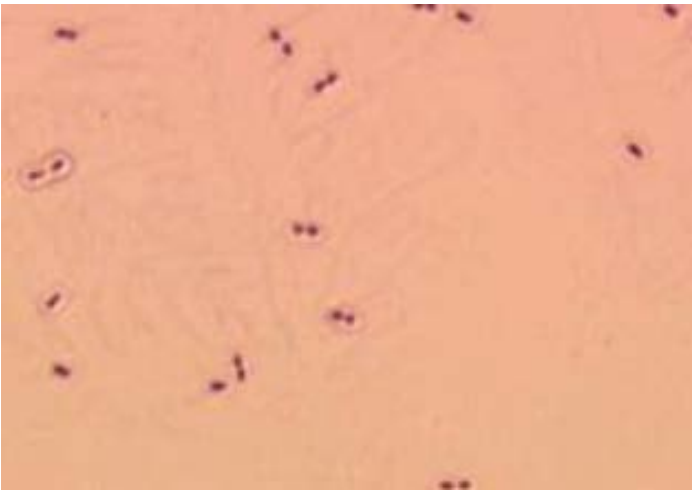
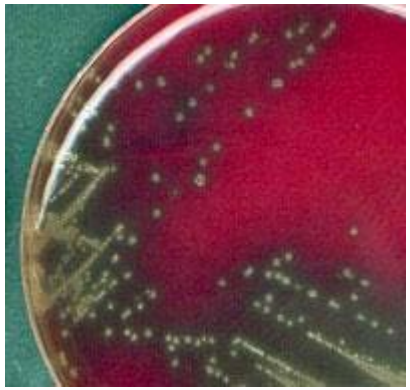
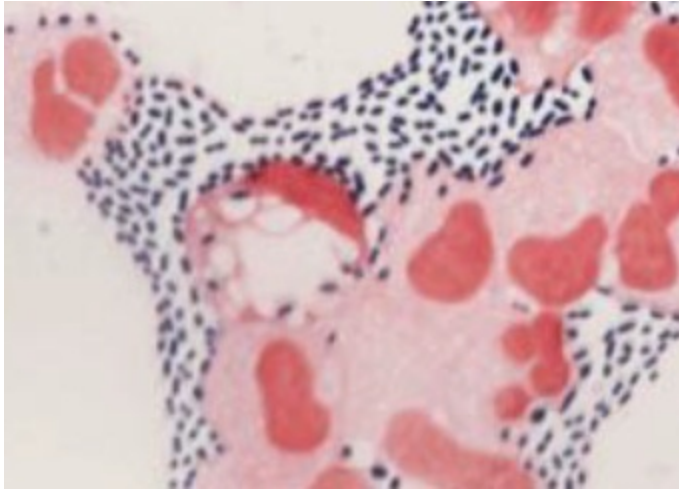






Souches invasives de *S. pneumoniae*: Résistance & Epidémiologie en Tunisie

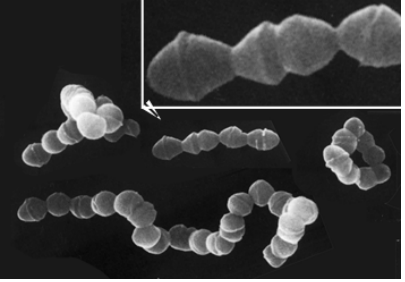
Boutiba-Ben Boubaker I

Laboratoire de Recherche ''Résistance aux Antimicrobiens'' Faculté de Médecine de Tunis – Université de Tunis ElManar

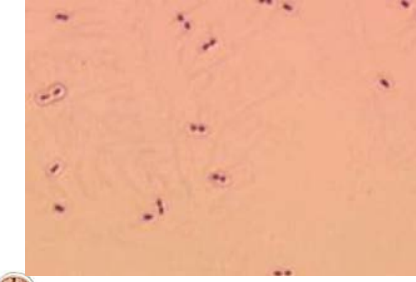
Laboratoire de Microbiologie EPS Charles Nicolle

XXIVème Congrès de la Société Tunisienne de Pathologie Infectieuse

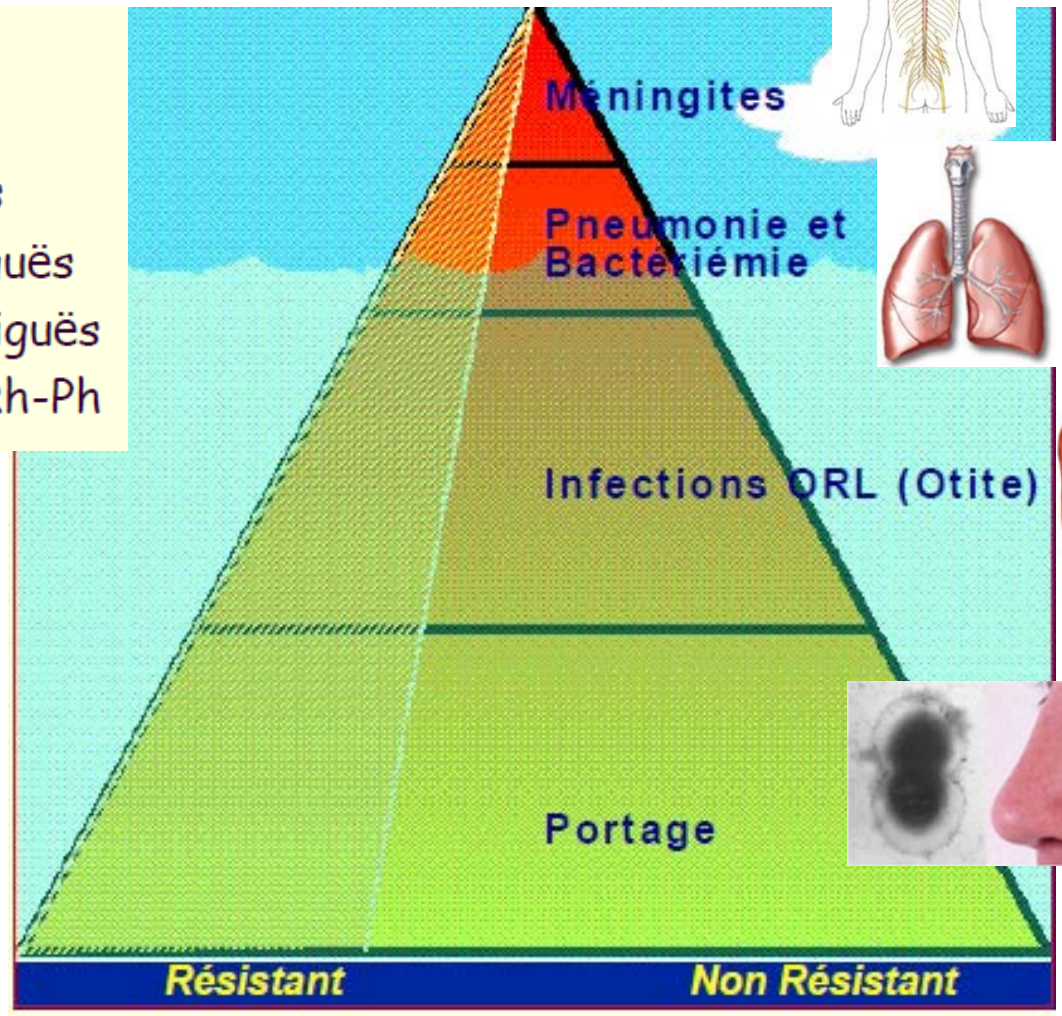
Golden Tulip El Mechtel - Tunis – 18 Avril 2014

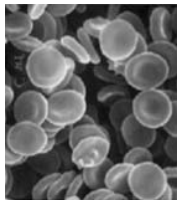


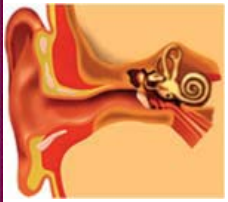
Infections à *S. pneumoniae*



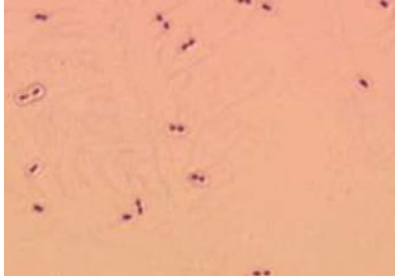
- XO Décès
- X00 Méningites
- X 000 Bactériémies
- X0 000 Pneumonies aiguës
- X00 000 Otites Moy. Aiguës
- X 000 000 de Portage Rh-Ph

