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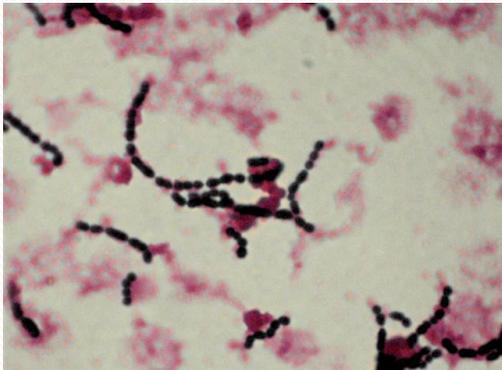
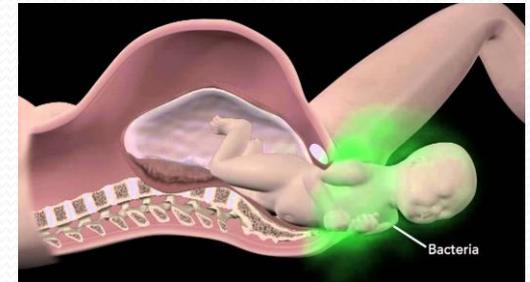
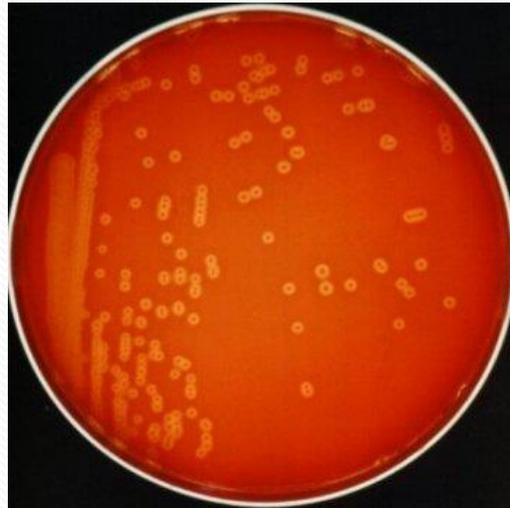
**UN** Nantes  
Université

# Physiopathologie des infections à *Streptococcus*

*Exemple de S. agalactiae*

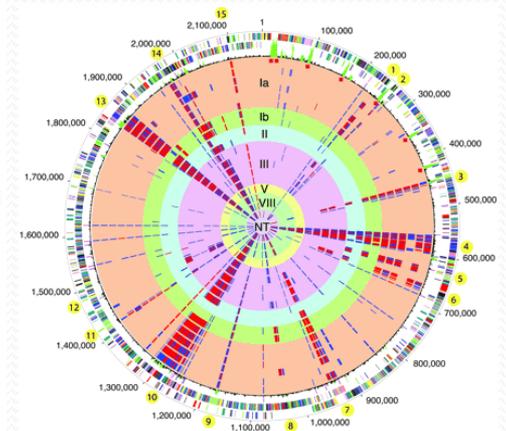
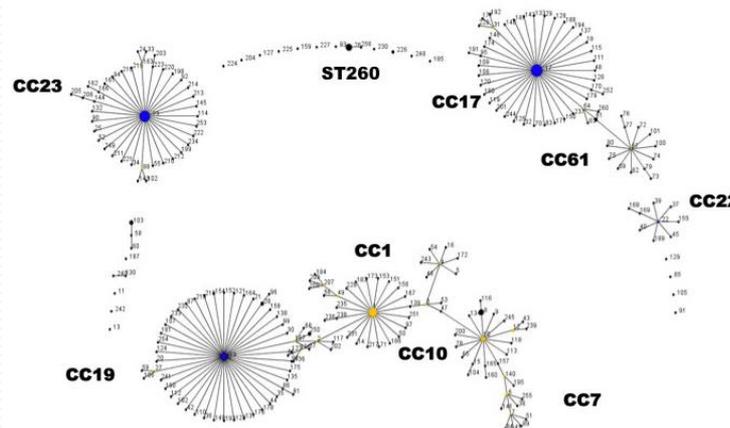
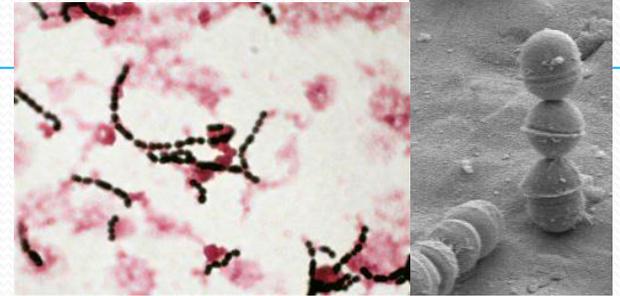
# ELEMENTS DE PHYSIOPATHOLOGIE DES INFECTIONS A STREPTOCOQUES

## *Streptococcus agalactiae*



# CONTEXTE GENERALE : *S. AGALACTIAE*

- ☞ *S. agalactiae*, commensal
- ☞ Flores digestive et vaginale
- ☞ Colonisant chez 15 à 30 % des adultes sains
- ☞ Leader des infections materno-fœtales => méningite  
Clone hyper-virulent ST17
- ☞ Important pathogène chez les personnes âgées 19% IOA



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- ☞ Important pathogène chez les personnes âgées
  
- ☞ **FQ, alternative traitement des infections sévères à SGB**
- ☞ **Caractérisation du résistome et mobilome de SGB**
- ☞ **Adaptation génomique et transmission materno-F**

# NOTIONS GENERALES

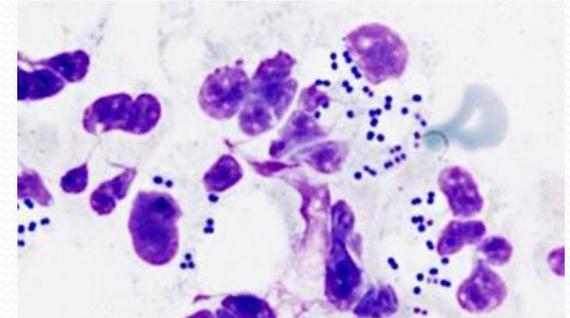
## ■ Deux contextes d'infections :

### - Infections néonatales :

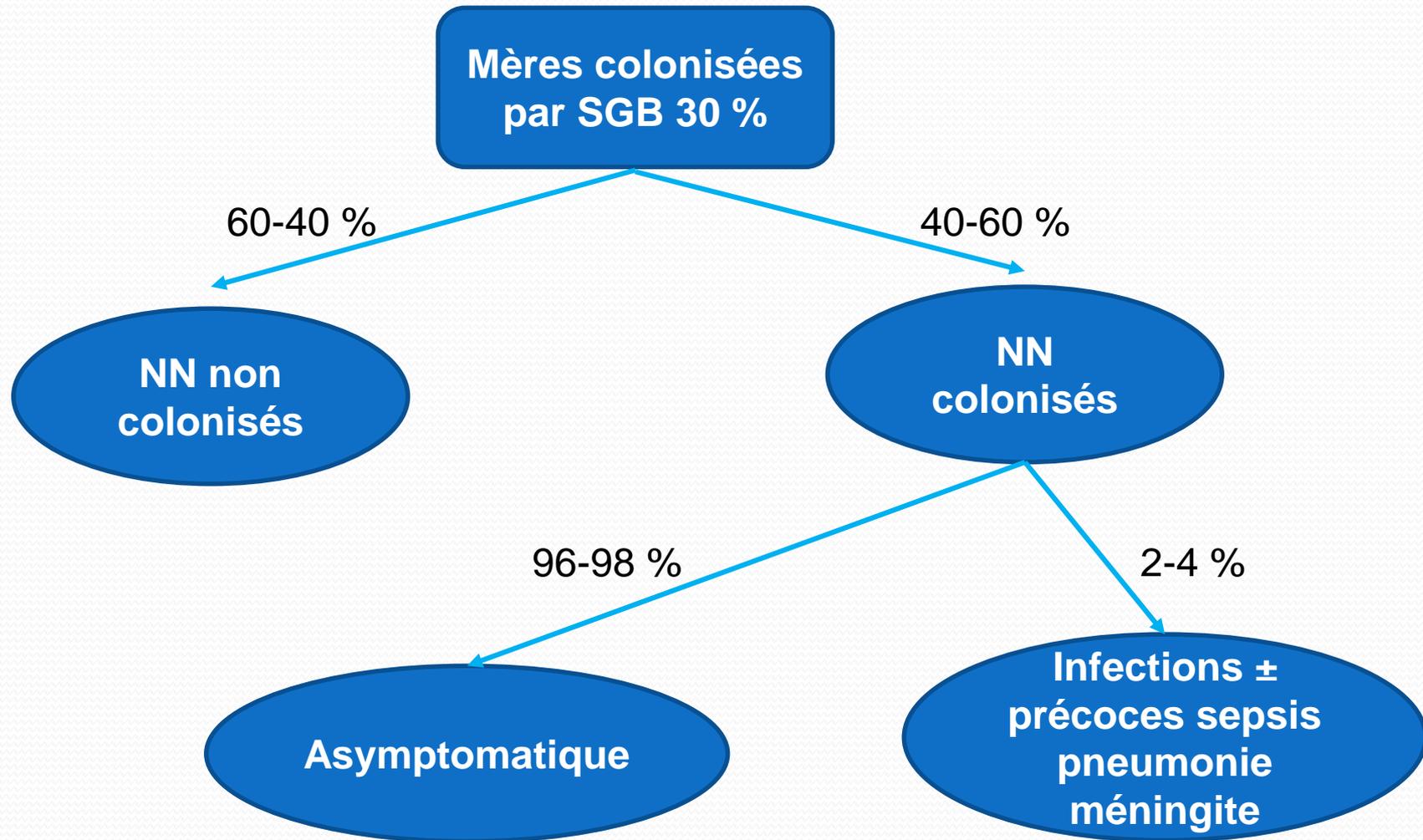
- . 1<sup>ère</sup> cause d'infections invasives :  
0,25-1,25 / 1000 naissances
  - . Infections précoces
  - . Infections tardives
- . 15-30 % femmes enceintes colonisées
  - 50 % enfants colonisés (en moyenne)
  - 1-2 % infections
- . Facteurs de risque

