



# Actualités MST



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CNR Syphilis  
Inserm U106



# Syphilis and gonorrhoea in Paris: the return

Dupin, Nicolas; Jdid, Randa; N'Guyen, Yen-Ti; Gorin, Isabelle; Franck, Nathalie; Escande, Jean-Paul

AIDS: April 13th, 2001 - Volume 15 - Issue 6 - p 814-815

Research Letters

**Table 1.** Mean clinical and biological features of the 10 gay men presenting with early syphilis.

Patient	Age (years)	HIV serology	Stage of syphilis	Serology of syphilis		
				VDRL (units)	TPHA (titre)	FTA (titre)
1	38	+ CD4 cells: 667/mm <sup>3</sup> VL: 17 000 copies/ml	Secondary	128 Positive dark-field on cutaneous lesion	1/10 240	1/640
2	42	+ CD4 cells: 824/mm <sup>3</sup> VL: 4490 copies/ml	Secondary	8	1/640	1/800
3	29	+ CD4 cells: 601/mm <sup>3</sup> VL: 427 copies/ml	Secondary	32	1/2560	NA
4	42	+ CD4 cells: 250/mm <sup>3</sup> VL: not detectable	Secondary	16	1/20 480	1/1600
5	25	+ CD4 cells: 260/mm <sup>3</sup> VL: NA	Secondary	64	1/640	NA
6	64	Negative	Secondary	4	1/20 480	1/3200
7	34	Negative	Primary	4	1/1280	1/200
8	40	Unknown	Primary	16	1/1280	1/800
9	41	Unknown	Primary	2 Positive dark-field result	±	±
10	41	Negative	Secondary	256 Positive dark-field on cutaneous lesion	> 1/20 480	NA

FTA, Fluorescent treponemal antibody; TPHA, *Treponema pallidum* haemagglutination antibody; VDRL, Venereal Disease Research Laboratory; VL, viral load.

**Table 2.** Number of gonococcal infections during 5 years

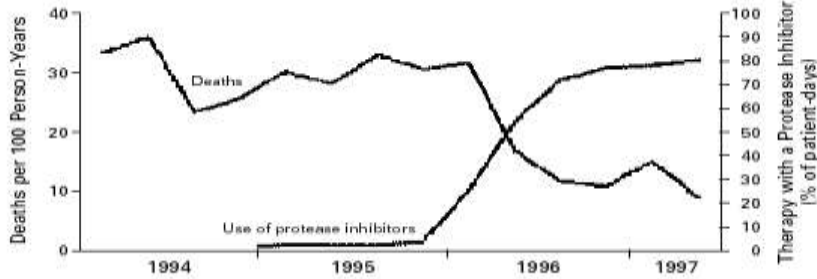
Year	BCGI	Total of patients treated for gonococcal infections	Visits to the STD centre (first 9 months) (no. of patients)
1996	23 <sup>a</sup>	24	4753
1997	34	48	6333
1998	35	69	6476
1999	43	72	5940
2000	47 <sup>a</sup>	86	5044

<sup>a</sup>There was a 104% overall increase in bacteriological confirmed gonococcal infections (BCGI) between 1996 and 2000 (for the first 9 months).

STD, Sexually transmitted diseases.

# Manifestations cliniques





HAART

2000

IST



terrence HIGGINS TRUST

14 European countries

1,166 couples: one HIV positive and on treatment, one HIV negative

58,000 acts of sex without condoms

ZERO HIV transmissions

TASP



IST



PrEP

Stratégie préventive  
- doxy (CT, sy. )  
- Vaccin méningo

ORIGINAL ARTICLE

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

J.-M. Molina, C. Capitant, B. Spire, G. Pialoux, L. Cotte, I. Charreau, C. Tremblay, J.-M. Le Gall, E. Cua, A. Pasquet, F. Raffi, C. Pintado, C. Chidiac, J. Chas, P. Charbonneau, C. Delaugerre, M. Suzani-Monti, B. Loze, J. Fonsart, G. Peytavin, A. Cheret, J. Timsit, G. Girard, N. Lorente, M. Prêau, J.F. Rooney, M.A. Wainberg, D. Thompson, W. Rozenbaum, V. Doré, L. Marchand, M.-C. Simon, N. Etien, J.-P. Aboulker, L. Meyer, and J.-F. Delfraissy, for the ANRS IPERGAY Study Group\*

# Augmentation des IST

- Les populations à risque sont beaucoup plus contrôlées tous les 3-4 mois
- On multiplie les recherches chez les mêmes patients, PCR NG/CT 3 sites, ce qui augmente aussi le taux de positivité
  - D'ailleurs quelle place accordée aux résultats + dans des sites asymptomatiques compte-tenu des possibilités de « clairance » spontanée pour NG (30%) et CT (50%) bien documentée à la gorge (Van Liere et al. STI 2019)



# Sexually Transmitted Infections

- 276 STIs were diagnosed in 141 participants (asymptomatic +++)

	TDF/FTC n=199		Placebo n=201		P value
	Nb Pt (%)	Nb Events	Nb Pt (%)	Nb Events	
<b>Chlamydia</b>	43 (22)	61	34 (17)	48	0.23
<b>Gonorrhoeae</b>	38 (19)	50	45 (22)	67	0.42
<b>Syphilis</b>	19 (19)	19	19 (19)	25	0.98
<b>HCV</b>	3 (3)	3	3 (3)	3	1.00
<b>Any STI</b>	<b>76 (38)</b>	<b>133</b>	<b>65 (32)</b>	<b>143</b>	<b>0.22</b>



Syndrome de Fiessinger-Leroy

Homme de 26 ans

Sous PrEP

Avec **balanite circonscrite**

Oligoarthritis invalidante +++

HLA B27

Sous étanercept + dipropionate  
de bétaméthasone



# Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection

Traeger et al, *Jama* 2019

Etude Australienne

PrEPX study

Les FDR associés à une IST:

- Jeune âge
- Le nombre élevé de partenaires
- Sex en groupe

Sur 1378 participants pour lesquels on avait les data à l'inclusion, On passe d'une incidence: de 69,5 pour 100 personnes-année à 98,4/100-année (IRR 1,41)

Tester régulièrement les prépeurs à la recherche de MST



Outcome (No. of Participants) <sup>b</sup>	PrEP-Naive Participants (n = 837)					
	IR 1 Year Before Enrollment <sup>c</sup>	IR During Follow-up <sup>c</sup>	IRR (95% CI)	P Value	Adjusted IRR (95% CI) <sup>d</sup>	P Value
All STIs (n = 1378)	55.1	94.2	1.71 (1.49-1.96)	<.001	1.21 (1.06-1.39)	.006
Chlamydia (n = 1318)	25.2	46.5	1.84 (1.55-2.20)	<.001	1.38 (1.13-1.66)	.001
Rectal (n = 1240)	19.4	34.4	1.78 (1.44-2.19)	<.001	1.20 (0.95-1.51)	.13
Urethral (n = 1304)	7.6	13.9	1.83 (1.30-2.56)	<.001	1.32 (0.91-1.90)	.14
Pharyngeal (n = 1061)	2.6	5.1	1.99 (1.10-3.62)	.02	1.64 (0.86-3.13)	.13
Gonorrhea (n = 1324)	24.6	41.5	1.69 (1.42-2.01)	<.001	1.11 (0.92-1.34)	.26
Rectal (n = 1241)	15.1	25.2	1.67 (1.33-2.09)	<.001	1.00 (0.78-1.28)	.99
Urethral (n = 1309)	3.6	7.5	2.06 (1.29-3.31)	.002	1.33 (0.84-2.09)	.23
Pharyngeal (n = 1274)	11.6	17.7	1.53 (1.17-1.99)	.002	1.04 (0.78-1.38)	.78
Syphilis (n = 1318)	6.4	7.9	1.24 (0.87-1.78)	.24	0.93 (0.62-1.40)	.74
Rectal infections (n = 1243)	34.7	59.6	1.72 (1.44-2.05)	<.001	1.10 (0.91-1.32)	.32
Urethral infections (n = 1310)	11.5	21.3	1.86 (1.40-2.48)	<.001	1.26 (0.91-1.74)	.13
Pharyngeal infections (n = 1276)	13.8	23.1	1.67 (1.31-2.14)	<.001	1.14 (0.88-1.47)	.44





# Les IST dans le monde

- C'est plus de  $350 \cdot 10^6$  nouveaux cas par an (soit  $10^6/j$ )
  - $130 \cdot 10^6$  infections à Chlamydia
  - $78 \cdot 10^6$  infections gonococciques
  - $5,5 \cdot 10^6$  syphilis
  - $142 \cdot 10^6$  infections à trichomonase
- Augmentation des résistances
  - *N gonorrhoeae*
  - *M genitalium*



# Les IST dans le monde

- Conséquences sur la fertilité (F >>>H)
- GEU, douleurs pelviennes chroniques  
Chlamydia ++, gono...)
- Complications CV et neurologiques (syphilis),  
arthropathies
- Transmission MF (syphilis, chlamydia,  
gonococcie)
- Acquisition du VIH (toutes)



# Les études et essais thérapeutiques sur les IST dans le monde

- **Syphilis** ( $5,5 \cdot 10^6$  /an): **71 études** dont 18 essais thérapeutiques (et)
- **Gonococcie** ( $78 \cdot 10^6$ ): **108 études** dont 29 et
- **Chlamydia** ( $130 \cdot 10^6$ ): **182 études** (y compris trachome...) dont 13 et, qqs essais vaccinaux
  
- Vs i.e. **mélanome** : 132000 cas / an et **2340 études** répertoriées sur CT.gov



# MST et VIH sont indissociables

une surreprésentation des hommes, des HSH et des VIH

- Syphilis précoce : 85% de HSH, **25% VIH+** dont 2% découvrent leur VIH au cours de la syphilis
- Gonococcie : 68% de HSH, **11% VIH+**
- LGV : 100% d'hommes, 100% de HSH, **76% VIH+**
- Anites Non LGV : 95% d'hommes, **30% VIH+**



# Problématiques sont différentes en fonction du type d'IST

- **Syphilis**

- Pas vraiment de pb de résistance
- Pénuries récurrentes, d'où la nécessité de valider une alternative (doxycycline ? d'autant plus qu'elle est proposée en PeP chez les Prépeurs)
- Les pbs sont plus la TMF et la neurosyphilis
  - Syphilis congénitale
  - NS pas d'alternative bien validée à la PénicG

- **Gonocoque et *M genitalium***

- Résistance
- Superbugs ?



# Problématiques sont différentes en fonction du type d'IST

- **Syphilis**

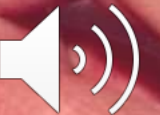
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  - Syphilis congénitale
  - NS pas d'alternative bien validée à la PénicG



# Complications neurologiques



# Syphilis néonatale





Syphilis is the great imitator

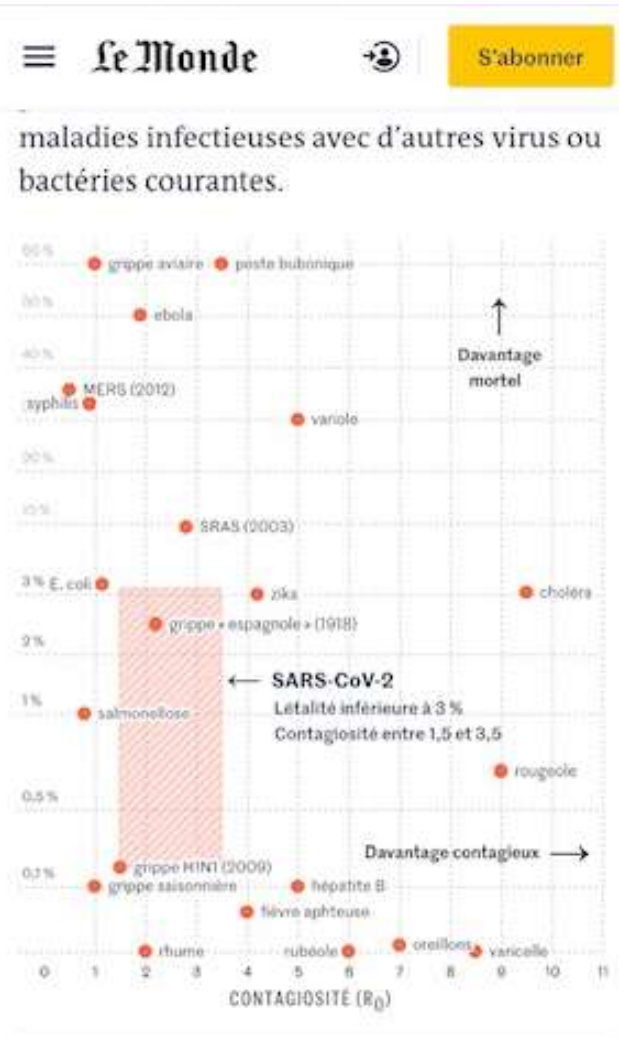




# Bacteriology



- *Treponema p*
- Infection is s
- Fragile (brittle)
- Family of spi
- Not cultivabl
- Sexual trans
- Vertical trans



pregnancy



# *T. Pallidum* genoma



## Complete Genome Sequence of *Treponema pallidum*, the Syphilis Spirochete

Claire M. Fraser,\* Steven J. Norris, George M. Weinstock,  
Owen White, Granger G. Sutton, Robert Dodson,  
Michelle Gwinn, Erin K. Hickey, Rebecca Clayton,  
Karen A. Ketchum, Erica Sodergren, John M. Hardham,  
Michael P. McLeod, Steven Salzberg, Jeremy Peterson,  
Hanif Khalak, Delwood Richardson, Jerrilyn K. Howell,  
Monjula Chidambaram, Teresa Utterback, Lisa McDonald,  
Patricia Artiach, Cheryl Bowman, Matthew D. Cotton,  
Claire Fujii, Stacey Garland, Bonnie Hatch, Kurt Horst,  
Kevin Roberts, Mina Sandusky, Janice Weidman,  
Hamilton O. Smith, J. Craig Venter

[www.sciencemag.org](http://www.sciencemag.org) SCIENCE VOL 281 17 JULY 1998

*Treponema pallidum pallidum* genoma is very  
small, 1.14 million BP with 1041 ORF



# Molecular subtyping of *T. pallidum*



Sexually Transmitted Diseases

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Volume 25(8)

September 1998

pp 408-414

## Molecular Subtyping of *Treponema pallidum* Subspecies *pallidum* [Original Articles]

PILLAY, ALLAN MS\*; LIU, HSI PhD†; CHEN, CHENG Y. PhD†; HOLLOWAY, BRIAN BS†; STURM, A. WILLEM MD\*; STEINER, BRET PhD†; MORSE, STEPHEN A. PhD†

## Enhanced Molecular Typing of *Treponema pallidum*: Geographical Distribution of Strain Types and Association with Neurosyphilis

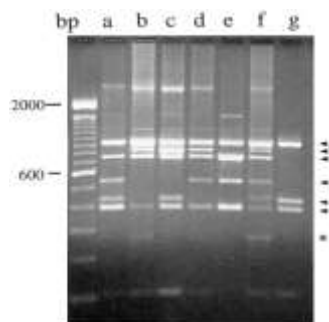
Christina M. Marra,<sup>1</sup> Sharon K. Sahi,<sup>1</sup> Lauren C. Tantalò,<sup>1</sup> Charmie Godornes,<sup>2</sup> Tara Reid,<sup>2</sup> Frieda Behets,<sup>3</sup> Anne Rompalo,<sup>4</sup> Jeffrey D. Klausner,<sup>2</sup> Yue-Ping Yin,<sup>4</sup> Fiona Mulcahy,<sup>4</sup> Matthew R. Golden,<sup>5\*</sup> Arturo Centurion-Lara,<sup>2</sup> and Sheila A. Lukehart<sup>2,3</sup>