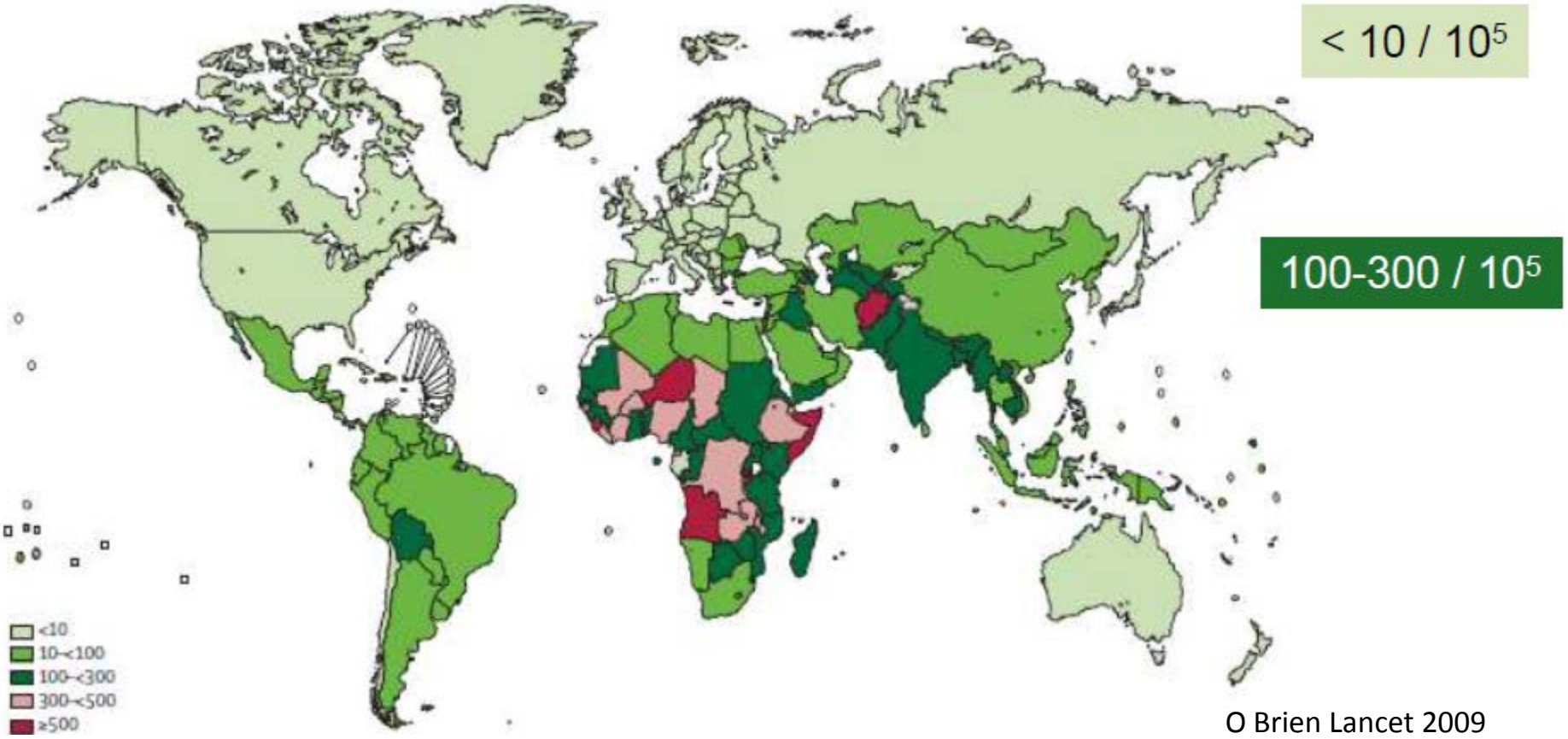






- ***S. pneumoniae*:**
  - Cause majeure de morbi-mortalité dans le monde
  - Mortalité > toute autre maladie infectieuse (VIH, TBc)
  - ≈ 1 Million de Dc (< 5ans) (CDC 2008)
    - Mortalité en Europe: 10 et 30%
    - Afrique → 60%

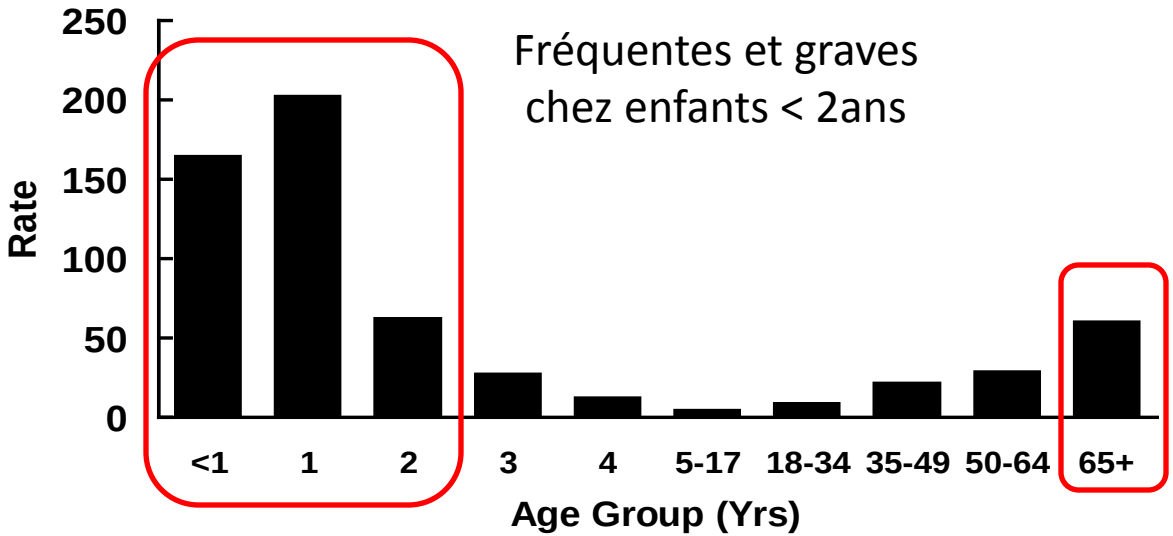




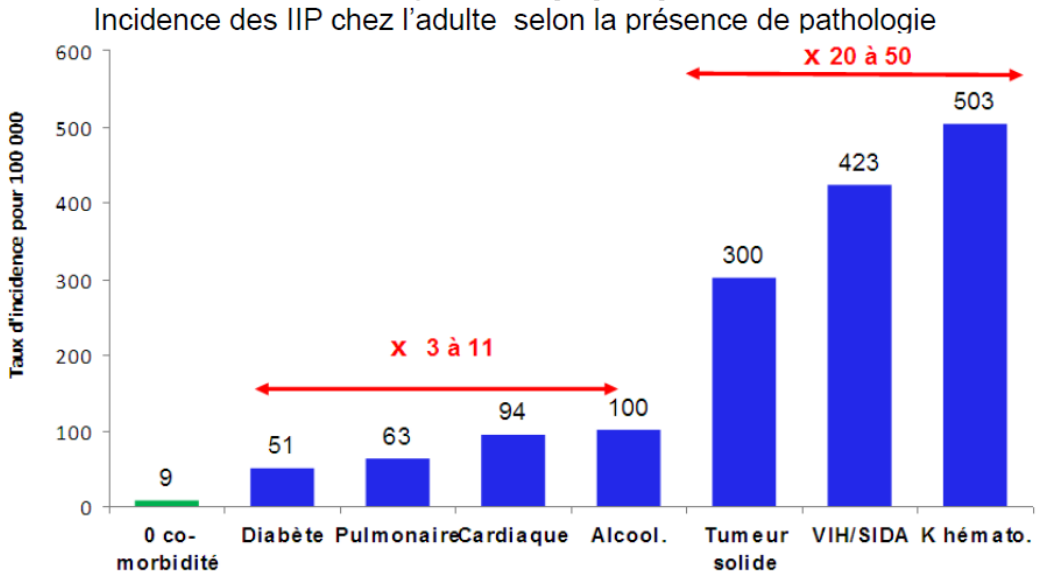
O Brien Lancet 2009

INCIDENCE: INFECTIONS INVASIVES PNEUMOCOCCIQUES (IIP)

Age

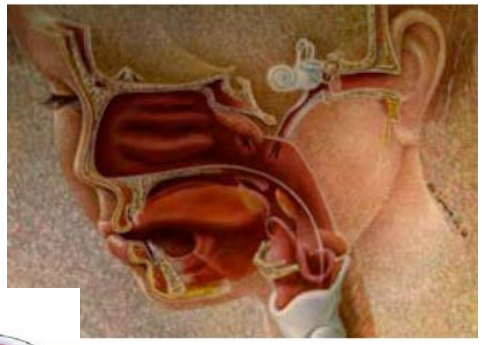


Co-morbidité



Plus rarement, épidémies dans les collectivités / crèches, prisons (Mhiri E et al. Diag Microbiol Infect Dis 2010)

Méningites à pneumocoque de sérotype 1, sensible aux ATB



- **Nasopharynx = Microbiome complexe** dans lequel nombreuses bactéries interagissent (synergie, coopération, interdépendance, redondance, stratégies d'espèce…)

***S. pneumoniae :* Rôle +++**

↳Transmission aérienne inter-humaine

↳ Adhésion à l'épithélium nasopharyngé

↳ Mise en place des mécanismes de défense mécaniques et immunologiques

↳ Stopper progression ↳ Colonisation

↳ Portage +++: Influencé par plusieurs facteurs (âge, entourage, saison, vaccination, antibiothérapie …

↳ Durée de colonisation et passage à invasivité dépend:

* Caractéristiques de l'**hôte**
* **Virulence** & **résistance** de la souche

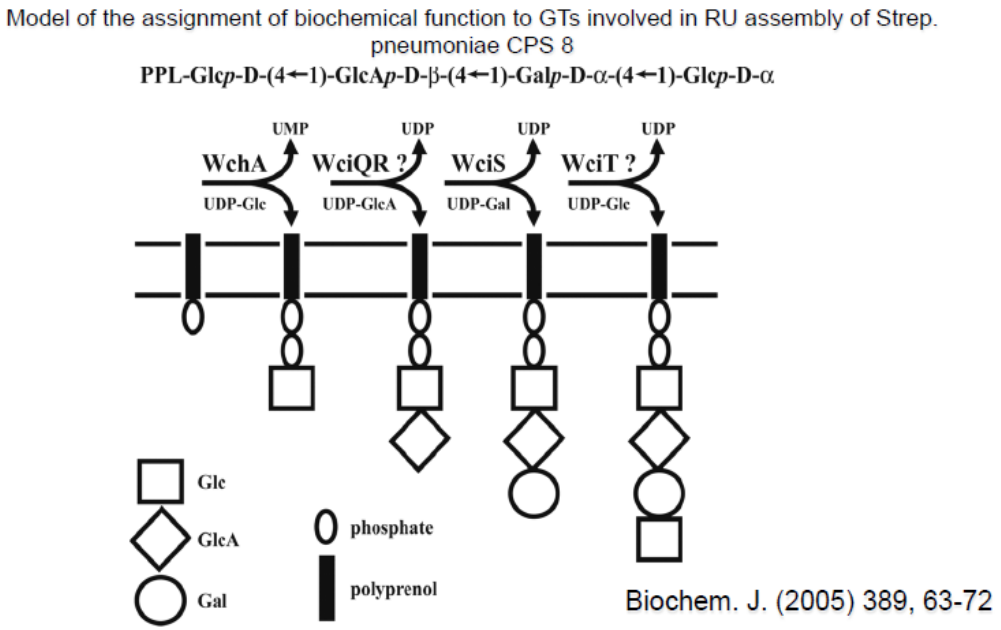
Etudes récentes ↳ Nouveau portage par certains sérotypes de *S. pneumonaie* (23F)

