iv§)</li></ul>	<ul style="list-style-type: none"><li>● Fluoroquinolone with some enhanced pneumococcal activity, e.g. levofloxacin 500 mg bd iv, po‡ <i>plus</i> benzylpenicillin 1.2 g qds iv</li></ul>

# CAP : FRENCH GUIDELINES



Outpatient with non severe CAP

Suspected pneumococcal infection

Oral Amoxicillin

If failure

- Oral Macrolide
- Or Telithromycin
- Or Pristinamycin
- Or anti-pneumococcal Fluoroquinolone

If failure

Doubt between : *S. pneumoniae* & atypical pathogens

- Oral Amoxicillin
- Or Telithromycin
- Or Pristinamycin

If failure

**HOSPITALIZATION**

- Severe pneumoniae,
- or complications,
- or failure of treatment change

Suspected infection with atypical pathogens

Oral Macrolide

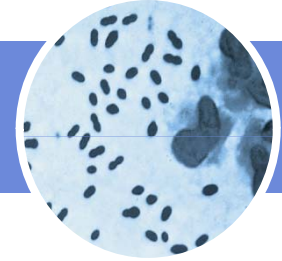
If failure

- Oral Amoxicillin
- Or Telithromycin
- Or Pristinamycin
- Or anti-pneumococcal Fluoroquinolone

AFSSAPS Oct, 2005



# CAP : **FRENCH** GUIDELINES



Adult patient with risk factors of mortality



**Third generation cephalosporin IV/IM**

Or

**Amoxicillin/Clavulanate**

Or

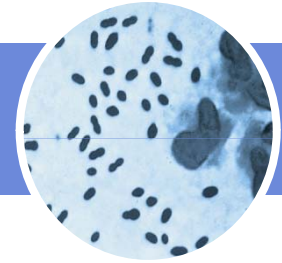
**Antipneumococcal Fluoroquinolone**



## **HOSPITALIZATION**

- Severe pneumoniae,
- or complications,
- or failure of treatment modification

# CAP : **TUNISIAN** PROPOSED GUIDELINES



Adult patient without risk factors  
Non severe CAP

Oral Amoxicillin 3g/24h  
Or  
Macrolide if suspected atypic pneumonia

No improvement within 72 h

## **Modify antibiotherapy**

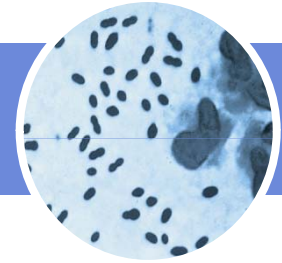
- Associate or substitute Amoxicillin/Macrolide
- Or prescribe an antipneumococcal FQ
- Pristinamycin? Telithromycin ?

**Hospitalization**



**Complication or Severe CAP**

# CAP : **TUNISIAN** PROPOSED GUIDELINES



Adult patient with Comorbidity  
Non severe CAP

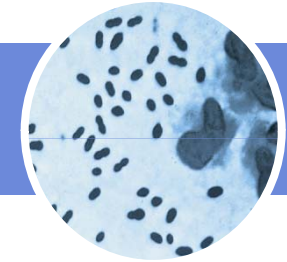
Oral Amoxicillin/Clavulanate 3g/24h Or  
Antipneumococcal Fluoroquinolone if  
suspected atypic pneumonia

No improvement within 48 h

## **HOSPITALIZATION**

- Severe pneumoniae,
- or complications,
- or failure of antibiotherapy

# CAP : **BTS** GUIDELINES



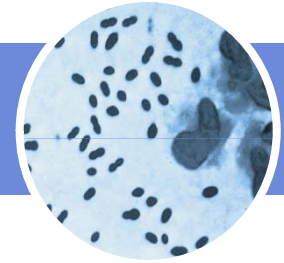
## Duration of antibiotic management by place of care, severity, and microbiological data