### - Infections de l'adulte :

- . Terrains à risque : alcool, lupus, drogue IV, maladie chronique
- . Peau (diabétique), os, bactériémie, tractus uro-génital, pneumonie

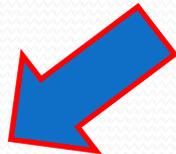


# TRANSMISSION MERE ENFANT



2-4 %

Infections ±  
précoces sepsis  
pneumonie  
méningite



**Porte d'entrée pulmonaire :**  
infection précoce 5/6 J

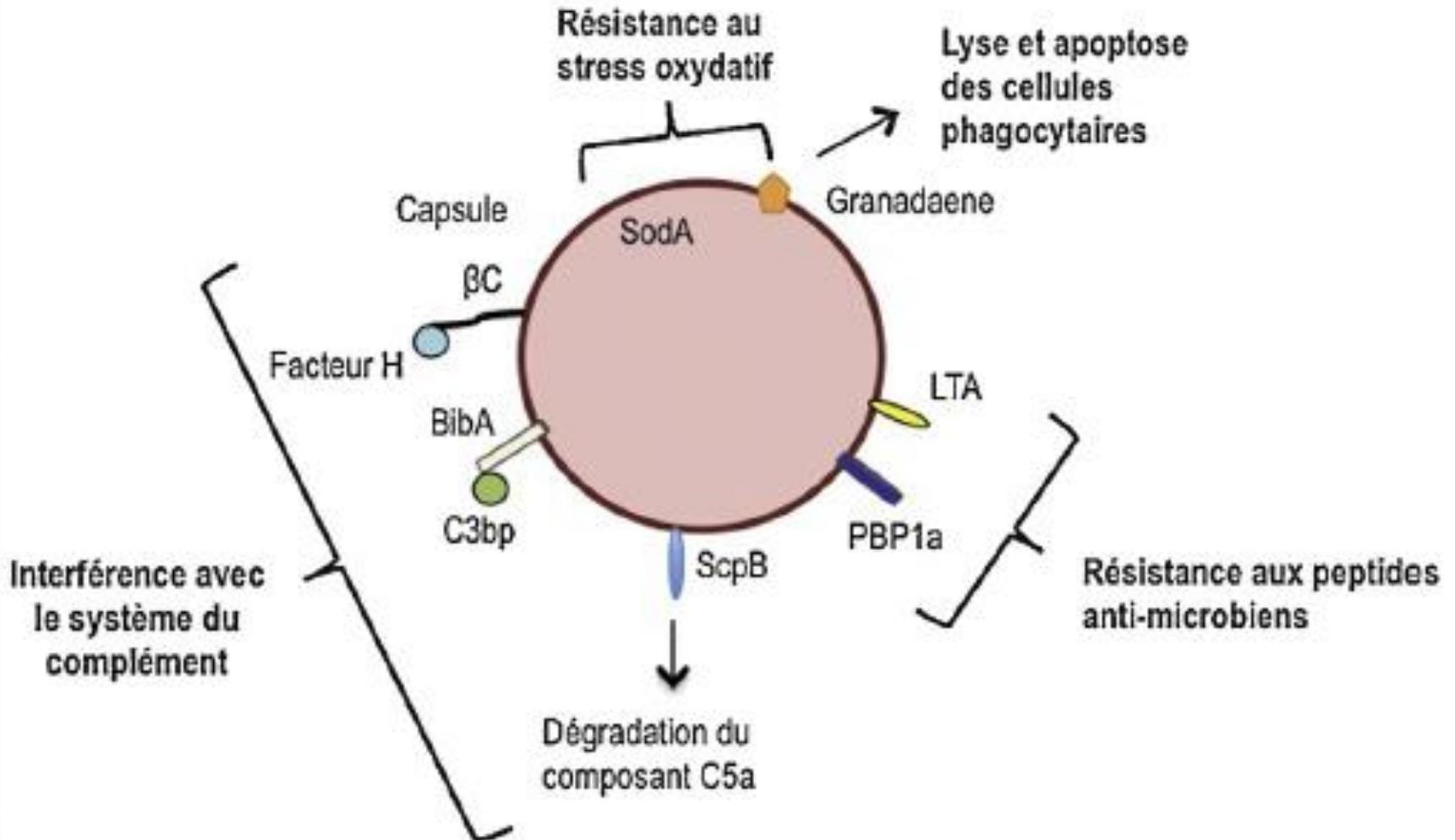


**Porte d'entrée digestive :**  
infection tardive 7/90 J

- 1- Réussite colonisation épithélium vaginal
- 2- Barrières épithéliales pulm ou dig
- 3- Atteinte circulation systémique
- 4- Résistance & persistance
- 5- Echappement SI
- 6- Franchissement barrière hémato méningée

## FV à la surface cellulaire

## FV sécrétés milieu extra-C

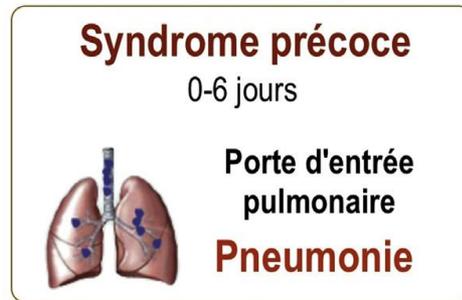


A



Transmission lors de l'accouchement

B



C



Translocation  
pulmonaire

Translocation  
intestinale



Franchissement de la barrière  
hémato-encéphalique

D



**Infections materno-fœtales à *Streptococcus agalactiae***

Anne Six<sup>1,2,3</sup>, Caroline Joubrel<sup>6,7</sup>, Asmaa Tazj<sup>1,2,3,6,7,8</sup>, Claire Poyart<sup>1,2,3,4,5,6,7,8</sup>