↳ Perturbation microbiome NP

Capsule = Virulence +++

- **> 90 Sérotypes≠ :** Composition structurale variable (2 à 8 sucres)

- **Exemples:**
  - 2 sucres⇘ sérotypes 3 et 37
  - 6 sucres ⇘ sérotypes 2 et 33F

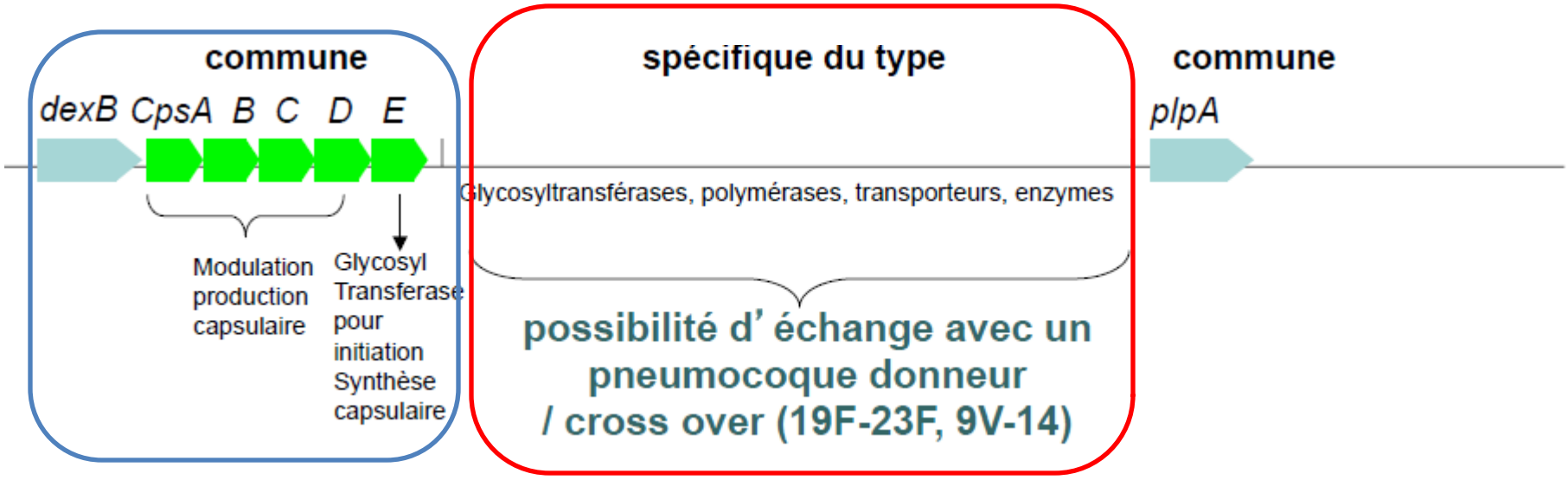


- Virulence liée à la composition de la capsule (pas quantité)

  ⇘Sérotypes invasifs / 3, 6B, 19F

Capsule : Contrôle génétique de l'expression

Organisation génomique similaire quelque soit le type capsulaire



Régulation et modulation de la synthèse

Transformation /recombinaison homologue
SWITCH CAPSULAIRE: Changement de sérotype

3 principaux phénotypes:

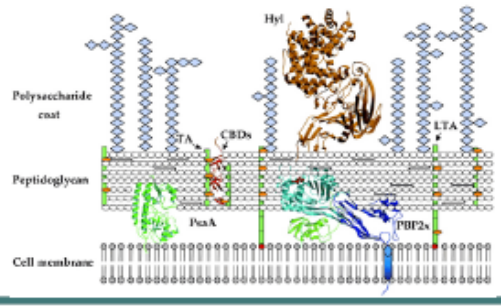
Acapsulé: colonisation +++ & virulence –
Capsulé: colonisation - & virulence +++
Intermédiaire

Souches capsulées 100.000 x plus virulentes que acapsulées

Capsule : Rôle

- Quelque soit sa diversité ↳ Même rôle
  - **Diminution de opsono-phagocytose** en limitant l'accés des récepteurs phagocytaires au complément fixé sur la membrane cellulaire de *S. pneumoniae*
  - **Echappement aux défenses immunitaires** de l'hôte
- **<u>Mais</u>**
  - Limiter l'expression des adhésines pariétales nécessaires pour la colonisation
  - Pas de rôle propre & pathogénicité de souches acapsulées bien démontrée (Martin et al 2003, Crum et al 2004, Reed et al 2005, Hanage et al 2006, Porat et al 2006)

PHYSIOPATHOLOGIE DES INFECTIONS

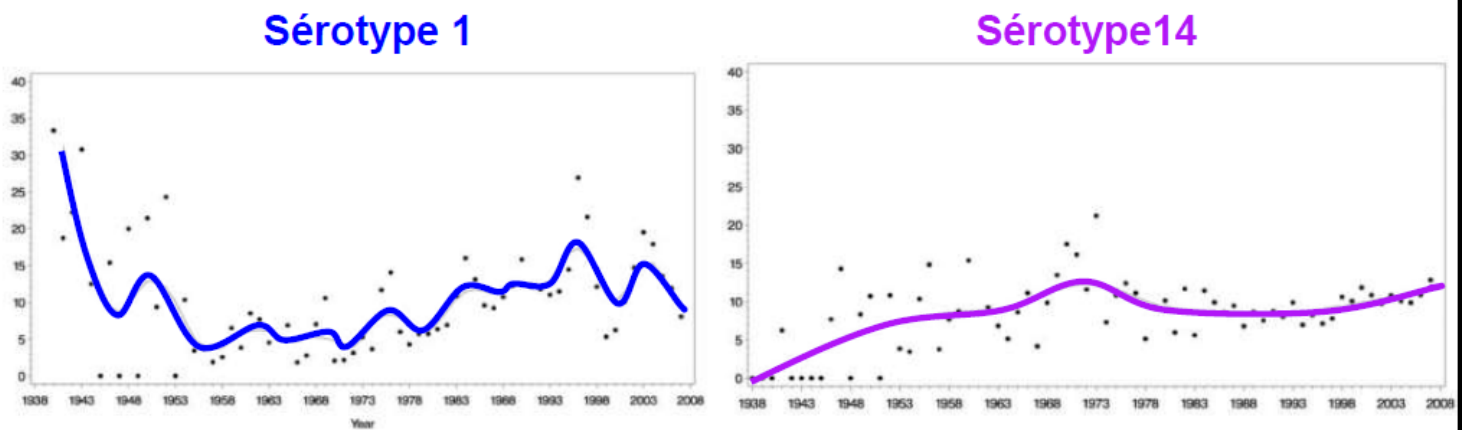


	adhésion/ colonisation	invasion	échappement aux défenses immunitaires	lésions tissulaires/ inflammation
Capsule	-	-	+++	-
Paroi cellulaire	-	-	-	+++
Psp A	-	-	+	-
Cbp A	+++	+ (BHE/méningite)	-	-
Psa A	+	-	-	-
Pneumolysine/ autolysine A	+/-	+	++	+++
Hyaluronate lyase	-	+	-	(++) (méningites)
Neuraminidase A	++	+	-	+
IgA1 protéase	+	-	+	-
Pyruvate oxydase	+	+	-	+++

Capsule: Rôle dans épidémiologie
↳Sérotypage +++

- ≈ 20 sérotypes ↳ > 70% des IIP
- Sérotypes associés aux profils de résistance & aux types moléculaires
- Distribution des sérotypes évolue dans le temps (swith capsulaire): Pression de sélection par antibiotiques + Vaccination
- Enfants: sérotypes de portage = sérotypes résistants / sérotypes invasifs
- Sérotypes épidémiques/ versus sérotypes stables

% of invasive pneumococcal disease cases according to serotypes, Denmark, 1938-2007,
Harboe et al. Trends in IPD over 7 Decades. CID 2010:50 (1 February)