<i>Place/severity or pathogen</i>	<i>Duration of treatment (days)</i>
Home treated, not severe (microbiologically undefined)	7
Hospital treated, not severe (microbiologically undefined)	7
Hospital treated, severe (microbiologically undefined)	10
Legionella infection	14–21
“Atypical” pathogen	14
Pneumococcal infection (uncomplicated)	7
Staphylococcal infection	14–21
Gram negative enteric bacilli	14–21

BTS Guidelines for the Management of Community Acquired Pneumonia in Adults

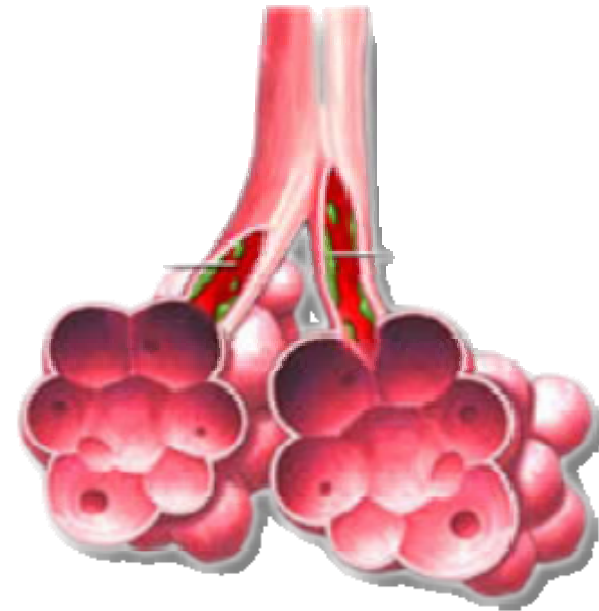
Thorax 2001; 56; 1-64

# ACUTE BRONCHITIS



## Causative pathogens :

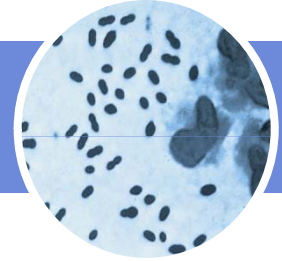
- ❖ Virus 95%
- ❖ Other pathogens :
  - *Chlamydia pneumoniae*
  - *Mycoplasma pneumoniae*
  - *Bordetella pertussis*



## Antibiotics

- ❖ Not effective,
- ❖ Not recommended.