JID 2010;202

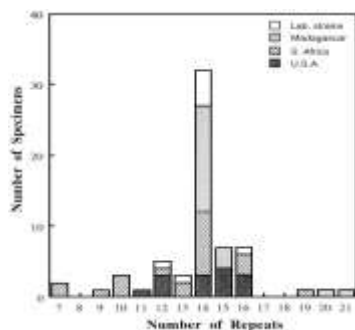
*arp*



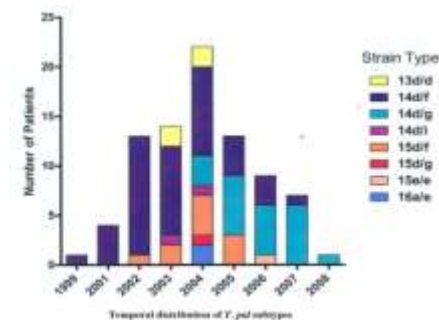
*tpr*

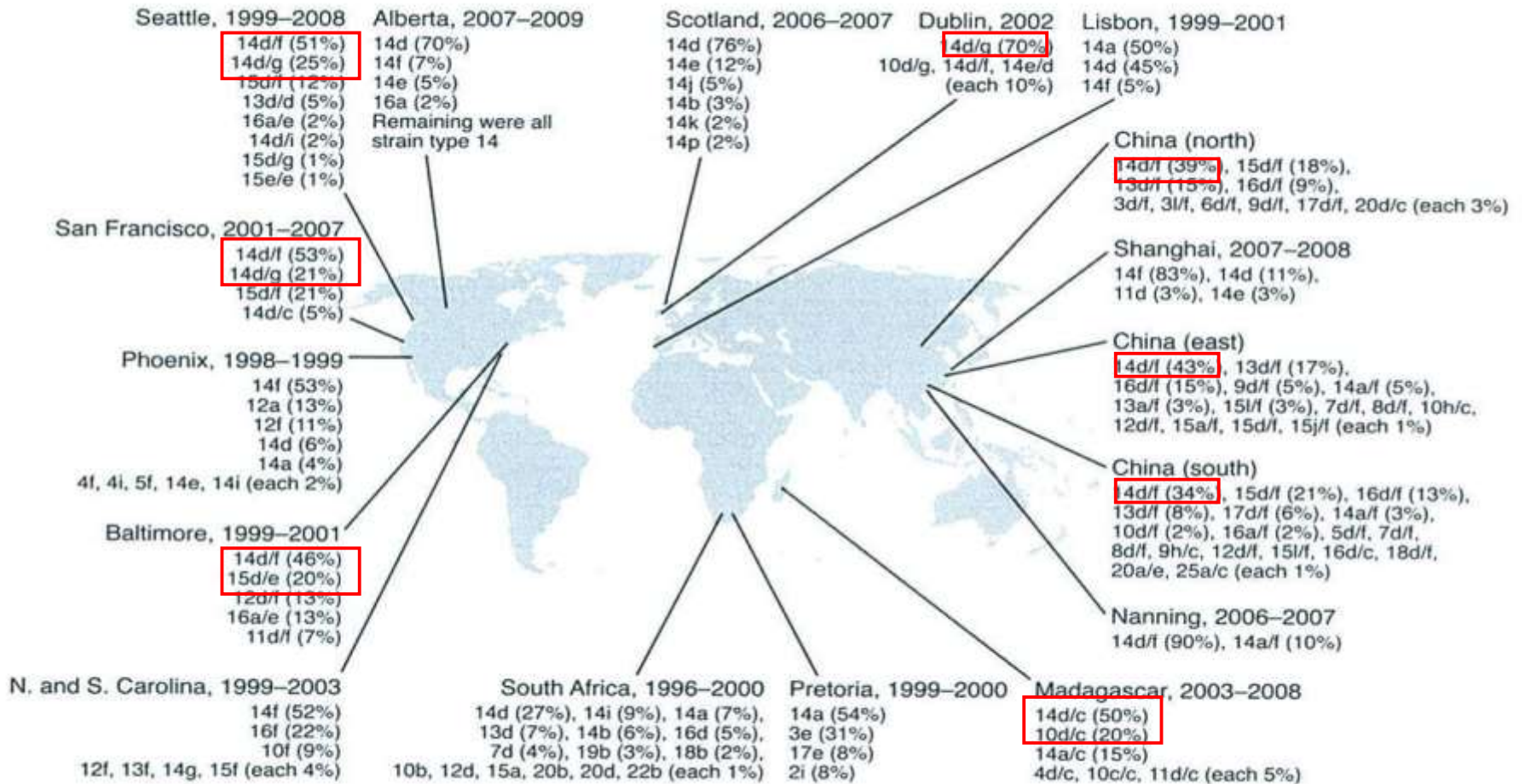


*tp0548*

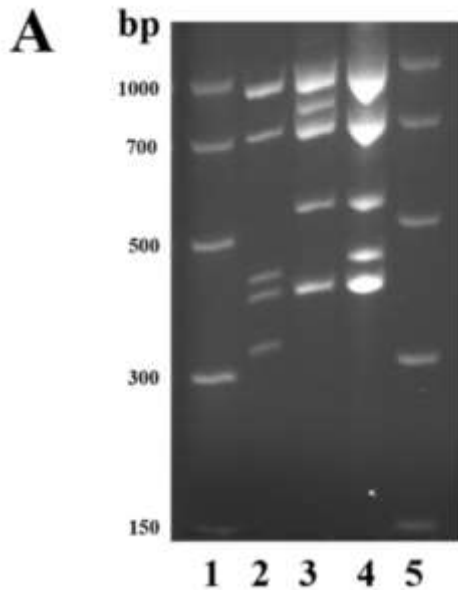


Fragment Size (bp)	Main RFLP Type						
	a	b	c	d	e	f	g
911	+	+	+	+	+	+	+
901	+	+	+	+	+	+	+
904	+	+	+	+	+	+	+
722	+	+	+	+	+	+	+
624	+	+	+	+	+	+	+
426	+	+	+	+	+	+	+
382	+	+	+	+	+	+	+





# En France, Grange et al. STD 2013



Subtype	<i>arp</i>	<i>tpr</i>	<i>tp0548</i>	No. of isolates
14d/g	████████████████████		CAGGCGCAGTGGCCACAGGCGCTGGAGGTCCTCCAGTGGTTCGCGCGATGGCAACACCCCGCAGGACAGTTCTCCAGTT	49
14d/f	████████████████████		CAGGCGCAGTGGCCACAGGCGCTGGAGGTCCTCCAGTGGTTCGCGCGATGGCAACACCCCGCAGGACAGTTCTCCAGTT	19
15d/f	████████████████████		CAGGCGCAGTGGCCACAGGCGCTGGAGGTCCTCCAGTGGTTCGCGCGATGGCAACACCCCGCAGGACAGTTCTCCAGTT	1
14d/d	████████████████████		CAGGCGCAGTGGCCACAGGCGCTGGAGGTCCTCCAGTGGTTCGCGCGATGGCAACACCCCGCAGGACAGTTCTCCAGTT	1
11q/j	██████████████		CAGGCGCAGTGGCCACAGGCGCTGGAGGTCCTCCAGTGGTTCGCGCGATGGCAACACCCCGCAGGACAGTTCTCCAGTT	1

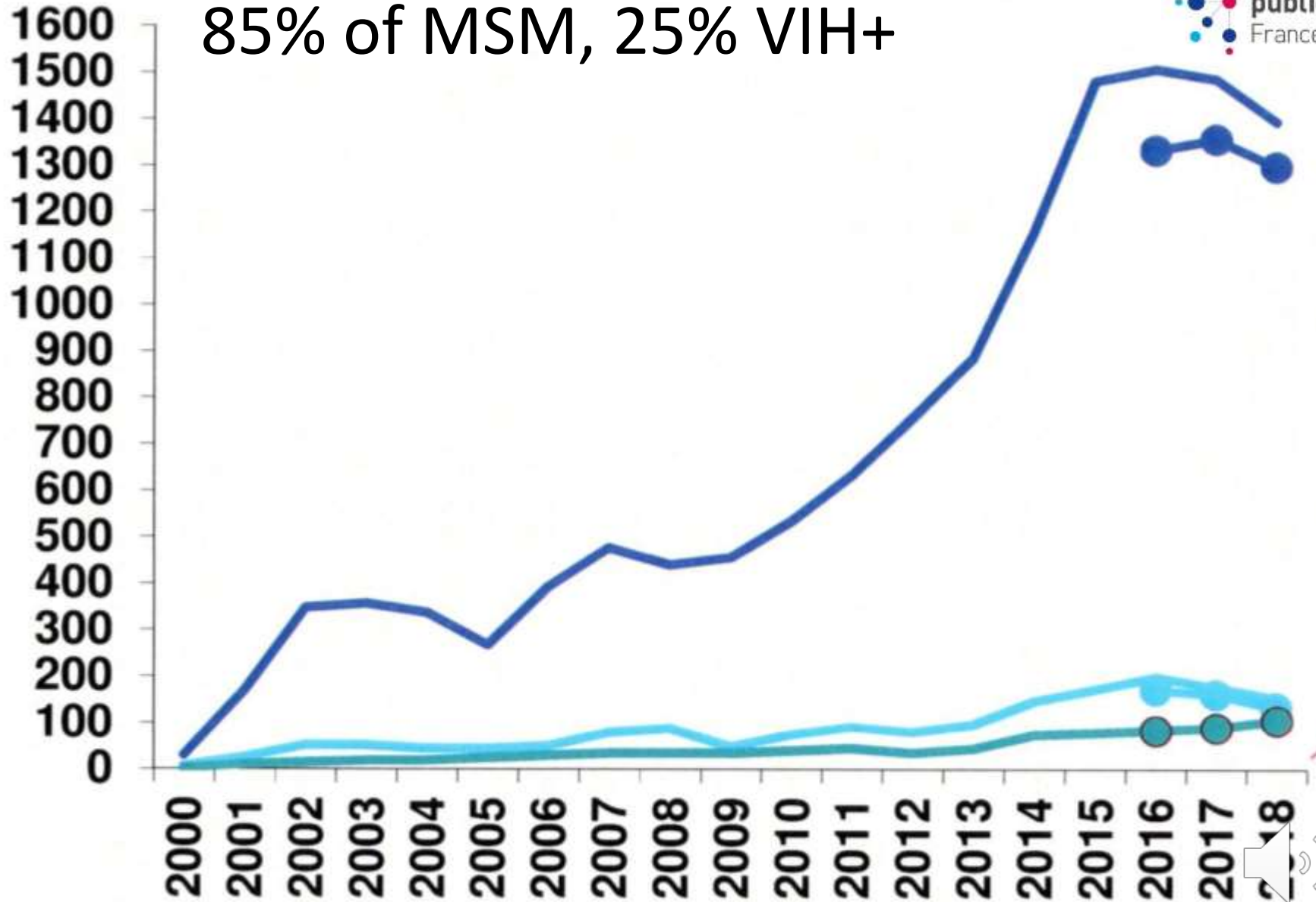
Consultation date	HIV status	Clinical lesion	DFM	Biological test		Strain subtype		
				TPHA	VDRL	<i>arp</i>	<i>tpr</i>	<i>tp0548</i>
Dec 2005	positive	papular on abdomen	positive	20480	16	14		CAGGCGCAGTGGCCACAGGCGCTGGAGGTCCTCCAGTGGTTCGCGCGATGGCAACACCCCGCAGGACAGTTCTCCAGTT
July 2007		genital and cutaneous on thorax	negative	20480	16	14		CAGGCGCAGTGGCCACAGGCGCTGGAGGTCCTCCAGTGGTTCGCGCGATGGCAACACCCCGCAGGACAGTTCTCCAGTT



# Incidence of early syphilis in France, ResIST network



85% of MSM, 25% VIH+





# Suède

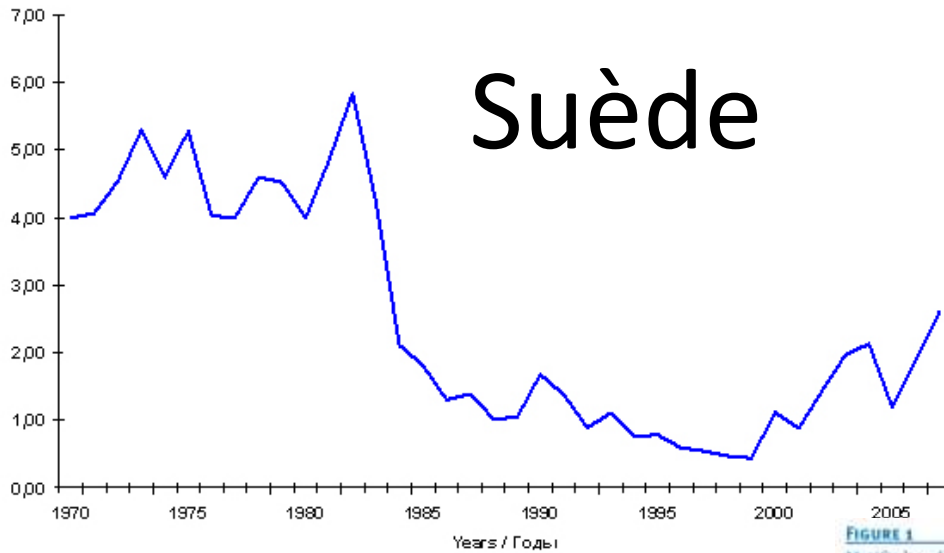
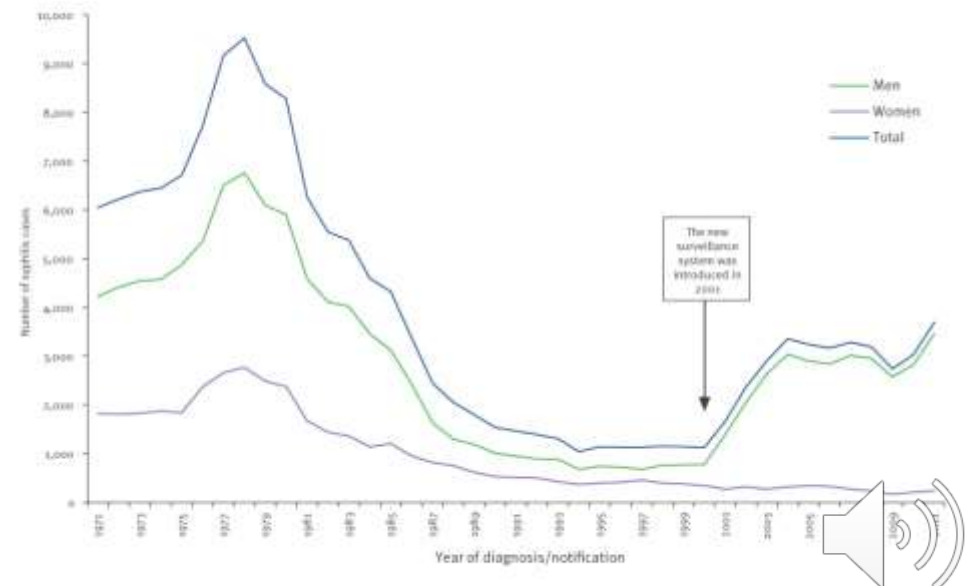


FIGURE 1

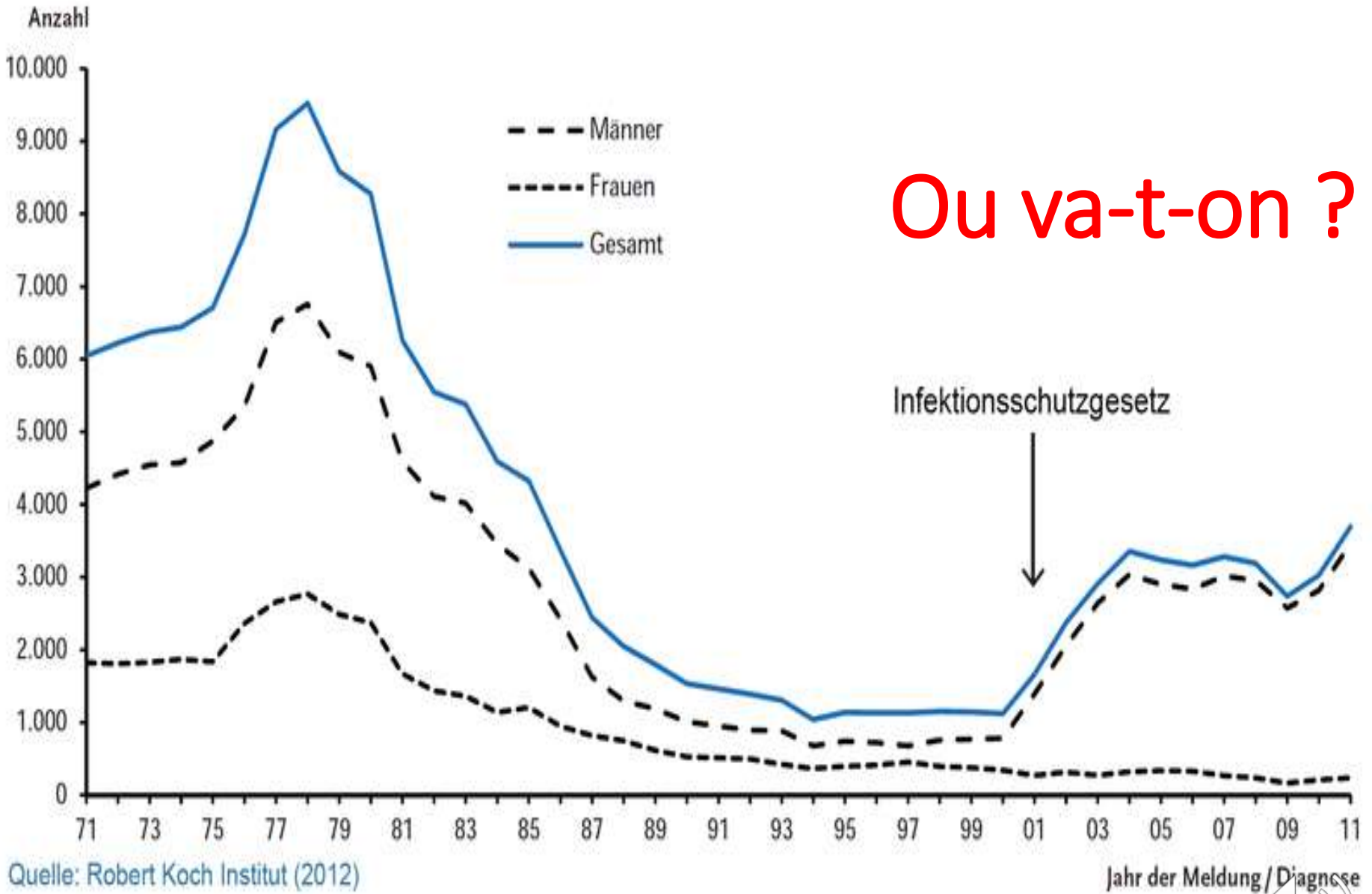
Notified syphilis cases by sex and year of notification or diagnosis, Germany, 1971-2011

# Allemagne



We used month of notification in case the date of diagnosis was missing.

Notification data according to the Sexually Transmitted Diseases Act (before 2001) and the Infection Protection Act (after 2001).



Ou va-t-on ?