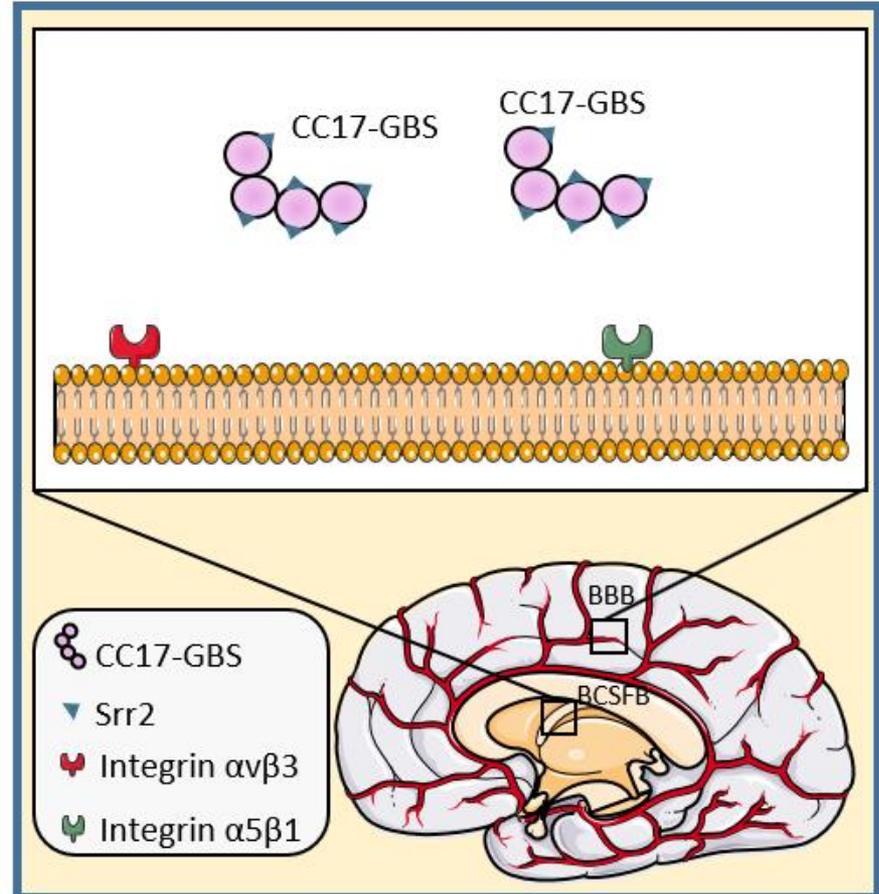
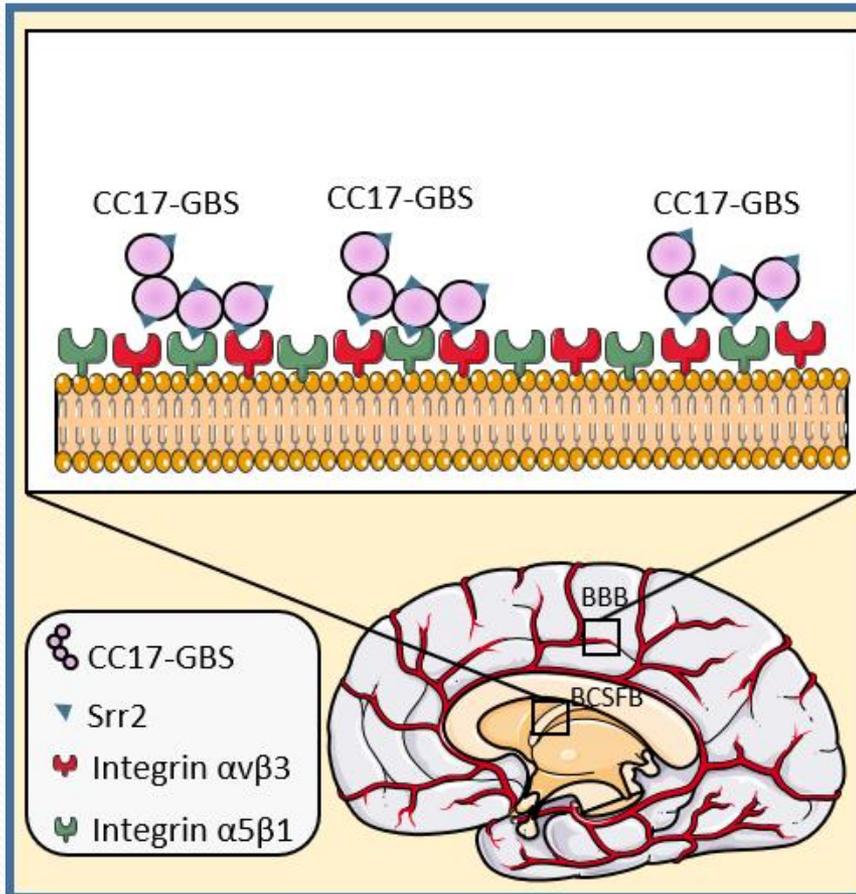
Presse Med. 2014; 00: 000  
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[www.sciencedirect.com](http://www.sciencedirect.com)

# Impact sur la physio pathologie Inf SNC

NEONATE

ADULT



Highly susceptible to meningitis

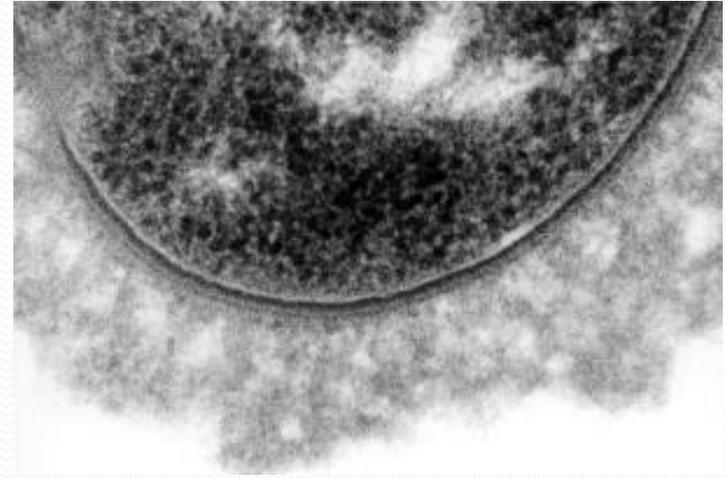
Poorly susceptible to meningitis

D'après Pr. C. Poyart

# PRINCIPAUX FACTEURS DE VIRULENCE

## ▪ CAPSULE :

- Polymère de haut PM
- **Unités répétitives :**  
glucose, galactose,  
N-acétyl glucosamine, acide sialique ;  
longueur variable.
- **10 types** Ia, Ib, II → IX ; Ia, Ib, III ↔ acide sialique terminal.
- Perturbe la fixation du C3b à la surface des bactéries  
→ inhibition voie alterne du C, opsono-phagocytose



Leurre du système immunitaire

# PRINCIPAUX FACTEURS DE VIRULENCE

## ▪ CAPSULE :

- ~ 15 gènes principaux impliqués dans régulation génétique :
  - . *cpsE* et *cpsF* : synthèse, activation de mono-saccharides ;
  - . *cps D, G, H, I, J* : formation de penta-saccharides ;
  - . *cps A, B, C, R* :

*Streptococcus agalactiae* Capsule Polymer Length and Attachment Is Determined by the Proteins CpsABCD

Received for publication, December 26, 2014, and in revised form, January 30, 2015. Published, JBC Papers in Press, February 9, 2015, DOI 10.1074/jbc.M114.631499

Chiara Toniolo, Evita Balducci, Maria Rosaria Romano, Daniela Proietti, Ilaria Ferlenghi, Guido Grandi, Francesco Berti, Immaculada Margarit Y Ros, and Robert Janulczyk<sup>1</sup>

### *CpsABCD* in *S. agalactiae* Capsule Biosynthesis

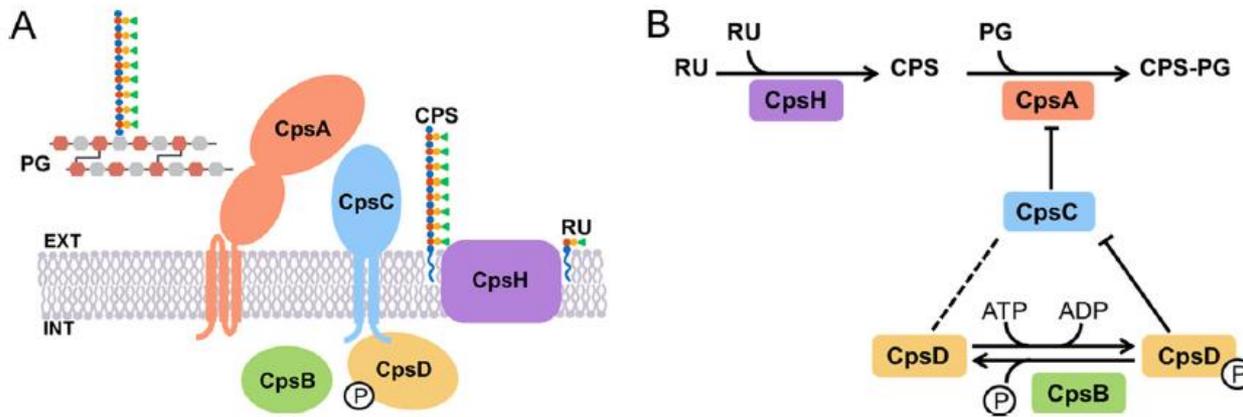


FIGURE 6. Model of CpsABCD involvement in CPS biosynthesis. A, topology and subcellular localization of the CpsABCD proteins and of the CpsH polymerase was predicted using PSORTb and Octopus. The repeating unit (RU), the capsular polysaccharide (CPS), and the cell wall peptidoglycan (PG) are also represented. B, schematic representation of the working model proposed for the CpsABCD proteins. Arrows, enzymatic reactions; bar-headed line, an inhibitory effect; dotted line, an interdependency.

