

# Actualités des microbiotes impact du microbiote vaginal en Obstétrique

## REVEAL Eu Project

Pr Florence Bretelle



- Disclosers



- No other link of interest

# Impact of the Microbiome in Obstetrics

## Preconception Period

- Fertility & Assisted Reproduction
- Pregnancy preparation



## Maternal Health

- Pregnancy complications
- Gestational diabetes



## Assisted Reproductive Technology (ART)

- Early pregnancy loss
- Preterm birth
- PROM or PPROM
- Preeclampsia
- Cesarean section



## Infant Health

- Immunity & development
- Noncommunicable Disease Risk



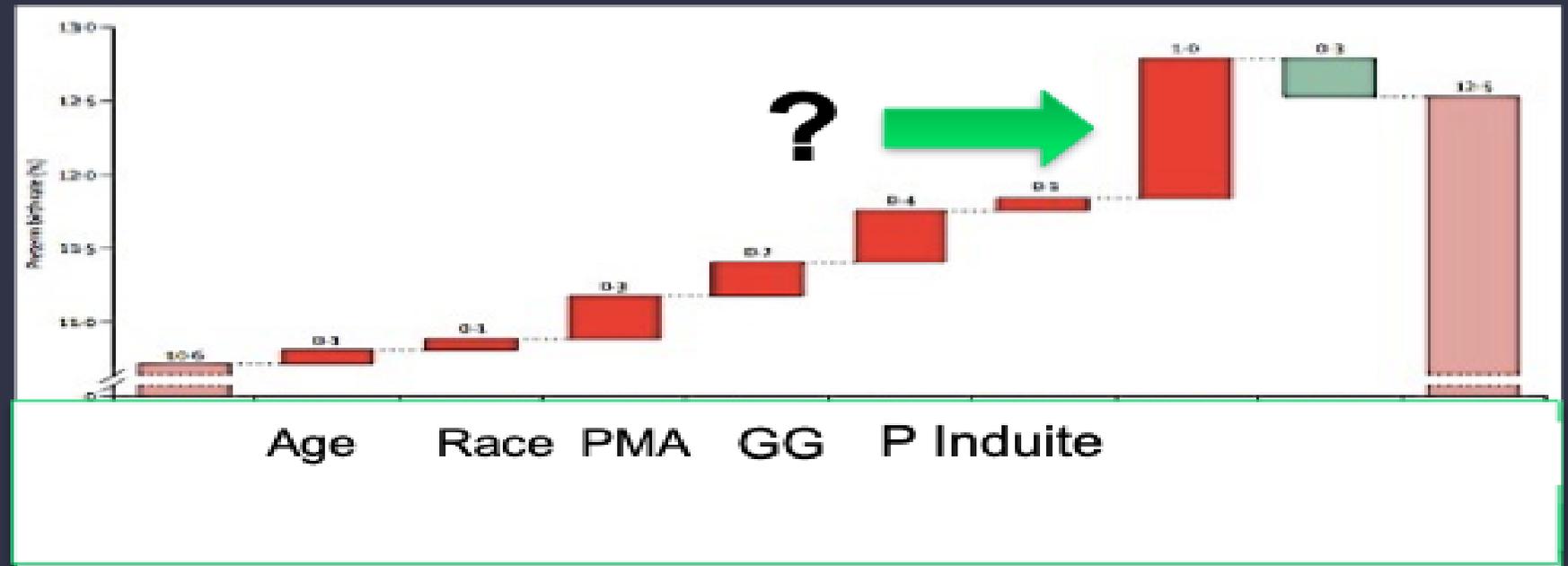
## Pregnancy Outcomes

- Early pregnancy loss
- Preterm birth
- PROM or PPROM
- Preeclampsia
- Cesarean section

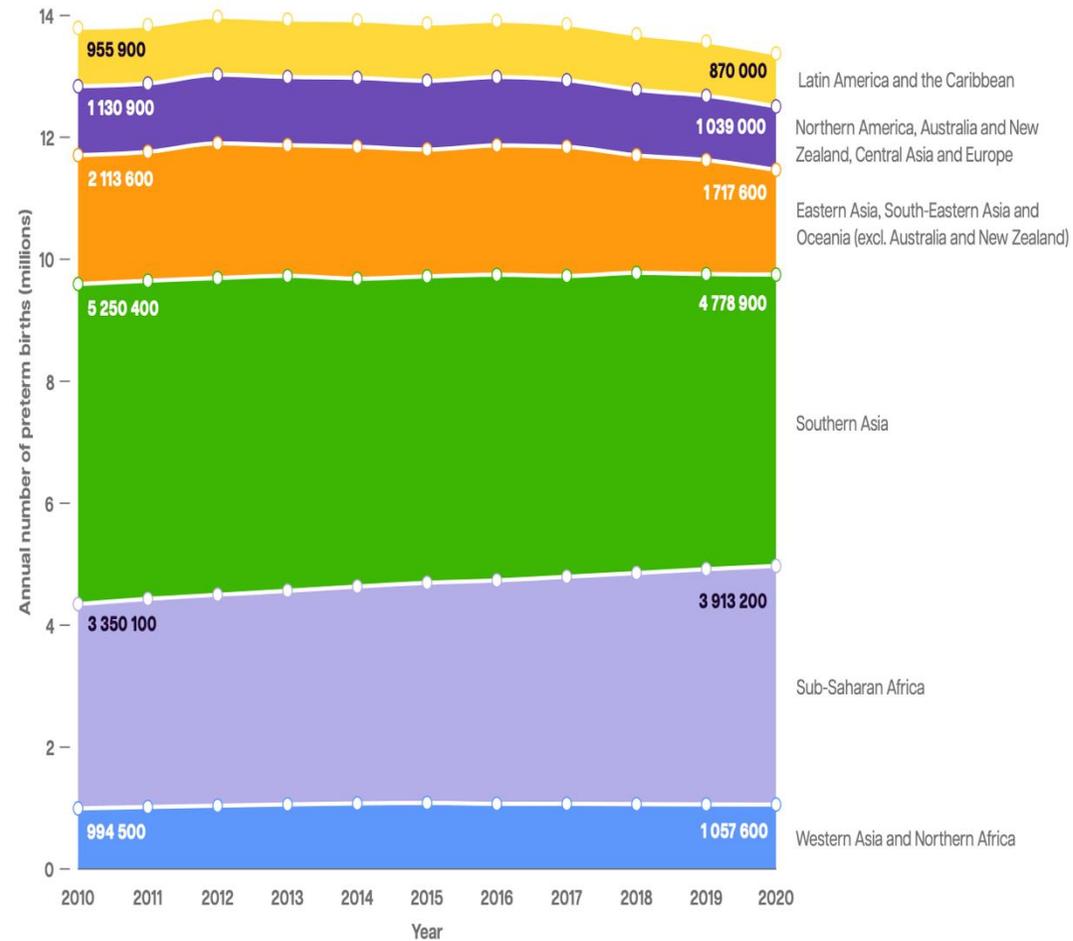


# Born to soon

- La majorité des AP surviennent chez les patientes sans ATCD
- 15 Millions d'AP en 2010
- 5% < 28 sa
- Objectif réduire la prématurité de 50% d'ici 2025

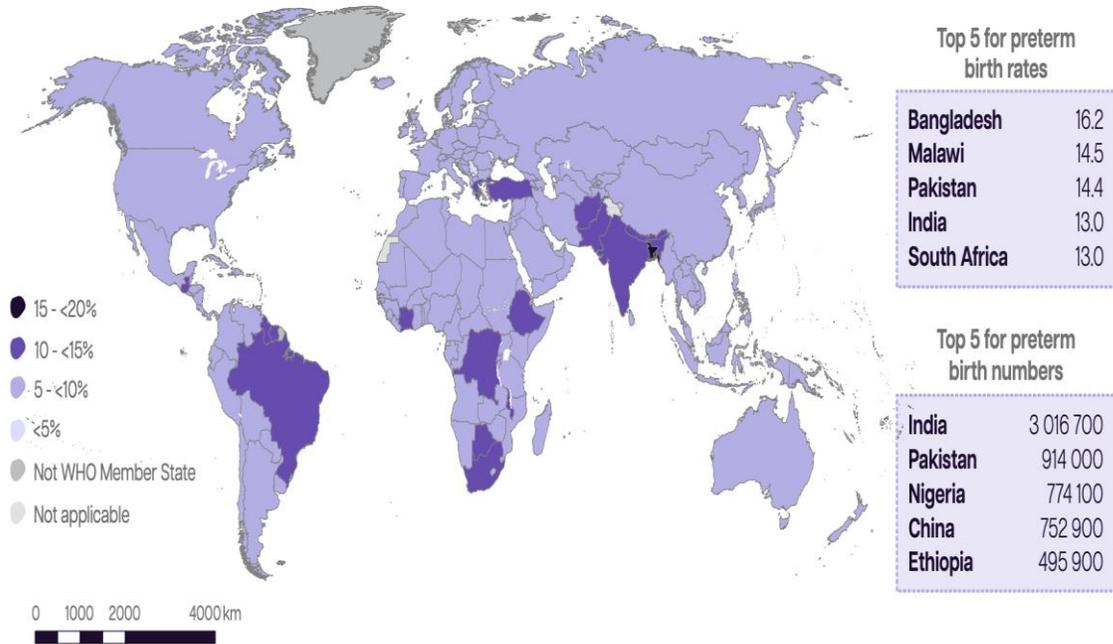


# Preterm Birth trends 2010-2020



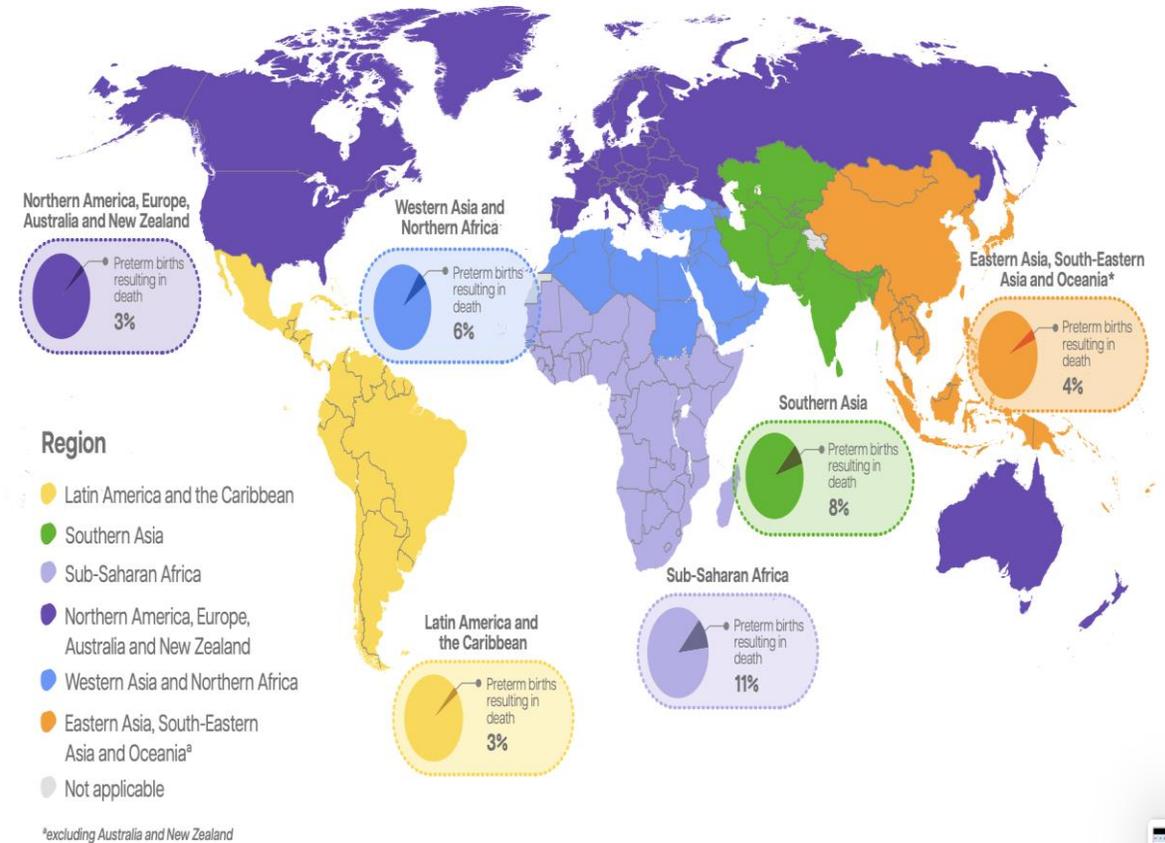
Data from WHO and UNICEF preterm birth estimates, Ohuma et al. (1).  
Source: Lawn et al. (12)

# National Preterm birth rate 2020



Source: UNICEF and WHO preterm estimates. Ohuma et al. (1)  
 Estimates are developed for international comparison and countries may decide to use their own national statistics for national planning and other purposes.