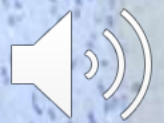
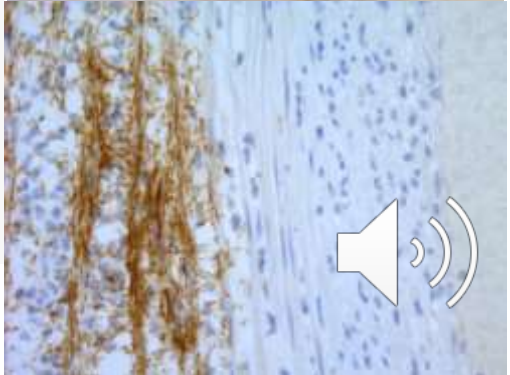
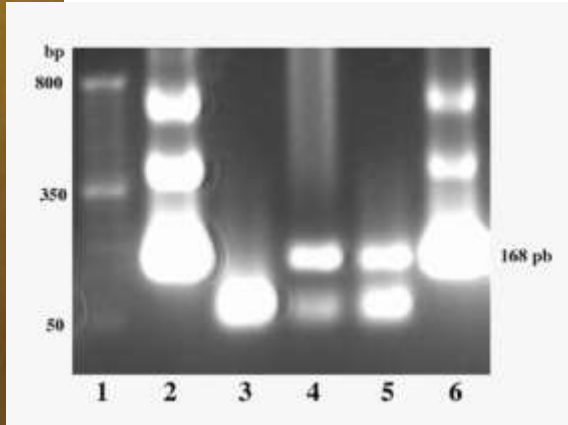
Quelle: Robert Koch Institut (2012)

Jahr der Meldung / Diagnose

Epidémiologie de la syphilis, Allemagne



# Le CNR Syphilis



# Classification of syphilis

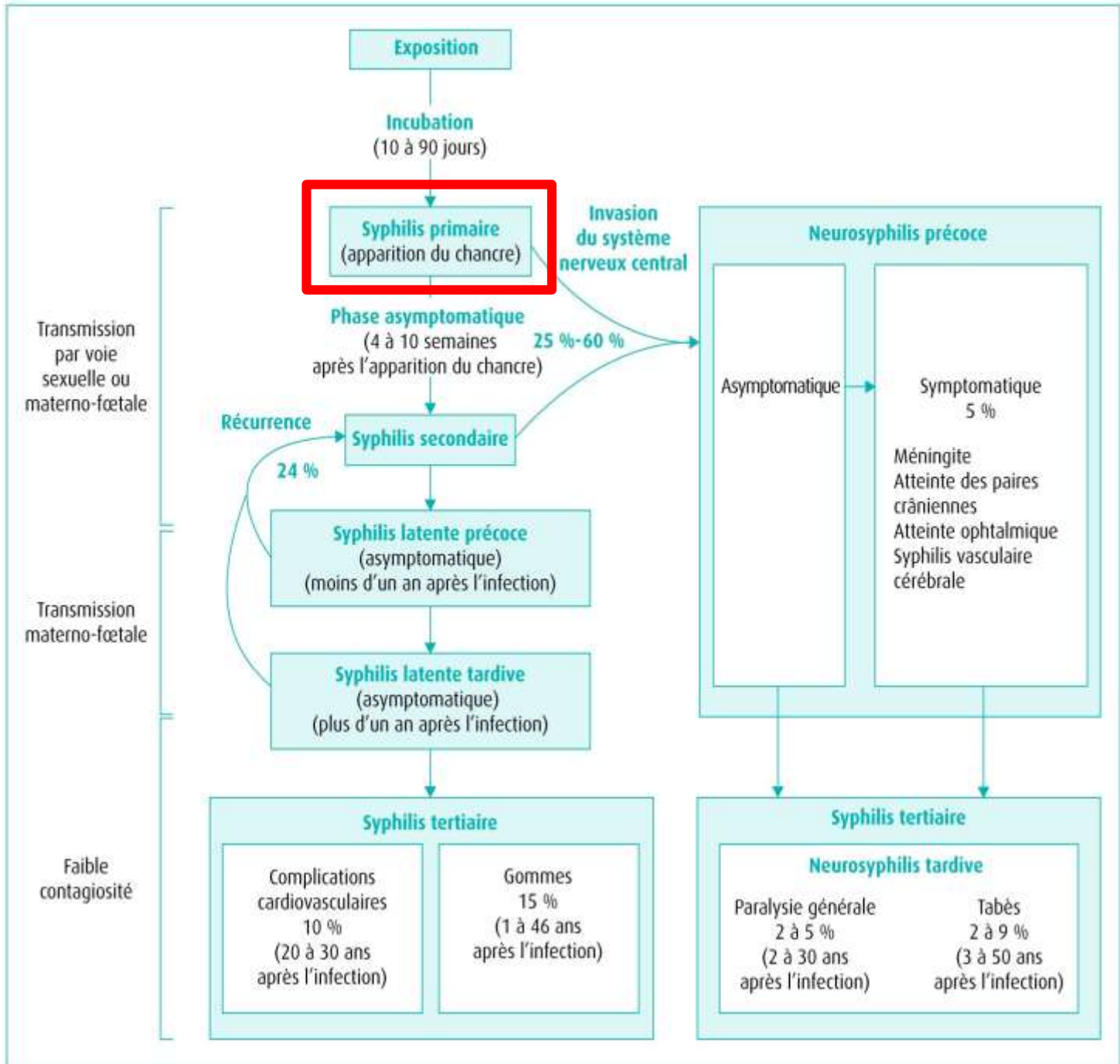
Early syphilis (less than 1 year) (highly contagious, neurosyphilis is rare but not so in fact...)

- Primary syphilis
- Secondary syphilis
- Early latent syphilis (less than one year duration 1)

Late syphilis (less contagious, treatment depends of neurological signs)

- Late latent syphilis (more than one year or unknown duration)
- Tertiary syphilis
  - cutaneous, cardiovascular syphilis
  - neurosyphilis





# Primary syphilis

The lesion is the **Chancre**

Erosion or exulceration more than an ulceration

Clean bottom

Painless

Hard based

Satellite adenopathy

Non inflammatory

Offset from the start of the chancre

None specific characteristics +++

**-> any mucosal ulceration is syphilis until proven otherwise**





# Test your self



??



??





# Test your self



**HSV-2**



**syphilis**

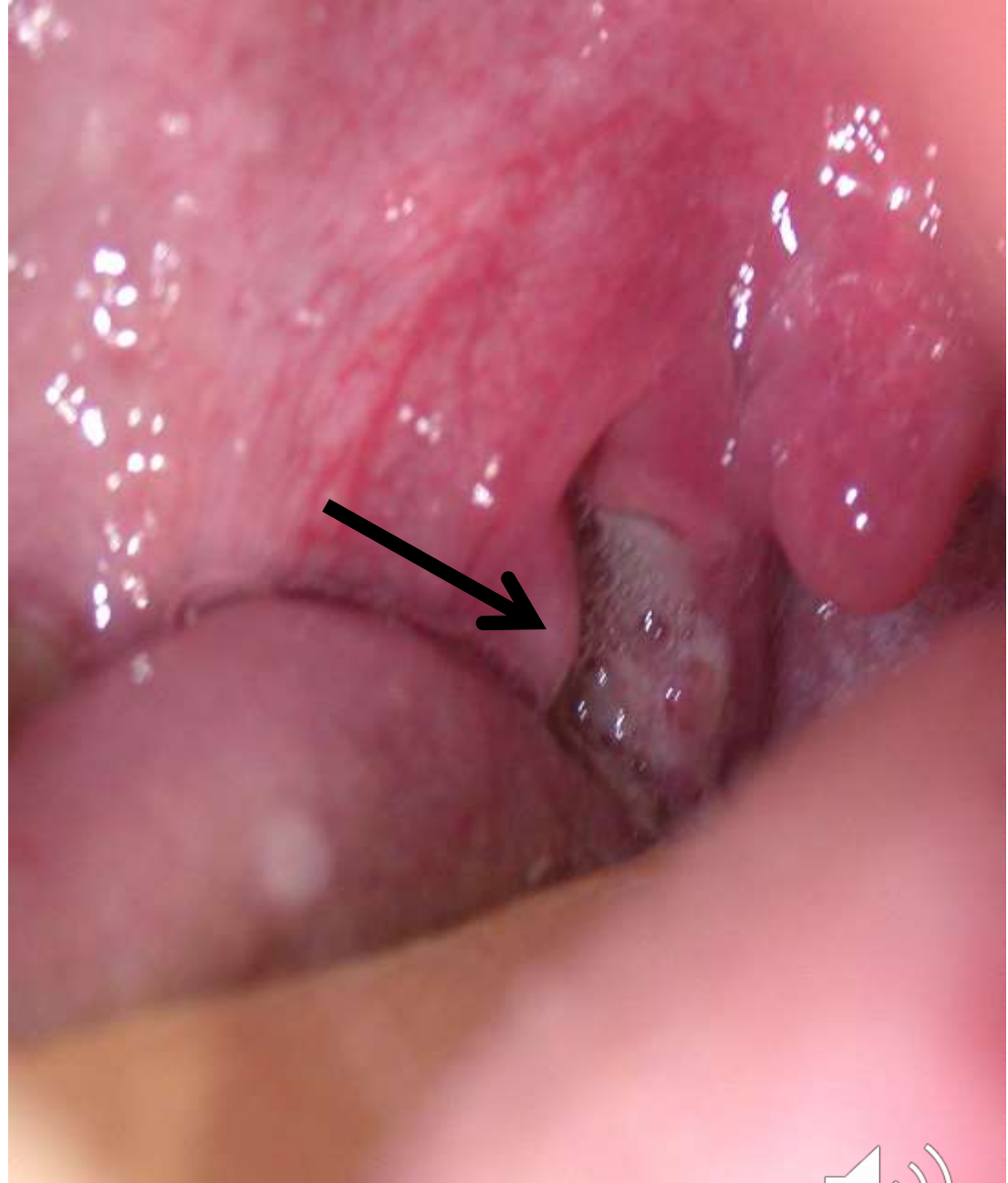
# Primary syphilis, anal chancre



**any mucosal ulceration is syphilis until proven otherwise**



# Tonsil chancre



**any mucosal ulceration is syphilis until proven otherwise**





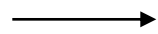
Lymphogranuloma venereum



# Lymphogranuloma venereum

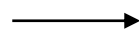


Diagnostic ?



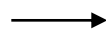
The diagnostic is frequently delayed  
Non specific anorectal signs in a MSM +++  
proctitis, anogenital ulcers, lymphadenopathies  
Fistulisation (bubo)  
Maladie de Nicolas Favre

What is the cause?



*Chlamydia trachomatis*  
Sérotype de L1 to L3

Diagnostic?



PCR on a rectal swab  
Ideally under rectoscopy or anoscopy  
If the PCR is positive  
Typing : L1 to L3

Traitement ?



Doxycycline 200 mg per day  
during 21 days  
  
Erythromycin in second line





*Haemophilus ducreyi* (a Gram-negative bacillus) Africa ++/south America  
Incubation 5-8 d  
Mixt with treponema 10%  
Ulcer has a ragged undermined edge  
It is not indurated and it is painful  
Multiple ulcers are common  
Satellite inguinal adenitis ++ which may suppurate leading to chronic draining lesions (bubo)  
Dg: Chain of cocobacilli in smears from the ulcers or of pus from the bubo  
Culture is difficult, PCR++  
DF and syphilis serology to be done +++

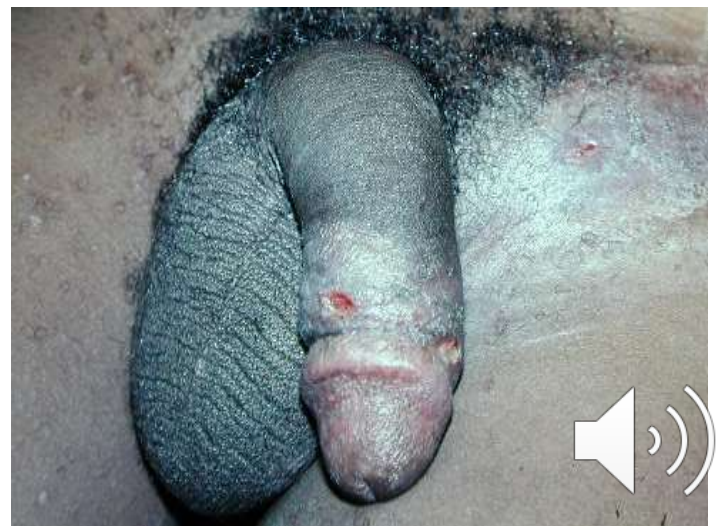
# Chancroid

Treatment:

Azithromycine, 1 gr orally, once time

Ceftriaxone, 250 or 500 mg IM

Erythromycin, 2 gr/d 7 d





*Klebsiella granulomatis* (Gram-negative bacillus)

South east Asia, Africa, New-Guinea,  
South-America

Incubation 9-50 days (difficult to determine)

The earliest lesion is a papule or a nodule

Ulcer is not painful

Localization: pubis, perigenital, not the mucosa

No adenopathy

Smears to search for Donovan bodies

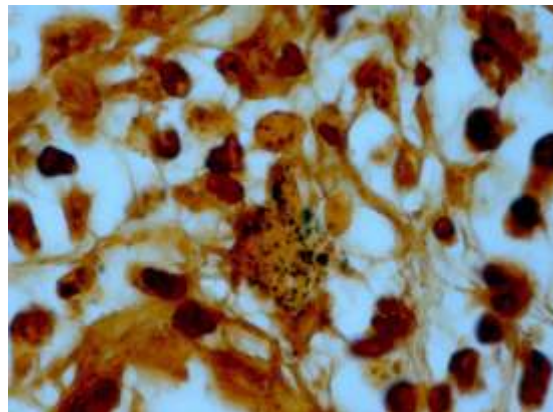
## Inguinal granuloma (Donovanosis)

Treatment:

Azithromycin, 1 gr per week  
for 4 weeks

Erythromycine, 2 gr /d /21 d

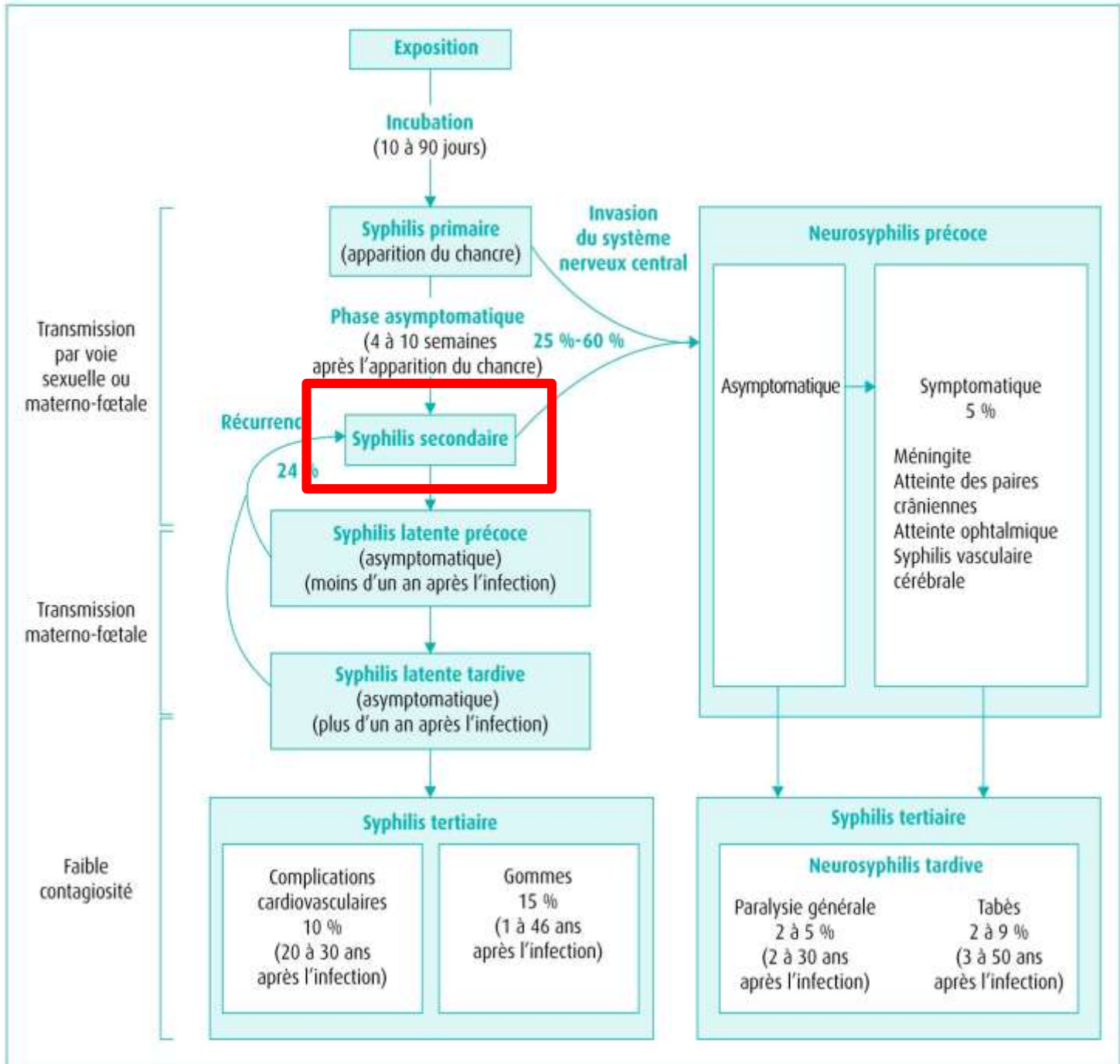
Gentamycin, tetracyclins...



Courtesy from Pr JJ Morand





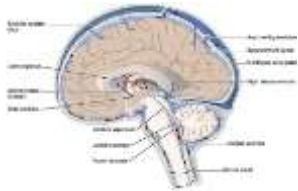


# Secondary syphilis can mimick all diseases

EYES



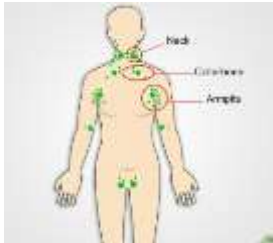
BRAIN AND MENINGES



BONES

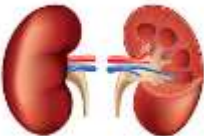


LYMPH NODES



$\Sigma$

KIDNEYS



LIVER



SKIN and MUCOSA





**1st  
flowering  
Roseole**

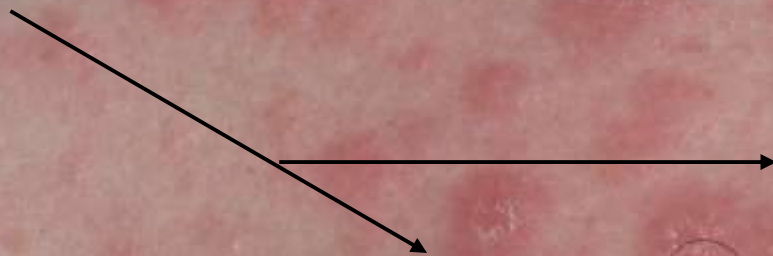




2nd  
flowering  
Papular  
eruption



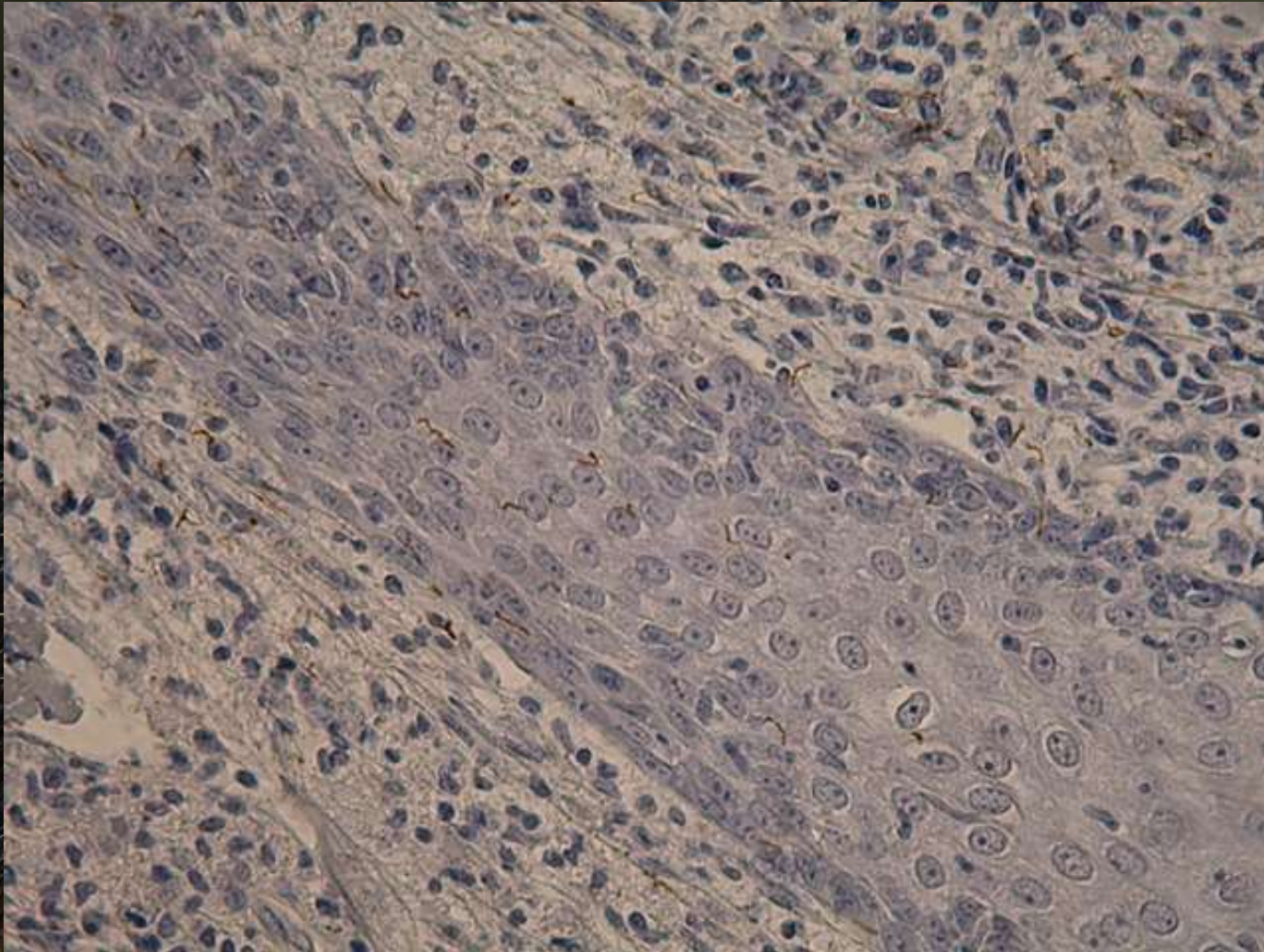
Biett's sign, collerette de Biett





Plants and soles papules in 30-40% II syphilis  
(copper coloured)