# IMPACT DU SÉROTYPE ET DU ST SUR LES FORMES CLINIQUES

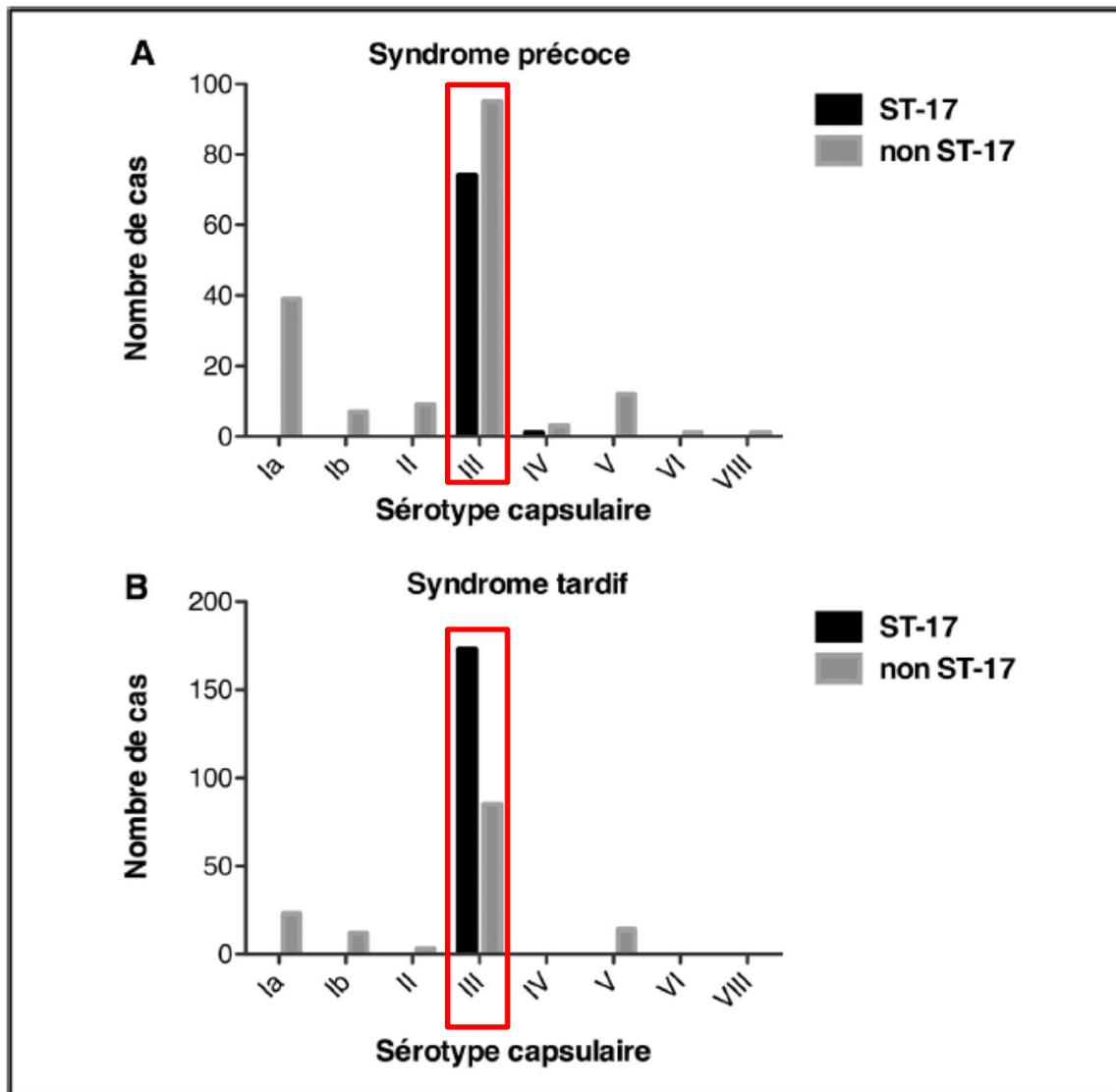


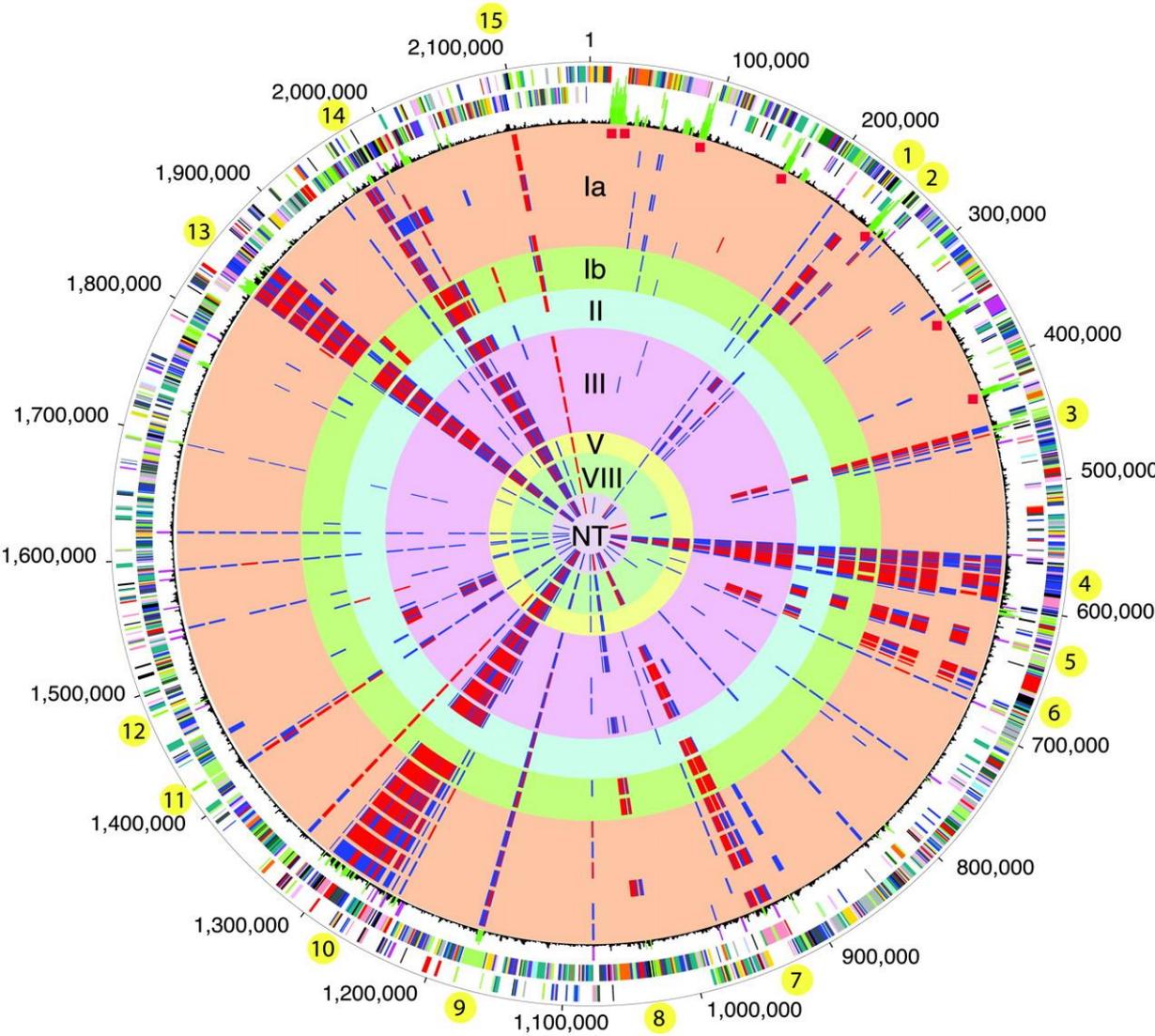
FIGURE 3

Répartition du nombre de cas, recensés par le CNR des streptocoques entre 2007 et 2012, de syndrome précoce (A) ou tardif (B) en fonction du sérotype capsulaire et du ST-17

# PRINCIPAUX FACTEURS DE VIRULENCE

## Complete genome sequence and comparative genomic analysis of an emerging human pathogen, serotype V *Streptococcus agalactiae*

Hervé Tettelin<sup>1</sup>, Vega Masignani<sup>2</sup>, Michael J. Cieslewicz<sup>5</sup>, Jonathan A. Eisen<sup>1</sup>, Scott Peterson<sup>7\*\*</sup>, Michael R. Wessels<sup>5††</sup>, Ian T. Paulsen<sup>1</sup>, Karen E. Nelson<sup>2</sup>, Immaculada Margarit<sup>4</sup>, Timothy D. Read<sup>2</sup>, Lawrence C. Madoff<sup>5</sup>, Alex M. Wolf<sup>1</sup>, Maureen J. Beanan<sup>2</sup>, Lauren M. Brinkac<sup>1</sup>, Sean C. Daugherty<sup>1</sup>, Robert T. DeBoy<sup>1</sup>, A. Scott Durkin<sup>1</sup>, James F. Kolonay<sup>1</sup>, Ramana Madupu<sup>1</sup>, Matthew R. Lewis<sup>1</sup>, Diana Radune<sup>1</sup>, Nadezhda B. Fedorova<sup>1</sup>, David Scanlan<sup>1</sup>, Hoda Khouri<sup>1</sup>, Stephanie Mulligan<sup>1</sup>, Heather A. Carty<sup>1</sup>, Robin T. Cline<sup>1</sup>, Susan E. Van Aken<sup>1</sup>, John Gill<sup>1</sup>, Maria Scarselli<sup>1</sup>, Marirosa Mora<sup>2</sup>, Emilia T. Iacobini<sup>2</sup>, Cecilia Brettoni<sup>2</sup>, Giuliano Galli<sup>2</sup>, Massimo Mariani<sup>2</sup>, Filippo Vegni<sup>2</sup>, Domenico Maione<sup>2</sup>, Daniela Rinaudo<sup>2</sup>, Rino Rappuoli<sup>2</sup>, John L. Telford<sup>2</sup>, Dennis L. Kasper<sup>5</sup>, Guido Grandi<sup>2</sup>, and Claire M. Fraser<sup>1\*\*\*†††</sup>



The **2,160,267 bp genome sequence of *Streptococcus agalactiae***, the leading cause of bacterial sepsis, pneumonia, and meningitis in neonates in the U.S. and Europe, is predicted to encode **2,175 genes**. These *in silico* analyses, combined with comparative genome hybridization experiments between the sequenced serotype V strain 2603 V/R and 19 *S. agalactiae* strains from several serotypes using whole-genome microarrays, **revealed the genetic heterogeneity among *S. agalactiae* strains, even of the same serotype, and provided insights into the evolution of virulence mechanisms.**