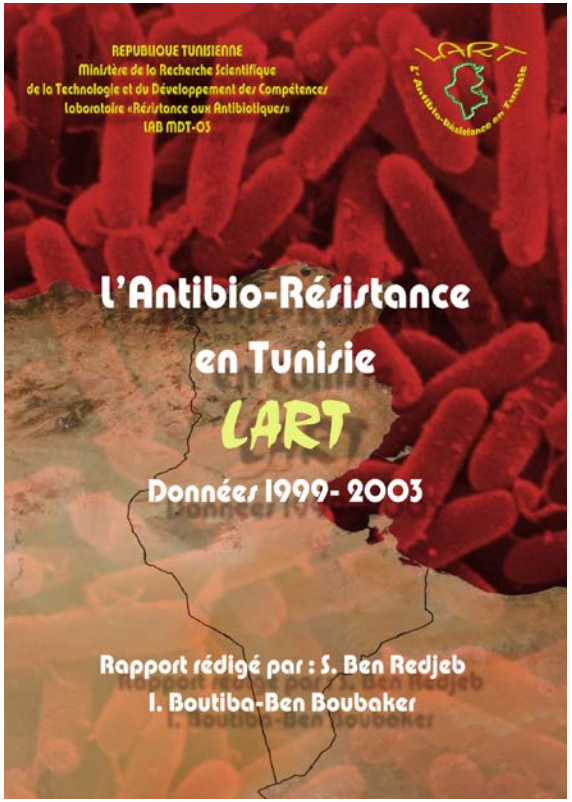


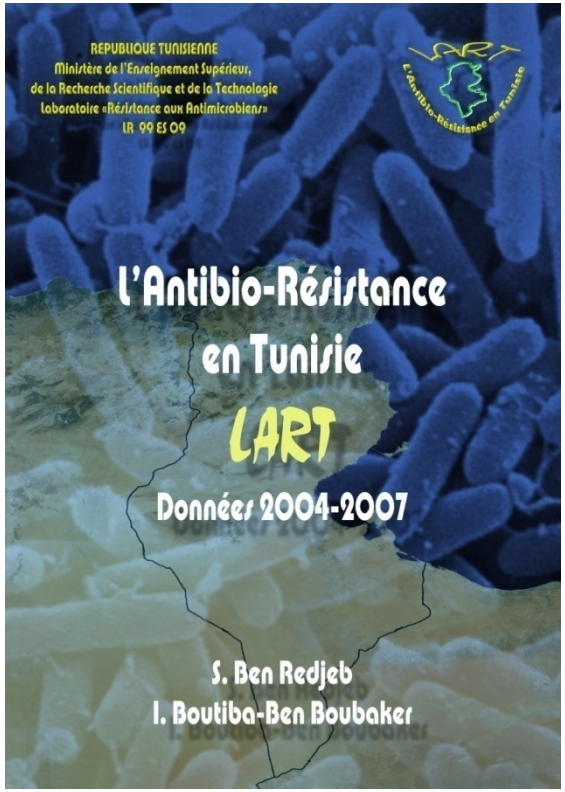
Effets des vaccins anti-pneumocciques

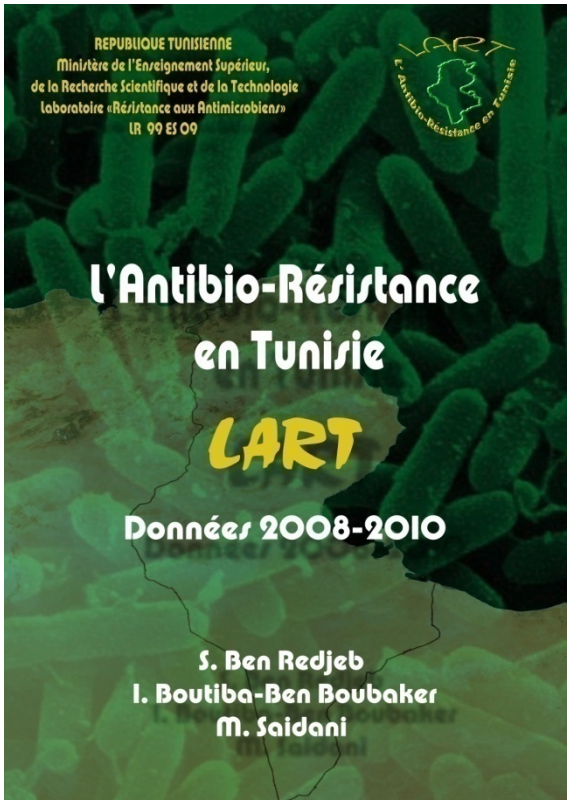
- **Effet direct:**
  - ↳Diminution de incidence IIP enfants vaccinés

- **Effet indirect à long terme**
  - ↳ Impact chez la population non vaccinée: diminution de incidence IIP
  - ↳ Impact écologique:
    - Réduction du portage des sérotypes vaccinaux
    - Réduction du portage des PSDP
    - Augmentation des souches de sérotypes non vaccinaux PSDP

Epidémiologie tunisienne







Streptococcus pneumoniae: N=1695

Données 2000-2011

Matériel & Méthodes

4 Centres Hospitalo-Universitaires totalisant 2839 lits: 2000 → 2010

- Centre Hospitalo-Universitaire de Sfax regroupant les hôpitaux Hédi Chaker et Habib Bourguiba
- Hôpital Charles Nicolle de Tunis
- Hôpital d'Enfants de Tunis
- Centre National de Greffe de Mœlle Osseuse de Tunis

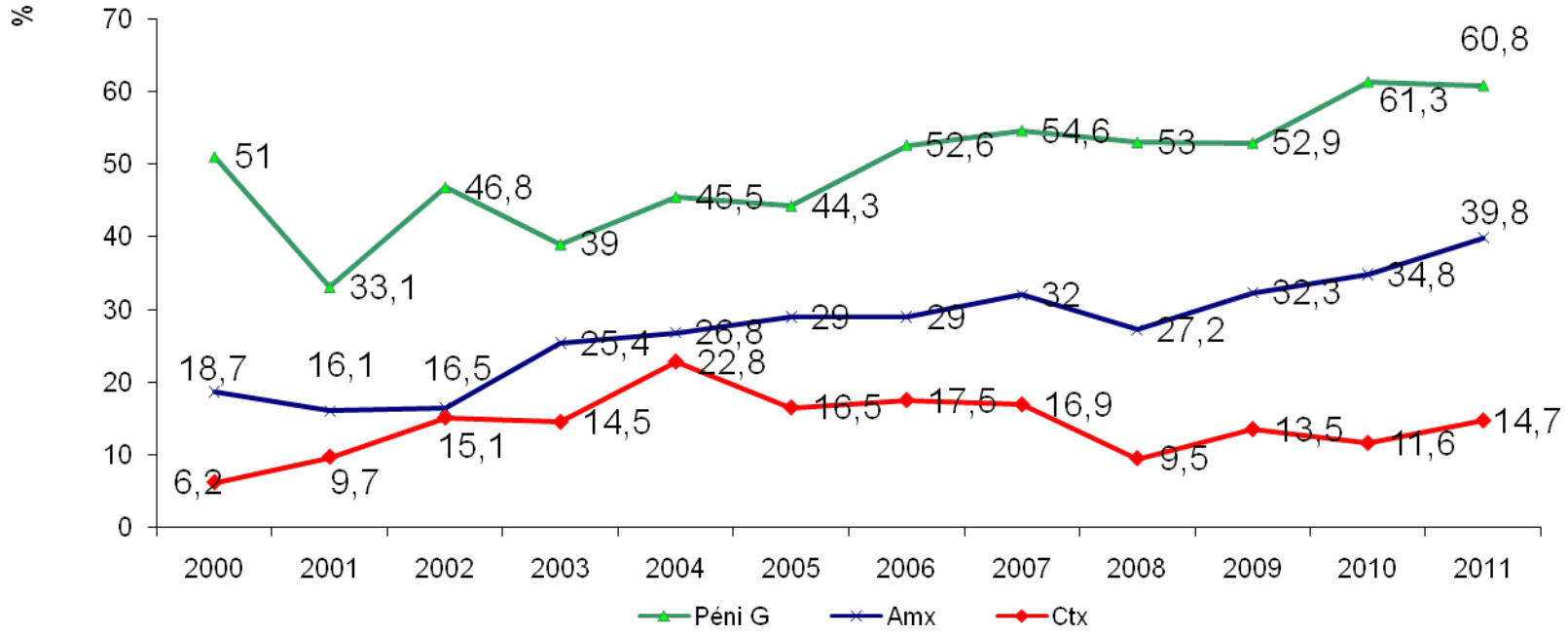
- Depuis, 2011 → élargissement du réseau à 8 centres (5656 lits)
  - Hôpital la Rabta de Tunis
  - Hôpital Militaire de Tunis
  - Institut Mohamed Kassab d'Orthopédie
  - Hôpital Fattouma Bourguiba de Monastir

- Méthodologie comparable:
  - Recueil des données
  - Contrôles de qualité (interne & externe)
  - Critères d'interprétation
  - Doublons épidémiologiques

