



UNIVERSITÉ
PARIS
DESCARTES

Perspectives vaccinales pendant la grossesse



Pr Odile Launay



Déclaration d'intérêts de 2014 à 2019

- Intérêts financiers : non
- Liens durables ou permanents : non
- Interventions ponctuelles : Sanofi Pasteur, Pfizer, Janssen, GSK bio, MSD
- Intérêts indirects : Fonds de recherche : Sanofi Pasteur, Pfizer, GSK bio, Janssen, MSD

Vaccination de la femme enceinte

- Objectifs: selon le vaccin,
 - protéger la mère
 - et/ou le fœtus
 - et/ou le nourrisson au cours des premières semaines de vie
- Elimination du tétanos néonatal
- Applications actuelles: grippe, coqueluche
- Applications futures:
VRS et strepto B

THE NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., Editor

Maternal Immunization

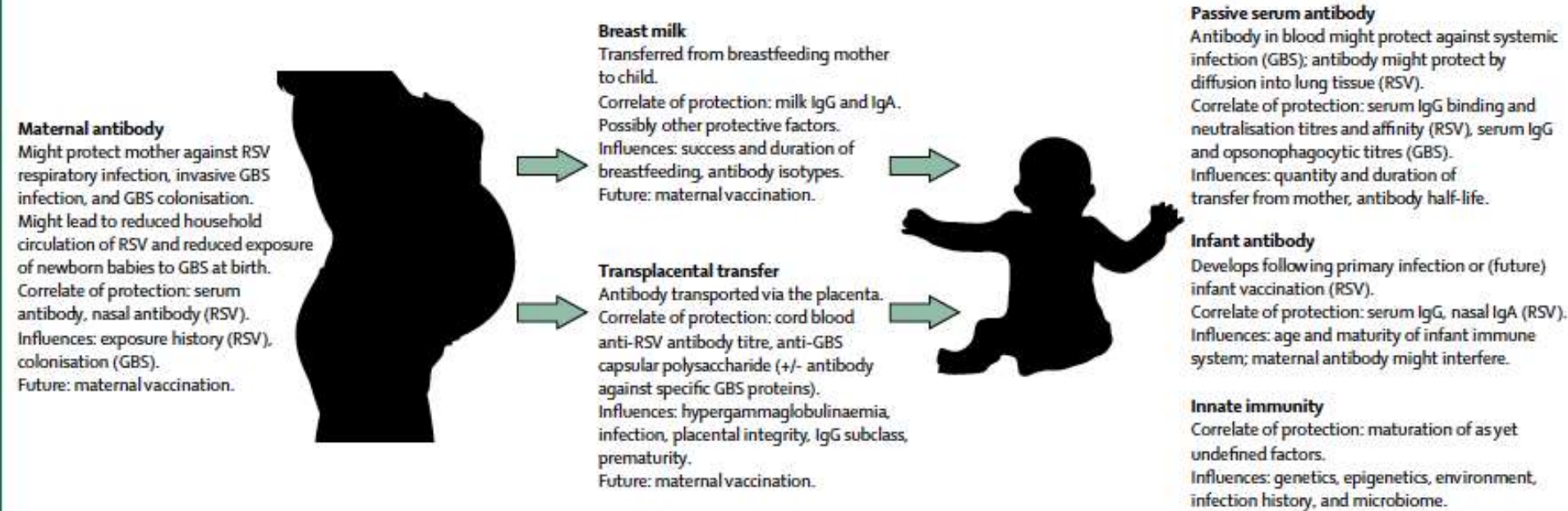
Saad B. Omer, M.B., B.S., M.P.H., Ph.D.

N ENGL J MED 376;13 NEJM.ORG MARCH 30, 2017

Vaccination de la femme enceinte

Group B streptococcus and respiratory syncytial virus immunisation during pregnancy: a landscape analysis

Pavli T Heath^{1*}, Fievas J Culley², Christine E Jones, Beetha Kangameen, Kirsty Le Deves, Maria C Nunes, Manish Sakranigari, Zain Chaudhry, Lenek Balam, Peter J M Openshaw



Le virus respiratoire syncytial: VRS (1)