# PRINCIPAUX FACTEURS DE VIRULENCE

## ▪ COMPOSANTS DE SURFACE :

- Protéines  $\alpha$  et  $\beta$  : 40-60 % souches, dont Ia, Ib
  - **Structure similaire**, séquence d'ancrage (LPXTG), Association fréquente, mais gènes non liés :
    - .  **$\alpha$**  : 62,5 à 167 KD - **protéine Rib #**, chez souches sérotype III ; codage par gènes *cba*.
    - . **protéine  $\beta$**  : 130 KD
  - **$\alpha$**  : variations antigéniques selon nombre unités répétitives  
→ **échappement / défenses immunitaires**
  - **Protéine  $\beta$**  :
    - . Liaison domaine N-terminal / fragment Fc des IgA  
→ **perturbation phagocytose après opsonisation**
    - . Liaison domaine C-terminal / protéine H, inhibitrice système C

# PRINCIPAUX FACTEURS DE VIRULENCE

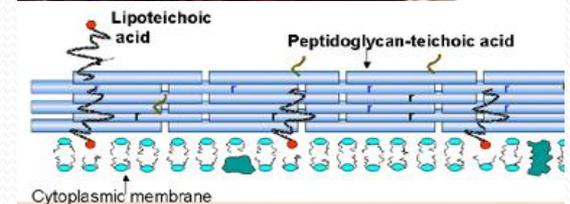
## ■ COMPOSANTS DE SURFACE :

### • C5a peptidase = ScpB

- 128 KD - séquence conservée Ser-Asp-His = site catalytique
- Codage par gène *scpB*
- Clivage du C5a → inhibition chimio-tactisme des leucocytes.
- Protéine de liaison / **fibronectine**.

### • Acides lipoteichoïques :

- Adhésines / cellules eucaryotes (cf. **fibronectine**, **laminine** du placenta...).
- Relargage cytokines par monocyte



Cytoplasm

# PRINCIPAUX FACTEURS DE VIRULENCE

## ■ COMPOSANTS DE SURFACE :

### • CAMP factor :

- 23,5 KD - gène *cfb*
- Fixation au fragment Fc des IgG et IgM  
→ ↓ **opsonisation**
- Formation de pores dans membranes,  
par oligomérisation
- Renforce l'activité hémolytique de l'hémolysine de *S. aureus*.



# PRINCIPAUX FACTEURS DE VIRULENCE

Protéines  
hydrophobes de la  
surface cellulaire

## ■ COMPOSANTS DE SURFACE :

### • Protéine Lmb :

- Protéine de surface : attachement à la **laminine** (placenta) ;  
adhérence /  $\phi$  endothéliales microvaisseaux cérébraux

### • Protéines FbsA / FbsB :

- Protéines de surface ;
- Séquences de liaison LPXTGX ;
- Séquences répétitives de longueur variables  
→ variabilité antigénique ;
- Liaison au **fibrinogène** → échappement (FbsA),
- Pénétration intra- $\phi$  (FbsB)

### • Protéine Pav A :

- protéine de liaison / **fibronectine**

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2005, p. 102-127  
0893-8512/05/\$08.00+0 doi:10.1128/CMR.18.1.102-127.2005  
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Vol. 18, No. 1

Surface Proteins of *Streptococcus agalactiae* and Related Proteins  
in Other Bacterial Pathogens

Gunnar Lindahl,\* Margaretha Ståhlhammar-Carlemalm, and Thomas Areschoug

Department of Medical Microbiology, Dermatology and Infection, Lund University, Sölvegatan 23, Lund, Sweden

# PRINCIPAUX FACTEURS DE VIRULENCE

## ▪ TOXINES/ENZYMES :

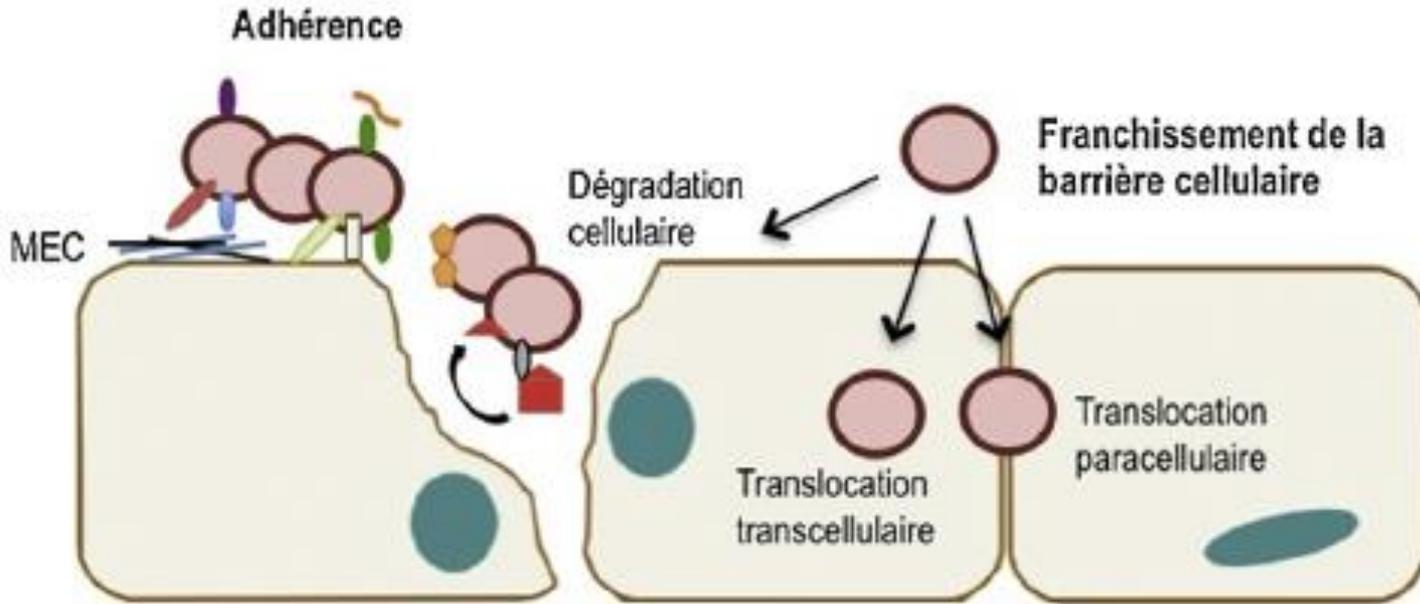
### • Hémolysine :

- Cytolysine, notamment / cellules épithéliales pulmonaires (pores)
- ↑ relargage dérivés NO toxiques et cytokines
- Codage par gènes *cyl* dont *cylA* et *cylB* :  
homologies avec gènes codant pour composants  
de systèmes de transport de type ABC (export)

### • Hyaluronate lyase :

- 110 KD - codage par gène *hylB*
- Niveau de production variable selon type et contexte d'isolement
- Clivage liaisons N-acétyl glucosamine - acide glucuronique  
(cf. acide hyaluronique tissu conjonctif, placenta, liq. amniotique...)

# PROCESSUS PHYSIOPATHOLOGIQUES



## Phénomène de transcytose

- |             |                      |             |              |          |
|-------------|----------------------|-------------|--------------|----------|
| Protéine αC | C5a peptidase (ScpB) | Pili        | Laminine     | Plasmine |
| Granadaene  | BibA/Hvga            | GAPDH       | Fibronectine |          |
| Lmb         | Srr1                 | Fibrinogène | Plasminogène |          |

Effet cytolytique : hémolysine

<b>Virulence factor</b>	<b>Mechanism</b>	Colonization	Adhesion	Invasion	Immune evasion	Neurotropism
Fibrinogen binding protein A (FbsA)		+	+			
Fibrinogen binding protein B (FbsB)				+		
Laminin binding protein (Lmb)				+		+
GBS surface adhesion (BsaB)		+	+	(+)		
Alpha C proteins (ACP)		+	+	+	+	
Serine rich repeat proteins (Srr)		+	+	+		
Pili		+	+	+	+	+
Hypervirulent GBS adhesiin (HvgA)		+	+	+	(+)	+
$\beta$ -hemolysin/cytolysin ( $\beta$ -H/C)		+	+	+	+	+
Capsular polysaccharides (CPS)					+	
Streptococcal C5a peptidase of GBS (ScpB)					+	
GBS immunogenic bacteria adhesion (BibA)					+	
Factor H					+	
IgA-binding beta-antigen					+	
D-alanylation					+	
Superoxide dismutase (SodA)					+	