THE NEW ENGLAND  
JOURNAL of MEDICINE



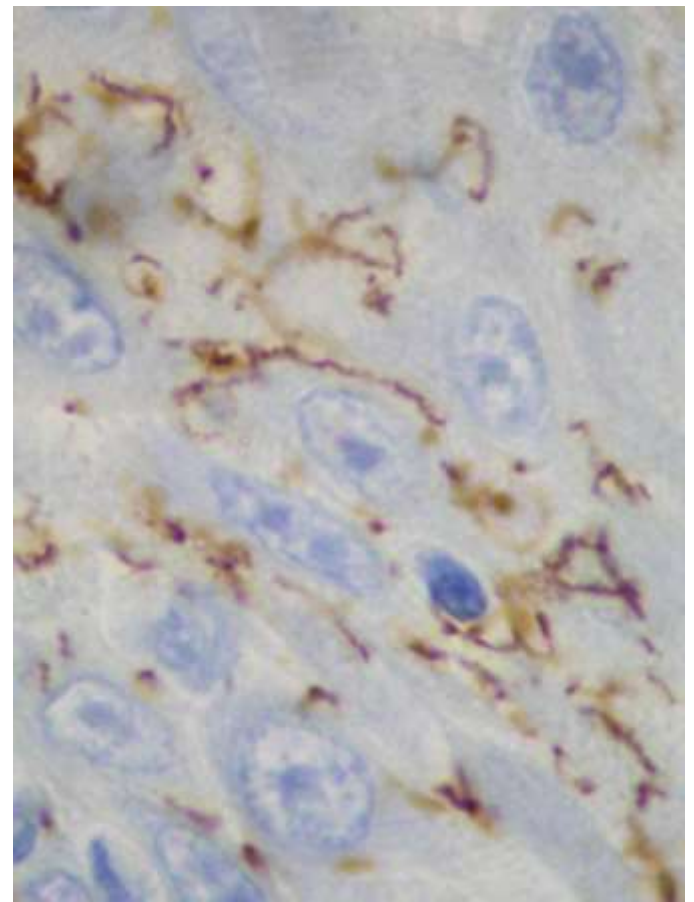
Moshiri, *NEJM* 2018

L'alopecie en clairiere, elle peut être isolée +++









TPHA = 1/2560

VDRL = 1/64



Syphilide secondaire

Syphilide érosive en carapace de tortue



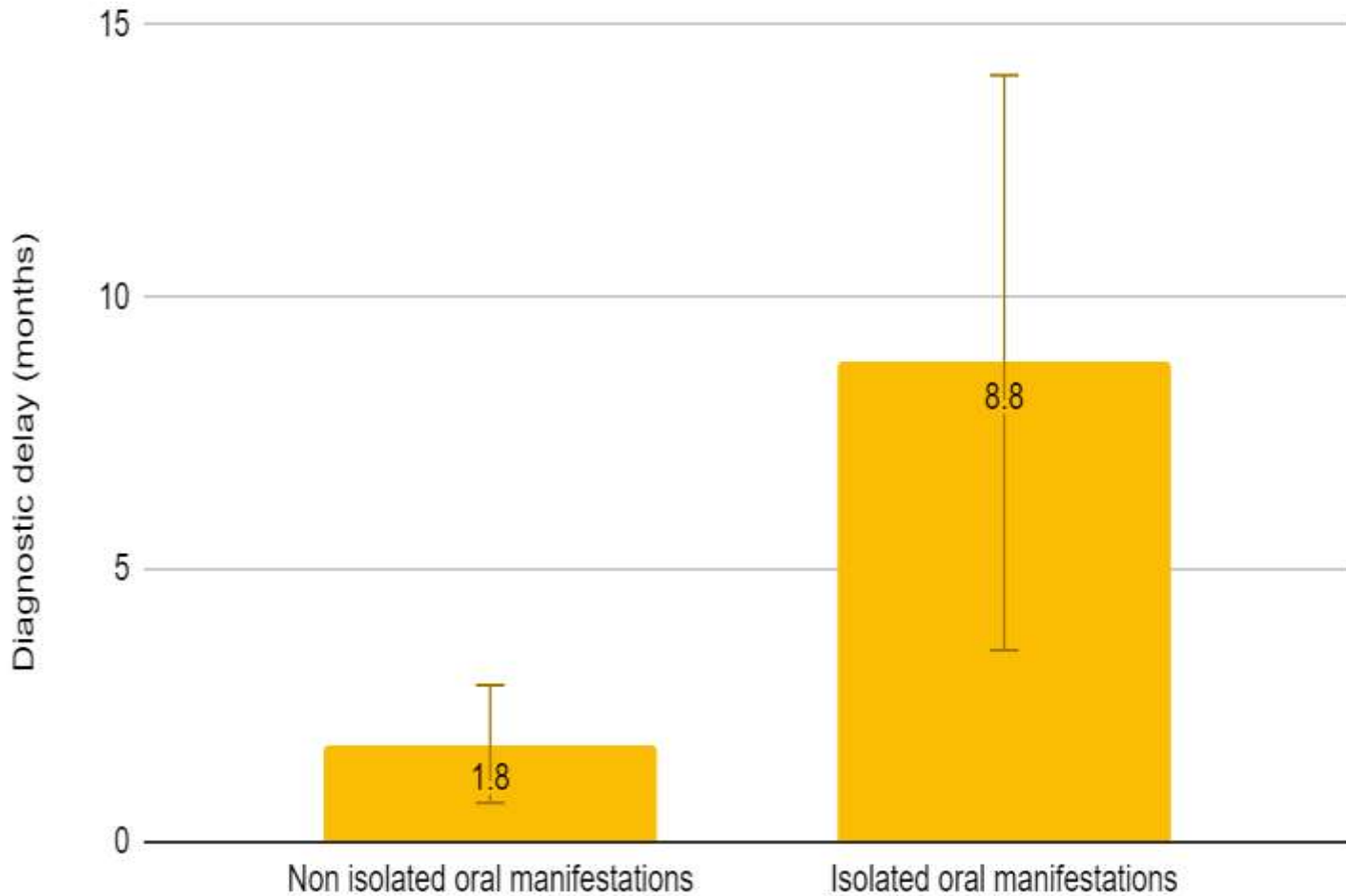


## Delay of diagnosis to frequent especially out of the target population !

- W, 28 ans
- Oral lesions since several months
- AAN +
- Supposed diagnosis was lupus
- Treatment with hydroxychloroquine
- Drop of visual acuity
- Papillary oedema toxicity of HCQ?
  - TPHA and VDRL +++
  - Meningitis on CSF



# Diagnostic Delay for patients with isolated vs non isolated oral



Pityriasis rosea or secondary syphilis ?

**In TROD we trust!**

The lesson of a rapid screening test



# POC=Rapid screening test = TROD

An ideal POC

« ASSURED »

- Affordable
- Sensitive
- Specific
- User friendly
- Rapid and robust
- Equipment free
- Delivered

## TROD INSTI Multiplex VIH1&2 / Syphilis

Lancement du premier TROD INSTI multiplex de dépistage des anticorps anti-VIH1/VIH2/Syphilis **disponible depuis juillet 2015.**

TROD présenté sous forme de set unitaire, marqué CE, avec tous les accessoires  
TROD validé par le Centre National de Référence de la Syphilis de l'Hopital Cochin (Paris)



- Sensibilité de **72,5%** (29/40) pour le diagnostic sérologique d'une **syphilis primaire**.
- La sensibilité est de **100%** lors du diagnostic de **syphilis secondaire** (41/41) et de **95.5%** (21/22) dans le diagnostic de **syphilis latente précoce**.
- Sa sensibilité sur l'ensemble du panel est de **88.3%** (91/103).
- La spécificité de **100%** pour le diagnostic sérologique de la syphilis (38/38).
- Une sensibilité de **100%** et une spécificité de **100%** pour le diagnostic d'infection à VIH comparé à un test ELISA classique.

[www.cnr-syphilis.fr](http://www.cnr-syphilis.fr) CNR Syphilis Service de Dermatologie – Vénérologie Hôpital Cochin  
Pr. Nicolas DUPIN / Dr. Philippe GRANGE / Dr. Nadjet BENHADDOU / Dr. Anne BIANCHI





Informations relatives à l'échantillon : SÉRUM ou Plasma / SÉRUM

## IMMUNOLOGIE BACTERIENNE

### Syphilis - Elisa

Dépistage des Ac anti-Tréponème  
Index

Positif  
25.12

Syphilis TP Architect System, Abbott (CMIA)

Négatif : <1

Positif : >=1

### Syphilis - VDRL

Dépistage VDRL

ASI RPR card test (Arlington Scientific)

Titre

Positif

(1)

(1) 1/128 (ou 128 UI/mL)

### Syphilis - Conclusion

Profil en faveur d'une tréponématose évolutive.

## SEROLOGIE VIRALE

### Virus de l'Immunodéficience Humaine (VIH)

Prélèvement: SÉRUM

Recherche Ag+Ac anti-VIH 1&2

Index

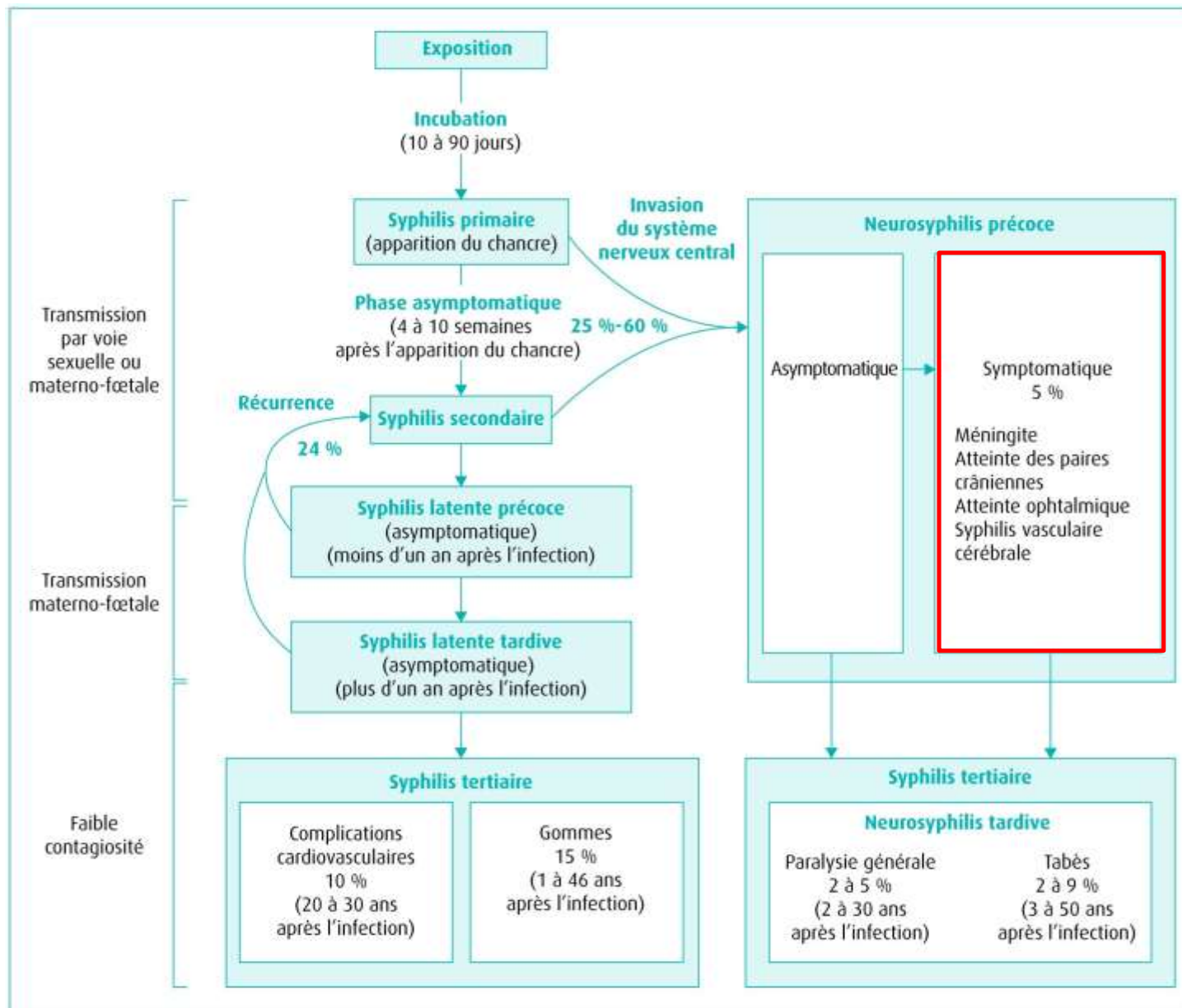
Négative  
0.16



# In (POC) TROD we trust...

- In this situation, the rapid test can easily establish the correct diagnosis
- The one who seems having not syphilis finally had
- The one who seems having syphilis finally had not
- As syphilis is the great imitator
- The famous adage: l'habit ne fait pas le moine is often true...
- TROD can help to make the correct diagnosis





# Clinical and Biological Characteristics of 40 Patients With Neurosyphilis and Evaluation of *Treponema pallidum* Nested Polymerase Chain Reaction in Cerebrospinal Fluid Samples

Clelia Vanhaccke,<sup>1</sup> Philippe Grange,<sup>1</sup> Nadjet Benhadou,<sup>2</sup> Philippe Blanche,<sup>3</sup> Dominique Sahnou,<sup>3</sup> Perrine Paris,<sup>4</sup> Olivier Lortholary,<sup>5</sup> Eric Couvres,<sup>6</sup> Isabelle Pelleux,<sup>7</sup> Olivier Epaillard,<sup>8</sup> Jérôme Guinant,<sup>9</sup> Nicolas Dupin<sup>1</sup> and the Neurosyphilis Network<sup>\*</sup>

Laboratoire de Rectevisse et Dermatologie, Institut Cochin (INSERM U1134), Centre National de Référence Syphilis, Faculté de Médecine, Université Paris Descartes, <sup>2</sup>Service de Bactériologie and <sup>3</sup>Service de Maladies Infectieuses, Hôpital Cochin, <sup>4</sup>Service de Maladies Infectieuses et Tropicales, Hôpital Necker Enfants Malades, Centre d'Intelligence Moléculaire (Paris), Hôpital Necker, <sup>5</sup>Service de Maladies Infectieuses et Tropicales, Hôpital Pitié Salpêtrière, AP-HP Paris, <sup>6</sup>Service de Bactériologie, and <sup>7</sup>Service de Maladies Infectieuses, Centre Hospitalier Universitaire de Grenoble, and <sup>8</sup>Service de Microbiologie, Centre Hospitalier Régional d'Orléans, France

# Prognostic Factors in Syphilitic Uveitis

Florence Hoogewoud, MD,<sup>1-6</sup> Laure Frumholtz, MD,<sup>1-6</sup> Paul Loubet, MD,<sup>1,4</sup> Caroline Chutlier, MD, PhD,<sup>5</sup> Philippe Blanche, MD,<sup>2,3</sup> David Lebeaux, MD, PhD,<sup>8</sup> Nadjet Benhadou, MD,<sup>2</sup> Neila Sedra, MD,<sup>6,11</sup> Laetitia Coste, MD,<sup>2,3</sup> Clelia Vanhaccke, MD,<sup>9</sup> Odile Lamy, MD, PhD,<sup>6</sup> Claire Le Jeunne, MD, PhD,<sup>12</sup> Emmanuel Héron, MD,<sup>8,11</sup> Dominique Monnet, MD, PhD,<sup>1</sup> Olivier Lortholary, MD, PhD,<sup>5</sup> José-Alain Sahel, MD, PhD,<sup>10,11</sup> Nicolas Dupin, MD, PhD,<sup>1,9</sup> Antoine Brézin, MD, PhD,<sup>1</sup> Marie-Hélène Errera, MD, PhD,<sup>10,11</sup> Sawsen Salah, MD,<sup>1</sup> Matthieu Groh, MD,<sup>1,12</sup>