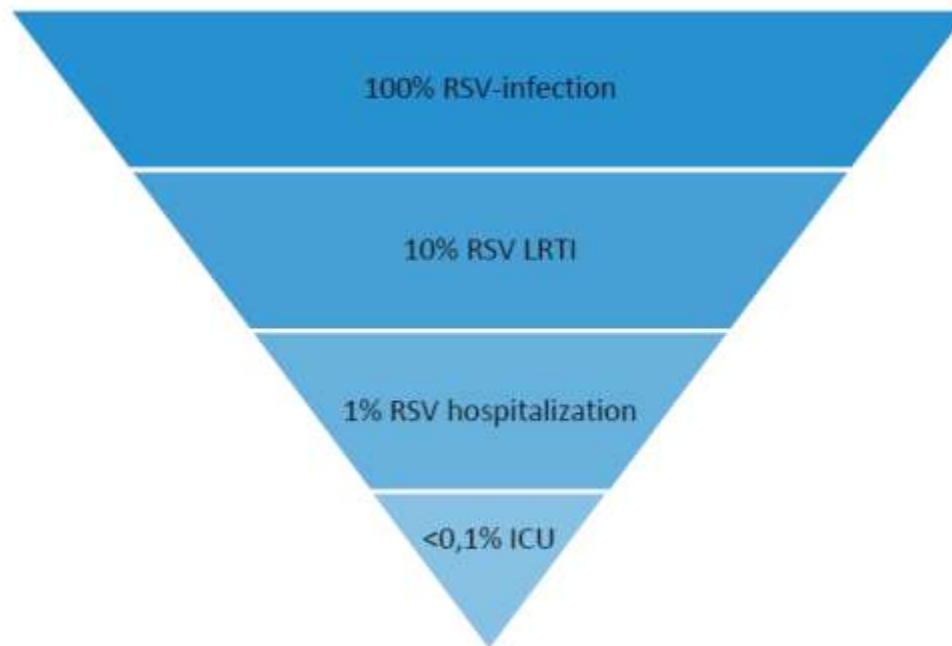
- Pneumovirus de la famille des paramyxoviridae
- virus à ARN simple brin
- Transmission par voie respiratoire (gouttelettes) et par contacts étroits avec des personnes infectées ou des objets contaminés
- 2 sérotypes: A et B (cross réactivité)
- Pathogénèse complexe: effet cytopathique direct sur les cellules épithéliales pulmonaire et infiltrat neutrophiles des peribronchiolaires entraînant un œdème et la formation d'un mucus lié à la réponse inflammatoire
- Sévérité variable d'un individu à l'autre

Le virus respiratoire syncytial: VRS (2)



- Principale cause virale d'infection respiratoire sévère et d'hospitalisation du jeune enfant
- > 60% des nourrissons avant l'âge de 1 an, 100% avant l'âge de 2 ans
- Pic d'hospitalisation chez le nourrisson entre 2 et 3 mois
- Risque d'infection sévère chez l'enfant jusqu'à l'âge de 5 ans
- Nourrissons à risque: prématurité, âge < 6mois, co morbidité cardiaque ou pulmonaire
- Pas d'immunité persistance, ré infection au cours de la vie tous les 3-5 ans
- Sévérité chez les personnes âgées et fragiles (co morbidités cardiaques ou pulmonaires) et en cas de déficit immunitaire portant sur l'immunité cellulaire CD8 (DCS, allogreffe de moelle, transplantation rénale ou sujets âgés)

Epidémiologie des infections à VRS





Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study



Ting Shi, David A McAllister, Katherine L O'Brien, Eric A F Simoes, Shabir A Madhi, Bradford D Gessner, Fernando P Polack, Evelyn Balsells, Socinho Acacio*, Claudia Aguayo*, Issifou Alassani*, Asad Ali*, Martin Antonio*, Shally Awasthi*, Juliet O Awori*, Eduardo Azziz-Baumgartner*,

Lancet 2017; 390: 946–58

Chez l'enfant de moins de 5 ans dans le Monde en 2015

- 33 millions de cas
- 3,2 millions d'hospitalisations
- 118 200 décès



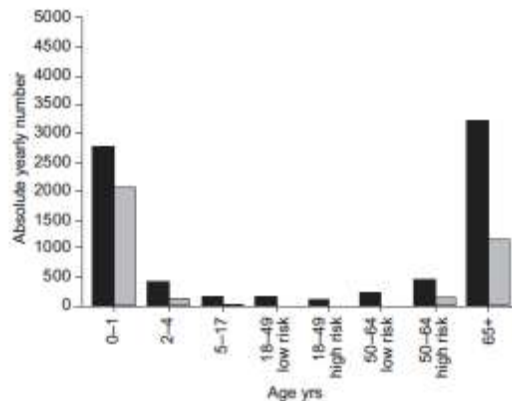


FIGURE 4. Respiratory syncytial virus-associated hospitalisation burden in the Netherlands. ■ versus summer baseline period, ▨ versus peri-seasonal baseline period.