Colonization of Pregnant Mother



Ascending Placental and Uterine Infection



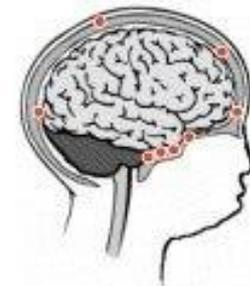
Pneumonia and Lung Injury



Bacteraemia and Sepsis Syndrome

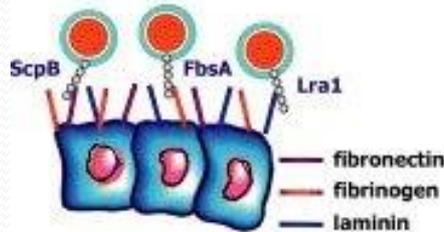


Blood-Brain Barrier Penetration and Meningitis

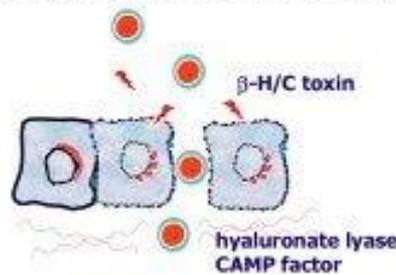


**Stages of Neonatal Infection**

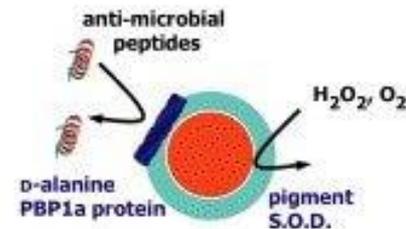
**Molecular and Cellular Pathogenesis**



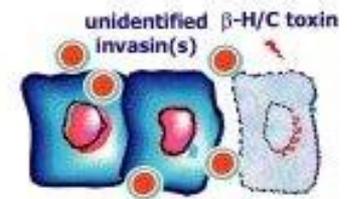
Extracellular Matrix Binding



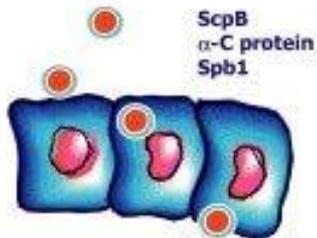
Direct Cellular Injury



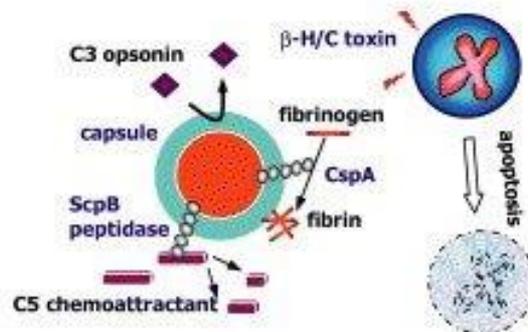
Resist Intracellular Killing



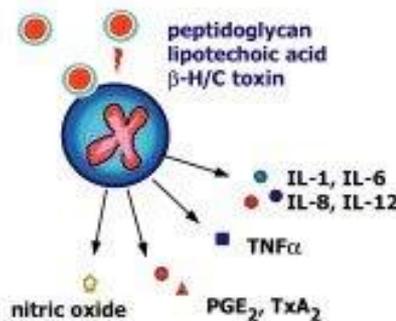
Brain Endothelial Invasion



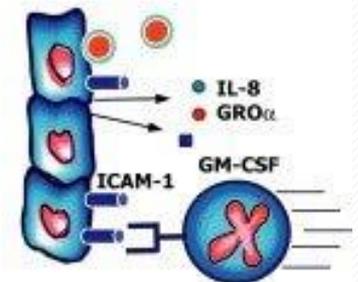
Epithelial Cell Invasion



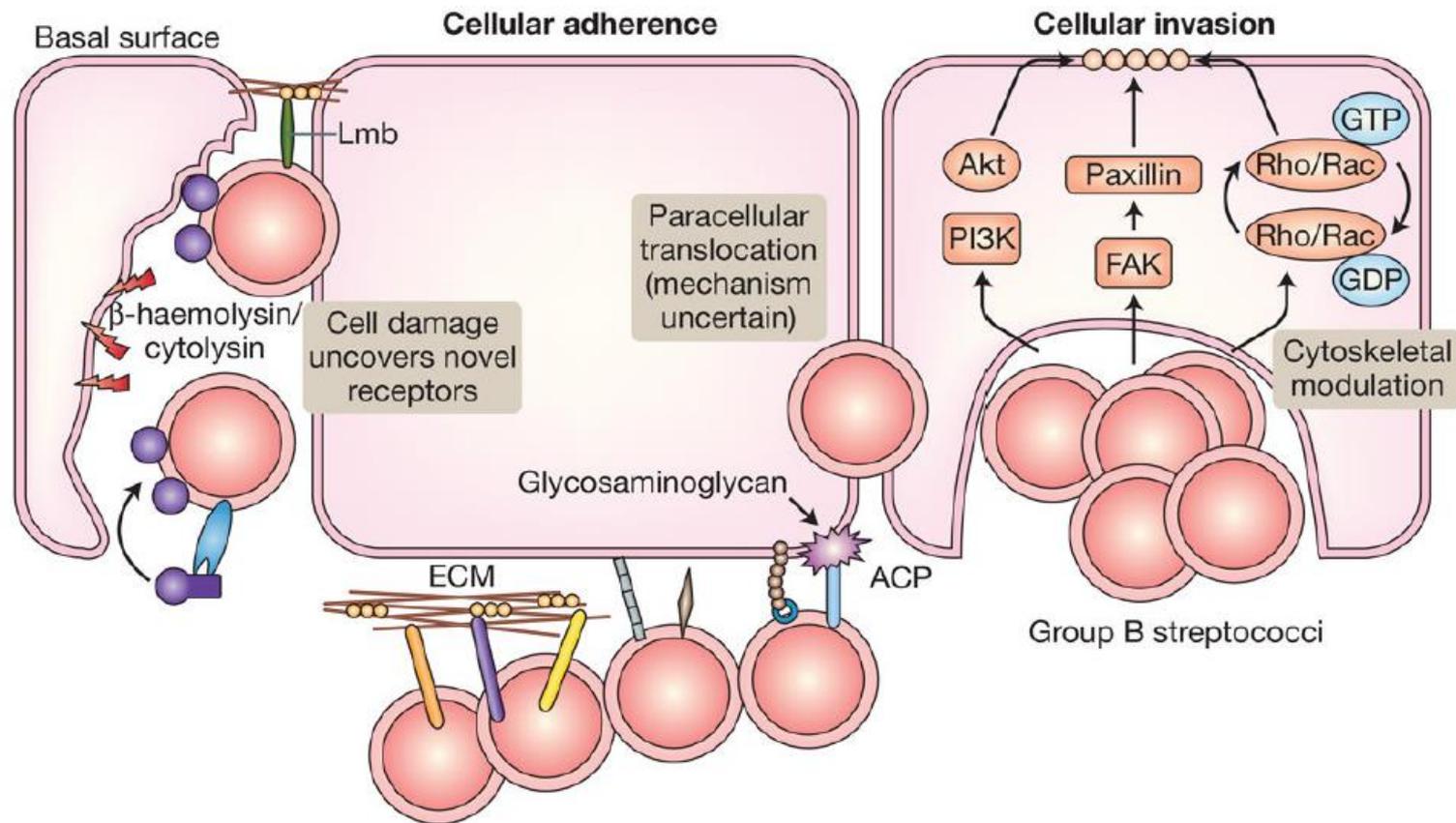
Resist Phagocytosis



Inflammatory Activation

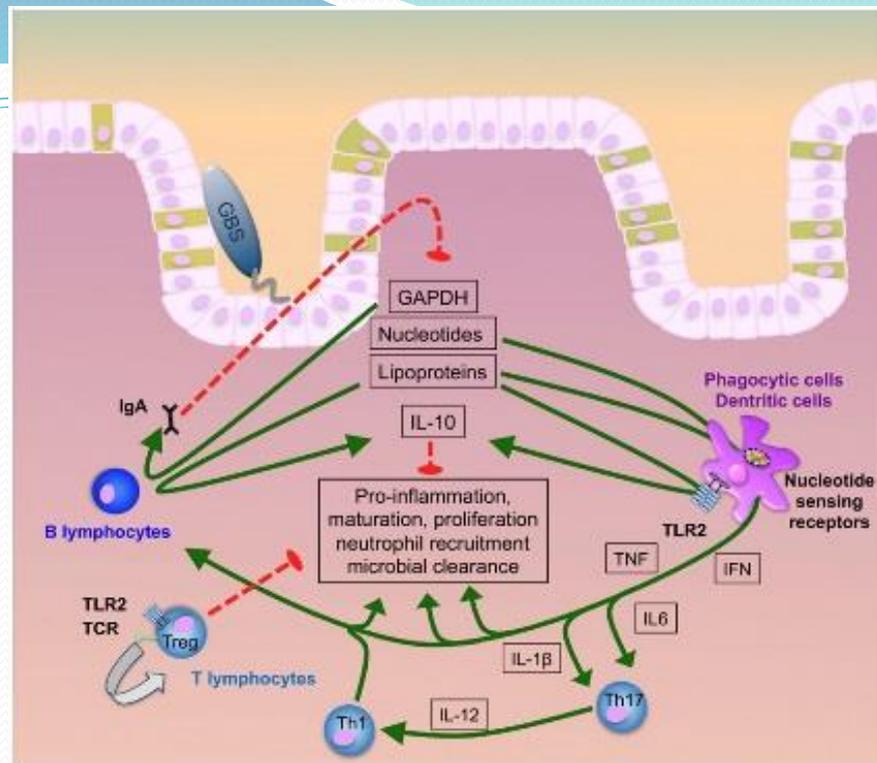


CNS Neutrophil Recruitment

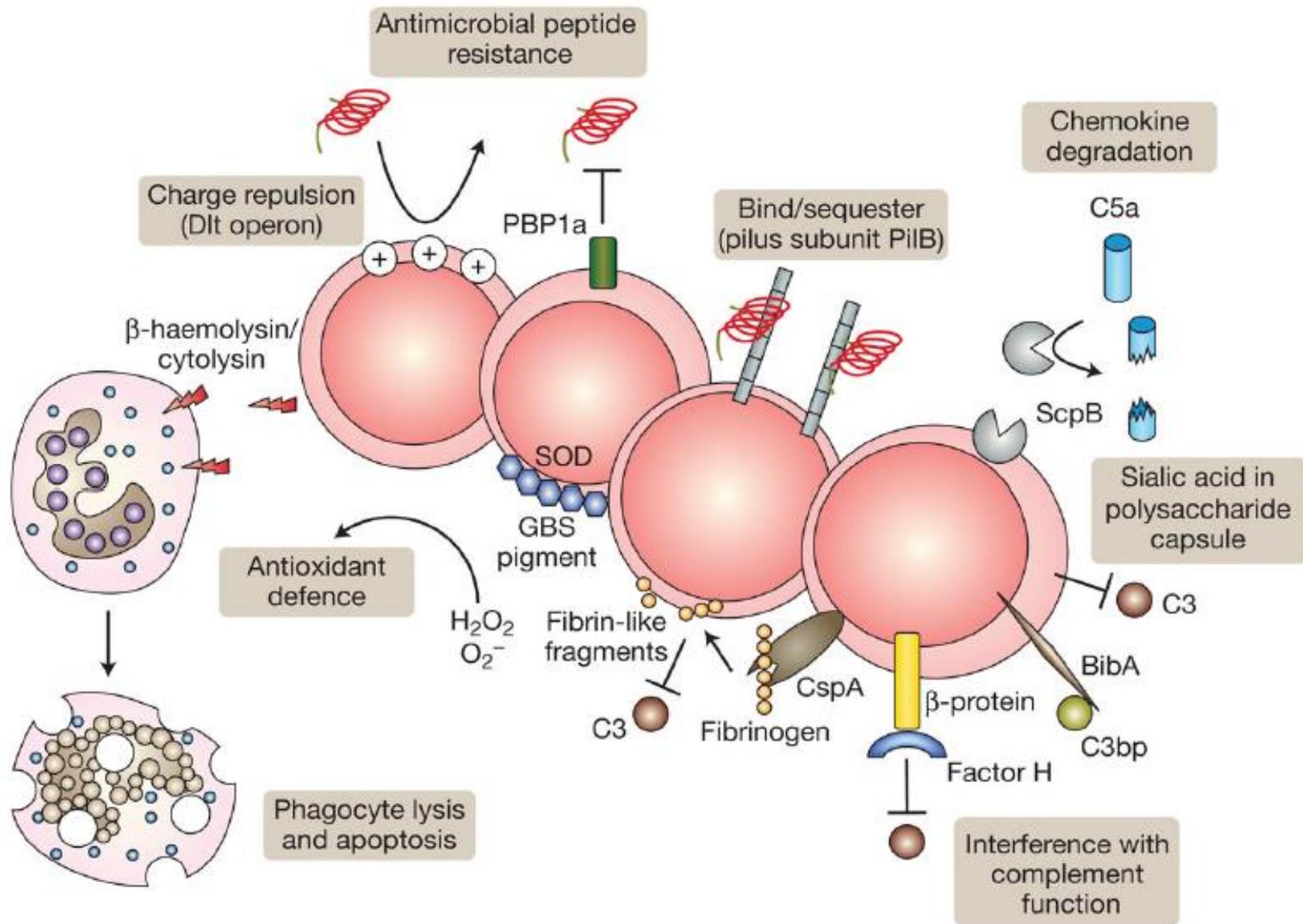


## Mechanisms of group B *Streptococcus* cellular adherence and invasion

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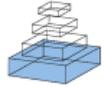


**Figure 1. GBS transition to invasive disease.** GBS lipoproteins, GAPDH, and nucleic acids majorly contribute to intestinal immune activation inducing pro-inflammatory responses, neutrophil recruitment, cellular proliferation, maturation and, finally, microbial clearance. Early induction of specific antibody release by B plasma cells and IL-10 secretion by both B-lymphocytes and phagocytes act as a negative feedback loop to counter-regulate hyperinflammation. Uncontrolled increase of IL-10, in contrast, hampers neutrophil recruitment and bacterial elimination. At the same time, T-lymphocytes can directly interact with GBS ligands or receive pro-inflammatory signals via monocytic cytokines. While Th1 and Th17 cells promote infection control, activation of regulatory T cells prevents hyperinflammation and supports post-infectious healing.



## Mechanisms of group B *Streptococcus* immune evasion

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# Interaction of *Streptococcus agalactiae* and cellular innate immunity in colonization and disease