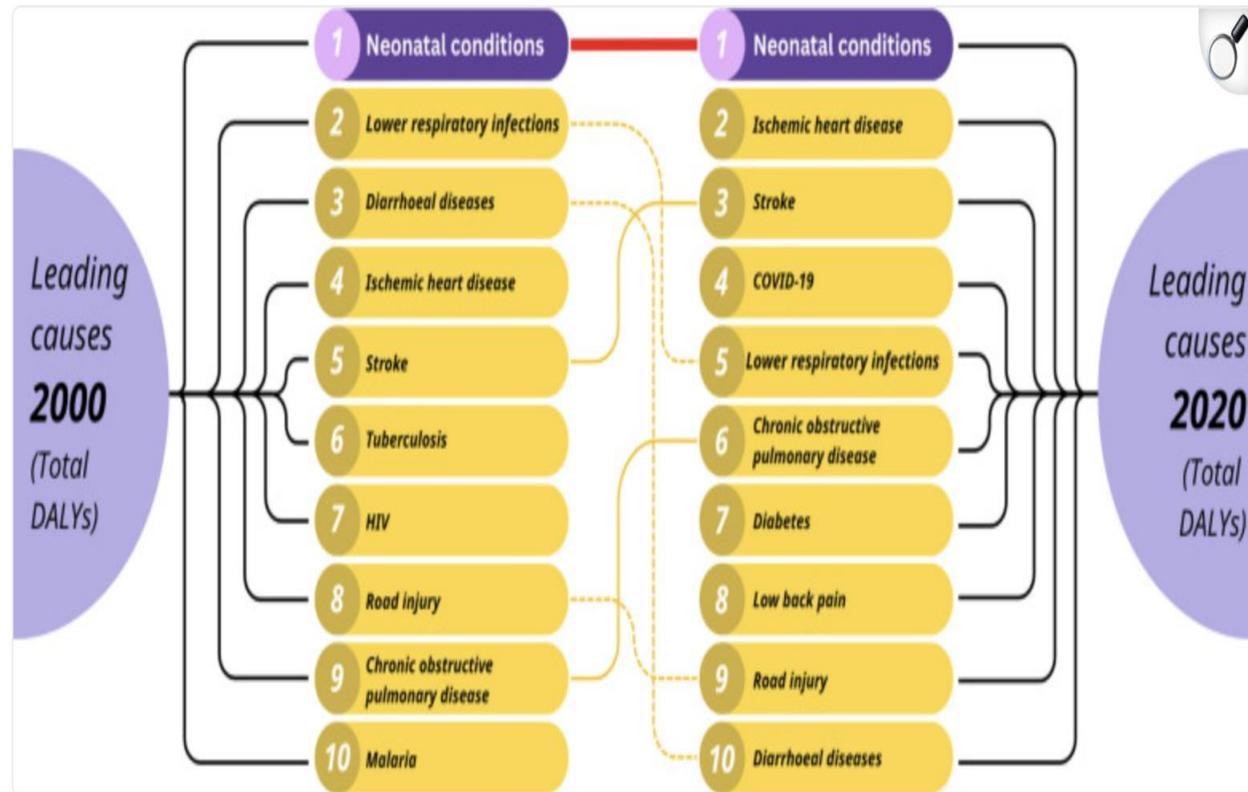
# Preterm birth mortality



**TABLE 2.1 Preterm birth risk factors and prevention strategies**

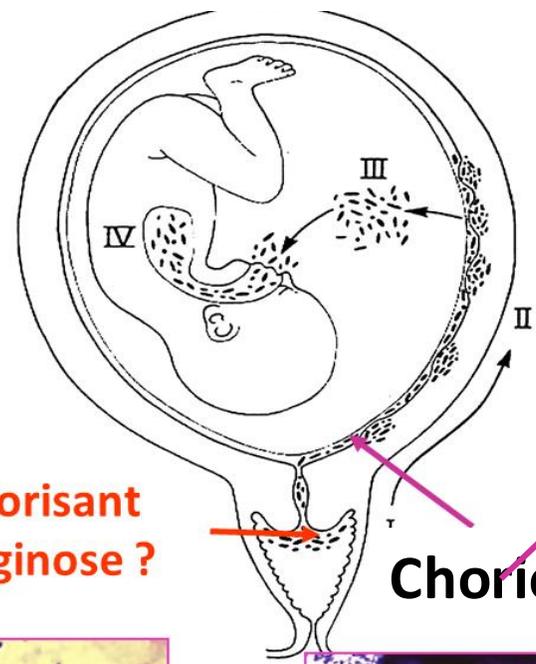
Type	Risk factors	Examples	Prevention strategies <sup>b</sup>
Spontaneous preterm birth <sup>c</sup>	Age at pregnancy and pregnancy spacing	Adolescent pregnancy, advanced maternal age, short inter-pregnancy interval	Preconception care, including access to family planning from adolescence, after birth and throughout reproductive years
	Multiple pregnancies	Increased rates of twin and higher-order pregnancies with assisted reproduction	Introduce and monitor policies for best practice in assisted reproduction
	Infection	Urinary tract infections, asymptomatic bacteriuria, malaria, HIV, syphilis, chorioamnionitis, bacterial vaginosis	Sexual health programmes aimed at prevention and treatment of infections prior to and during pregnancy  Intermittent preventive treatment of malaria (context-specific), antenatal screening for lower genital tract infections and asymptomatic bacteriuria
	Underlying chronic medical conditions	Diabetes, hypertension, anaemia, asthma, thyroid disease, HIV	Maximize preconception control for pre-existing conditions, as well as screening and prompt management during pregnancy
	Nutritional	Undernutrition, micronutrient deficiencies	Assess and treat low nutritional status prior to conception and in early pregnancy  Consider supplementation (e.g. iron folate and zinc supplementation) for pregnant women without systemic illness
	Lifestyle and work-related	Smoking, excess alcohol consumption, recreational drug use, excess physical work and activity	Adopt laws and rights-based approaches to protect pregnant women, and ensure maternity leave  Behavioural and community public health interventions targeting pregnant women and women of reproductive age, e.g. pharmacological interventions for smoking cessation
	Environmental	Exposure to indoor and ambient air pollution, heat stress	Public health measures, antenatal counselling, avoidance of air pollution and excessive heat where possible

Fig. 1.



Neonatal disorders: the leading condition of global burden of disease, 2000 and 2020

# Bacterial vaginosis (BV): a risk factor for preterm birth



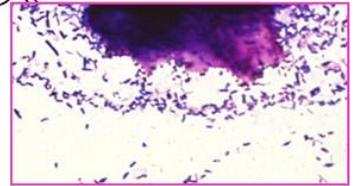
Rôle favorisant de la vaginose ?

**Chorioamnionitis**



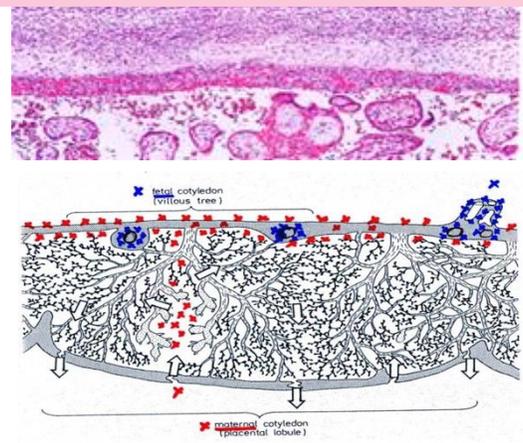
Nugent = 0 à 6 (flore équilibrée)

**Normal Flora**



Nugent = 7 à 10 (=vaginose)

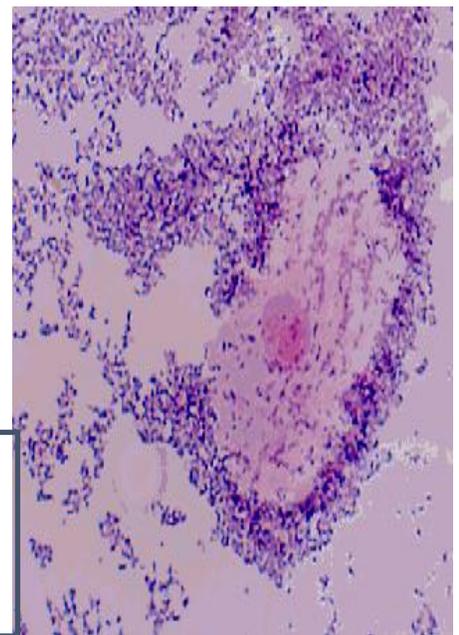
**Bacterial Vaginosis**



BV is asymptomatic in up to 50%

- Preterm Rupture of Membranes +++ (OR = 3)
- Preterm Birth (OR = 1.5)
- Early PTB++ (OR=2)

OR= 6 < 16 weeks of gestation



Hillier et al, N Engl J Med 1995

# Bacterial Vaginosis and Pregnancy Loss

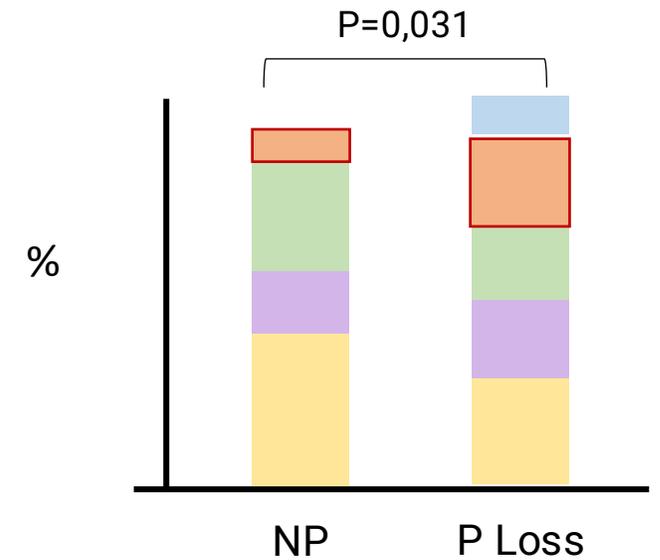
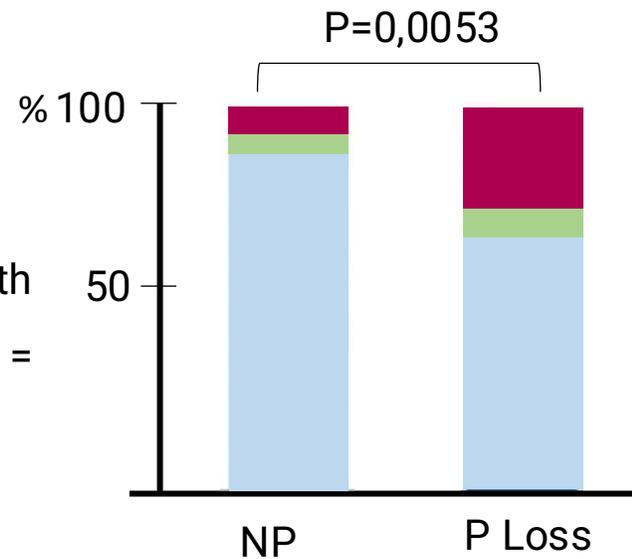
## Vaginal microbiote analysis :

- 1st and 2<sup>nd</sup> Pregnancy Loss (n = 77)
- Normal Pregnancy (n = 81)

**Lactobacillus**

- Lack
- Intermediate
- Dominant

✓ Pregnancy loss is associated with Lack of **Lactobacillus** spp. (P = 0,0053)



**CST**

- I
- II
- III
- IV
- V

# Preterm Birth prevention guidelines

- Only cessation of smoking is associated with decreased prematurity (LE 1) => recommended (Grade A).
- Routine screening and treatment of bacterial vaginosis is not recommended in the general population (Grade A).....