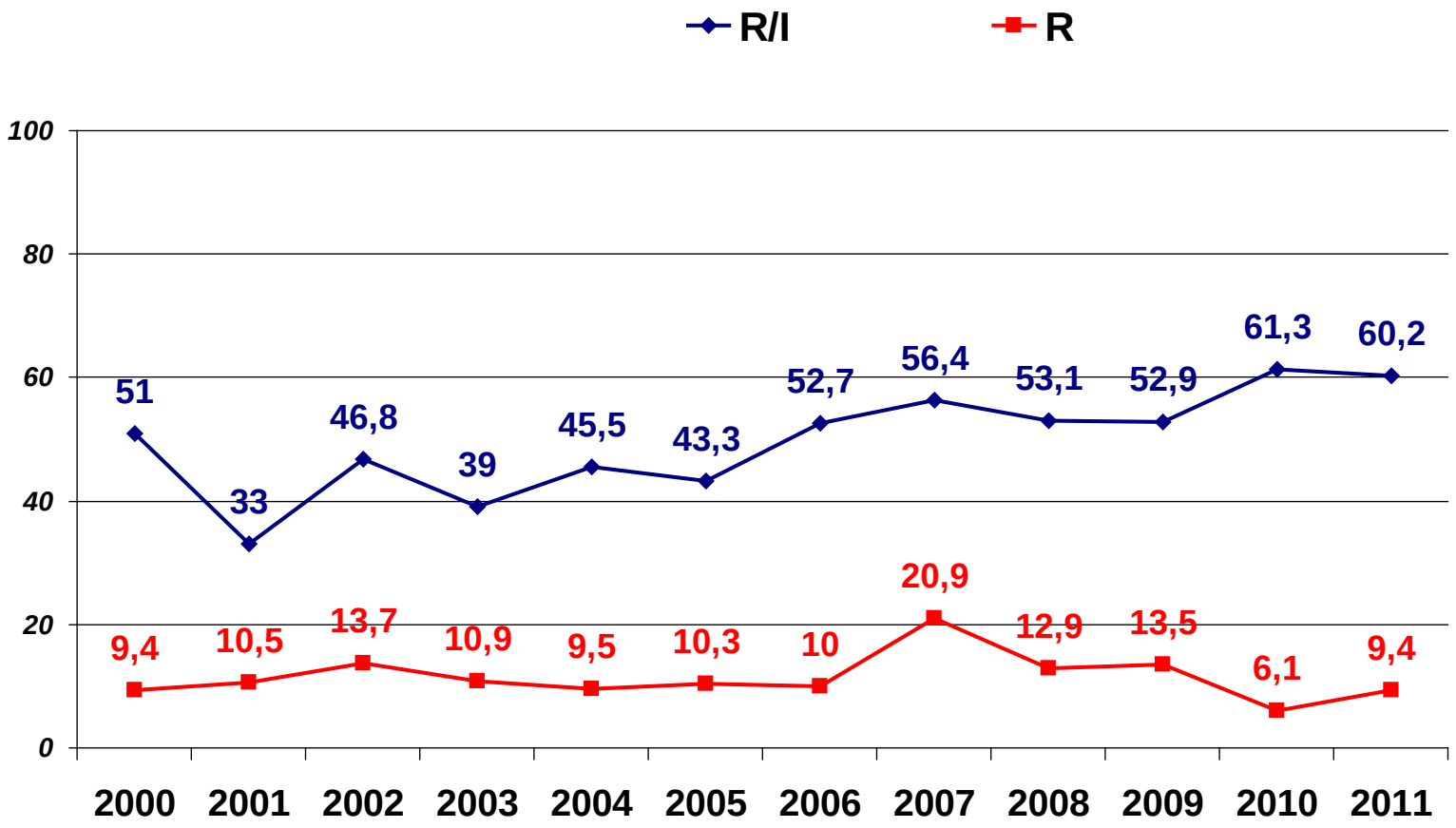
S. pneumoniae (n=1695)

	2000 - 2011 (1695)	
	I	NI
Total	647	1052
%	**38**	**62**

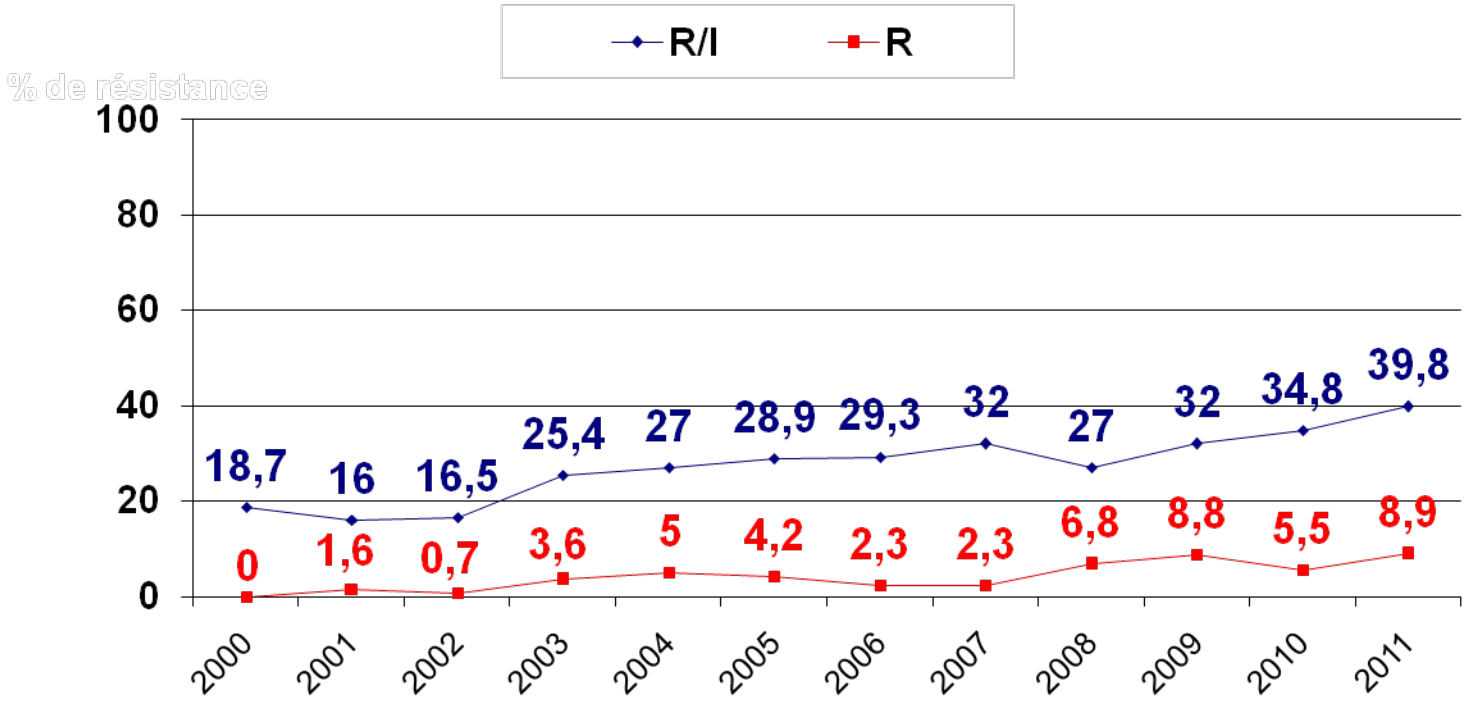
Evolution annuelle de la résistance des souches de *S. pneumoniae* aux β-lactamines



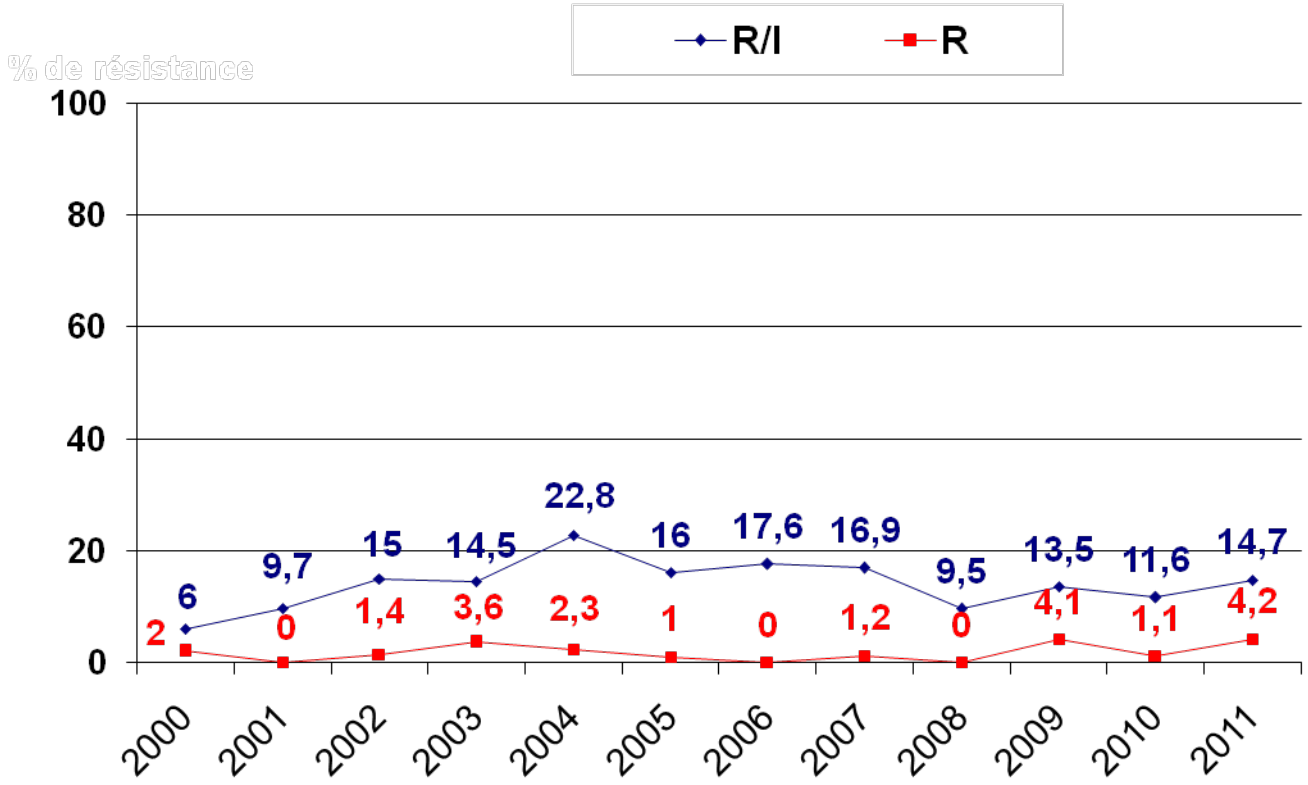
Evolution annuelle de la résistance des souches de *S. pneumoniae* à la Pénicilline G