Eur Respir J 2007; 30: 1158-1166
DOI: 10.1183/09031506.00034407
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Influenza- and respiratory syncytial virus-associated mortality and hospitalisations

A.G.S.C. Jansen*, E.A.M. Sanders*, A.W. Hoes*, A.M. van Loon[†] and E. Hak*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 28, 2005

VOL. 352 NO. 17

Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults

Ain K. Faleg, M.D., Patricia A. Hennessy, R.N., Maria A. Formica, M.S., Christopher Cox, Ph.D., and Edward E. Walsh, M.D.

Clinical Microbiology and Infection (2005) 50, 258

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

Journal homepage: www.clinicalmicrobiologyandinfection.com



Original article

Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France

P. Loubet^{1,2}, N. Lenzi³, M. Valette⁴, V. Foulongue⁵, A. Krivine⁶, N. Houhou⁷, G. Lagathu⁸, S. Rogez⁹, S. Alain¹⁰, X. Duval¹¹, F. Galtier¹², D. Postil¹³, P. Tattevin¹⁴, P. Vanhems^{15,16}, F. Carrat^{17,18}, B. Lina^{4,19}, O. Launay^{1,20,21,22}, the FLUVAC Study Group

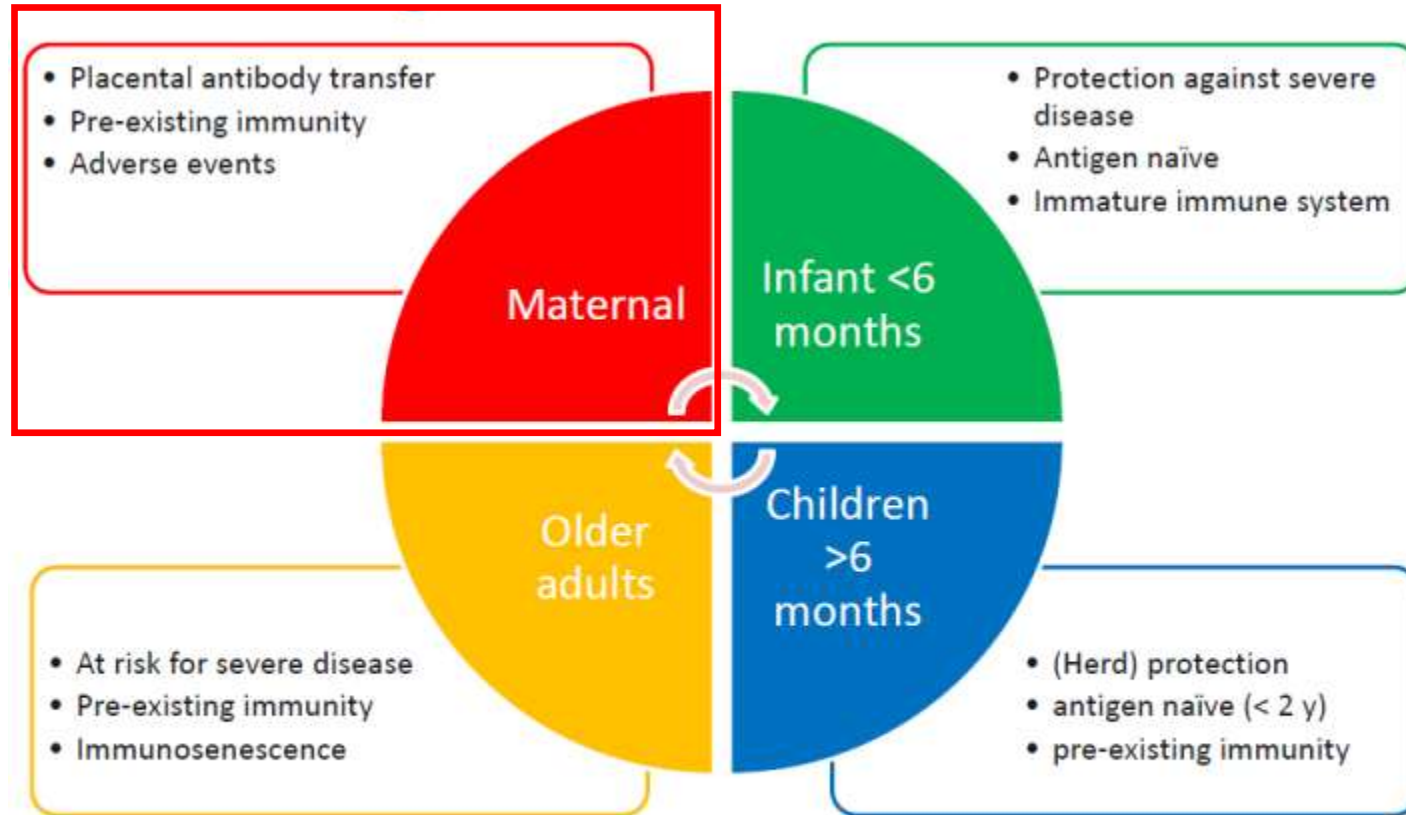
Chez l'adulte:

- 10 000 décès par an aux USA chez l'adulte de plus de 65 ans
- Autres terrains à risque:
 - Immunodéprimés
 - BPCO

Traitement de l'infection à VRS

- Traitement **symptomatique**: hydratation, ventilation assistée
- Ribavirine peu utilisé chez l'enfant
- Traitement préventif:
 - anticorps monoclonal anti protéine F: Palivizumab (Synoagis)
 - prévention des infections sévères à VRS chez le prématuré(<35SA)
 - 5 injections mensuelles
 - cout élevé
 - pas/peu d'effet sur l'infection
 - pas de vaccin disponible

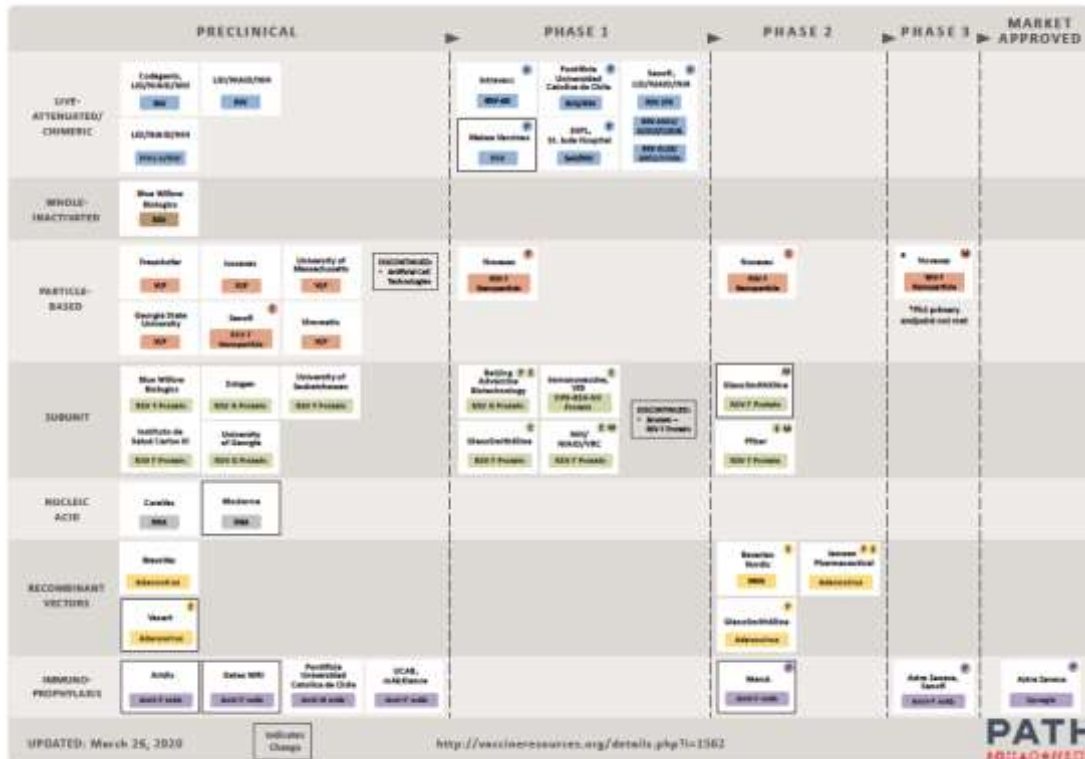
Les cibles pour un vaccin anti VRS



Vaccin contre le VRS

RSV Vaccine and mAb Snapshot

TARGET INDICATION: ☒ PEDIATRIC ☒ MATERNAL ☒ ELDERLY



UPDATED: March 25, 2020

Indicates Change

<http://vaccine-resources.org/details.php?id=1562>

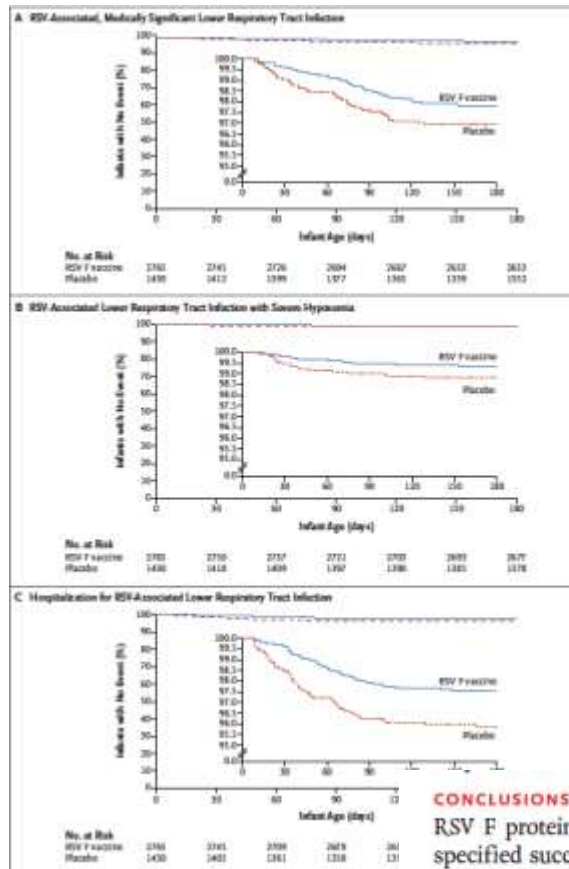
PATH
FORWARD

Vaccin nanoparticule (Novavax) Protein F VRS Vaccination 2:1 vs placebo Entre 28SA et 36 S

Suivi enfants jusqu'à M6
pour l'efficacité
1 an pour la sécurité