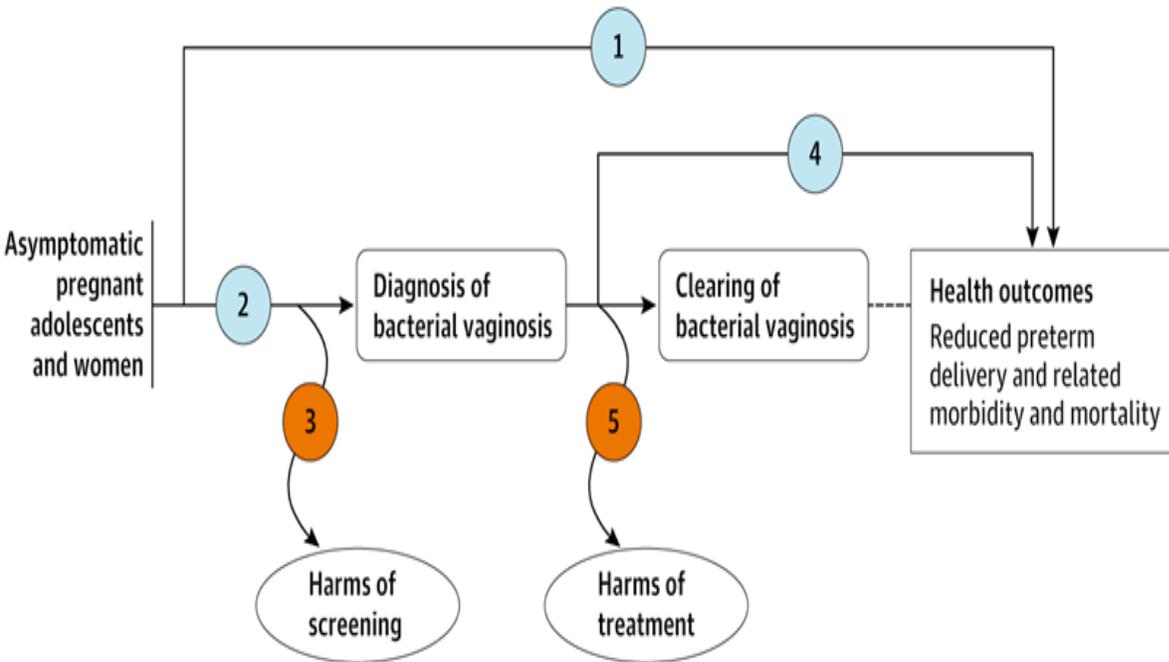
CNGOF 2016

## International guidelines

Key recommendations	Yes	Conditional Yes	No	Not enough evidence to recommend
<b>Guidelines endorsed...</b>				
Cervical length as screening in high-risk women only	5	3*	0	1
Screening for asymptomatic bacteriuria to prevent PTB	2	0	0	0
<b>Guidelines advised against...</b>				
Cervical length as universal screening in each pregnancy	2	0	4	2
Screening for bacterial vaginosis to prevent PTB in women without signs of PTL or PPROM	0	2**	5	0

Medley BJOG 2018

# Screen&Treat during pregnancy to prevent Preterm Birth



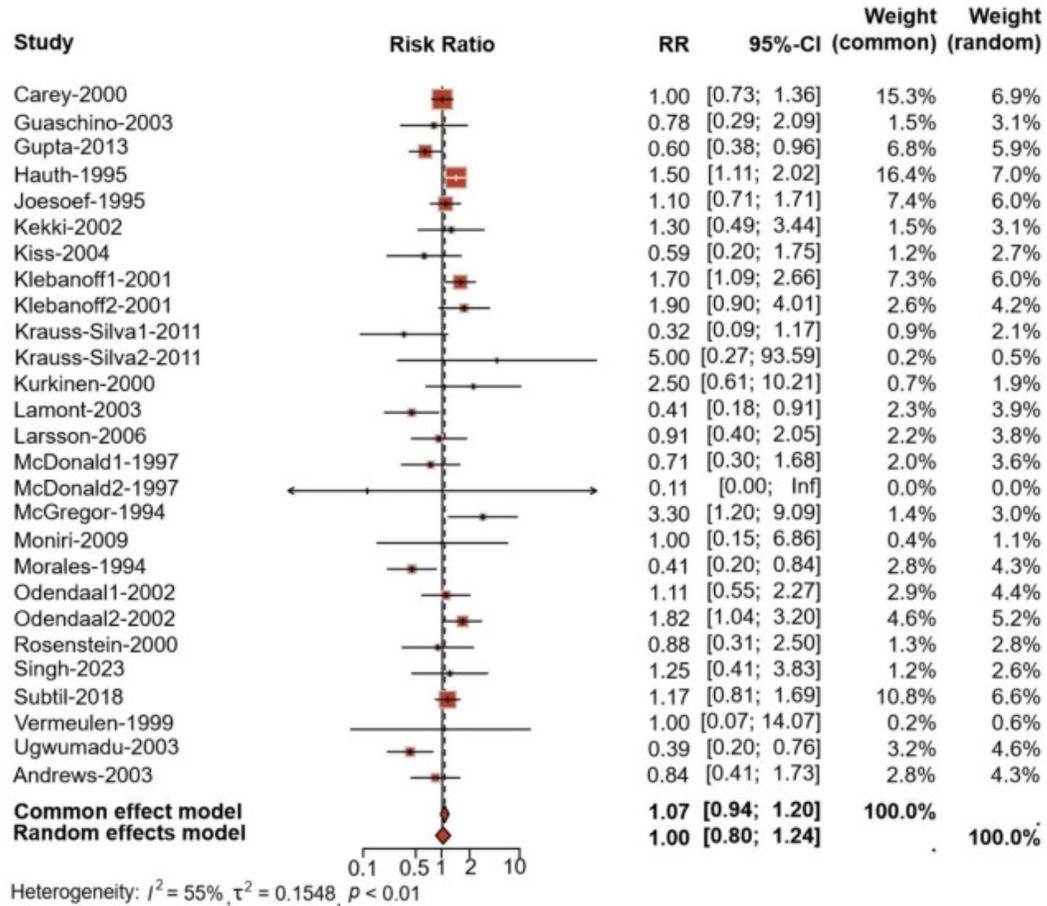
## Accuracy of S&T

- Meta-analysis of Conventional Tools
- Sensitivity 0,36-1 and Specificity 0,49-1 ( n=7853 Pregnancies) => No PTB reduction
- For at risk Pregnancy: inconclusive

JAMA

FULL  
TEXT

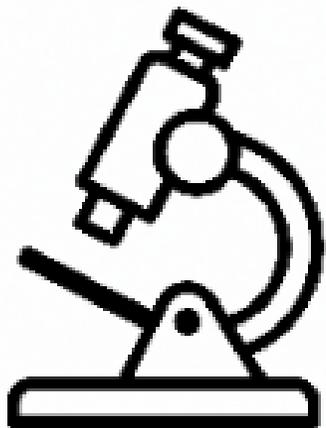
# Screen&Treat during pregnancy to prevent Preterm Birth



Screen and Treat Doesn't work

Except in UK and Austria :  
Screen & Treat for BV works  
RR 0.39

# It's all about diagnosis



# It's all about diagnosis: Standard Diagnosis

Points	<i>Lactobacillus</i>	<i>Gardnerella et Bacteroides spp</i> (BGN et/ou clue cells)	<i>Mobiluncus</i> (BGN incurvés)	
0	> 30 / champs	Absence	Absence	
1	5 – 30 / champs	< 1 / champs	< 1 – 4 / champs	
2	1 – 4 / champs	1 – 4 / champs	≥ 5/champs	
3	< 1/champs	5 – 30 / champs		
4	Absence	> 30 / champs		
Sous-scores	A	B	C	Score : A+B+C



Nugent > 4 :  
intermediate Flora

Nugent > 7 : BV

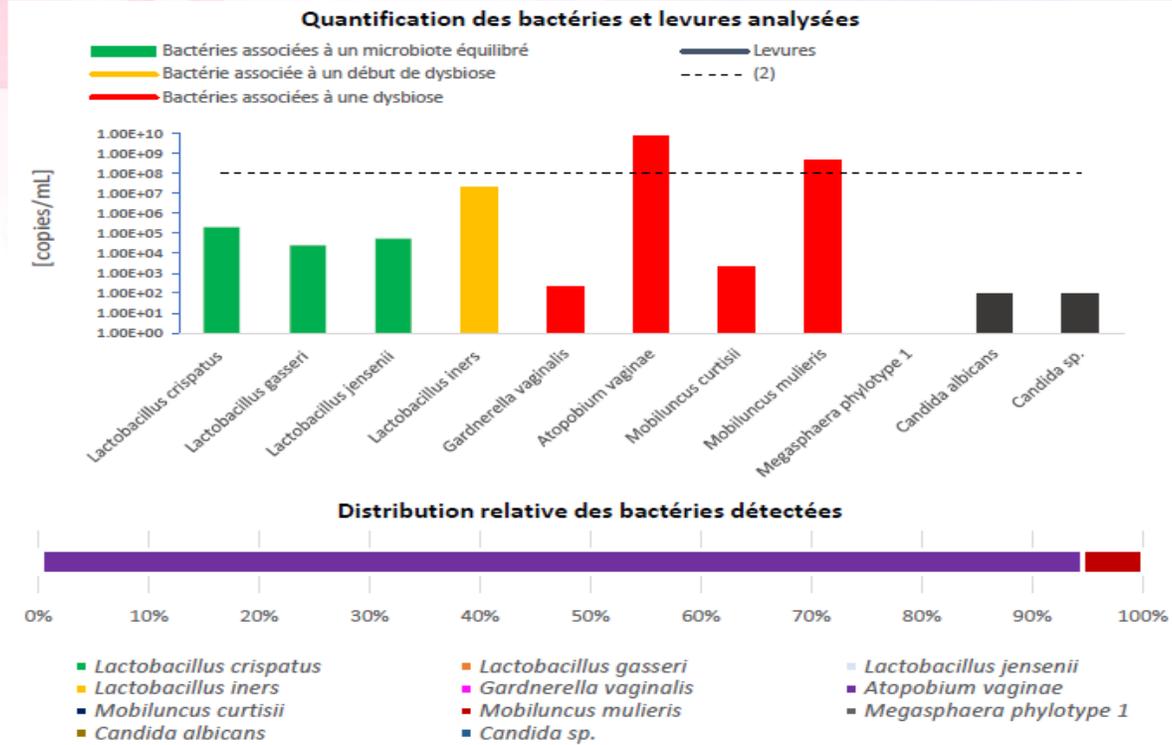
## Amsel's Criteria

- Pertes vaginales homogènes blanches et adhérentes à la paroi vaginale
- pH vaginal supérieur à 4.5 déterminé par papier pH
- une odeur des pertes vaginales à type de poisson avarié spontanée ou provoquée par l'addition d'un réactif à la potasse (test à la potasse).

## Nugent Score

# It's all about diagnosis: PCR

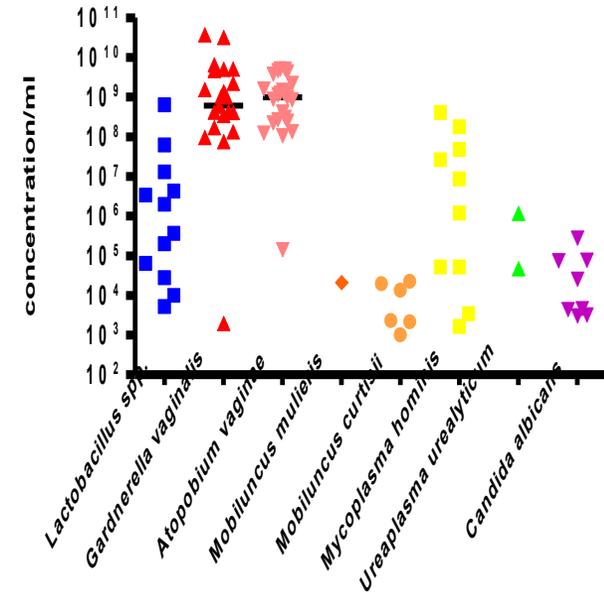
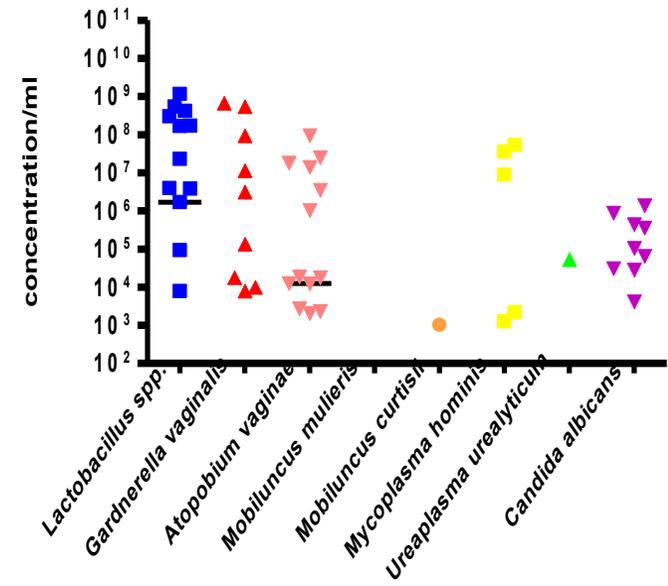
Résultats:



**Interprétation:**

Flore vaginale avec prédominance de bactéries anaérobies, correspondant à la classe 4 d'après la norme de classification CST(1) : écosystème déséquilibré, signe de la présence d'une vaginose bactérienne.