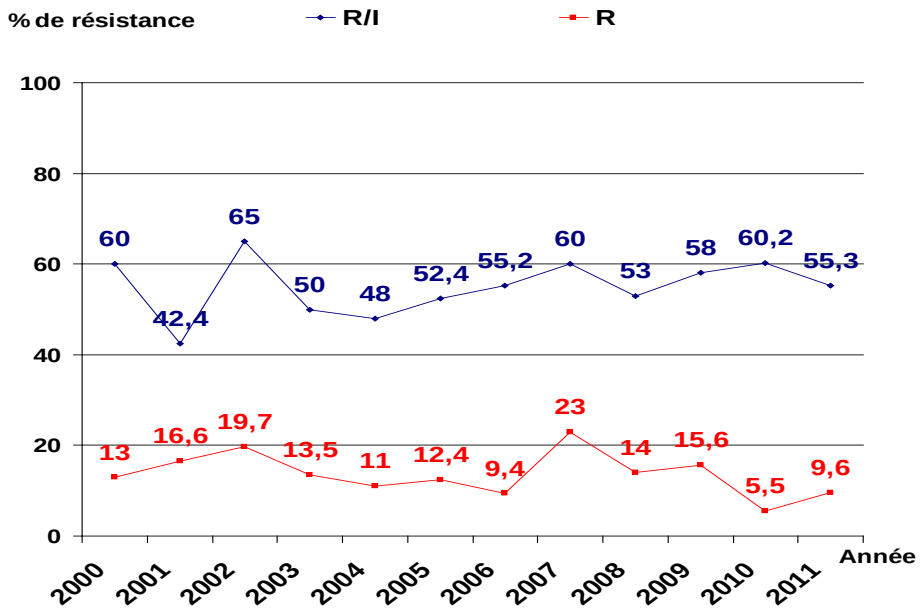
Evolution annuelle de la résistance des souches de *S. pneumoniae* à l'amoxicilline



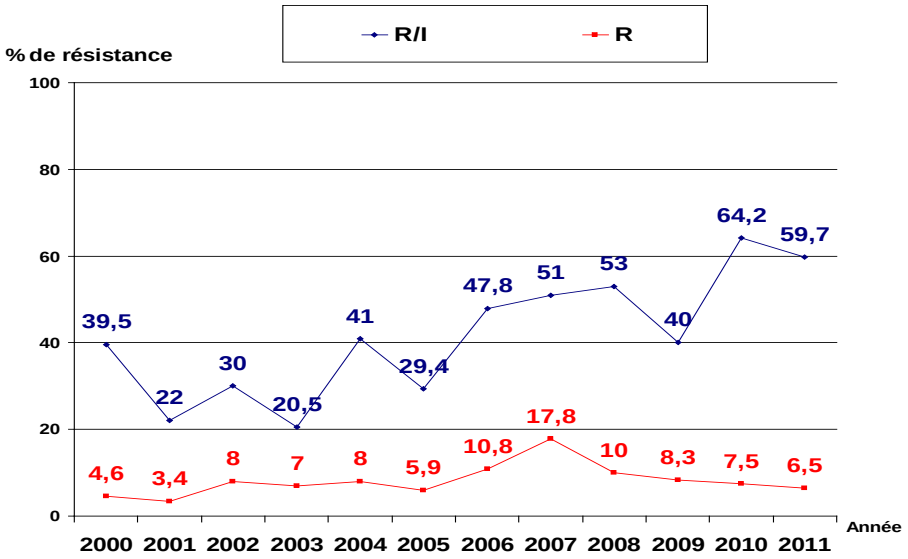
Evolution annuelle de la résistance des souches de *S. pneumoniae* au céfotaxime



Evolution annuelle de la résistance à la pénicilline G

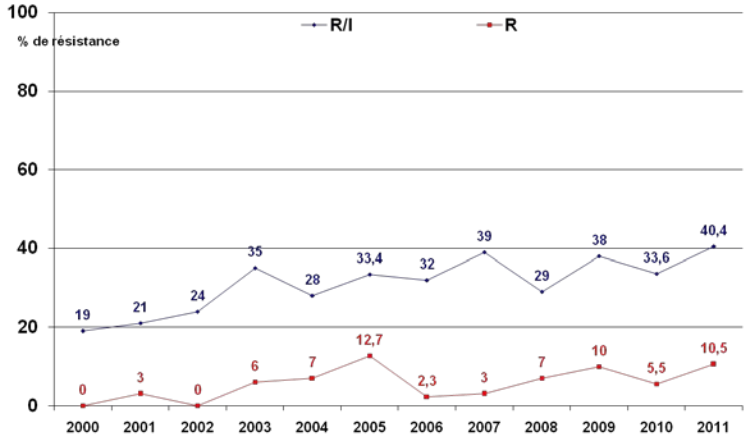


Souches non invasives

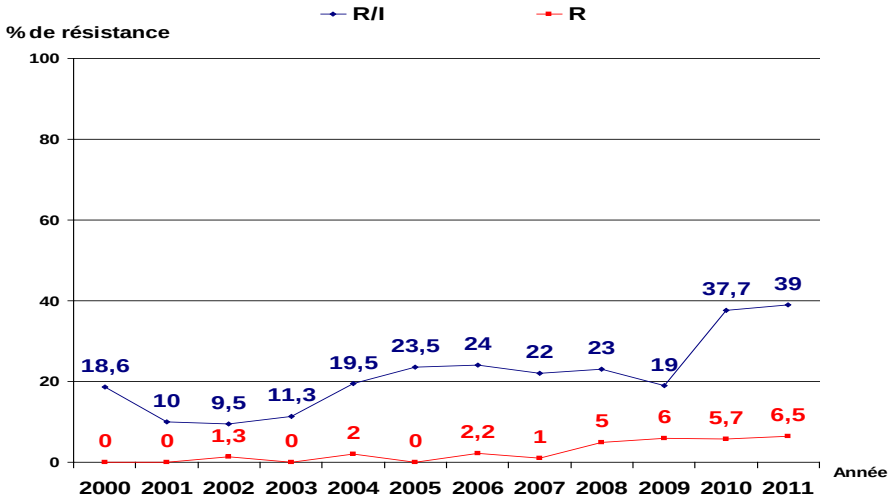


Souches invasives

Evolution annuelle de la résistance à l'amoxicilline

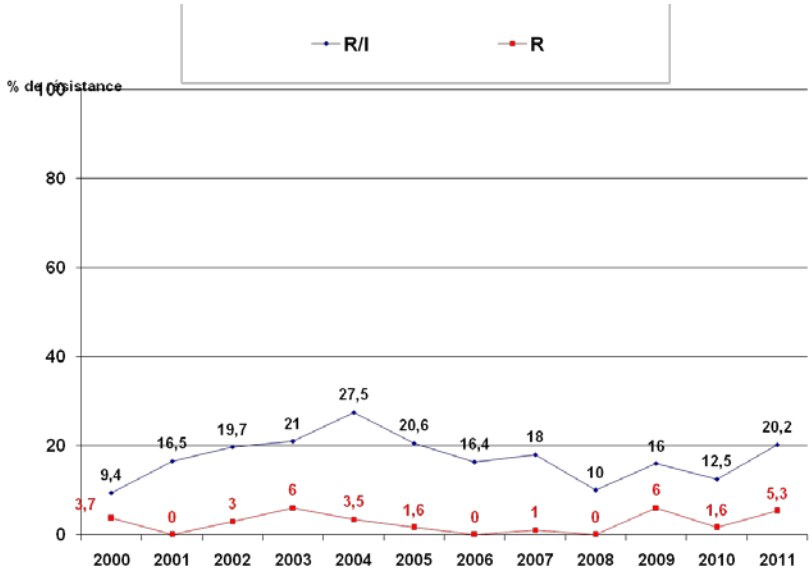


Souches non invasives

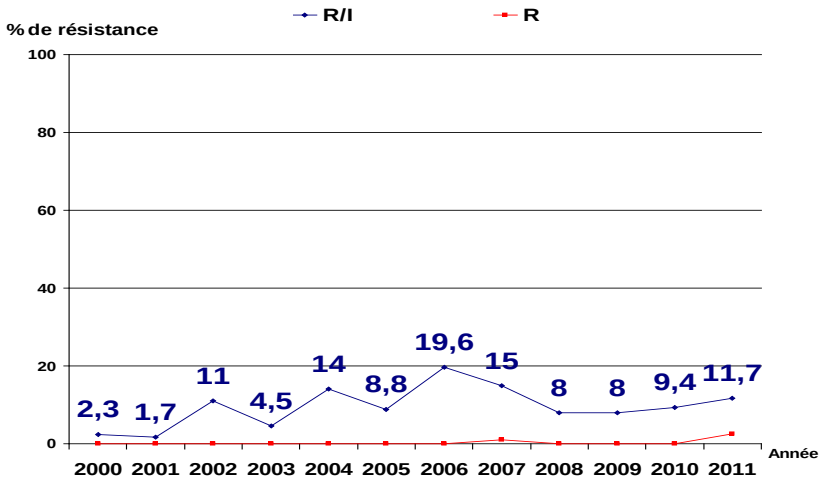


Souches invasives

Evolution annuelle de la résistance au céfotaxime



Souches non invasives



Souches invasives

Fréquence de résistance des souches de *S. pneumoniae* souches non invasives (NI) VS invasives (I)

ATB	2000 (53/43)	2001 (66/58)	2002 (66/73)	2003 (66/44)	2004 (83/51)	2005 (63/34)	2006 (85/64)	2007 (100/73)	2008 (107/40)	2009 (122/48)	2010 (128/53)	2011 (113/82)
C	13/2	15/2	18/8	9/4	7/4	18/3	12/10	9/12	9/2	14/6	16/4	12/4
E	**53/28**	**53/26**	**59/33**	**53/27**	**58/33**	**66/35**	**57/43**	**63/61**	**63/67**	**73/57**	**72/70**	**76/62**
Pris	0	0	0	0	0	0	0	0	0	0	0	0
Rif	0/2	0/0	0/4	1/0	3/0	3/3	0/0	0/0	1/0	8/0	8/1	7/1
Van	0	0	0	0	0	0	0	0	0	0	0	0
Lévo	-	-	-	-	-	-	-	-	-	-	-	**1/0**