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<sup>5</sup> Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany

## CONCLUSION

Group B *Streptococcus* comprises several regulatory systems that respond to the microenvironment and, by steering adhesion and virulence factors, allow for colonization of mucosal niches in the genital and (lower) intestinal tract. Colonization is further propagated by the GBS-intrinsic ability to manipulate local cellular immunity. Yet, under only partially understood conditions GBS loses its colonizing trait and invades the host. Then, immune mechanisms that usually stabilize the natural GBS niche may lead to detrimental immunopathology. Rather subtle changes on the single immune cell level in newborn infants appear to facilitate the escalation from a beneficial site-specific response to sepsis and meningitis. Better understanding of the dynamic expression of virulence traits in GBS, and of the cellular immunology that shapes the GBS niche, will hopefully pave the way for preventing lifelong disabilities inflicted by a normal component of the microbiota.

# REGULATION GENETIQUE

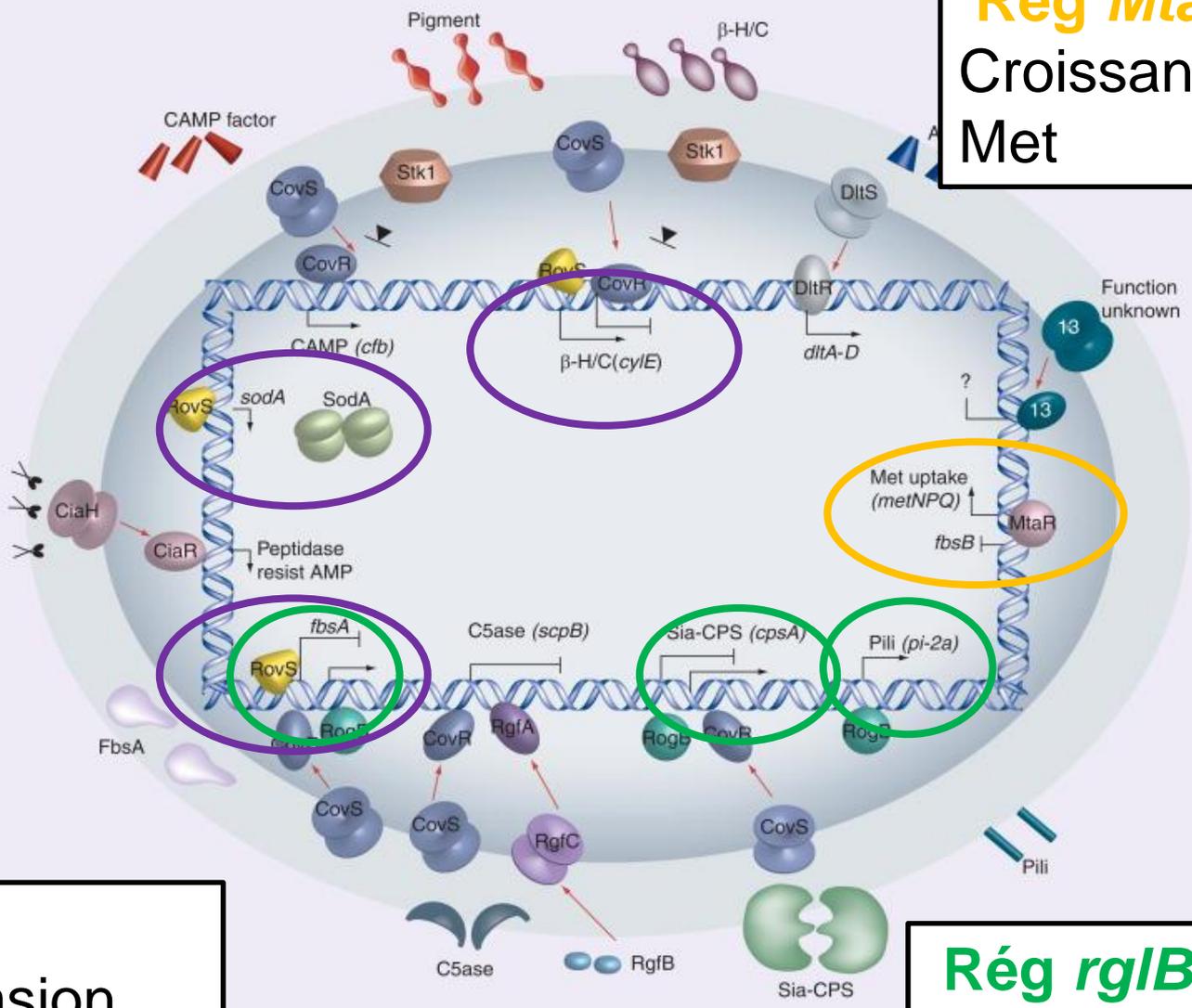
- **Système à 2 composants, codé par gènes du locus *rgfBDCA*** (regulator of fibrinogen binding) :
  - Histidine-kinase ("sensor" - *rgfC*) + 1 régulateur (*rgfA*)
  - **Phosphorylation d'une histidine**, puis transfert d'un groupement phosphate à un résidu aspartate
    - modification structurale
    - modification expression de gènes.
  - **Implication démontrée dans la régulation de :**
    - . L'adhérence au fibrinogène,
    - . La production de C5a-peptidase : mutation / *rgfC* affecte transcription de *scpB* codant pour C5a-peptidase