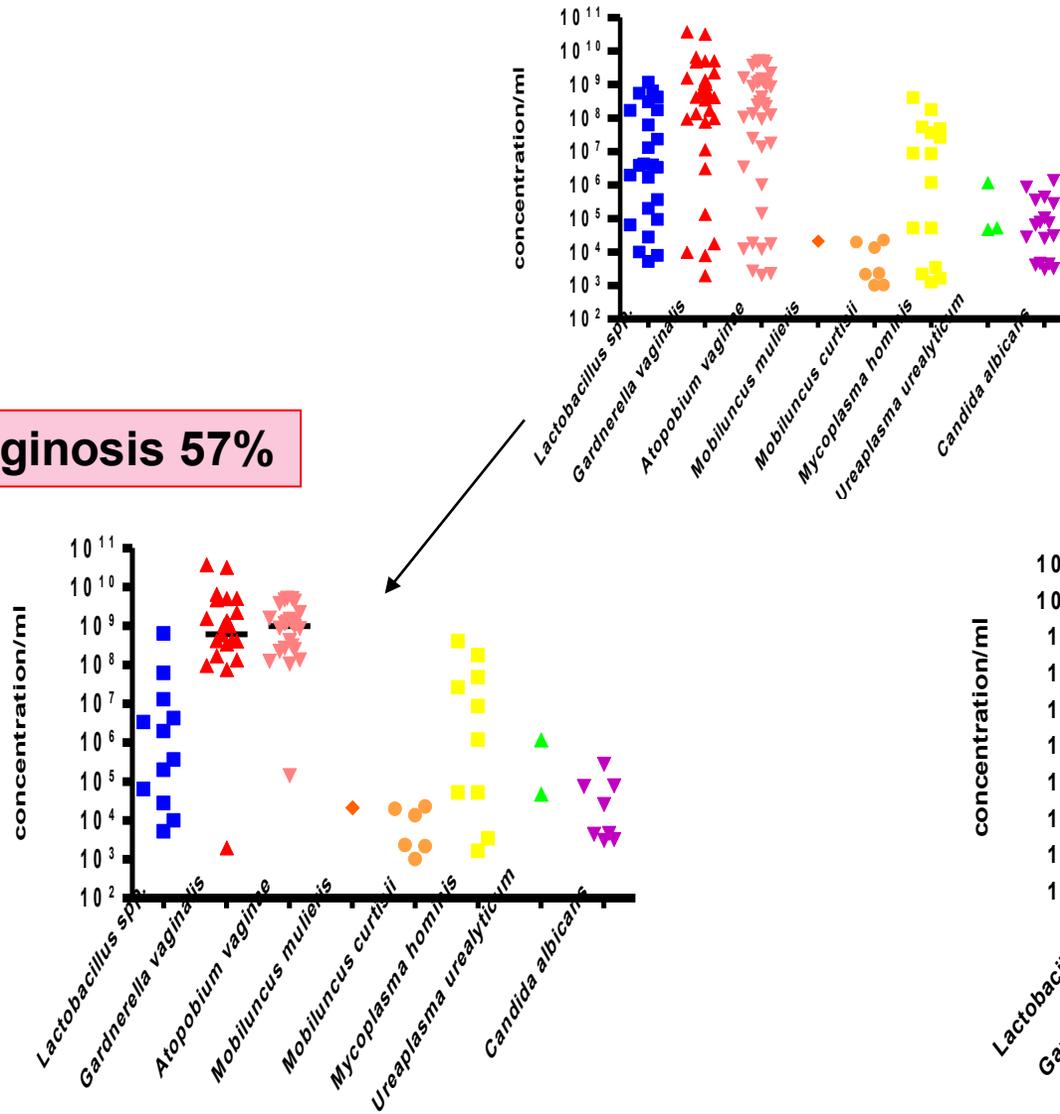
Dr. Philippe HALFON



Ménard, Bretelle 2018; Ménard, Bretelle 2010

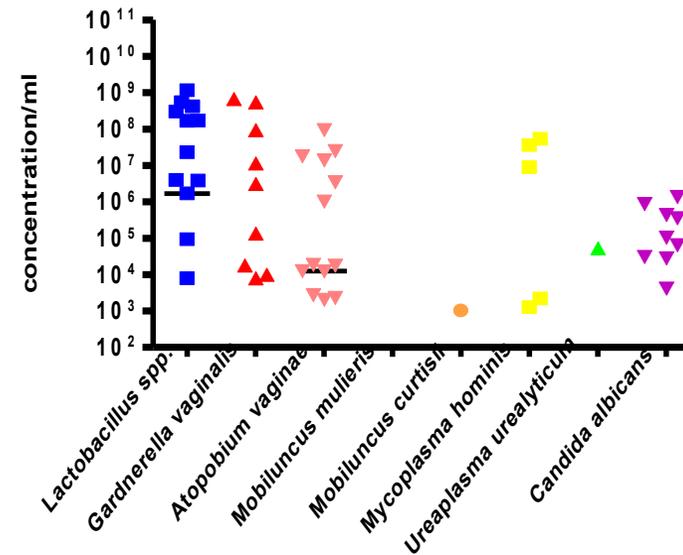
# Bacterial Vaginosis diagnosis: Molecular biology analysis ( PCR) > Nugent score

**Bacterial Vaginosis 57%**



**Intermediate Flora or Nugent score 3-7**

**Normal Flora 43%**



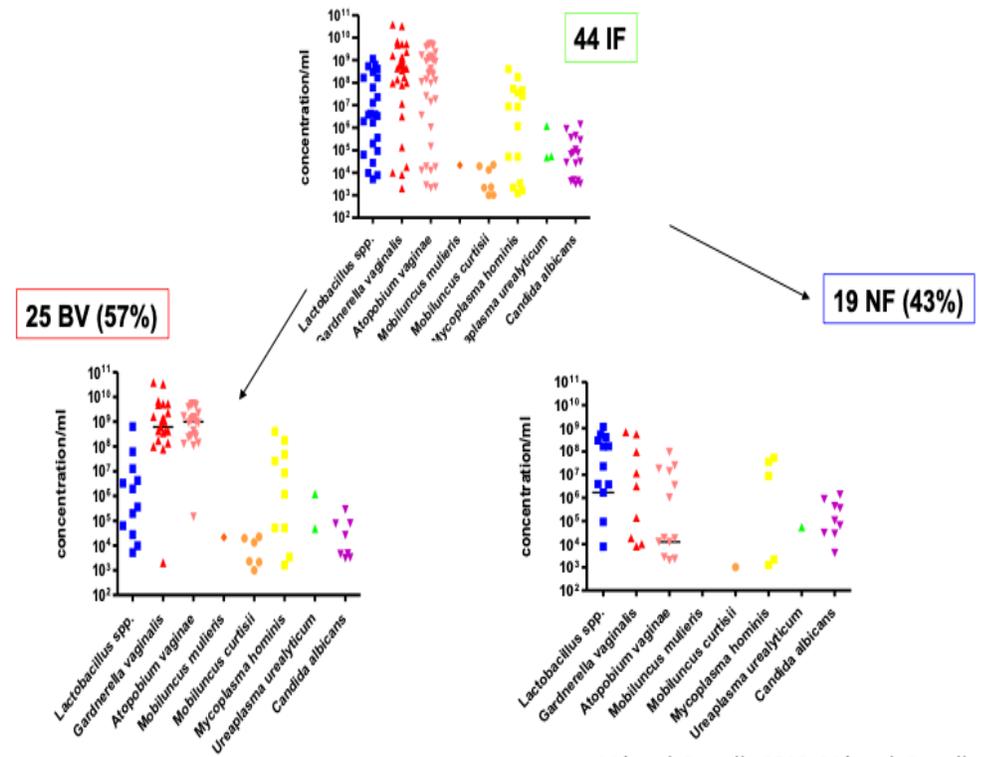
# It's all about diagnosis: PCR >> Nugent

Using standard diagnosis means:

-> Wrongly including 43% of Normal Women if inclusion is Nugent score >4

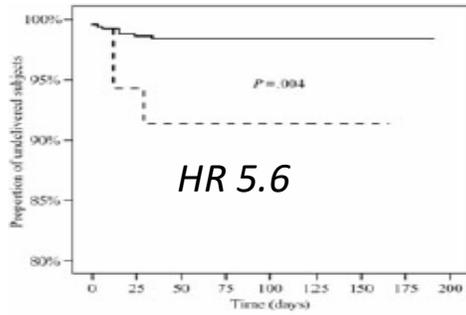
-> Missing 57% of patient if inclusion criteria is Nugent score >7

## PCR Molecular analysis > Nugent score

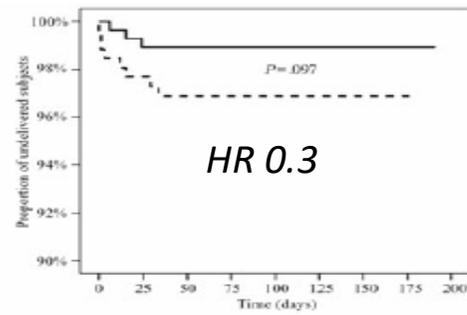


# PCR *A. vaginae* et *G. vaginalis* portage decrease the time to delivery

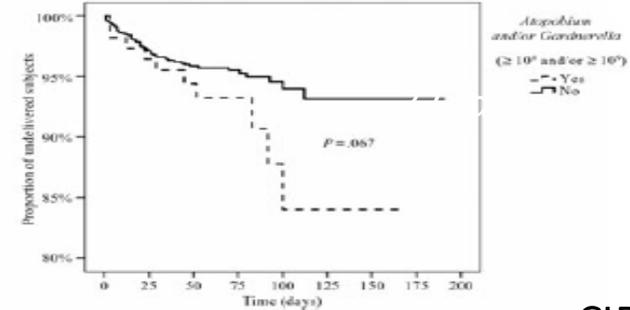
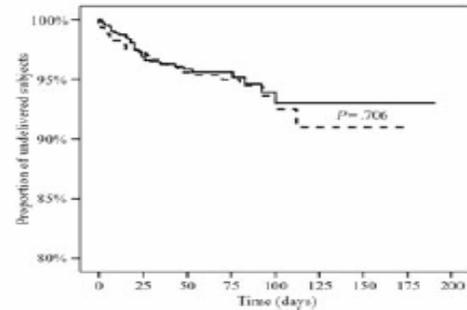
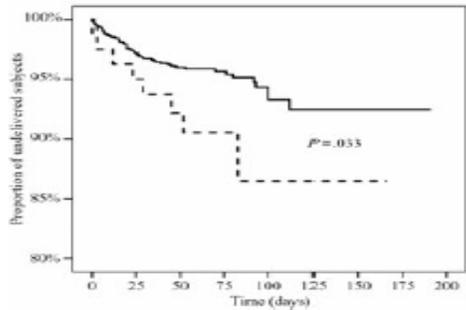
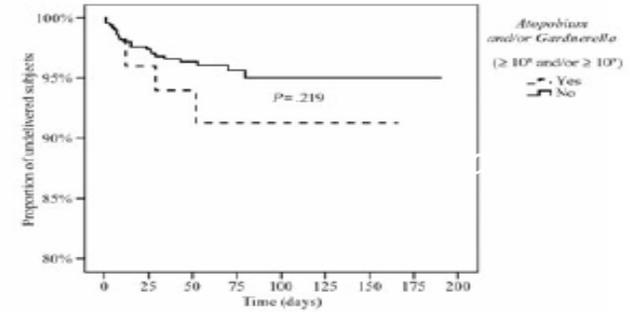
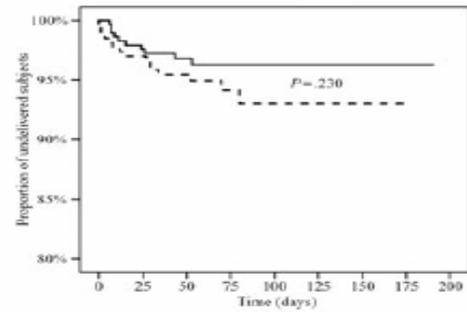
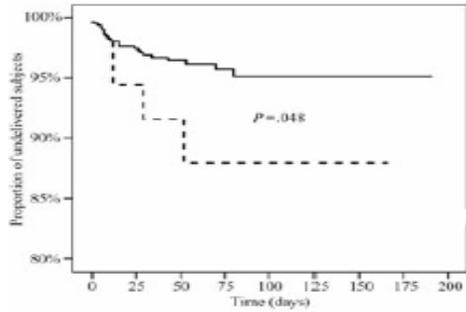
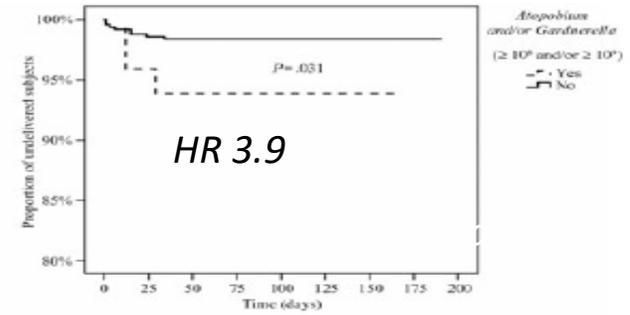
*A. vaginae* / *F.vaginae*