Le CNR Syphilis





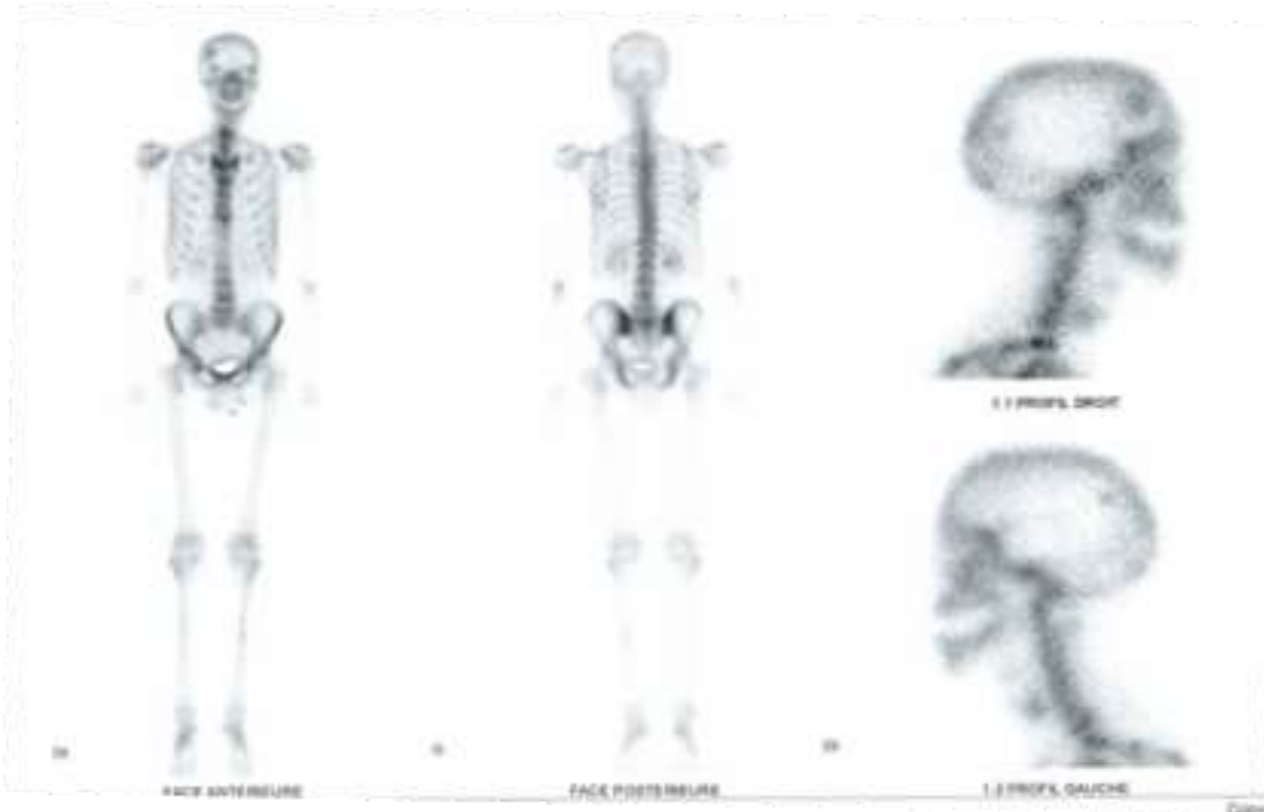
*From Dr Michel Janier*



Clinical Characteristics	Patient with neurosyphilis (n = 46)				Negative control
	Only ophtalmological (OPH) symptoms	Only neurological (N) symptoms	Both OPH and N symptoms	Total	
Number of patient	18	17	11	46	147
<i>CSF nPCR</i>					
<b>Positive (42%)</b>	8	9	4	21	5
Negative	10	8	7	25	142
HIV Infection (%)	10 (55)	5 (29)	5 (45)	20(43)	26
<i>Syphilis serology</i>					
<b>CSF VDRL (32%)</b>					
Positive	6	3	4	13	0
Negative	8	12	7	27	147
Serum VDRL					
Positive	18	16	11	46	0
<i>Clinical</i>					
Early NS	18	8	9	35	28
Late NS	0	4	2	6	100
Meningovascular NS	0	5	0	5	
<i>CSF white cells count</i>					
Mean	40,5	16	81	41	126
Intervalle	0-167	0-60	0-304	0-304	0-2750
>20/mm <sup>3</sup>	10	4	5	19	97
<i>CSF protein level</i>					
Mean	0,83	0,75	0,9	1,01	0,92
Intervalle	0,4-2,63	0,2-6,96	0,38-1,7	0,2-6,96	0,27-8,63
>0,5g/l	14	12	9	35	113



# Headaches = periostitis...





# Diagnosis procedures

- Serology ++
  - Place to automatized assays (farewell to IFA...)
  - Wellcome to:
    - EIA
    - Elisa
    - CMIA
- Dark field is not used in practice, PCR is not officially recommended
- Point of care (POC) can help



# Serology (screening)

- Used a treponemic test (EIA...)
  - If negative and no context of syphilis STOP
  - If negative and context of syphilis do it again 1 month later
  - If positive do a TNT (VDRL, RPR)
    - If TNT +, make a titration (pure, 1/2, 1/4...)
    - If TNT -,
      - could be a serological scar
      - Could be too early (repeat it 2 weeks later...)



# Serology (diagnostic)

- When you have a suspicion of primary or secondary syphilis
- Ask both a treponememic test (EIA...) and TNT
- Primary syphilis
  - If both tests negative, it could still be primary syphilis
    - Help with dark field microscopy
    - Help with PCR
    - Treat without any biological proof (40% will never come back...)
- Secondary syphilis
  - Both test are positive with high titers for the TNT
  - If both tests are negative, this is not a secondary syph





*Dark field*

	<i>Positif</i> <i>n (%)</i>	<i>Negatif</i> <i>n (%)</i>	<i>Non</i> <i>Fait</i>
<b>VDRL+ TPHA -</b>	6 (15%)	4 (7%)	1
<b>VDRL- TPHA +</b>	8 (20%)	19 (35%)	0
<b>VDRL+ TPHA +</b>	19 (48%)	32 (58%)	6
<b>VDRL - TPHA -</b>	7 (17%)	0	0
<b>TOTAL</b>	40(100%)	55 (100%)	7



Michel Janier

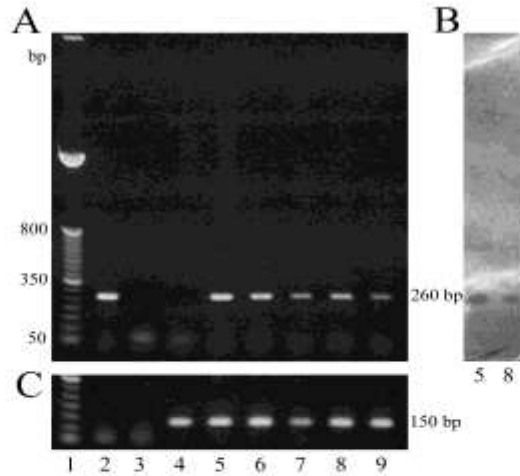
PCR can be useful



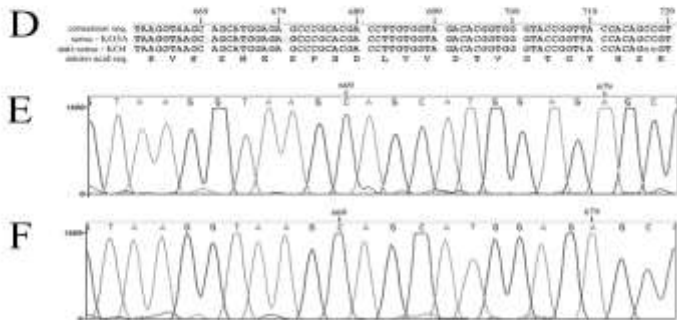
# Detection of *T. pallidum* *tp47* gene by PCR

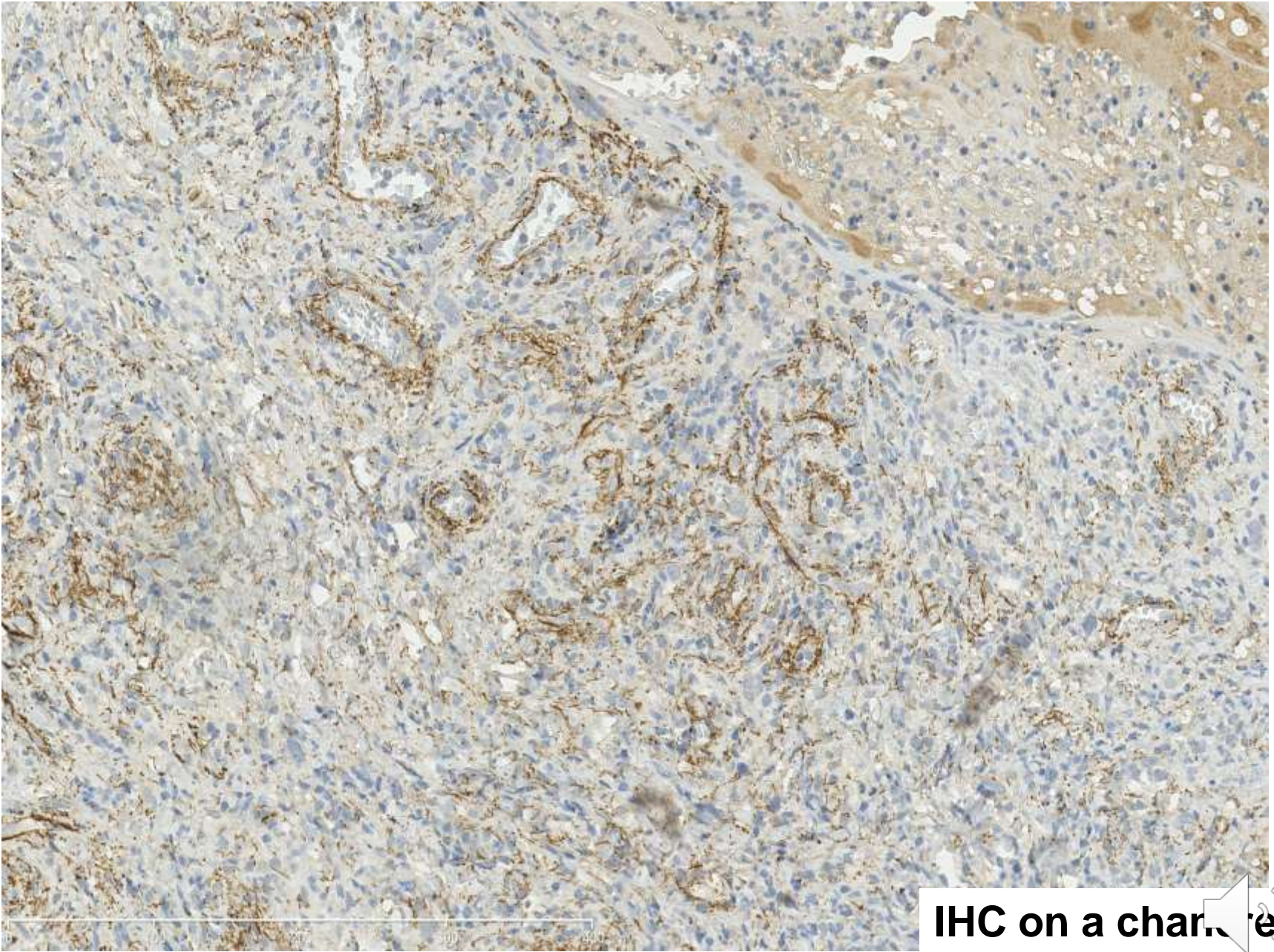
Grange, JCM 2012

245 patients with syphilis  
 72 patients with an ulceration of another origin  
 35 healthy controls

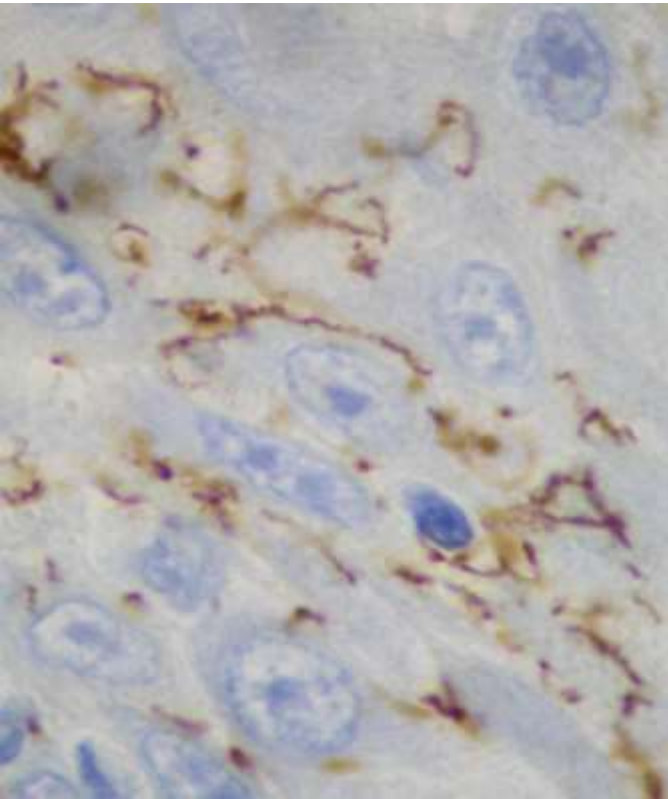


Nested PCR	ss	sp
swabs	79,6%	97,2%
Pbmc	29%	95,6%
Total blood	24%	97,3%
Serum	14,7%	93,3%
Plasma	18,5%	92%

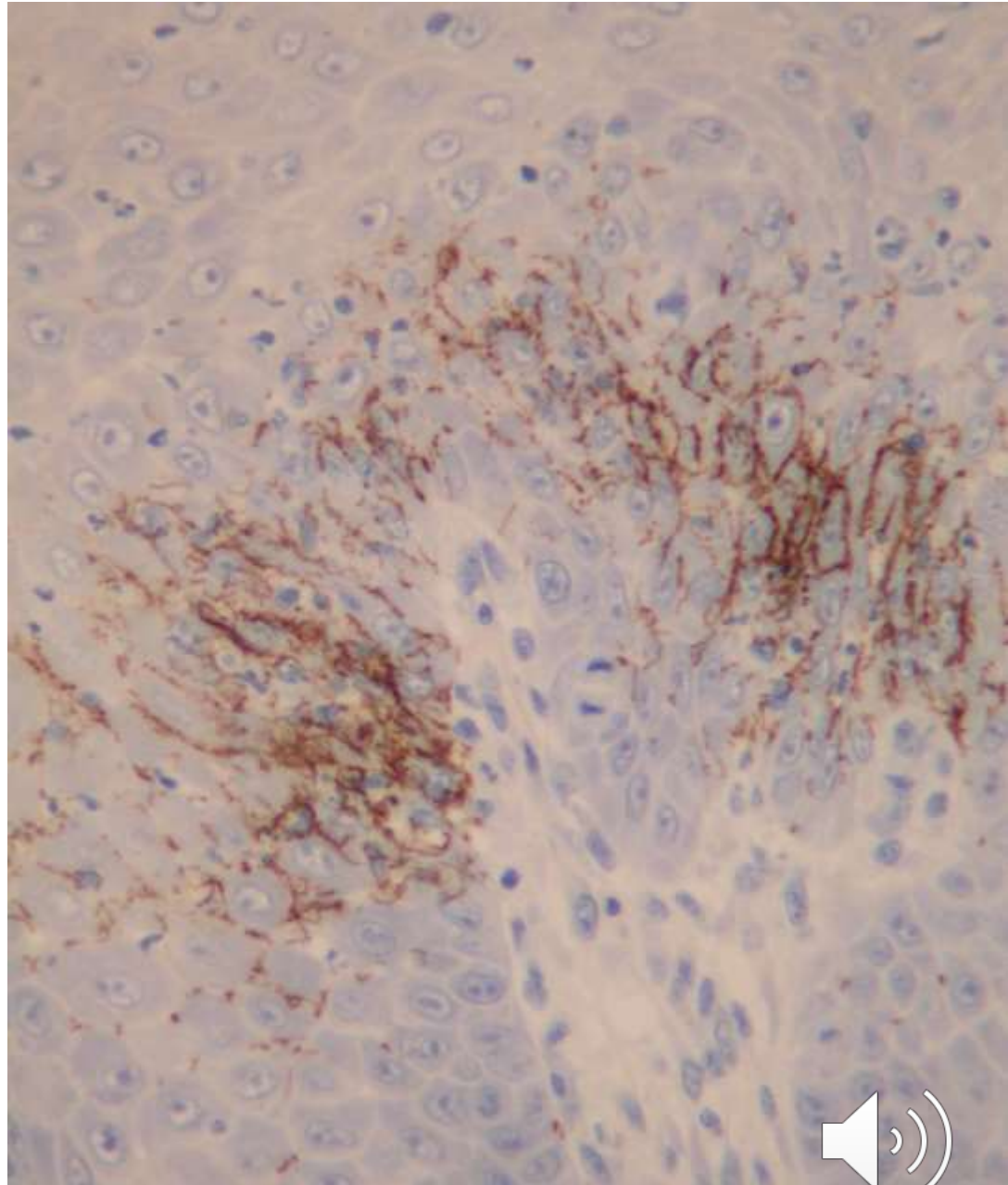




IHC on a chondrocyte



Immunohistochemistry  
on syphilides



# Syphilis treatment (idem for HIV)

Early syphilis

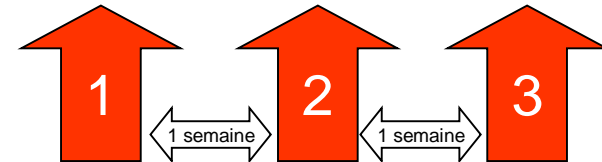
Late syphilis

<b>I Syphilis</b>	<b>II syphilis</b> Early latent	<b>III syphilis (not neurosyphilis)</b> Late latent
-------------------	------------------------------------	--