# REGULATION GENETIQUE

- Autres systèmes impliqués :
  - Système **DltS/DltR** :
    - Régulation synthèse acides lipoteichoïques
  - Système **CovS/CovR** :
    - régulation hémolyse et adhérence

# Rég *MtaR*

## Croissance sang Met



# Rég *rovS*

## Impact invasion

# Rég *rglB*

↗ adhérence  
 ◻ ↘ synthèse capsule

- Transcriptional activation
- | Transcriptional repression
- ? Indicates 'unknown' genes or function
- Activation through post-translational modification
- ▼ Repression/loss of function through post-translational modification

## Clinical Features of Group B *Streptococcus* Prosthetic Joint Infections and Molecular Characterization of Isolates<sup>▽</sup>

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Sepsis aigus

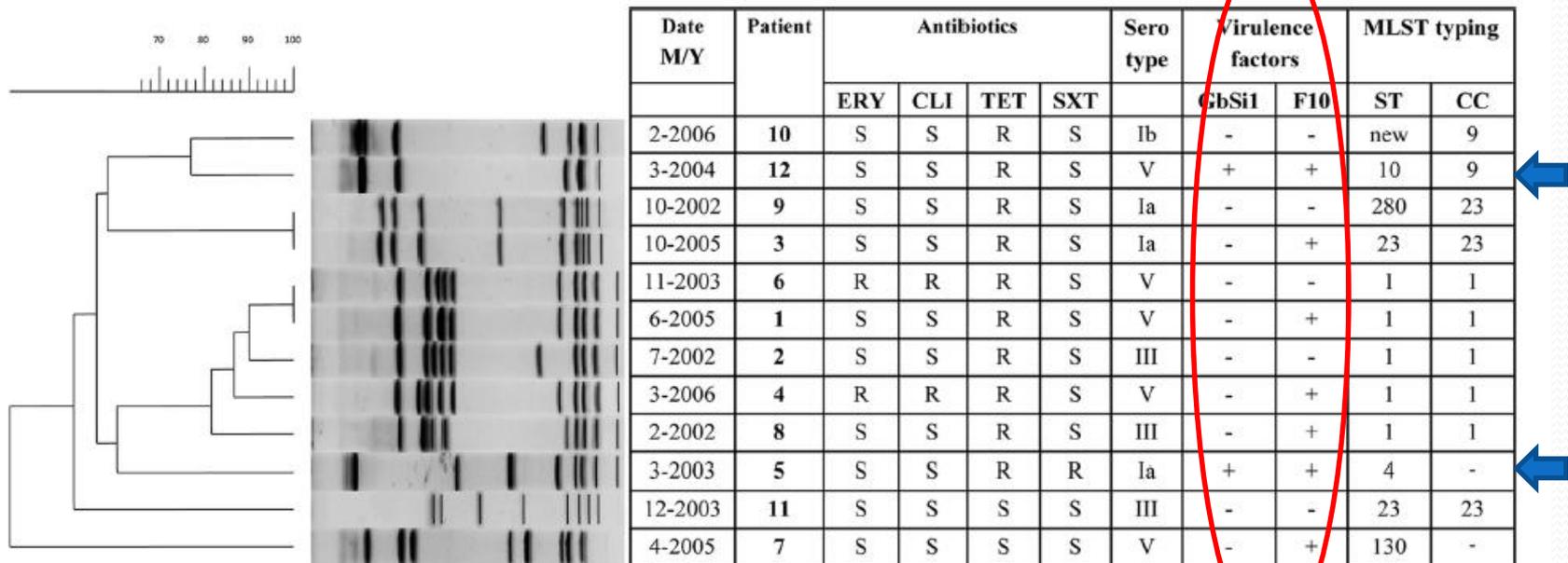


FIG. 1. Characteristics of 12 *Streptococcus agalactiae* prosthetic joint infection clinical isolates. Pulsed-field gel electrophoresis banding patterns after SmaI digestion are shown. Percentages of similarity are shown above the dendrogram. ERY, erythromycin; CLI, clindamycin; TET, tetracycline; SXT, co-trimoxazole; S, susceptible; R, resistant.

Prophage Groupe II intron = C5a peptidase *scpB* et IS1548 *hylB*

### **Investigating the genomic adaptation of group B *Streptococcus* following maternal transmission**

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## **👉 Du portage de SGB à l'infection et adaptation génétique**

### **👉 47 isolats analysés dont 19 paires**

- \* Bio-informatique +++
- \* Variation génomique SNP
- \* Variation chez l'hôte
- \* Expression de certains gènes de résistance

### **👉 Découverte de 21 SNP et 7 insertions/délétions**

14 mutations *covRS* locus = système de régulation virulence

1 mutation gène *rib* protéine de surface très immunogène

### **👉 Q-PCR = influence des mutations**

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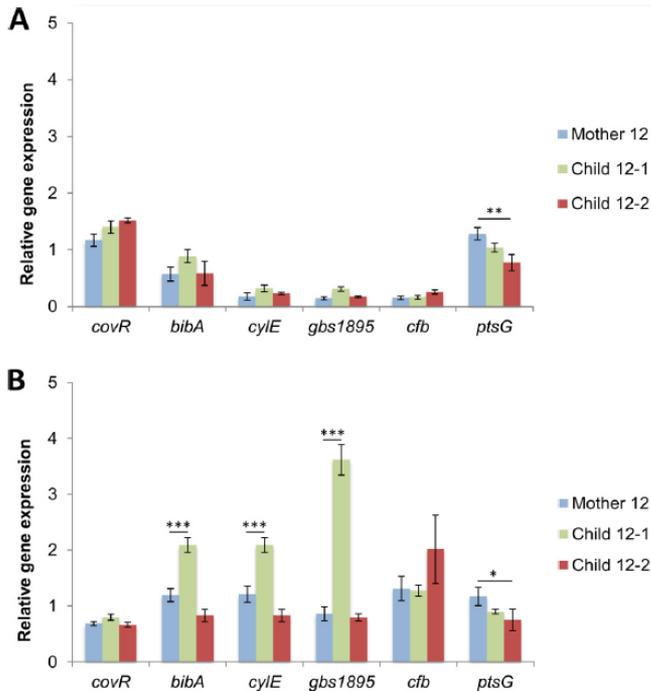


FIG 3 Relative expression of mutated genes (pair 12). RT-qPCR results obtained with GBS strains from pair 12 in TH medium (A) and after incubation for 1 h in human blood (B). The mother 12 isolate was mutated in the 5' UTR of *gbs1946* (*ptsG*), and both child strains were mutated in *gbs0668* (D-lactate dehydrogenase) and *gbs1038* (permease). The isolate from child 12-1 tested presented additional mutations affecting *gbs1946* (*ptsG*), *gbs1377* (homocysteine S-methyltransferase), and a phage terminase, while the child 12-2 strain specifically was mutated in the 5' UTR of *gbs1672* (*covR*) and *gbs0231* (putative transporter). Gene expression is represented after normalization to the house-keeping gene *gyrA*. Gene names are indicated below each graph. Experiments were performed in triplicate with three independent cultures. Error bars represent standard deviations. \*\*\*,  $P < 0.001$ ; \*\*,  $P < 0.01$ ; \*,  $P < 0.05$ .

☞ **Modifications adaptatives après colonisation**

☞ **Types, localisations des mutations et impact phénotypiques**

⇒ **Sélection « positive » avec transition d'un état commensal à strict pathogène = maladie**

☞ **Absence de mutations chez isolat de NN donc virulence intrinsèque du SGB !!!**

*Annu Rev Microbiol.* 2014 ; 68: 439–458. doi:10.1146/annurev-micro-092412-155711.

## Subterfuge and Sabotage:

### Evasion of Host Innate Defenses by Invasive Gram-Positive Bacterial Pathogens

**Cheryl Y.M. Okumura**<sup>1</sup> and **Victor Nizet**<sup>2</sup>

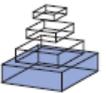
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frontiers in  
**CELLULAR AND INFECTION MICROBIOLOGY**

**MINI REVIEW ARTICLE**

published: 04 February 2015  
doi: 10.3389/fcimb.2015.00006



## Biofilm formation by *Streptococcus agalactiae*: influence of environmental conditions and implicated virulence factors

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