*Lactobacillus*

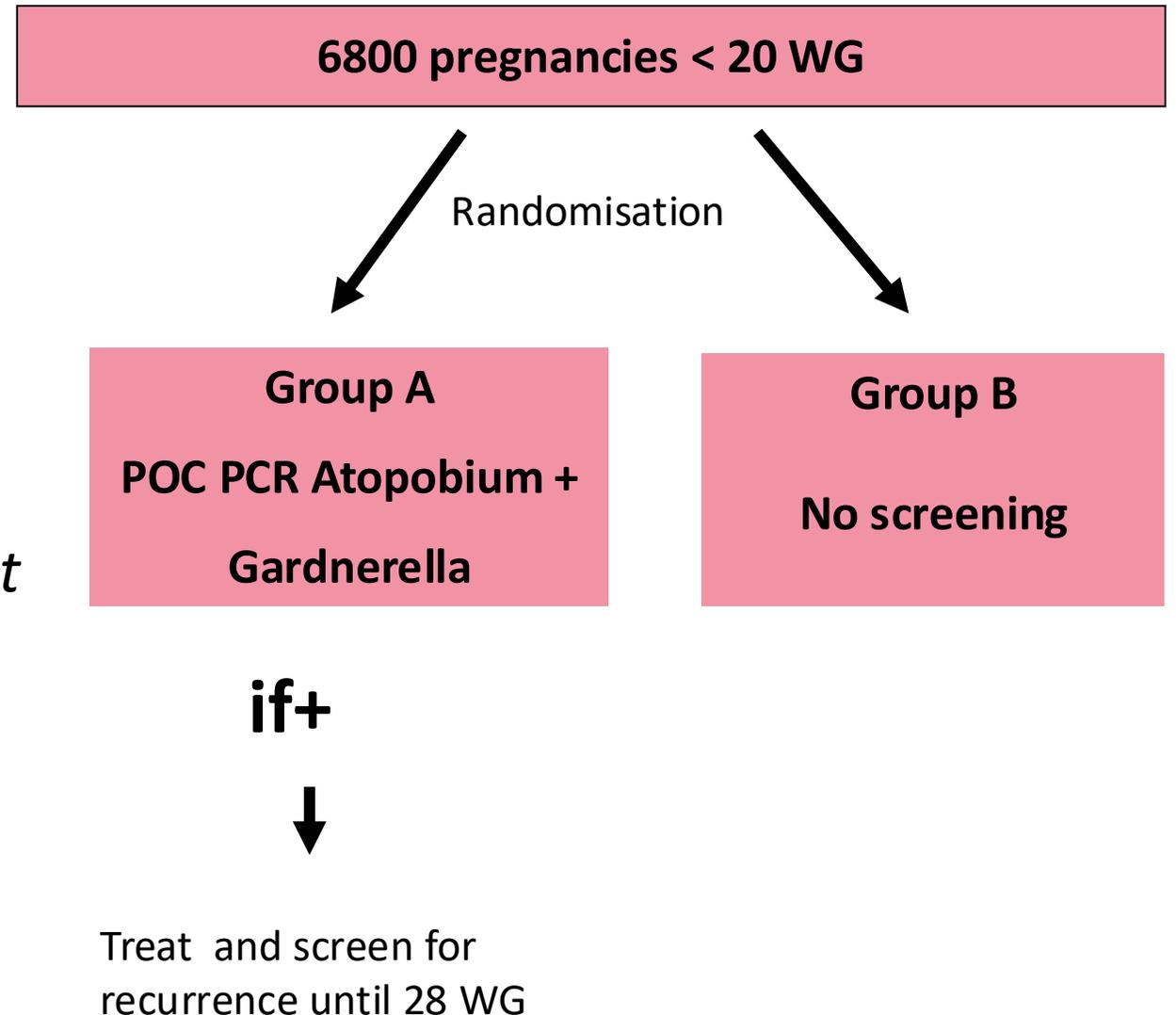


*G vaginalis*



# AuTOP!

- Cost effectiveness study
- Screen and Treat *Atopobium vaginae* et de *Gardnerella vaginalis*
- French national study Prospective, 20 inclusion centers
- Two Point of Care Marseille Poissy



## RCT: Effectiveness and Costs of Molecular Screening and Treatment for Bacterial Vaginosis to Prevent Preterm Birth

### POPULATION

6671 Women



Low-risk pregnant women before 20 wk gestation without previous preterm births or late miscarriages

Mean age, 30.6 y

Mean gestational age, 15.5 wk

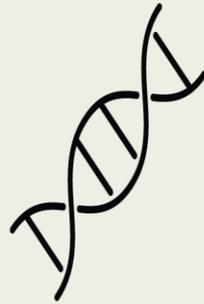
### SETTINGS / LOCATIONS



19 French perinatal centers

### INTERVENTION

6671 Pregnant women randomized



#### 3333 Screen and Treat

Point-of-care quantitative real-time polymerase chain reaction screening and treatment for bacterial vaginosis



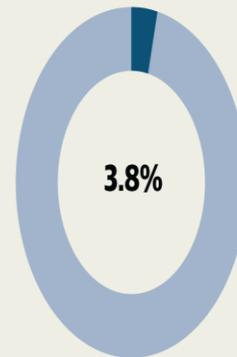
#### 3338 Usual care

Usual care according to standard practices with no systematic screening of bacterial vaginosis

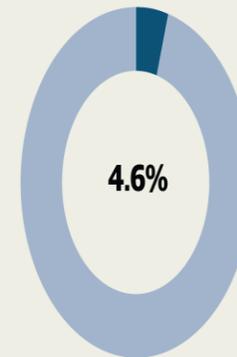
### FINDINGS

There was no significant difference in the rate of preterm birth or cost between the screen and treat and control groups

#### Screen and treat



#### Control



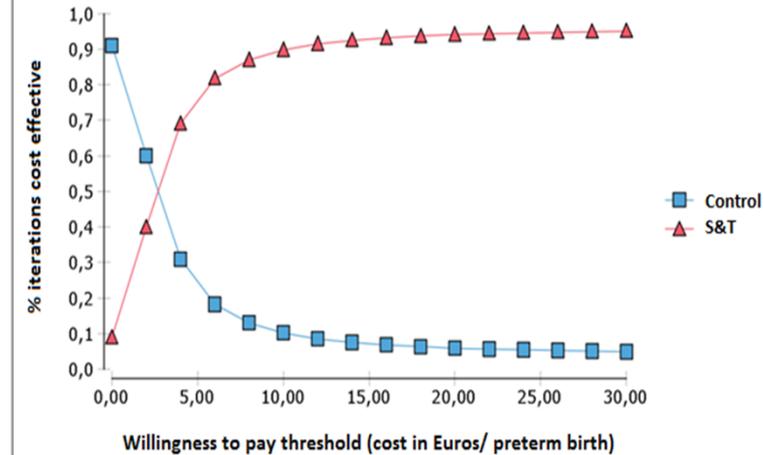
#### Preterm births in the screen and treat vs control groups:

3.8% vs 4.6%; risk ratio, 0.83; 95% CI, 0.66-1.05; P=.12

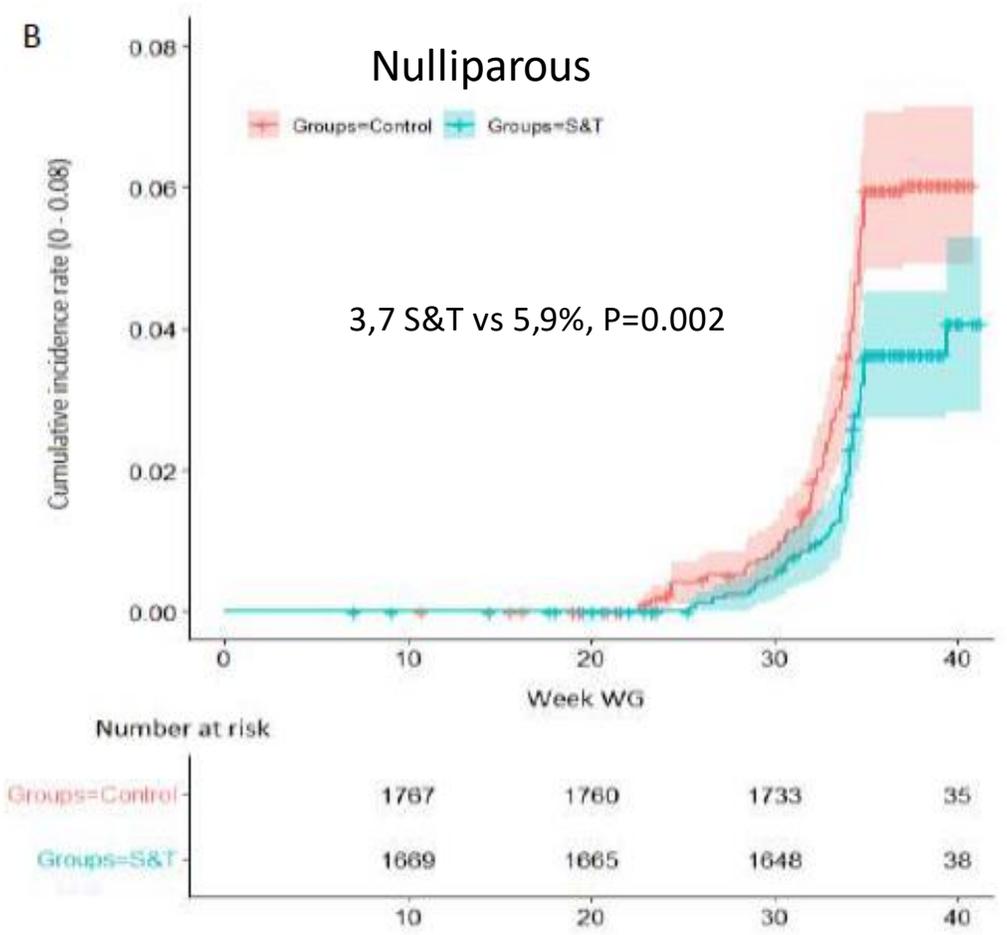
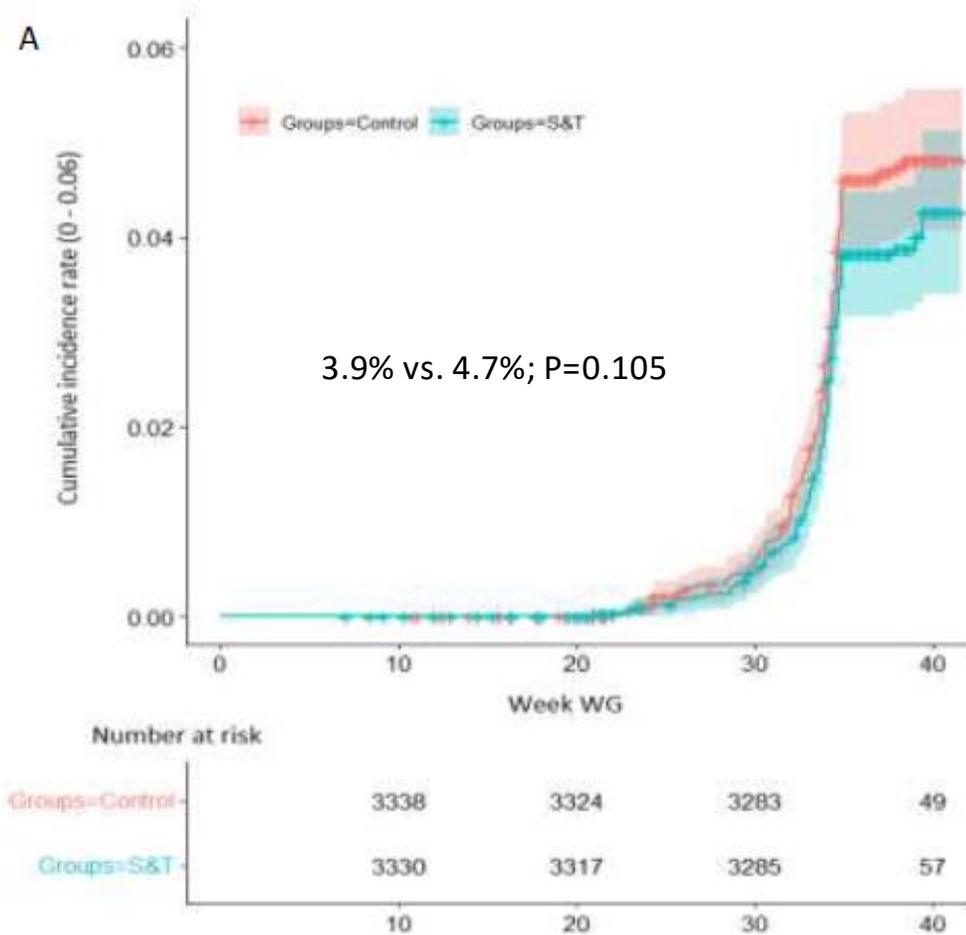
#### Total cost:

€3344.3 (US \$3580.5) vs €3272.9 (US \$3504.1); P=.23

### Cost effective among nulliparous



**Results** The cumulative incidence of preterm births was 3.6% for 1,670 patients who received S&T vs 5.9% for 1,764 patients who received usual care (aSHR 0.61, 95%CI: 0.44 to 0.83; P=0.002).