Fréquences de R souches non invasives >> souches invasives

Celles des souches isolées chez enfants >> adultes

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Original article

Phenotypic and genotypic characterization of macrolide resistant *Streptococcus pneumoniae* in Tunisia

Caractérisation phénotypique et génotypique des souches de *Streptococcus pneumoniae* isolées en Tunisie

M. Rachdi, I. Boutiba-Ben Boubaker *, S. Moalla, H. Smaoui, A. Hammami, A. Kechrid, S. Ben Redjeb

Laboratoire de recherche « résistance aux antibiotiques », faculté de médecine de Tunis, Tunisia

Table 3
Correlation between the phenotypes and the genotypes of MLS resistance of *S. pneumoniae* isolates

Phenotypes	Strains number	Genotypes		
		erm(B)	*mef*(A)	*erm*(B)+ *mef*(A)
$cMLS_B$	83	81	0	2
$iMLS_B$	5	5	0	0
M	12	0	12	0

Bull. Soc. Pathol. Exot. (2011) 104:42-48
DOI 10.1007/s13149-010-0077-5

SANTÉ PUBLIQUE / *PUBLIC HEALTH*

Les méningites purulentes dans la région de Monastir, Tunisie (1999–2006) : aspects bactériologiques et état de résistance aux antibiotiques

Acquired bacterial meningitis in Monastir region, Tunisia (1999–2006): bacteriological aspects and susceptibility patterns

A. Ben Haj Khalifa · M. Mastouri · H. Ben Abdallah · S. Noomen · M. Kheder

Tableau 1 Profil bactériologique des méningites selon l'âge / *Bacteria responsible for bacterial meningitis according to age*

	Total		0–3 mois		3 mois–2 ans		2–5 ans		5–16 ans		16–50 ans		> 50 ans	
	Nombre	(%)	Nombre	(%)	Nombre	(%)	Nombre	(%)	Nombre	(%)	Nombre	(%)	Nombre	(%)
Streptococcus pneumoniae	49	19,4	2	8	7	20	17	37,8	9	22	11	11,8	3	21,6
Haemophilus influenzae	35	13,8	1	4	19	54,3	10	22,2	3	7,3	2	2,2	0	–
Neisseria meningitidis	16	6,3	0	-	1	2,8	2	4,4	5	12,2	7	7,5	1	7,1
Streptocoque B	14	5,5	14	56	0	–	0	–	0	–	0	–	0	–
Escherichia coli	18	7,1	6	24	1	2,8	1	2,2	6	14,6	3	3,2	1	7,1
Klebsiella pneumoniae	35	13,8	0	–	2	5,7								
E. cloacae	13	5,1	0	–	0	–								
Proteus spp	4	1,6	0	–	0	–								
Salmonella spp	6	2,4	0	–	5	14,4								
P. rettgeri	5	2	0	–	0	–								
S. marcescens	3	1,2	0	–	0	–								
P. aeruginosa	15	5,9	0	–	0	–								
A. baumannii	7	2,8	0	–	0	–								
Staphylococcus epidermidis	13	5,1	0	–	0	–								
S. aureus	9	3,5	0	–	0	–								
Enterococcus spp	5	2	0	–	0	–								
Streptocoque D	4	1,6	0	–	0	–								
Streptocoque A	2	0,8	2	8	0	–								
Total	253	100	25	100	35	100								

Tableau 4 Sensibilité aux antibiotiques pour les principales espèces bactériennes isolées de LCR / *Antibiotic susceptibility of the main bacteria identified in CSF*

Antibiotiques	Sensible	Intermédiaire (I) ; résistant (R)
Streptococcus pneumoniae ($n = 49$)		
Pénicilline G	57,1	I = 38,8 ; R = 4,1
Amoxicilline	67,3	I = 28,6 ; R = 4,1
Céfotaxime	69,4	I = 26,5 ; R = 4,1
Rifampicine	100	–
Vancomycine	100	–

J Infect Chemother (2012) 18:324–331
DOI 10.1007/s10156-011-0337-8

ORIGINAL ARTICLE

Severe pneumococcal community-acquired pneumonia admitted to medical Tunisian ICU

Khairallah Belkhouja · Kaïs Ben Romdhane · Asma Ghariani · Afef Hammami · Emna M'hiri · Leila Slim-Saidi · Jalila Ben Khelil · Mohamed Besbes

Abstract *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia (CAP). There are no available data about this disease in Tunisian intensive care patients. The objective of this study is to describe the clinical and microbiological features of pneumococcal CAP and determine the prognostic factors. This is a retrospective cohort study of all pneumococcal CAP cases hospitalized in the medical intensive care unit (ICU) of Hospital A. Mami of Ariana (Tunisia) between January 1999 and August 2008. Included were 132 patients (mean age, 49.5 years; 82.6% males); 30 patients had received antimicrobial treatment before hospital admission. The mean of the Simplified Acute Physiology Score II was 32.9. All patients had an acute respiratory failure; 34 patients (25.8%) had pneumococcal bacteremic CAP. Among the isolated strains, 125 antimicrobial susceptibility tests were performed. The use of the new Clinical and Laboratory Standards Institute breakpoints for susceptibility when testing penicillin against *S. pneumoniae* showed that all isolated strains were susceptible to penicillin. The mortality rate was 25%. The need of mechanical ventilation at admission [odds ratio (OR), 3.4; 95% confidence interval (CI), 1.67–6.94; $P = 0.001$), Sepsis-related Organ Failure Assessment (SOFA) score at admission ≥4 (OR, 3.1; 95% CI, 1.56–6.13; $P = 0.001$), and serum creatinine at admission ≥102 μmol/l (OR, 1.8; 95% CI, 1.02–3.17; $P = 0.043$) were independent factors related to ICU mortality. In conclusion, pneumococcal CAP requiring hospitalization in the ICU is associated with high mortality. All isolated stains were susceptible to penicillin.

Keywords Community-acquired pneumonia · *Streptococcus pneumoniae* · Intensive care · Prognosis

Introduction

Taux de mortalité : 25%

Table 6 Multivariate analysis of prognostic factors

Factor	OR	95% CI	*P*
MV required at admission	3.4	1.67–6.94	0.001
SOFA at admission ≥4	3.1	1.56–6.13	0.001
Serum creatinine at admission ≥102 µmol/l	1.8	1.02–3.17	0.043

SOFA Sequential Organ Failure Assessment, *MV* mechanical ventilation

Table 2 Susceptibility testing of 125 isolated pneumococci stains

Antimicrobial	Susceptible	Intermediate	Resistant
Penicillin[a]	125 (100)	0	0
Erythromycin	80 (64)	0	45 (36)
Lincomycine	82 (65.6)	0	43 (34.4)
Pristinamycine	118 (94.4)	1 (0.8)	6 (4.8)
Chloramphenicol	111 (88.8)	2 (1.6)	12 (9.6)
Tetracycline[b]	50 (65.8)	2 (2.6)	24 (31.6)
Levofloxacin[c]	74 (100)	0	0
Trimethoprim–sulfamethoxazole[d]	53 (45.7)	23 (19.8)	40 (34.5)
Rifampicin	125 (100)	0	0
Vancomycin	125 (100)	0	0

Rachdi et al, JMM 2011

Table 1. Distribution of serotypes and antimicrobial resistance of *S. pneumoniae* isolated in Tunisia

Values represent number of isolates.

Serotype/serogroup	Non-invasive	Invasive	PIR	PRP	CNS*	Multidrug-resistant (%)†	
19F (*n*=34)	15	19	25	3	9	25 (73.5)	P=0.002
19A (*n*=22)	11	11	9	5	7	15 (68.1)	P=0.02
14 (*n*=22)	13	9	8	7	10	14 (63.6)	
23F (*n*=19)	4	15	10	2	5	13 (68.4)	P=0.05
6B (*n*=18)	2	16	3	5	6	8 (44.4)	
6A (*n*=11)	3	8	0	1	0	1 (9)	P=0.01
9V (*n*=9)	1	8	6	2	0	4 (44.4)	
35F (*n*=8)	5	3	0	0	0	0	
24F (*n*=8)	2	6	6	2	1	4 (50)	
4 (*n*=7)	3	4	0	0	0	0	
1 (*n*=7)	1	6	0	0	0	0	
18C (*n*=7)	4	3	5	0	0	4 (57.1)	
9A (*n*=4)	3	1	2	2	1	2 (50)	
34 (*n*=4)	1	3	0	0	0	0	
10A (*n*=3)	1	2	0	0	0	0	
15A (*n*=3)	0	3	0	0	0	1 (33.3)	
35B (*n*=3)	3	0	0	0	0	0	
8 (*n*=3)	1	2	0	0	0	0	
11A (*n*=1)	0	1	0	0	0	0	
16F (*n*=1)	1	0	0	0	0	0	
31 (*n*=1)	1	0	0	0	0	0	
33F (*n*=1)	0	1	0	0	0	0	
20 (*n*=1)	0	1	0	0	0	0	
17F (*n*=1)	0	1	0	0	0	0	
3F (*n*=1)	0	1	0	0	0	0	
23B (*n*=1)	0	1	0	0	0	0	
Total (*n*=200)	75	125	74	29	39	90 (45)	

*CNS, Cefotaxime non-susceptible.

†Multidrug resistance was defined as resistance to penicillin and to two or more classes of antimicrobial agents.