Critère principal: infection
respiratoire basse avant 3
mois

4636 femmes incluses`
87 sites dans le Monde



CONCLUSIONS

RSV F protein nanoparticle vaccination in pregnant women did not meet the pre-specified success criterion for efficacy against RSV-associated, medically significant lower respiratory tract infection in infants up to 90 days of life. The suggestion of a possible benefit with respect to other end-point events involving RSV-associated respiratory disease in infants warrants further study. (Funded by Novavax and the Bill and Melinda Gates Foundation; ClinicalTrials.gov NCT02624947.)

Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants

S.A. Madhi, F.P. Polack, P.A. Piedra, F.M. Munoz, A.A. Trenholme, E.A.F. Simões, C.V. Simões, C. Arora, V. Akhond, A. Amarat, A. Al-Barrak, A. Al-Ghazal, I. Chan

- Nirsevimab
- IgG1 kappa monoclonale
- Proteine recombinante

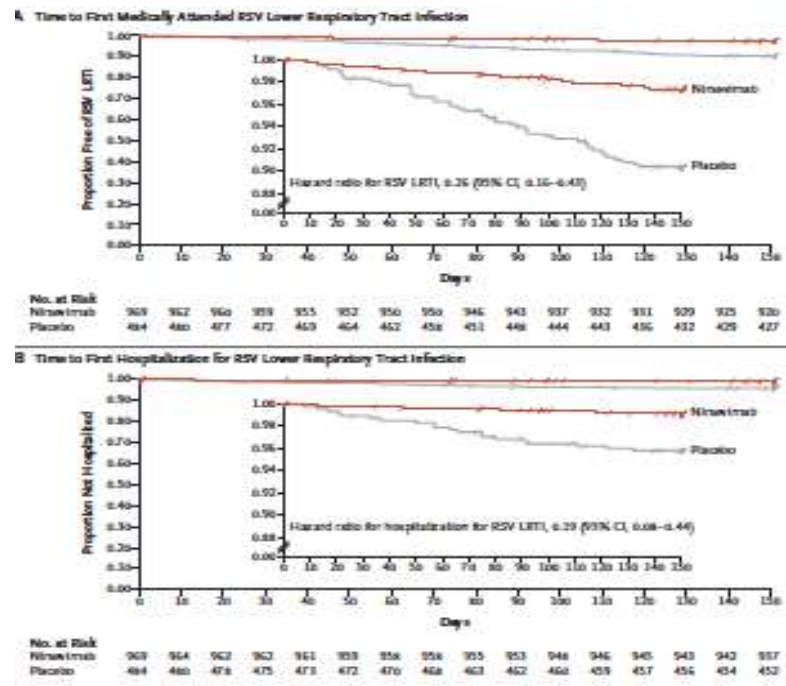
dirigée contre un épitope conservé présent sur la protéine de fusion du VRS