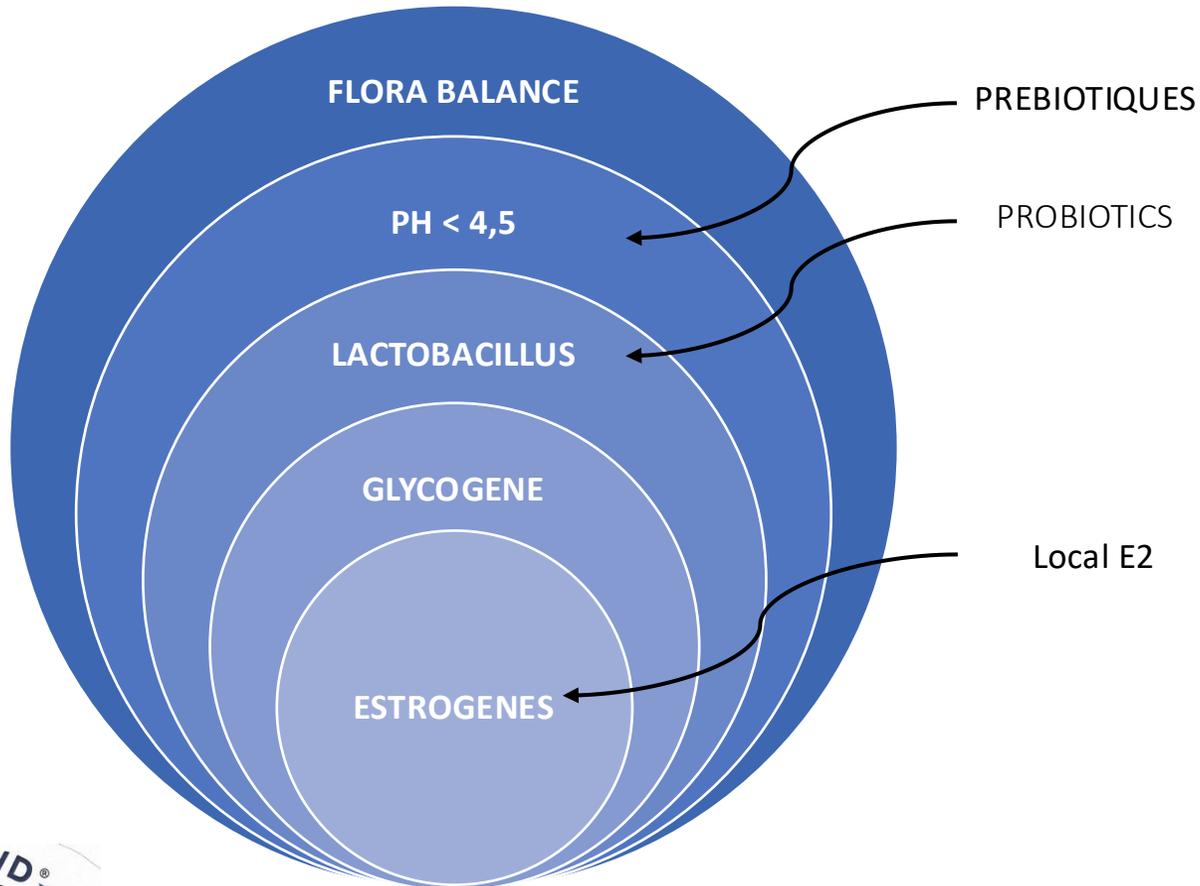


S&T strategy was significantly more effective in primiparous women than usual care (aSHR 0.61 (95% CI 0.44 to 0.84), p=0.003)  
30 euros/PTB avoid

# Bacterial Vaginosis: Which Treatment during pregnancy?



# BV: Which Treatments ?



## BV



Metronidazole 400 or 500 mg x 2/j 7 Days

Metronidazole gel 0,75 %  
1 (5g) 1 /d 5 Days

Clindamycin or Gel of clindamycin 2% 2/j 7 days

Risk factors reduction

Amoxicillin  
Azithromycin 1g

50% of efficacy  
80% of recurrence

Main Treatments



**Metronidazole and Clindamycine NS**

*Beigi RH et al 2004, Bradshaw CS et al 2006, Oduyebo et al 2009*

**Metronidazole ORAL or VAGINAL same efficacy**

*Brand M et al 2008*

**Less side effect for Vaginal administration ( Metronidazole and Clindamycine)**

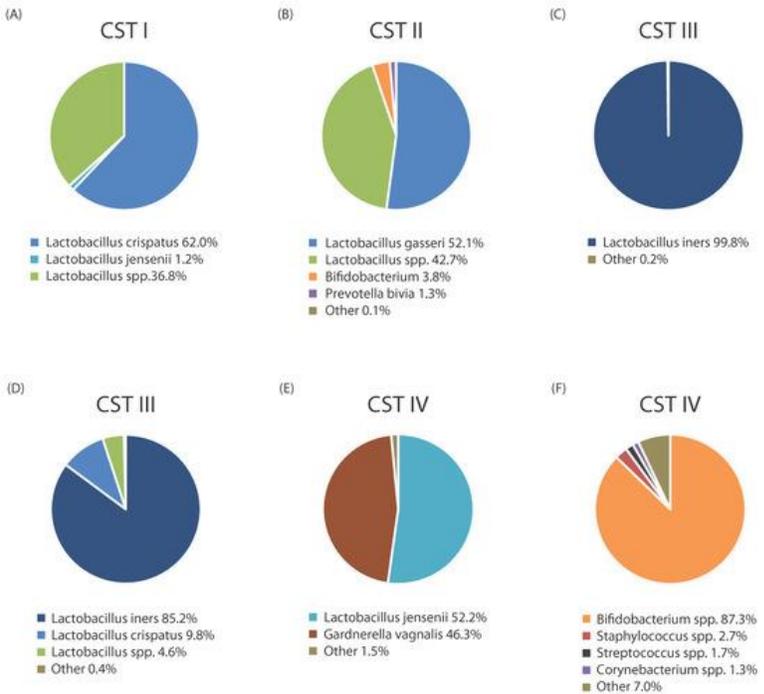
*Brand M et al 2008, Oduyebo et al 2009*

**Other treatments: Tindazole, Ornidazole, secnidazole, Azithromycin, Amoxicilline**

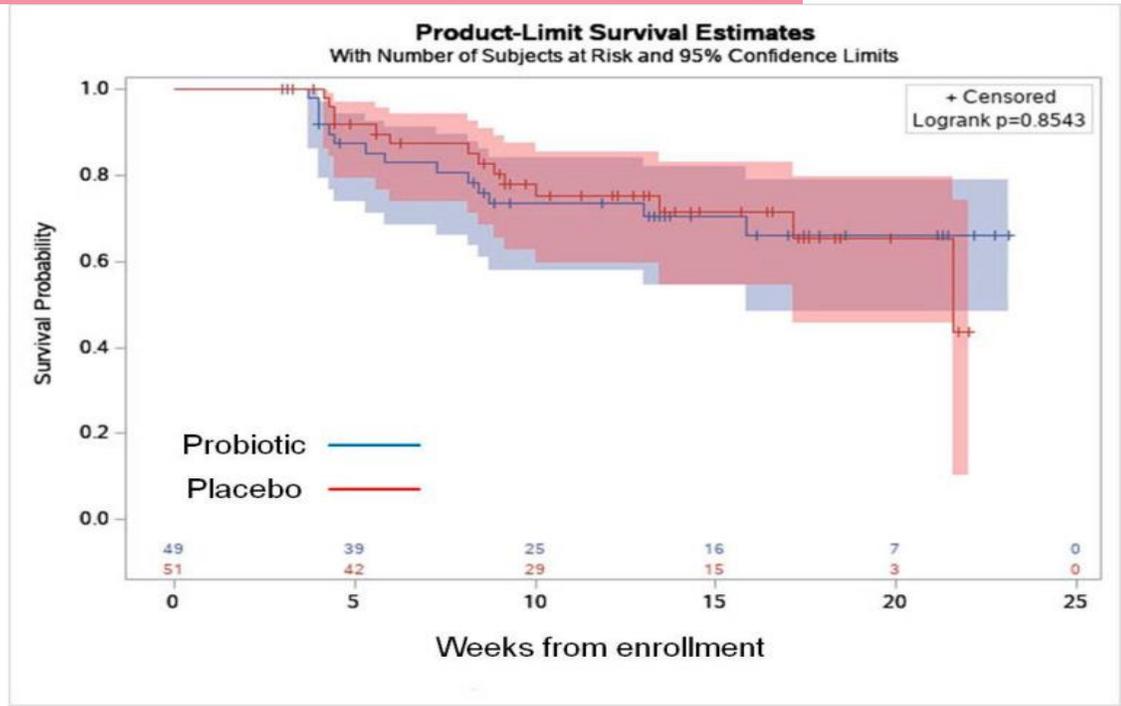
*De Backer E et al 2006, Schwebke JR et al 2007, Thulkar J et al 2012, Donders G et al 2016  
Hillier L et al 2017, Petrina MA et al 2017*

**CNGOF, 2007**  
**SOGC, 2015**

# Probiotics in Prevention of BV in pregnancy



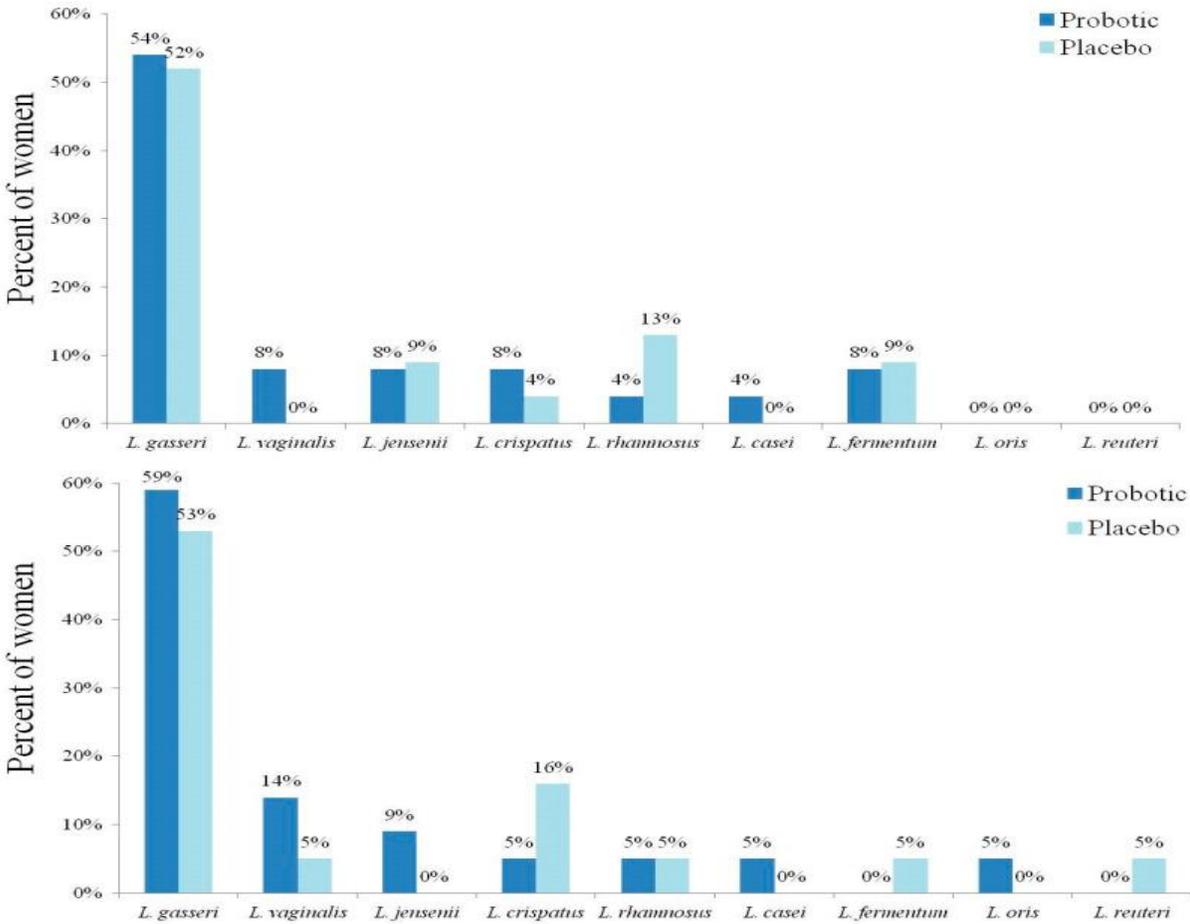
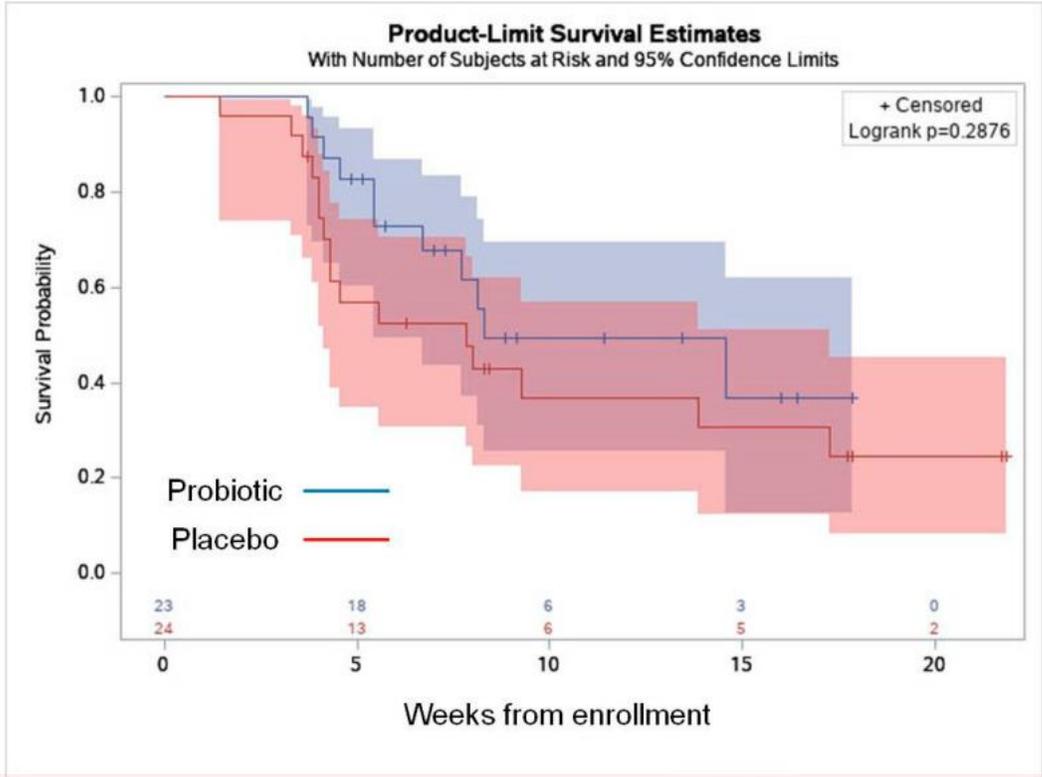
Probiotics:  
*Bifidobacterium bifidum*, *B.lactis*, *Lacto bacillus acidophilus*, *casei*, *paracasei*, *rhamnosus*, and *Streptococcus thermophilus*