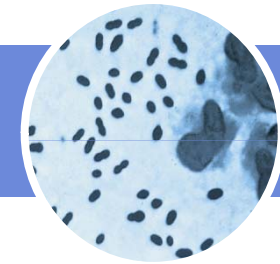
# CAUSATIVE PATHOGENS IN AECB



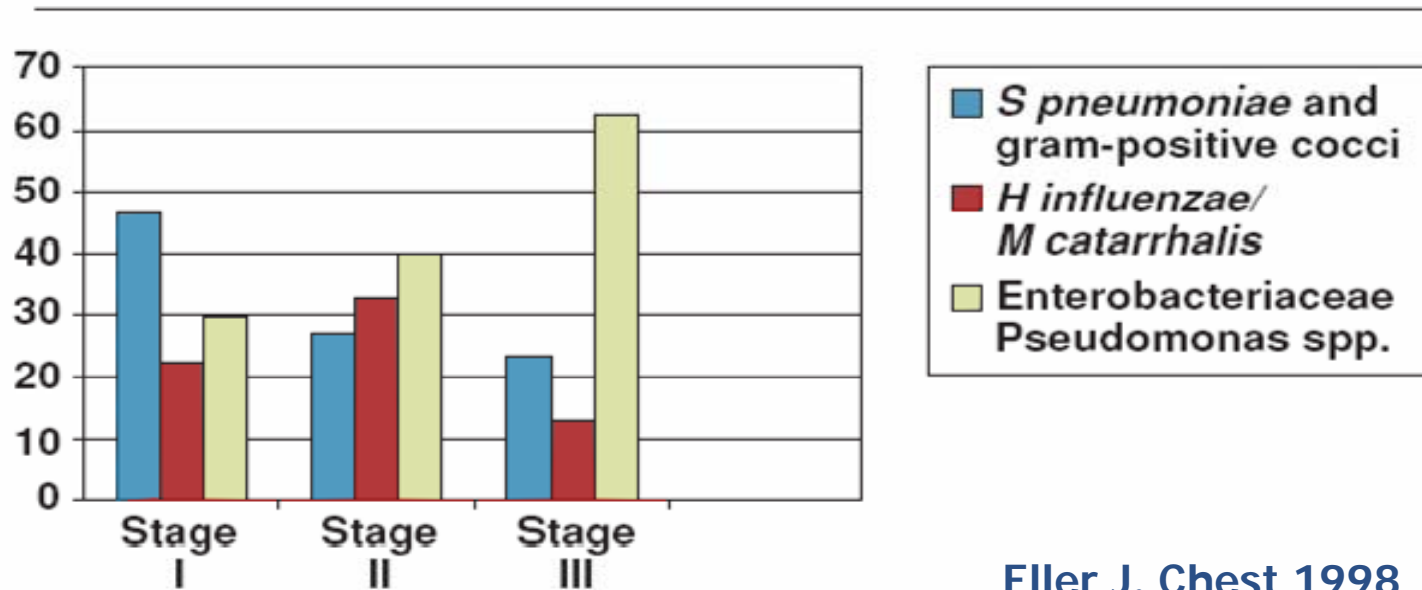
- ❖ *Haemophilus influenzae*,
- ❖ *Streptococcus pneumoniae*,
- ❖ Rarely :
  - *Branhamella catarrhalis*
  - *Mycoplasma pneumoniae*
  - *Chlamydia pneumoniae*



# RESPIRATORY TRACT INFECTIONS & COPD



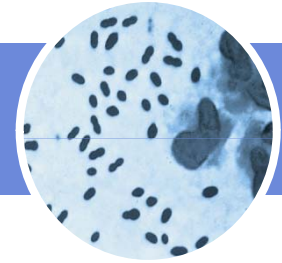
## Relation of lung function and bacterial infection in patients with COPD Flare



Eller J. Chest 1998

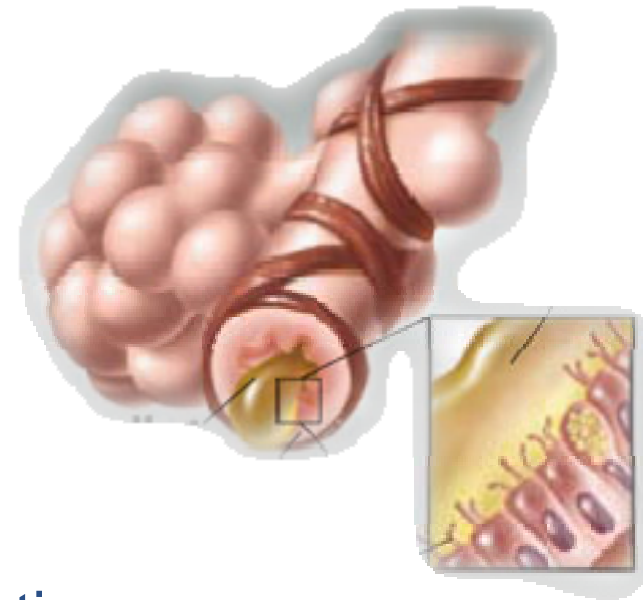
Stage I = Forced expiratory volume in 1 second (FEV-1), greater than 50% predicted;  
Stage II = FEV-1, between 35% and 50% predicted; Stage III = FEV-1, less than 35% predicted; COPD: chronic obstructive pulmonary diseases.

# ANTIBIOTICS IN AECB



## ❖ COPD Stage (0) :

- No antibiotics
- If no improvement within 5 days : amoxicillin, macrolides or doxycycline



## ❖ COPD Stage (I, II, III) :

- Require systematically antibiotics.
- Spectrum coverage is enlarged with COPD severity : Oral cephalosporin, or Amoxicillin/Clavulanate, or Oral anti-pneumococcal Fluoroquinolone



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