½ vie prolongée permettant une injection couvrant la période de circulation du VRS (5 mois)

- Une injection chez des nourrissons nés prématurés
- Randomisation 2:1 (969:484)
- Efficacité:
 - réduction de 70% des infections respiratoires basses
 - 78% des infections respiratoires basses hospitalisées

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

M. Pamela Griffin, M.D., Yuan Yuan, Ph.D., Theresa Takas, B.S., Joseph B. Dymally, M.D., Shafiq A. Madhi, M.B., B.Ch., Ph.D., Paolo Manzoni, M.D., Ph.D., Eric A.F. Simoes, M.D., Mark T. Esser, Ph.D., Anis A. Khan, Ph.D., Filip Dubovsky, M.D., Tanya Vilafans, Ph.D., and John P. DeVincenzo, M.D., for the Nirsevimab Study Group¹



Infections à Strepto B

- 800 cas d'infections invasives à Strepto B par an en France
- principalement transmission mère/enfant,
- 10% mortalité, séquelles neurologique
- Problème: immunité contre tous les serotypes.

	Mean incidence per 1000 livebirths (95% CI)
Europe	0.57 (0.44-0.71)
The Americas	0.67 (0.54-0.80)
Africa	1.21 (0.50-1.91)
Eastern Mediterranean	0.35 (0.07-0.62)
Western Pacific	0.15 (0.04-0.27)
Southeast Asia	0.02 (-0.03-0.07)

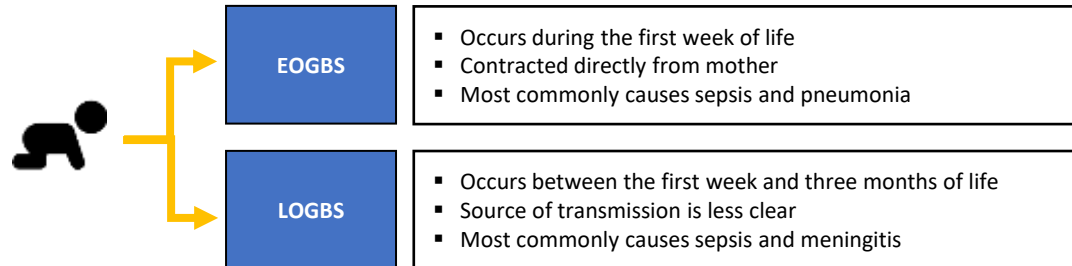
Table: Incidence of group B streptococcus disease in infants with disease onset 0-89 days between 2000 and 2011 by WHO region²⁹

www.thelancet.com/infection Published online April 29, 2016 [http://dx.doi.org/10.1016/S1473-3099\(16\)00152-3](http://dx.doi.org/10.1016/S1473-3099(16)00152-3)

Group B Streptococcus is a bacteria commonly found in women, which can be transmitted to infants during pregnancy

Disease Overview

- Group B streptococcus (GBS) is a bacteria that lives in the body and usually does not cause serious illness; however, in pregnant women GBS can result in maternal infections including uterine (amnionitis), urinary, and bloodstream infections (sepsis)
- A woman who is colonized with GBS late in her pregnancy can pass it to her baby during labor
 - Infection is caused by direct transfer of GBS from the mother to the baby, usually after the water breaks where the bacteria travel up from the vagina into the amniotic fluid
- While GBS infections can affect anyone, newborns are at the highest risk of serious complications, such as sepsis, meningitis, and death
- There are 2 types of patient types with GBS: **early onset** (EOGBS) and **late onset** (LOGBS)