49 and 51 women were analyzed in the probiotic and placebo cohorts, respectively. No difference in the rate of BV between probiotic and placebo groups 14 (29%) versus 14 (27%), respectively;  $p = 0.80$ ). No woman had vaginal colonization with lactobacilli from the probiotic capsule.

A multicenter-prospective-randomized, double-blind, placebo-controlled trial was conducted during 2016-2019. Women with normal vaginal flora (Nugent score < 4 and no candida)

# Oral Probiotics during Pregnancy



RCT ( n=47 pregnant women) With BV and initial treatments: 2 capsules/day of oral probiotic containing *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *L. acidophilus*, *L. paracasei*, *L. rhamnosus* and *Streptococcus thermophilus* vs and placebo (two capsules/day) until delivery.

**No difference recurrence before delivery 67% vs 48% for placebo - No colonisation with new strains of probiotics**

# Conventional treatment

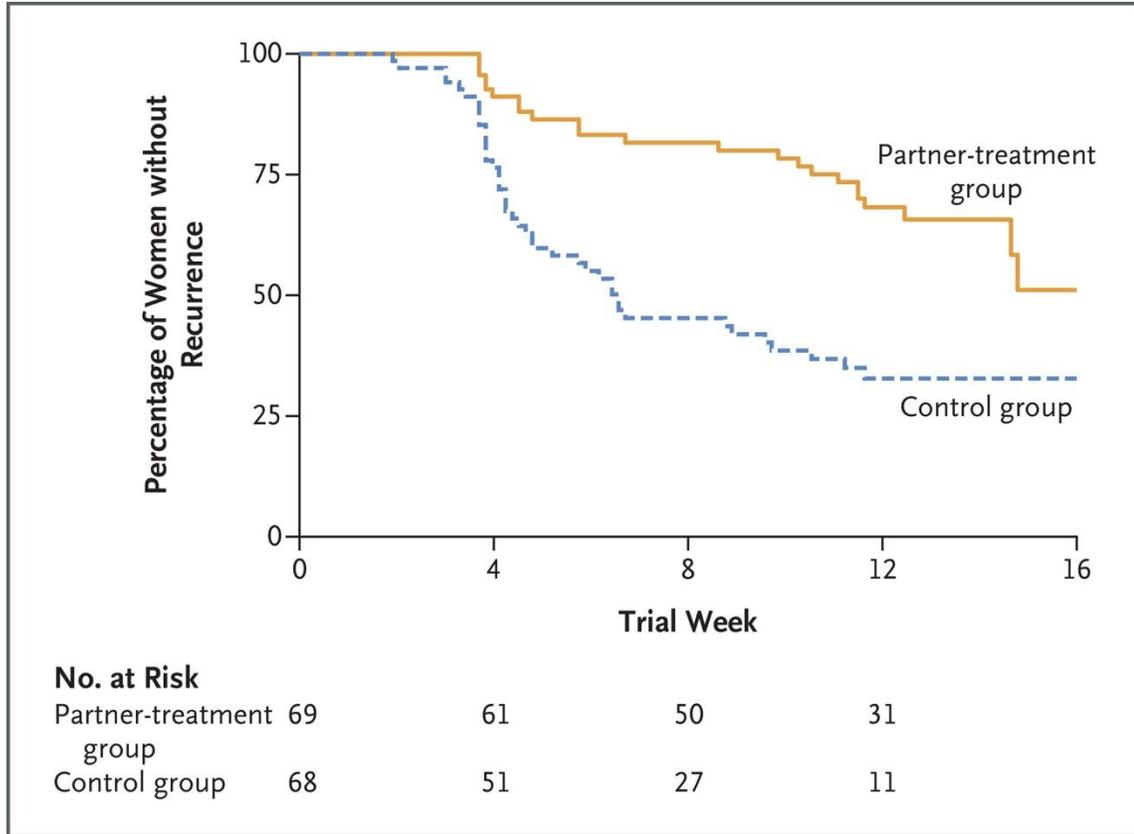
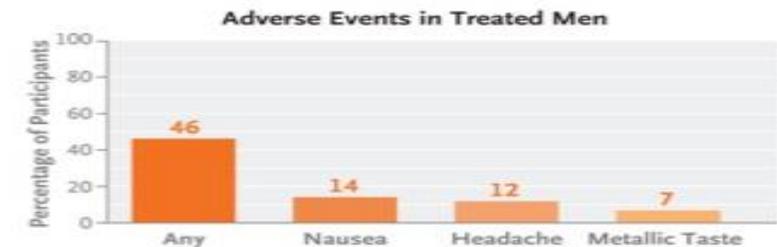
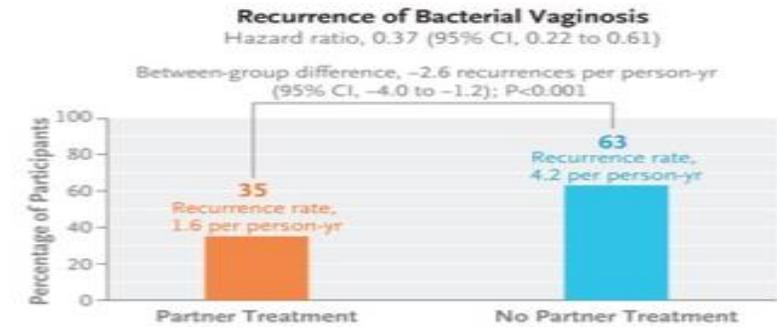
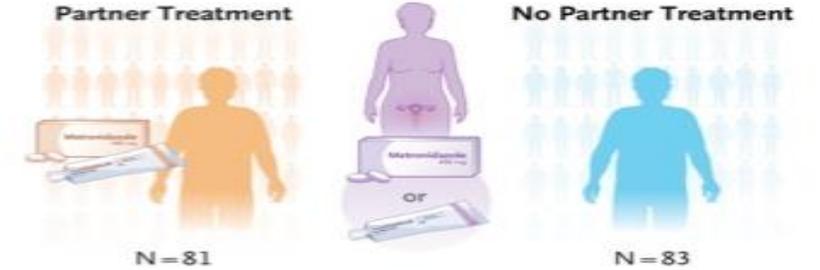
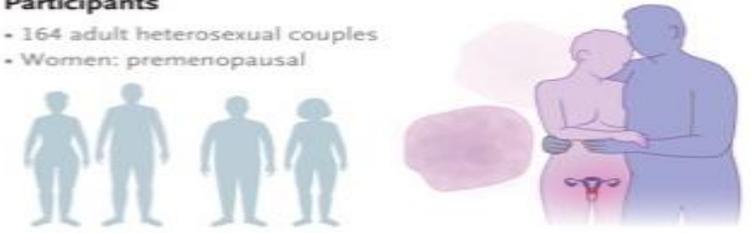
- Metronidazole *per os*, for 7 days  
or vaginal route, for 5 days

Benefits	Limits
Quickly effective	50% risk of recurrence > after 6 to 12 months
	Limited efficacy on <i>Atopobium vaginae</i> and some strains of <i>Gardnerella vaginalis</i> ...
	Not effective on <b>mixed infections</b>
	Local and/or systemic side effects

# New clue: Male-Partner Treatment to Prevent Recurrence of Bacterial Vaginosis

## Participants

- 164 adult heterosexual couples
- Women: premenopausal



First line treatment Metronidazole+clindamycine 2%

Lenka A. Vodstrcil, 2025



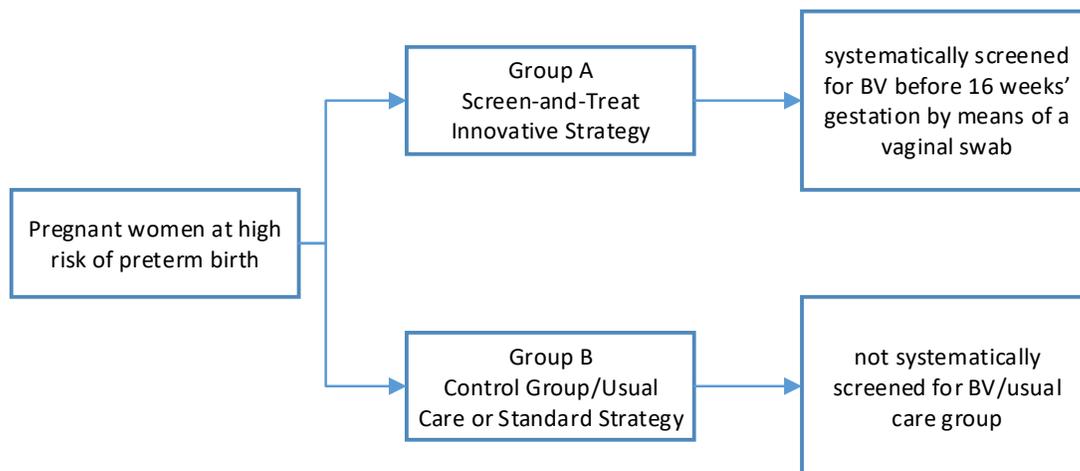
The NEW ENGLAND JOURNAL of MEDICINE

# AUTOP 2 2026



**Screen-and-treat strategy for vaginal flora abnormalities by multiplex molecular biology using POC technology in pregnant women at high risk of preterm birth:**

## A Multicentre, Randomized Study PHRC N 2023



N=1800 women

**Intervention Screen and Treat par PCR pour *Chlamydia*, *Atopobium*, *Gardnerella*, *Neisseria Trichomonas* infections, *Candida* infections, *Lactobacillus* deficiency**

# Answer to an European Call : fighting against Preterm birth a public health issue

## Contexte

- 15 million babies were born preterm in 2020 (< 37 weeks of gestation)
- PB occurs from 4–16% in 2020
- PB complications are the leading cause of death < 5 years, responsible for 900 000 deaths in 2019
- **3/4 of these deaths could be avoid**

## Why and when does preterm birth happen?

- Infections ( such as Bacterial Vaginosis) , chronic conditions or unknown
- **Inequity:**
  - PB is high in southern Asia & sub-Saharan Africa, but preterm birth is truly a global problem.
- **Premature babies survival :**
  - 90% of extremely preterm babies born in low-income countries die
  - 10% in high-income settings

# REVEAL Objectives

- To demonstrate that molecular biology should be the reference method of diagnosis
- To demonstrate that BV is a sexual transmitted disease
- To evaluate the impact of screening and treating partners for BV during pregnancy and to prove its efficacy