**Benzathine penicillin G**



**Benzathine penicillin G**



**TRAITEMENT : Benzathine penicillin G**  
Injection IM de 2,4 Millions d'unités

In case of allergy  
Doxycycline 100 mg/12 h PO 14 days

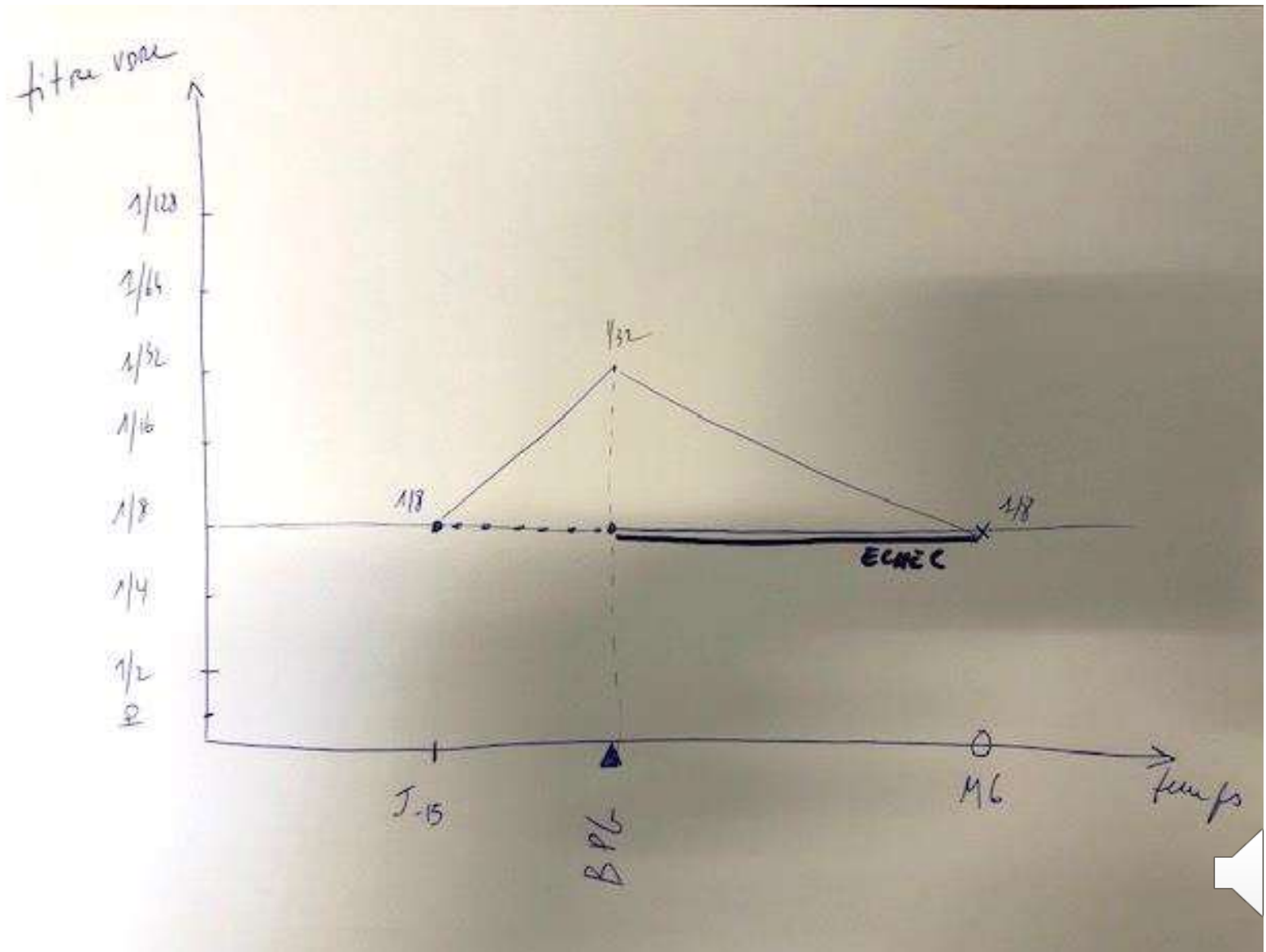
In case of allergy  
And no NEUROSYPHILIS  
Doxycycline 100 mg/12 h PO 28 days



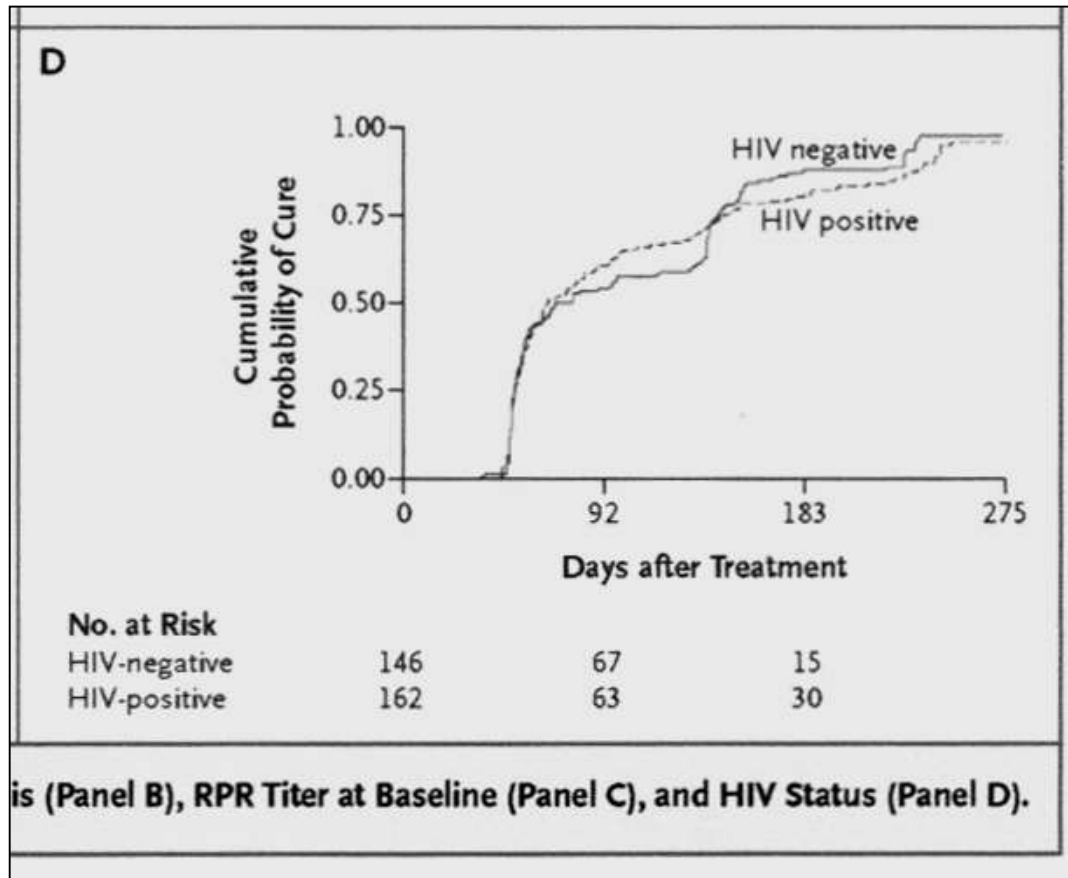
# Follow up of serology

- In the same laboratory +++
- You must look only to the decrease of the titer of the TNT (VDRL/RPR)
- TNT should be performed the day of administration of BPG
- You want TNT to decrease of 2 dilutions at M6 (i.e. 1/32 to 1/8, this is good)
- You should perform TNT at 3, 6, 12 and 24 months and more if the patient develops new lesions or symptoms
- TNT should be negative at 1 year for a I syphilis
- TNT should be negative at 2 years for a II syphilis

# Why perform the TNT the day of BPG ?



# Quel traitement pour la syphilis en 2020 ? Place de l'azithromycine en France ?



Mbeya, Tanzania



## BRIEF REPORT

Macrolide Resistance in *Treponema pallidum*  
in the United States and Ireland

## Mutation A2058G ARNr 23S

**Table 1.** The Presence of the 23S rRNA Gene Mutation in *T. pallidum* Samples Collected from Sites in the United States and Ireland from 1912 through 2003.

Geographic Site	Date Sample Collected	Samples with Mutation/ Total Amplifiable Samples
		no./total no. (%)
San Francisco	1999–2002	1/25 (4)
	2003	11/30 (37)
Seattle	2001–2003	3/23 (13)
Baltimore	1998–2000	2/19 (11)
Dublin	2002	15/17 (88)
Historical strains from multiple locations	1912–1987	1/18 (6)

**Table 2.** Efficacy of Therapy for Primary *T. pallidum* Infection in the Rabbit Model, According to Strain and Type of Therapy.\*

Outcome	Nichols Strain				Street 14 Strain			
	Untreated Control	Penicillin G Benzathine	Erythromycin	Azithromycin	Untreated Control	Penicillin G Benzathine	Erythromycin	Azithromycin
No. of animals with DF-positive lesions at completion of therapy/total no. studied	3/3	0/3	0/3	0/3	3/3	0/3	3/3	3/3
Days to DF negativity — median (range)	>14	1 (1)	3 (3–4)	3 (2–3)	>14	1 (1)	>14	>14
VDRL titer six weeks after initiation of therapy — median (range)	8 (4–8)	0 (0–WR)†	2 (2–4)†	1 (1)†	8 (4–8)	0 (0)†	4 (4–8)	1 (0–8)

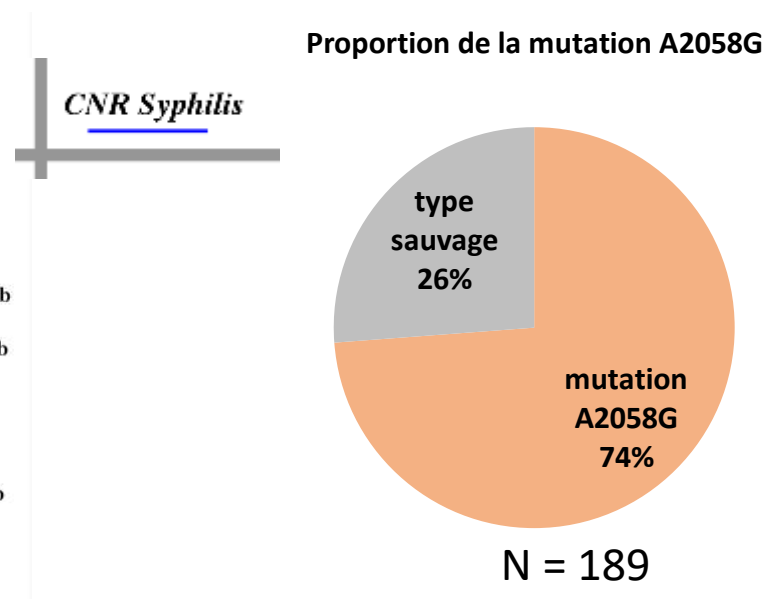
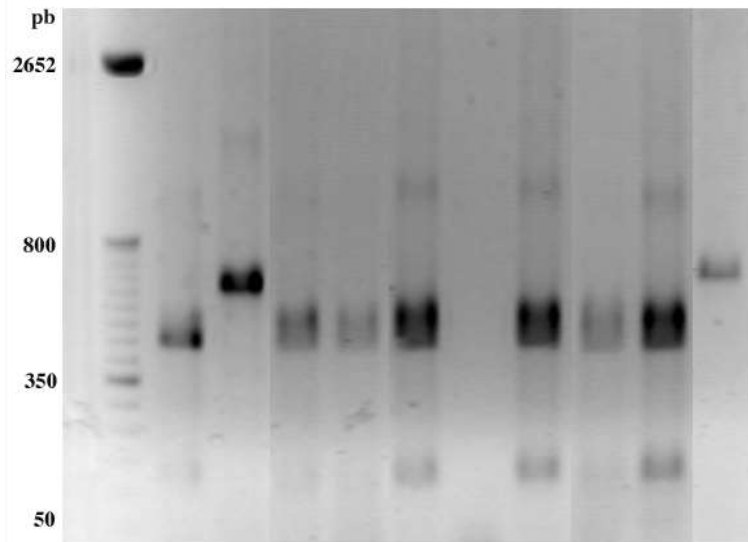
\* DF denotes dark-field microscopical examination of lesions for presence of *T. pallidum*, VDRL Venereal Disease Research Laboratory, and WR weakly reactive.

† P<0.05 for the comparison with untreated controls for each strain, by means of analysis of variance.



Depuis 2013, le CNR syphilis analyse la présence de la mutation A2058G sur tous les échantillons positifs en PCR de criblage (nPCR, gène *tpp47*).

## Très forte proportion de *T. pallidum* muté



CNR Syphilis

Pospisilova et al, Plos One 2018 -> A2058G = 86% des souches en France

# Problématique de la doxycycline

- La doxycycline apparait comme l'alternative proposée par toutes les guidelines (UE, EU)
- Confrontation aux pénuries et recours à la doxycycline en prophylaxie nécessitent de valider:
  - l'absence de résistance microbiologique
  - que la doxy n'est pas inférieur au tt de référence de la syphilis précoce (BPG) par un essai

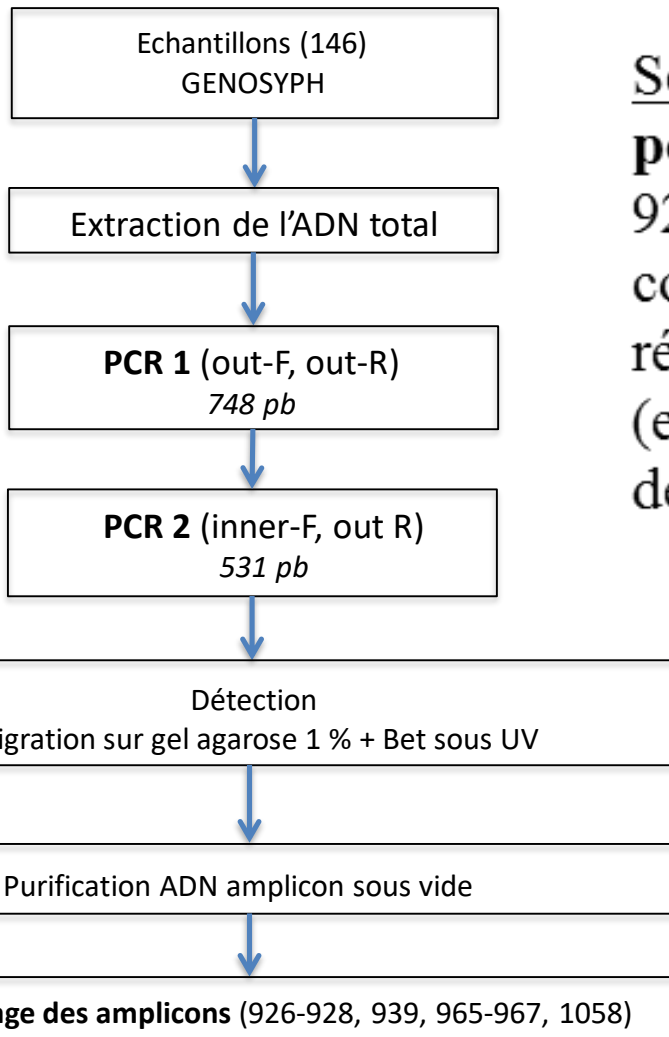


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  - l'absence de résistance microbiologique



# Recherche mutation ARNr 16S



Séquençage : **aucune mutations ponctuelles retrouvées** en position 926-928, 939, 965-967 et 1058 comparativement à la séquence de référence du gène de l'ARNr 16S de TPA (exemple sur 7 amplicons représentatifs de 124/139 amplicons séquençés).

**Absence de résistance microbiologique du Tp à la doxycycline**





# Problématique de la doxycycline

- La doxycycline apparait comme l'alternative proposée par toutes les guidelines (UE, EU)
- Confrontation aux pénuries et recours à la doxycycline en prophylaxie nécessitent de valider:
  - que la doxy n'est pas inférieur au tt de référence de la syphilis précoce (BPG) par un essai



# Etat des lieux sur la doxycycline pour le traitement de la syphilis

- Peu de données dans la littérature
  - 0 RCT (TTC vs BPG)
  - Séries rétrospectives
  - Une revue systématique dans Plos one 2017...  
Méta-analyse en réseau
  - Encore moins de données chez les VIH, Long et al. STD 2006; Ghanem et al CID 2006, trop peu de patients VIH inclus dans ces études pour faire des recommandations
  - Des échecs cliniques décrites, Zenilman et al STD 2013



Table 3. Summary of data on serological response rates of interventions at 6-month follow-up.

Study	Intervention	Response	Total patients	Response rate	<i>P</i> value
Tsai 2014	Doxycycline	78	123	63.4%	0.094
	Penicillin	196	271	72.3%	
Li 2014	Doxycycline/tetracycline	29	35	82.9%	0.157
	Penicillin	554	606	91.4%	
Schofer 1989	Ceftriaxone	5	6	83.3%	1.000
	Penicillin	2	2	100%	
Moorthy 1986	Ceftriaxone	11	13	84.6%	1.000
	Penicillin	4	5	80%	
Schroeter 1972	Tetracycline	82	87	94.3%	0.592
	Penicillin	191	198	96.6%	

<https://doi.org/10.1371/journal.pone.0180001.t003>

Liu Hy, Han Y, Chen Xs, Bai L, Guo Sp, et al. (2017) Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies. PLOS ONE 12(6): e0180001.

<https://doi.org/10.1371/journal.pone.0180001>

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0180001>

Table 4. Summary of data on serological response rates of interventions at 12-month follow-up.

Study	Intervention	Response	Total patients	Response rate	P value
Tsai 2014	Doxycycline	60	91	65.9%	0.681
	Penicillin	185	271	68.3%	
Psomas 2012	Doxycycline	11	15	73.3%	0.928
	Ceftriaxone	38	49	77.6%	
	Penicillin	39	52	75.0%	
Spornraft-Ragaller 2011	Ceftriaxone	11	12	91.7%	1.000
	Penicillin	11	11	100%	
Potthoff 2009	Ceftriaxone	16	27	59.3%	0.542
	Penicillin	34	65	52.3%	
Wong 2008	Doxycycline/ tetracycline	25	25	100%	1.000
	Penicillin	409	420	97.4%	
Ghanem 2006	Doxycycline	34	34	100%	0.399
	Penicillin	69	73	94.5%	
Schofer 1989	Ceftriaxone	5	5	100%	-
	Penicillin	7	7	100%	
Moorthy 1986	Ceftriaxone	12	13	92.3%	1.000
	Penicillin	4	4	100%	
Schroeter 1972	Tetracycline	61	67	91.0%	0.357
	Penicillin	143	150	95.3%	

<https://doi.org/10.1371/journal.pone.0180001.t004>

Liu Hy, Han Y, Chen Xs, Bai L, Guo Sp, et al. (2017) Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies. PLOS ONE 12(6): e0180001.