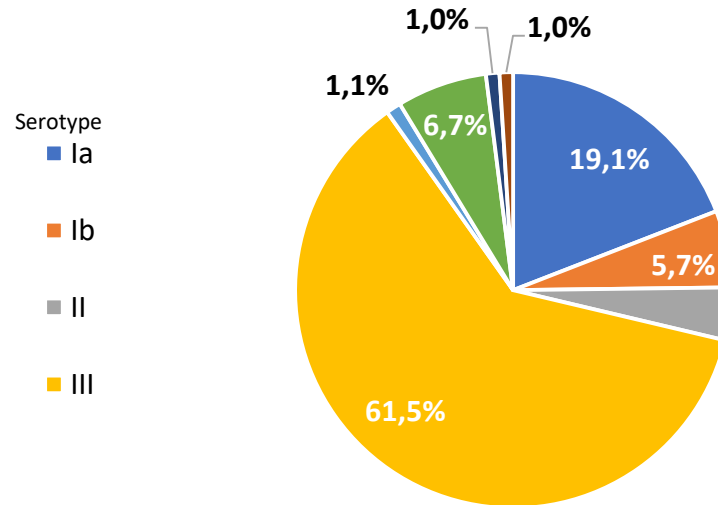
Invasive GBS Syndromes and Common Clinical Presentations*

Sepsis	▪ Hypothermia, lethargy, poor feeding, and respiratory symptoms such as tachypnea, grunting, hypoxia; may vary by gestational age and severity of infection
Pneumonia	▪ Respiratory symptoms including apnea, tachypnea, grunting, nasal flaring, and intercostal retractions²
Meningitis	▪ Temperature instability, irritability or lethargy, poor feeding, vomiting and signs of upper respiratory infection such as apnea, tachypnea or grunting
Focal Infections	▪ Less frequent infections in organs such as bones, joints, skin and lymph nodes presenting with range of symptoms

Six serotypes, Ia, Ib, II, III, IV and V, account for 98% of isolates found in invasive infant GBS

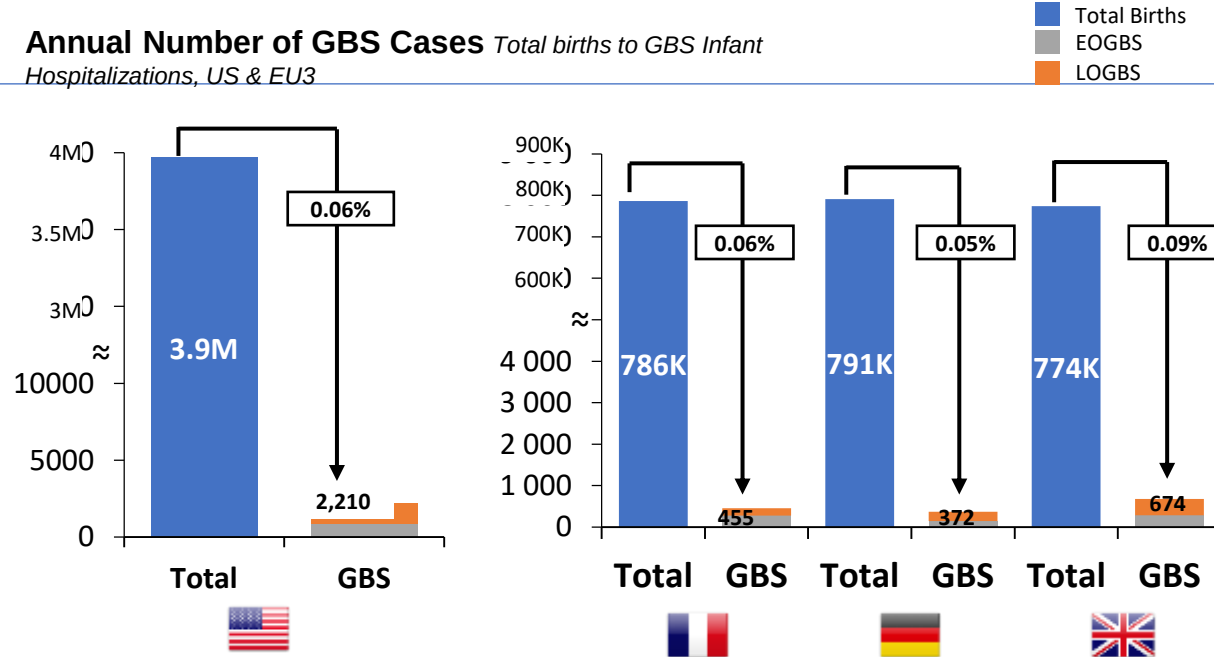
Distribution of GBS Serotypes in Infants