# Methodology

## Waiting for a Call:

- European Call Horizon HLTH 2025-01-Disease 07
- Europe AMU

## Consortium :

- Social Human Health Department
- Start Up ( to create an Antigenic Diagnosis test)
- Biology ( referral Diagnosis)
- Countries
- Low incomes countries

**Budget : 6.2MEuros**



The screenshot shows the EU Funding & Tenders Portal interface. The main heading is "Tackling high-burden for patients and under-researched medical conditions" with the call ID "HORIZON-HLTH-2025-01-DISEASE-07". A "Topic" label indicates it is a "Call for proposal". The "Internal navigation" sidebar lists: General information, Topic description, Topic updates, Destination, Conditions and documents, Budget overview, Start submission, Topic Q&As, and Get support. The main content area displays "General information" with the following details:

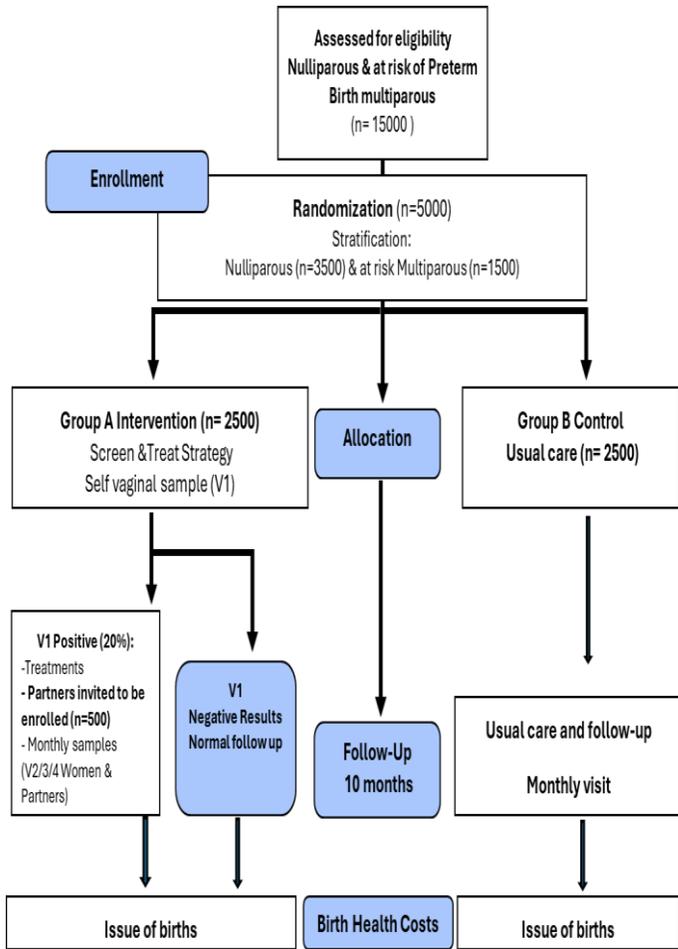
<b>Programme</b> Horizon Europe (HORIZON)		
<b>Call</b> Cluster 1 - Health (Single stage - 2025) (HORIZON-HLTH-2025-01)		
<b>Type of action</b> HORIZON-RIA HORIZON Research and Innovation Actions	<b>Type of MGA</b> HORIZON Action Grant Budget-Based [HORIZON-AG]	<b>Fermé</b>
<b>Deadline model</b> single-stage	<b>Opening date</b> 22 May 2025	<b>Deadline date</b> 16 September 2025 17:00:00 Brussels time

The "Topic description" section is partially visible, showing "Expected Outcome:".

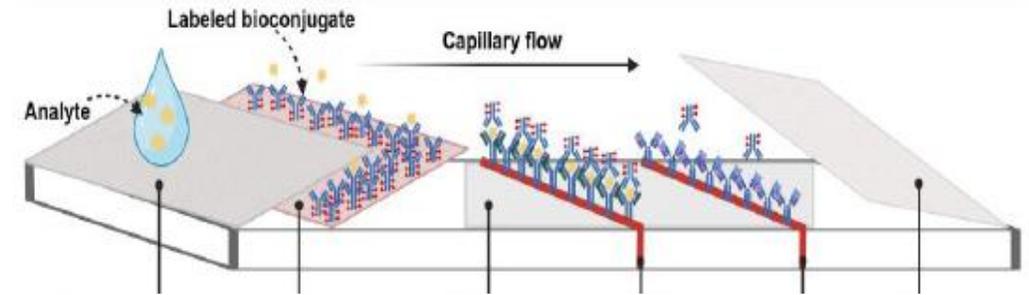
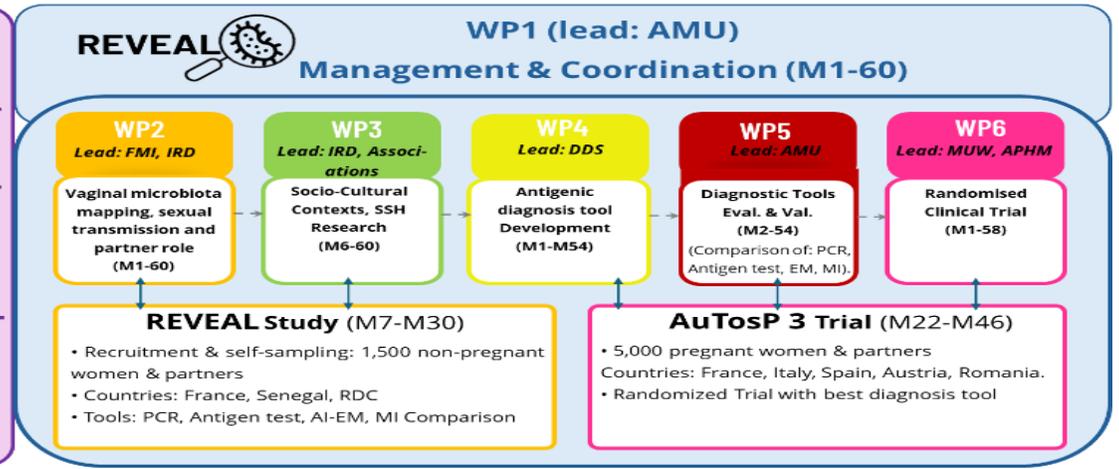
# Results: REVEAL

Topic: HORIZON-HLTH-2025-01-DISEASE-07

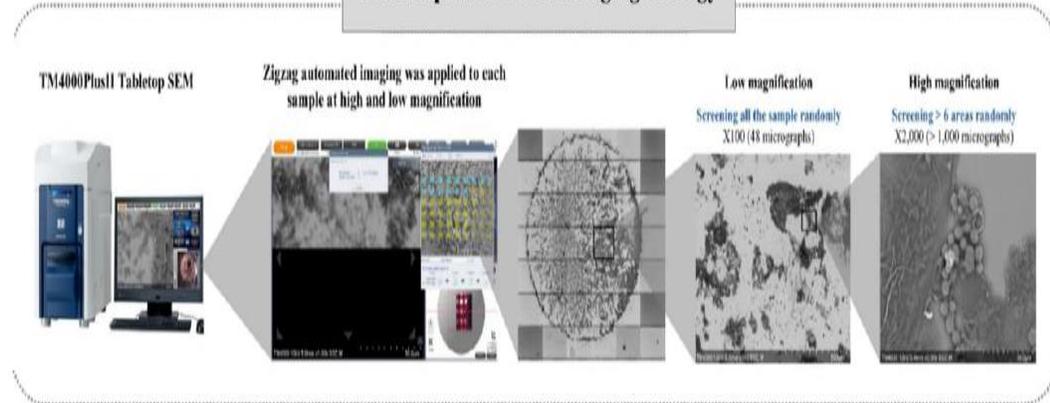
Type of Action: HORIZON-RIA  
(HORIZON Research and Innovation Actions)



WP7 (lead: Supervisime)  
Communication, dissemination, Exploitation (M1-60)

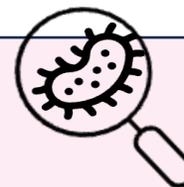


## First steps in the SEM imaging strategy



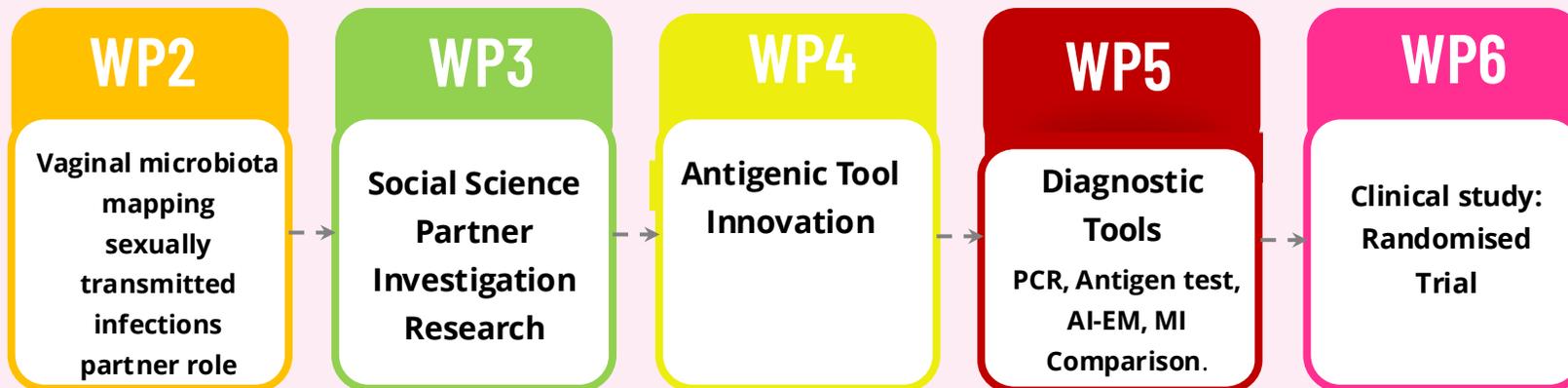
# WP1 REVEAL

## Management & Coordination



WP7  
Communication, dissemination, exploitation

WP7  
Communication, dissemination, exploitation



### REVEAL Study

- Recruitment & self-sampling: 2,500 non-pregnant women & partners.
- Countries: France, Senegal, RDC.
- Tools: PCR, Antigen test, AI-EM, MI Comparison.

### AuToPs 3 Study

- 5,000 pregnant women & partners.
- Countries: France, Italy, Spain, Austria, Romania.
- Randomized Trial with best tool

## WP3 Social Sciences & Humanities

Focus groups, questionnaires, interviews, Determinants, Stigma, Acceptability  
**Research**

# Results : EU Funding & Tenders Portal

- European Call Horizon HLTH 2025-01-Disease 07
- Answer between 25.1.2026 and 16.2.2026

The screenshot displays the 'RESEARCH & INNOVATION Grant Management Services' interface. The user is logged in as 'Florence Bretelle'. The main section is titled 'MY PROPOSAL' and shows details for 'Proposal Management & Grant Preparation 101290224 - REVEAL'. A progress timeline indicates the proposal was 'Submitted' on 16 Sep 2025 and is currently 'Informed' until 16 Feb 2026 (69/153 days). The timeline includes stages: Submitted, Informed, Invited, Prepared, Signed, and Paid. Below the timeline, there are sections for 'Process documents' (Proposal (1)), 'Process communications' (No topics), and 'Process history' (EU registered the proposal on 16 Sep 2025 00:00). A sidebar on the left provides additional details: Call: HORIZON-HLTH-2025-01, Type of Action: HORIZON-RIA, Acronym: REVEAL, Number: 101290224, Duration: 60 months, Estimated Project Cost: €6,214,891.25, and Requested EU Contribution: €6,214,891.25. At the bottom of the sidebar are buttons for 'Latest Legal Data', 'Active Processes', and 'Document Library'.

RESEARCH & INNOVATION  
Grant Management Services

European Commission

Help

Florence Bretelle

MY PROPOSAL

Proposal Management & Grant Preparation  
101290224 - REVEAL

16 Sep 2025 16 Feb 2026 (69/153 days)

Submitted Informed Invited Prepared Signed Paid

Process documents  
▶ Proposal (1) [Expand All](#) [Collapse All](#)

Process communications  
No topics

Process history  
⚙️ EU registered the proposal on 16 Sep 2025 00:00

Latest Legal Data

Active Processes

Document Library

# Perspectives

If REVEAL is not funded:

- New answer to HORIZON-HLTH-2027-02-IND-02-two-stage:  
Portable and versatile Point-of-care diagnostics  
Call: Cluster 1 - Health (Two stage - 2027)

# Take home message for BV and Pregnancy

- Use PCR diagnosis if possible to treat women that need it and don't miss the other
- Antibigram is the future
- Treat with first line option + check for efficacy and recurrence
- Tell women to keep their money for oral probiotics during pregnancy
- If recurrences: think to treat partners ( Not recommend yet)



Thanks