<https://doi.org/10.1371/journal.pone.0180001>

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0180001>

# Chez les patients infectés par le VIH

*Salado-Rasmussen, et al. Acta Dermatol Venereol 2016*

- Danemark, étude multicentrique, rétrospective
- 202 patients doxy ou BPG
- À 12 mois 15% d'échec sérologique dans le gpe Doxy vs 17% dans le gpe BPG
- La réponse sérologique dépend du stade de la syphilis
  - 100% Syp I
  - 89% Syp II
  - 75% Lat précoce
  - 69% Lat tardive



Un essai clinique randomisé de non-infériorité de la Doxycycline vs BPG dans le traitement de la syphilis précoce

- SY-DOXY -

*N Dupin Invest principal*

- **essai clinique en ouvert, de phase III, comparatif et randomisé**
- L'objectif principal de notre étude est de montrer qu'une dose de 100 mg de doxycycline deux fois par jour pendant 14 jours n'est pas inférieure à une injection intramusculaire unique de  $2,4 \times 10^6$  UI de BPG dans le traitement de la syphilis précoce, évaluée comme une diminution de 4 fois du titre dans le test non tréponémique (VDRL ou RPR) à 6 mois (largement utilisé comme définition du traitement dans des conditions réelles)
- 100 patients dans chaque groupe
- Durée de l'étude 30 mois avec une période d'inclusion de 24 mois
- 18 sites référents
- Début de l'étude T1 2020

# syphilis

- High prevalence in MSM in western countries
- Effect of the HAART, the TASP and recently the PrEP...
- Always think that *treponema* hides under a skin or a mucosal lesion and other variable clinical manifestations...delay of diagnosis is too frequent even in 2020
- Biological diagnostic is based on serology in most cases
- BPG is safe (used since more than 70 years) for treating early syphilis
- Doxycycline, although never demonstrated by RCT, can be an alternative treatment but needs 14 days of administration which is not ideal for treating a STD

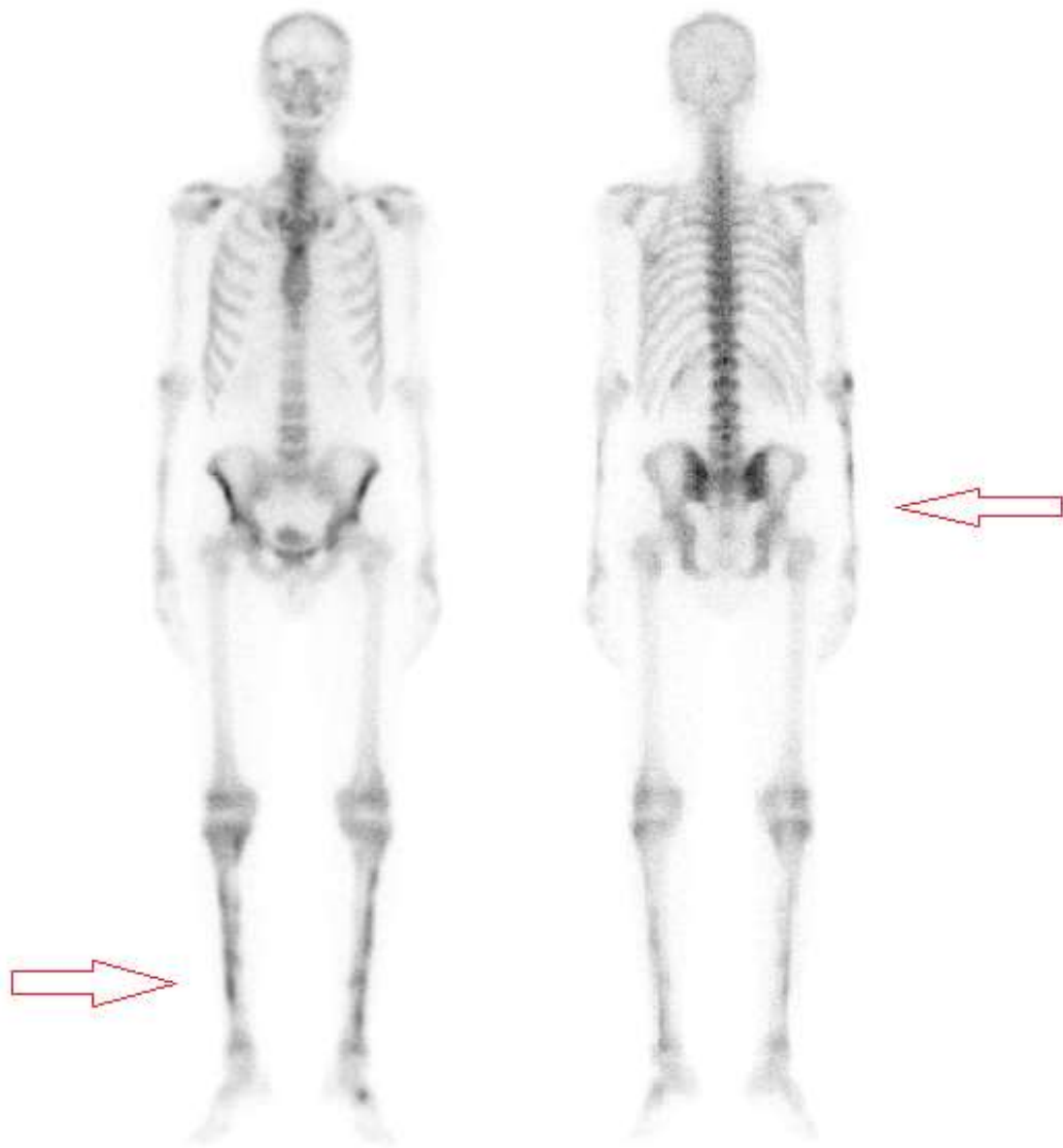


- A man in his 50's year was hospitalized in our department for investigation of a skin rash associated with diffuse bone pain
- He has few red papules over the body predominantly on the trunk and on the upper and lower limbs. He has also an hyperkeratosis of the plants
- He has no mucosal lesion. The joints were not painful but he has bone pain of the humerus and the tibia and he cannot walk and sleep since one week









Among the following proposal, what is the diagnosis you privilege ?

- A. yaws
- B. Behçet disease
- C. Secondary syphilis
- D. psoriasis
- E. Lyme disease (secondary phase)



Among the following proposal, what is the diagnosis you privilege ?

- A. yaws
- B. Behçet disease
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- D. psoriasis
- E. Lyme disease (secondary phase)



You suspect a secondary syphilis, among the following exams, which you will prescribe ?

- A. Western blot
- B. VDRL or RPR
- C. FTA
- D. Elisa
- E. Nelson



You suspect a secondary syphilis, among the following exams, which you will prescribe ?

A. Western blot

B. VDRL or RPR

C. FTA

D. Elisa

E. Nelson



You have prescribe an Elisa and a VDRL ,what is(are) the possible result(s) for these serologies if the patient has a secondary syphilis ?

- A. Both tests can be negative
- B. Elisa is always positive
- C. Both test should be positive
- D. VDRL is frequently negative
- E. None of these proposals is correct



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- B. Elisa is always positive
- C. Both test should be positive
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- E. None of these proposals is correct





You receive the result:

Elisa is positive with an index at 47 (cutt off 1)

VDRL is negative

Your resident told you that it cannot be a secondary syphilis because during secondary syphilis both test should be positive with a high titre...

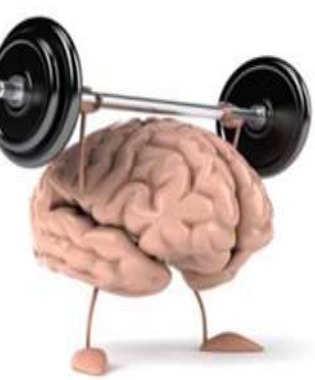
Are you agree with him/her ?

Do you have any explanation ?

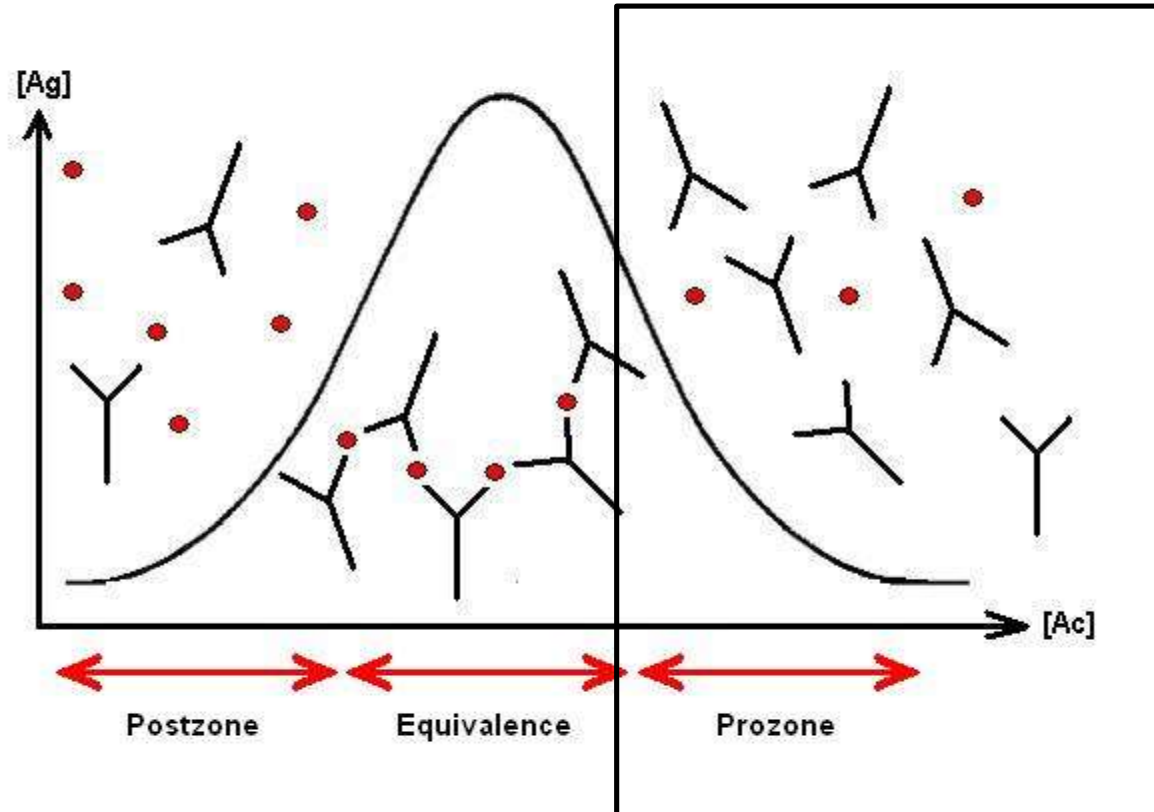
How you can go further ?







# Prozone phenomenon



You should perform dilution to control the VDRL, in this case, the VDRL was only positive at dilution 1/128 !!! And it was still positive at dilution 1/1024 +++  
This case was reported by the resident: Mahevas T, et al Rheumatology 2016



# Take home messages

- this case illustrates that bone pain can be very frequent during secondary syphilis and can lead also to headache ++
- Prozone phenomenon is very rare, and can also be observed with the new test (Elisa here and not TPHA)
- The incidence of prozone phenomenon is less than 1%, in a chinese study it was reported to be 0,83% (Liu et a; Clin Infect Dis 2014)
- Risk factors for prozone phenomenon are:
  - HIV
  - Pregnancy
  - neurosyphilis



# Problématiques sont différentes en fonction du type d'IST

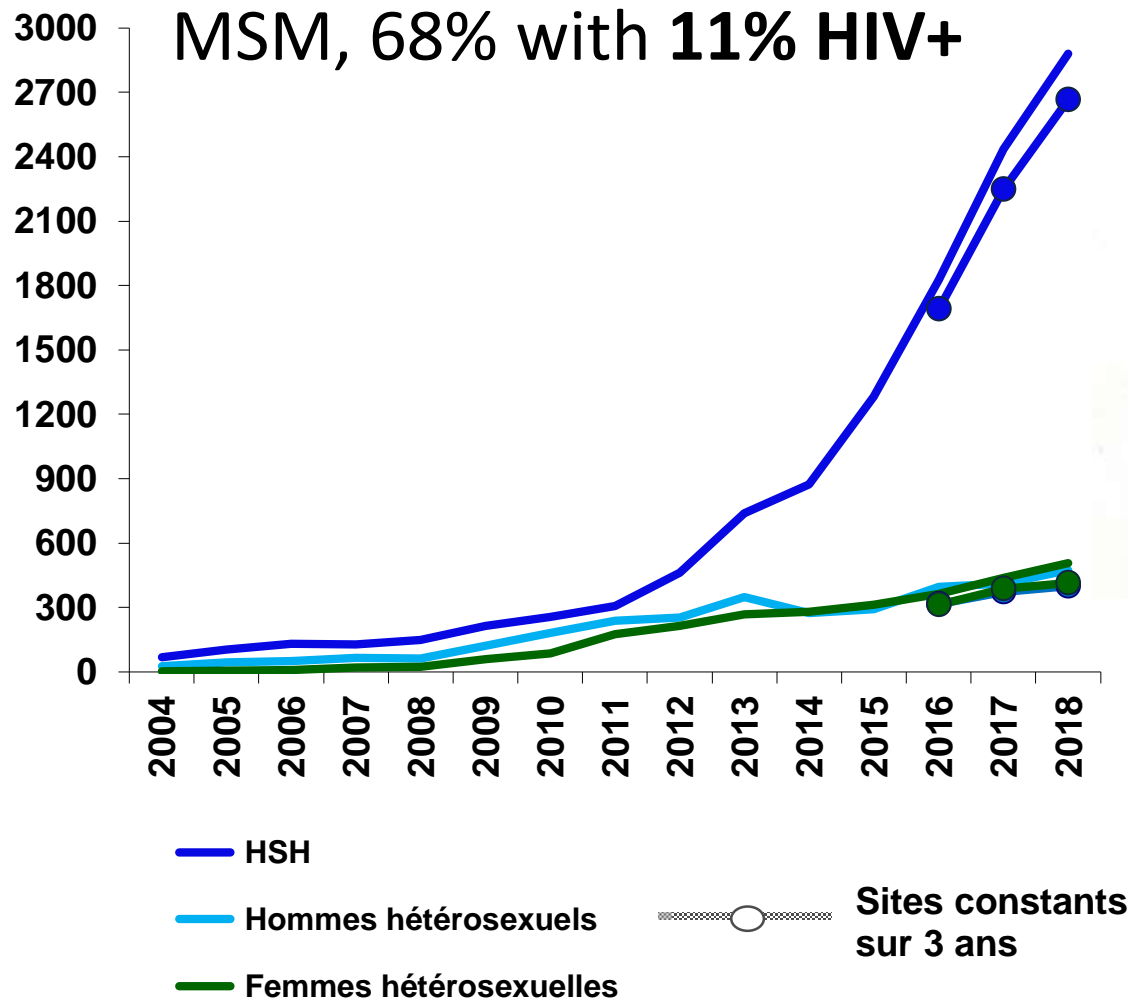
- **Gonocoque et *M genitalium***
  - Résistance
  - Superbugs ?



# *Neisseria gonorrhoeae*



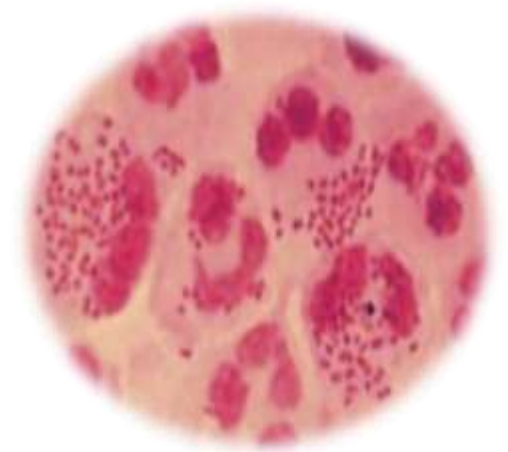
# Gonococcal infections are increasing



?



# *N gonorrhoeae*

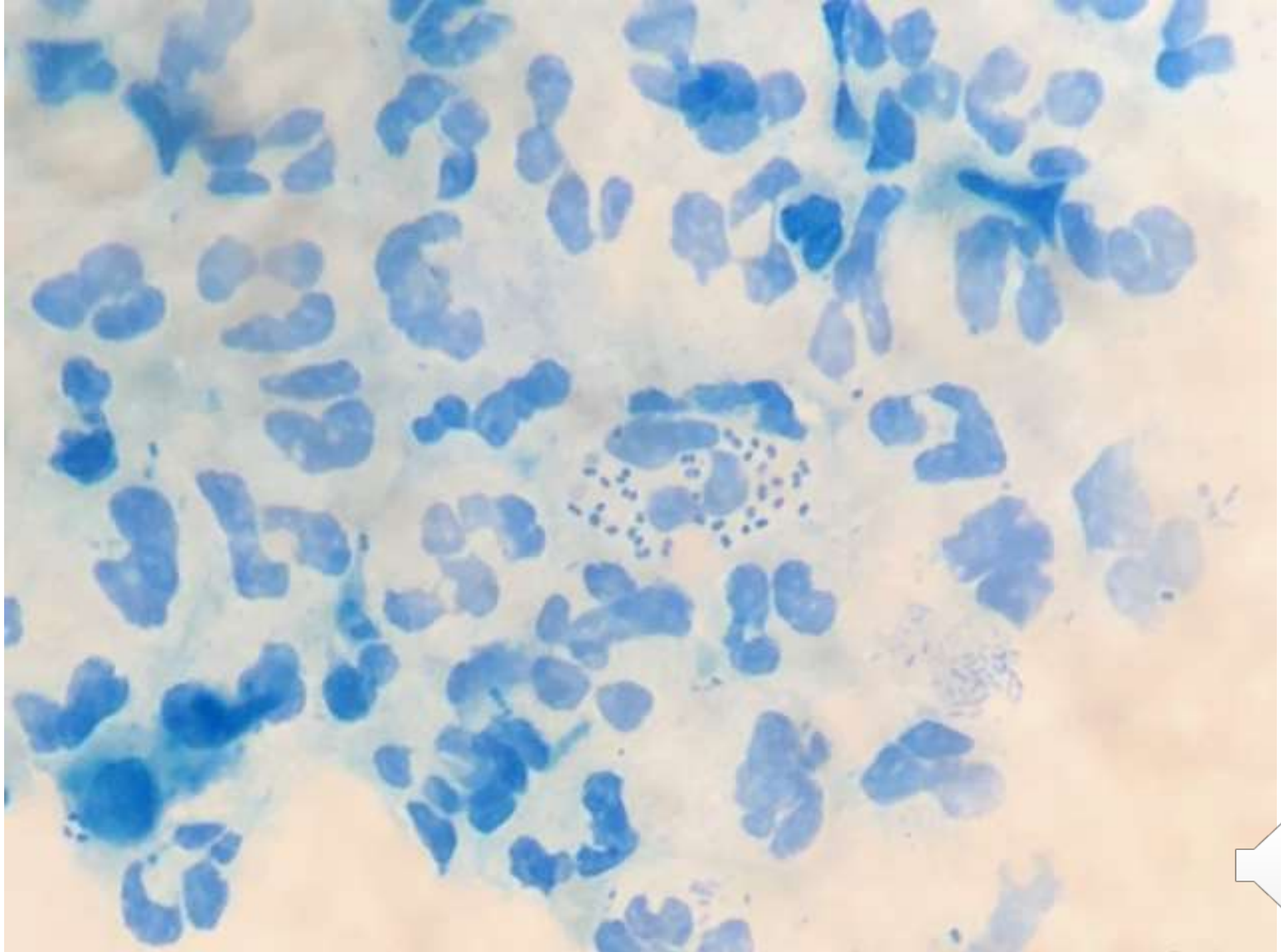


- Cocci Gram –
- Intra and extra cellular
- Very brittle (fragile)
- Very sensitive to desiccation and to temperature < 37°C
- Culture is the gold standard, and the best is to seed in the lab (if not possible to send it very quickly)
- Culture permits antibiogram
- However for screening and/or for diagnostic PCR is more sensitive than culture especially in throat, and in the cervix





direct smear is very sensitive when performed at uretra (nearly 90%)



# NG in men-urethritis

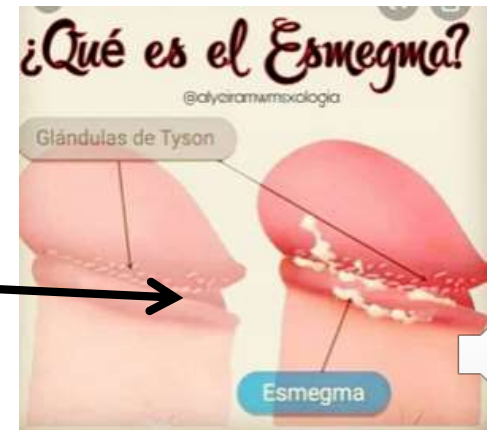
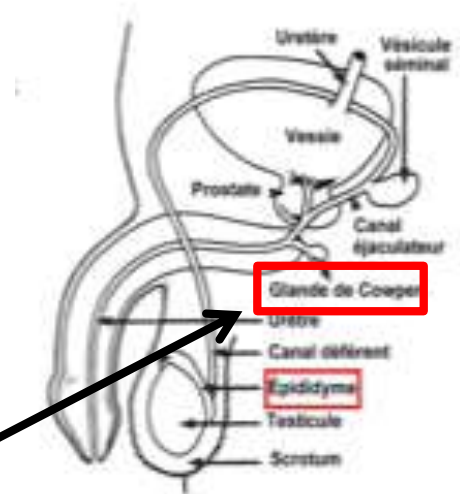
- 10 to 20% of all urethritis
- Easily transmitted, 20% after just one sexual contact
- All type of sexual contact (oral, anal, genital)
- Short incubation 2 to 5 days rarely more (*sex on Saturday, gonorrhoeae on Monday*)
- Highly symptomatic ++ 90%
  - Purulent discharge (very rarely a clear discharge)
  - « *pissing razor blades* »
- Balanitis possible,
- No fever, no adenopathy, no other signs



# NG-complications in male

(very rare, only when the diagnostic is delay)

- Orchitis
- Orchi-epididymitis
- Prostatitis
  - Dysuria
  - High fever
  - Chills
  - Perineal pains
- Cowperitis, Tysonitis...