Infants (< 90 days), % of Invasive Isolates



GBS impacts 0.06% of births in the US, with similar infection rates across all other markets

Annual Number of GBS Cases *Total births to GBS Infant*
Hospitalizations, US & EU3

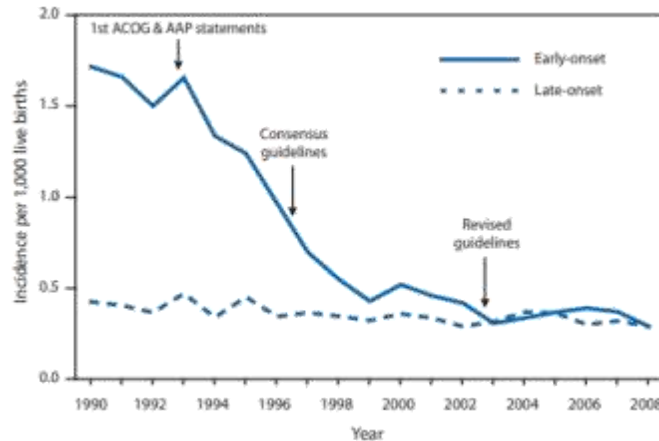


- 25% of pregnant women carry GBS, and if untreated, 1-2% of babies will develop GBS
- However, with current GBS prevention approaches, only ~0.06% of newborns develop GBS infections

Dépistage et traitement de la colonisation à strepto B (35-37 SA) : impact sur les formes précoces

Incidence of Infant GBS over Time

US, 1990-2008



- Use of IAP decreased early-onset infection from 1.7 cases per 1,000 live births (1993) to 0.22 cases per 1,000 live births (2016) in the US

Intérêt de la vaccination pour le formes tardives
Mais aussi pour les formes précoces en cas de difficulté de dépistage

GBS vaccine

- Vaccin conjugué
- Strepto B sérotype 3
- Efficacité sur le délai d'acquisition vaginale (36%) et rectal (43%)

Nécessité de démontrer:

- l'efficacité sur la transmission chez le nouveau né
- autres serotypes

A Phase 2, Randomized, Control Trial of Group B *Streptococcus* (GBS) Type III Capsular Polysaccharide-tetanus Toxoid (GBS III-TT) Vaccine to Prevent Vaginal Colonization With GBS III

Sharon L. Hillier,¹ Patricia Ferrieri,² Morven S. Edwards,³ Marian Ewell,⁴ Daron Ferris,⁵ Paul Fine,⁶ Vincent Carey,⁷ Leslie Meyn,¹ Dakota Hoagland,⁸ Dennis L. Kasper,⁹ Lawrence C. Paoletti,⁸ Heather Hill,⁴ and Carol J. Baker¹⁰

Table 2. Estimate of Group B *Streptococcus* (GBS) Type III Capsular Polysaccharide-tetanus Toxoid Conjugate Vaccine Efficacy Against Acquisition of Vaginal and Rectal Colonization With Type III GBS

	Vaccine Efficacy	Confidence Interval	P Value
Time to first positive swab			
Vaginal	0.35	0.01 to 0.58	.047 ^a
Rectal	0.42	0.10 to 0.63	.015 ^a
Proportion of positive swabs			
Vaginal			
Not adjusted	0.36	−0.07 to 0.61	.089
Adjusted ^b	0.36	−0.06 to 0.62	.085
Rectal			
Not adjusted	0.41	−0.01 to 0.66	.055
Adjusted	0.49	0.13 to 0.70	.014 ^a

^aStatistically significant at the 0.05 level of significance.

Vaccination de la femme enceinte-perspectives

Approche ayant démontrée son efficacité pour le tetanos, la grippe et la coqueluche

Pour le VRS: 2 approches : vaccination de la mère et immunisation passive du nné

Strepto B?

The first RSV vaccine failed

- Formalin inactivated (FI)
- Children 2 months – 7 year
- FI-RSV (n=23) and controls (n=39)