48.5% PSP, 37% PIP & 14.5% PRP (+ R aux autres antibiotiques que PSP)

Plus de 50% des sérotypes 19F & 14 → résistantes à amoxicilline

59.6% des souches résistantes au céfotaxime → sérotypes 19F, 19A, 14, 23F & 6B

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Review

Non-susceptibility trends and serotype coverage by conjugate pneumococcal vaccines in a Tunisian paediatric population: A 10-year study

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Distribution of pneumococcal strains according to age and specimen type.

Age years	Invasive specimens ($n=200$)			Non-invasive specimens ($n=310$)			Total
	CSF[a]	Blood	Other punctions[b]	Pulmonary[c]	Ear pus	Others[d]	
<2	62	51	19	148	11	42	333 (65.3%)
2–5	17	9	3	34	2	11	76 (14.9%)
>5	20	13	6	49	2	11	101 (19.8%)
Total	99	73	28	231	15	64	510

Penicillin susceptibility of *S. pneumonia* strains according to specimen type.

Invasive specimens ($n=200$)				
Specimens	Blood ($n=73$)	CSF[a] ($n=99$)	Other punctions[b] ($n=28$)	Total
LLR[d]	25 (34.2%)	34 (34.3%)	11 (39.2%)	70 (35%)
HLR[e]	14 (19.2%)	3 (3.0%)	2 (7.1%)	19 (9.5%)

Non invasive specimens ($n=310$)			
Pulmonary ($n=231$)	Ear pus ($n=15$)	Others[c] ($n=64$)	Total
102 (44.1%)	6 (40%)	37 (57.8%)	145 (46.7%)
38 (16.4%)	0 (0%)	6 (9.4%)	44 (14.2%)

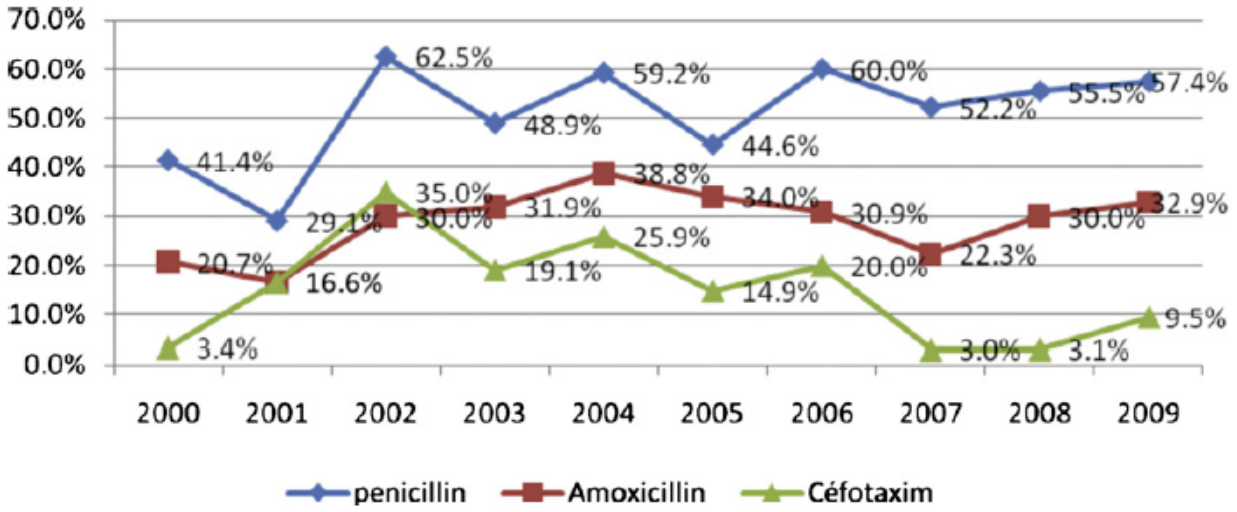

Fig. 1. Evolution of *S. pneumoniae* strain beta lactam resistance from 2000 to 2009.

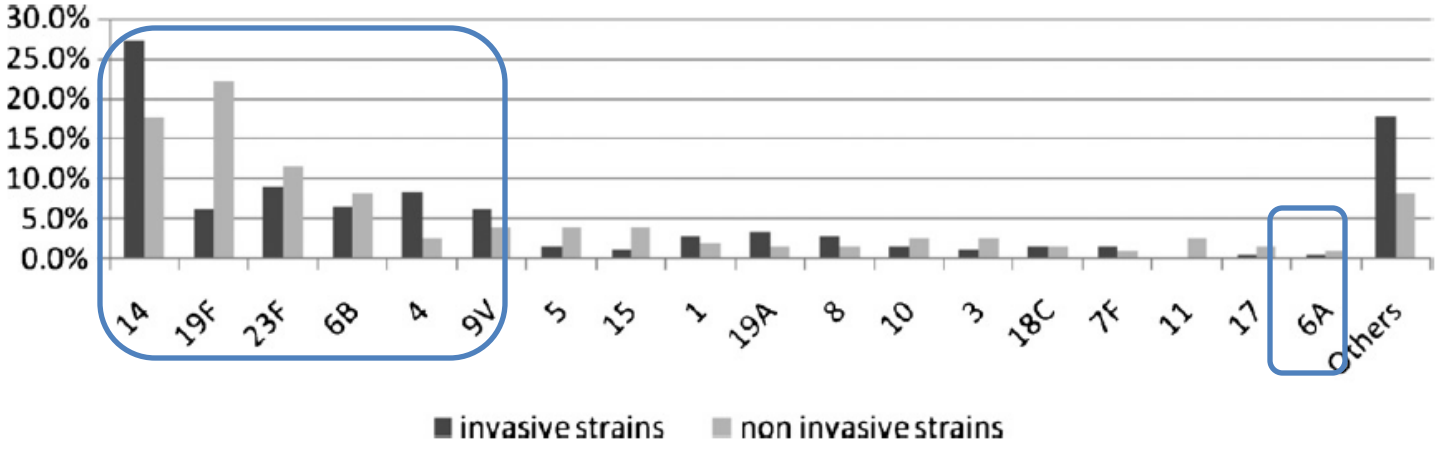

Fig. 3. Serogroups and serotype distribution of invasive and non-invasive *S. pneumoniae* strains. Other strains are: 2, 12, 20, 33 and non typable.

Distribution of *S. pneumoniae* vaccine serotypes according to age and specimen type.

Serotype	Invasive ($n = 180$)		
	<2 years ($n = 119$) Number (%)	2–5 years ($n = 26$) Number (%)	>5 years ($n = 35$) Number (%)
1	4 (3.3)	0	1 (2.8)
3	0	1 (3.8)	1 (2.8)
4	12 (10.0)	1 (3.8)	2 (5.7)
5	1 (0.8)	1 (3.8)	1 (2.8)
6A	1 (0.8)	0	0
6B	11 (9.2)	0	1 (2.8)
7F	2 (1.6)	0	1 (2.8)
9V	8 (6.7)	2 (7.6)	1 (2.8)
14	36 (30.2)	7 (26.9)	6 (17.1)
18C	3 (2.5)	0	0
19A	5 (4.2)	1 (3.8)	0
19F	8 (6.7)	0	3 (8.5)
23F	8 (6.7)	5 (19.2)	3 (8.5)
Total vaccine serotypes	99 (83.1)	18 (69.2)	20 (57.1)
Non-vaccine serotypes	20 (16.8)	8 (30.7)	15 (42.8)

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SEROTYPE PREVALENCE AND ANTIBIOTIC RESISTANCE IN STREPTOCOCCUS PNEUMONIAE CLINICAL ISOLATES IN SFAX,SOUTH OF TUNISIA

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Background and Aims: *Streptococcus pneumoniae* causes a wide range of infections that could be deliterious. Prevention through vaccination is a valuable tool to decrease the burden of disease. Nevertheless, none of the marketed internationally vaccines, PCV 7, PCV 10 and PCV 13 is currently part of the national program of immunization in Tunisia. We undertook this study to determine the serotype distribution and to analyze the antimicrobial resistance of *S. pneumoniae* isolates .
Methods: All pneumococcal strains isolated in the microbiology laboratory of the University Hospital, Sfax, Tunisia, from January 2012 to August 2013 were included. *S. pneumoniae* was identified by Gram straining, optochin susceptibility and bile solubility. Antimicrobial susceptibility was determined by the disk diffusion and E test methods. Serotyping was performed by multiplex PCR. Statistical analysis was done using SPSS 20.
Results: Among 125 collected pneumococcal isolates, 39 were invasive isolates (31%). The mean age of patients was 29.7 years. Seventy four percent of the strains were penicillin non-susceptible (PNSP). Forty four percent had decreased susceptibility to amoxicillin and 23.2% to cefotaxim. The PNSP were more frequently resistant to other antibiotics. Serotype 14 was the most frequently isolated (21.4%) followed by serotypes 19F (20.4%), 6A/6B (10.2%), 23F (9%) and 3(8.2%). Serotype 19F was associated with higher level of PNSP (p = 0.03). The potential coverage by the 7, 10 and 13 valent pneumococcal conjugate vaccines were 65.3%, 65.3% and 77.6% respectively.
Conclusion: A high rate of *S. pneumoniae* antibiotic resistance is observed in Tunisia. Conjugate vaccines and particularly PCV 13 provide good coverage for pneumococcal isolates .

CONCLUSION

S. pneumoniae:

- ✓Infections invasives +++ ⬎ Mortalité +++
- ✓Résistance aux antibiotiques +++

- ✓**Phénomènes réversibles:**
  - ✓ Vaccination
  - ✓ Meilleur usage des antibiotiques

- ✓**Surveillance continue indispensable:**
  - ✓Sérotypes
  - ✓Résistances

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