# NG in women-cervicitis

- Contrary to men, asymptomatic infections are frequent 50%
- Purulent leucorrhea, sometimes hemorrhagical
- Isolated Uretral symptoms
- At speculum, purulent cervicitis, sometimes normal
- Complications
  - Salpingitis ++
  - Endometritis
  - Bartholinitis
  - Fitz-Hugh-Curtis (perihepatitis)



# NG other clinical manifestations

- Anorectal infections: 10 to 20%
  - In women and MSM
  - Isolated in less than 10% in women
  - Can be symptomatic or asymptomatic
  - Systematic samplings in MSM, women with cervicitis
- Pharyngitis
  - In 85% asymptomatic
  - Systematic samplings in MSM
- Conjunctivitis ++,
  - « Manuportage »
  - systematic prevention in new borns

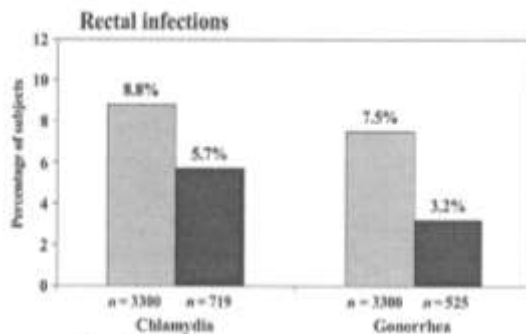


# Prevalence of Rectal, Urethral, and Pharyngeal Chlamydia and Gonorrhea Detected in 2 Clinical Settings among Men Who Have Sex with Men: San Francisco, California, 2003

Charlotte K. Kent,<sup>1</sup> Janice K. Chaw,<sup>1</sup> William Wong,<sup>1\*</sup> Sally Liska,<sup>1</sup> Steven Gibson,<sup>2</sup> Gregory Hubbard,<sup>2</sup> and Jeffrey D. Klausner<sup>1</sup>

MSM

MSM-STDs

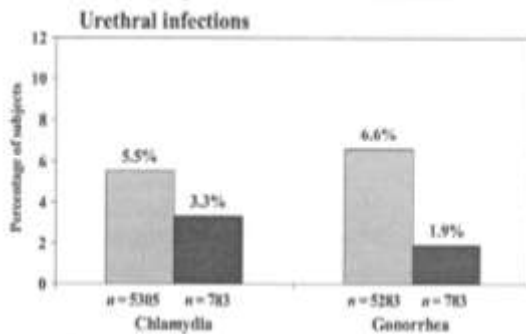


Rectum

NG

3,2%

7,5%

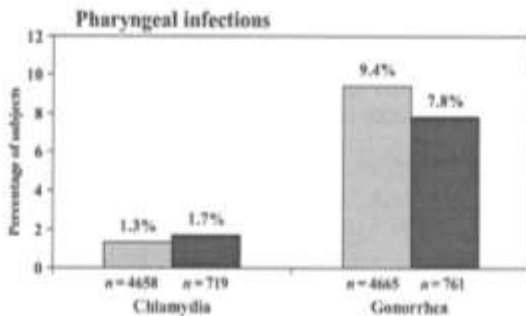


Urètre

NG

1,9%

6,6%



Pharynx

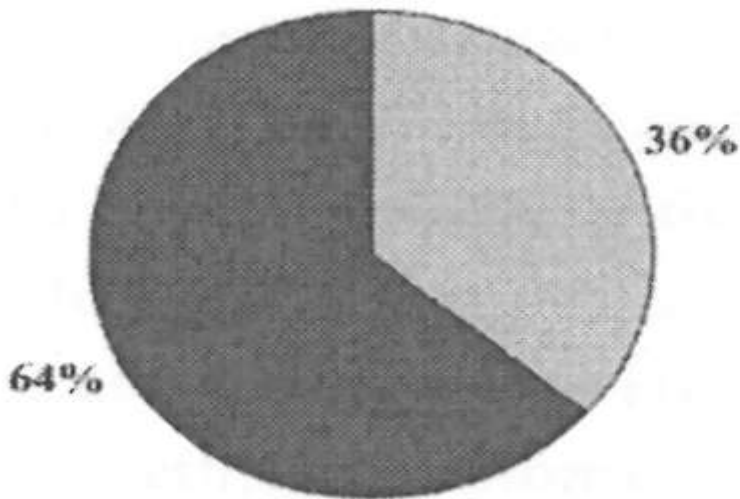
NG

7,8%

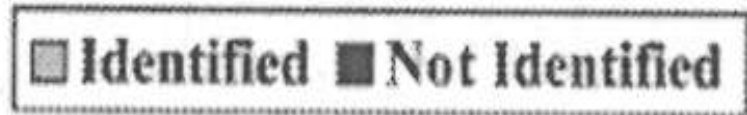
9,4%

STD  
 Gay men's health center





**Gonorrhoea**  
*n* = 785



In MSM, if you practice only the urethral sampling (first urine stream), 64% of NG infections will not be detected



# NG complications in both sex subacute septicemia

- More frequent in women (delay of diagnostic)
- Fever
- Rash with few papules and or pustules surrounded by an erythematous halo around the joints
- Then after 3-4 days
  - Oligo or polyarthritits 70%  
(wrists, knees, ankles)
  - Monoarthritits (wrist, knee)
  - Rare disseminations to other organs
    - Heart: myocarditis, endocarditis
    - Meningitis
    - Liver abcess
    - Splenic abcess





# Traitement des infections gonococciques

- Très simple, mais...
- 10-20% produisent pénicillinase
- Haut niveau de R aux TTC
- Résistance établie aux quinolones (40%)
- Restent les C3G mais des résistances sont rapportées
- Et arsenal AB très limité...
- Prb de diffusion des ATB, difficulté de tt des gonococcies pharyngées (rôle et implication de ce portage ?)...



# What is a good antibiotic for treating NG ?

- A microbiological cure of more than 95%
- Needs to have a good anti microbiological activity
- Needs to have a good pharmacological profile
  - Diffusion to anorectal tissues
  - Diffusion to tonsils
- Needs to be administered in one shot (like for other STDs)



# What is a good antibiotic for treating NG ?



Only, ceftriaxone gives this security



# Gonocoque, résistance et C3G...

- En France :
- 2010: 2 souches résistantes
- Depuis 6 souches isolées au CNR avec CMI égale à la concentration critique de 0,125 mg/l.
- 2017, une souche R au Cegidd StLouis
- *penA* avec 100% d'homologie avec la souche japonaise FC428
- Dans le monde:
- Souches de *N. gonorrhoeae* multirésistantes aux ATB avec un haut niveau de résistance à la ceftriaxone (Danemark, Canada, Australie)

# Traitement des gonococcies

- **Gonococcie non compliquée:**
  - Culture indispensable (+ pharynx et anus femme et HSH)
  - Ceftriaxone : 500 mg IM – dose unique (peut-être utilisé en sous-cutané ? ou en IV en cas d'anomalie de l'hémostase)
  - Nouvelles reco IUSTI
    - Ceftriaxone 1 gr (Unemo, et al. 2020)
  - Traitement antichlamydien systématique
    - 1 gr d'azithromycine ?
    - 2 gr d'azithromycine pour IUSTI
  - Contrôle clinique nécessaire à J7
  - Contrôle bactériologique à J7 recommandé en cas d'échec clinique
- **Sujet allergique aux bétalactamines:**
  - Azithromycine : 2g - dose unique
  - ou Gentamicine : 240 mg IM dose unique
  - ou Ciprofloxacine : 500 mg per os - dose unique (si atbgramme...)
  - Contrôle bactériologique à J7 obligatoire à tous les sites infectés à J0.
  - Contrôle clinique nécessaire à J7 avec contrôle de la sensibilité de la souche fait à J0 et éventuelle prescription d'un autre traitement alternatif

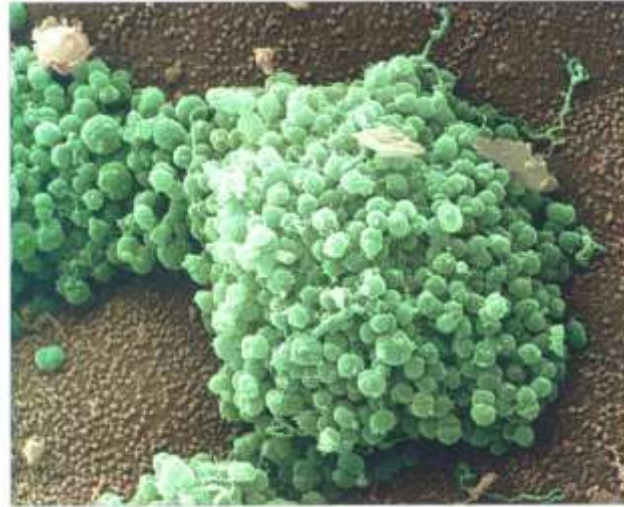


# Traitement des gonococcies

- Validation de la gentamycine ?
- Nouvelles molécules
  - Zoliflodacine
  - Solithromycine
  - gepoditacine



# Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): a randomised non-inferiority trial



	Ceftriaxone group (n=362)	Gentamicin group (n=358)	Adjusted risk difference for clearance* (95% CI)
Participants cleared at all sites	299/306 (98%, 95 to 99)	267/292 (91%, 88 to 94)	-6.4% (-10.4 to -2.4%)
Participants with genital gonorrhoea cleared	151/154 (98%, 96 to 100)	163/174 (94%, 90 to 97)	-4.4% (-8.7 to 0)
Participants with pharyngeal gonorrhoea cleared	108/113 (96%, 92 to 99)	82/102 (80%, 72 to 88)	-15.3% (-24.0 to -6.5)
Participants with rectal gonorrhoea cleared	134/137 (98%, 95 to 100)	107/119 (90%, 84 to 95)	-7.8% (-13.6 to -2.0)

Data are n/N (%; 95% CI) unless otherwise specified. \*Adjusted by recruiting site (for gentamicin group vs ceftriaxone group).

Table 2: Clearance of *Neisseria gonorrhoeae* at infected sites at 2 weeks



# Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): a randomised non-inferiority trial

	Ceftriaxone group (n=320)	Gentamicin group (n=298)
Nausea	38 (12%)	41 (14%)
Vomiting	3 (1%)	12 (4%)
Reduction in hearing	5 (2%)	3 (1%)
Dizziness or unsteadiness	24 (7%)	21 (7%)
Skin rash	5 (2%)	12 (4%)
Injection pain	315 (98%)	294 (99%)
Participants with at least one adverse event	48 (15%)	38 (13%)
Total number of adverse events	54	43
Adverse event severity		
Mild	45/54	35/43
Moderate	8/54	6/43
Severe	1/54	2/43
Participants with at least one adverse event thought to be related to trial medication	15 (5%)	17 (6%)
Total number of adverse events thought to be related to trial medication	16	19
Serious adverse events	1 (<1%)	0
Most frequently reported adverse events (>5%)		
Gastrointestinal disorders	14/54	22/43
Nervous system disorders	10/54	3/43
General disorders and administration site conditions	6/54	3/43
Infections and infestations	6/54	5/43

Data are n (%) for the number of participants, or n/N for the number of adverse events. All side-effects and adverse events were self-reported by the participant. Adverse event categories are from MedDRA coding.

**Table 4: Side-effects and adverse events**

- Gentamycine 240 mg im n'est pas non-inférieure à la CFT à 500 mg im associée à l'AZTh pour le tt des infections gonococciques
- La gentamycine ne peut pas être recommandée en 1<sup>ère</sup> intention
- Elle reste indiquée en cas d'infection génitale isolée, d'allergie ou d'intolérance à la CFT ou chez les patients infectés par une souche R à la CFT





# Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

- spiropyrimidinetrione
- Cible: DNA gyrase et topoisomérase IV
- Jusqu'à maintenant, pas de souches cliniques résistantes
- Essai de phase 2, 179 patients dont 12 femmes comparant 2 doses de Zoliflodacin à 500 mg de ceftriaxone
- Comparable sur les IU et cervicales
- Id rectales mais peu de patients
- Moins bien pour les gono pharyngés

**Table 2. Microbiologic Cure Rates at Test-of-Cure Visit — Micro-ITT and Per-Protocol Populations.**

Population, Site, and Treatment	Confirmed Infections <i>number</i>	Cures	Microbiologic Cure <i>% (95% CI)</i>
<b>Micro-ITT</b>			
Urethra or cervix			
Zoliflodacin, 2 g	57	55	96 (88–100)
Zoliflodacin, 3 g	56	54	96 (88–100)
Ceftriaxone, 500 mg	28	28	100 (88–100)
Rectum			
Zoliflodacin, 2 g	5	5	100 (48–100)
Zoliflodacin, 3 g	7	7	100 (59–100)
Ceftriaxone 500 mg	3	3	100 (29–100)
Pharynx			
Zoliflodacin, 2 g	8	4	50 (16–84)
Zoliflodacin, 3 g	11	9	82 (48–98)
Ceftriaxone, 500 mg	4	4	100 (40–100)
<b>Per protocol</b>			
Urethra or cervix			
Zoliflodacin, 2 g	49	48	98 (89–100)
Zoliflodacin, 3 g	47	47	100 (92–100)
Ceftriaxone, 500 mg	21	21	100 (84–100)
Rectum			
Zoliflodacin, 2 g	4	4	100 (40–100)
Zoliflodacin, 3 g	6	6	100 (54–100)
Ceftriaxone, 500 mg	3	3	100 (29–100)
Pharynx			
Zoliflodacin, 2 g	6	4	67 (22–96)
Zoliflodacin, 3 g	9	7	78 (40–96)
Ceftriaxone, 500 mg	4	4	100 (40–100)

# Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial

*Marcus Y Chen, Anna McNulty, Ann Avery, David Whiley, Sepehr N Tabrizi, Dwight Hardy, Anita F Das, Ashley Nenninger, Christopher K Fairley, Jane S Hocking, Catriona S Bradshaw, Basil Donovan, Benjamin P Howden, David Oldach, on behalf of the Solitaire-U Team*

- Solithromycin, un macrolide de la 4<sup>ème</sup> génération, actif sur des souches R aux anciens macrolides, appartient à la classe des fluoroketolides
- La cible est l'ARNr 23S
- Essai de phase 3 de non infériorité de la solithromycin vs ceftriaxone + azithromycine pour les infections gonococciques
- 130 patients sous solithromycin vs 131 sous CFT+AZTh
- Non infériorité si la limite inférieure de l'IC 95% est de plus de -10%



# Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial

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	Solithromycin (n=123)	Ceftriaxone plus azithromycin (n=129)	Difference (95% CI)
<b>Primary outcome</b>			
Eradication	99 (80%)	109 (84%)	-4.0% (-13.6 to 5.5)*
Persistence	8 (7%)	0	..
Indeterminate	16 (13%)	20 (16%)	..
<b>Secondary outcomes†</b>			
Eradication of genital gonorrhoea			
Overall	97/105 (92%)	107/107 (100%)	-7.6 (-14.3 to -3.9)
Women	5/5 (100%)	5/5 (100%)	..
Men	92/100 (92%)	102/102 (100%)	..
Eradication of pharyngeal gonorrhoea			
Overall	15/16 (94%)	19/19 (100%)	-6.3 (-28.8 to 11.6)
Women	2/2 (100%)	1/1 (100%)	..
Men	13/14 (93%)	18/18 (100%)	..
Eradication of rectal gonorrhoea			
Overall	5/6 (83%)	12/12 (100%)	-16.7 (-57.4 to 11.6)
Women	1/1 (100%)	1/1 (100%)	..
Men	4/5 (80%)	11/11 (100%)	..
Eradication of gonorrhoea at all anatomical sites (by-patient analysis)‡			
Overall	95/104 (91%)	107/107 (100%)	-8.7 (-15.7 to -4.6)
Women	5/5 (100%)	5/5 (100%)	..
Men	90/99 (91%)	102/102 (100%)	-9.1 (-16.4 to -4.8)
Heterosexual men	20/21 (95%)	24/24 (100%)	-4.8 (-23.0 to 9.7)
Men who have sex with men	70/78 (90%)	78/78 (100%)	-10.3 (-19.0 to -5.3)

	Solithromycin (n=130)	Ceftriaxone plus azithromycin (n=131)
One or more adverse events	69 (53%)	45 (34%)
Adverse events related to study drug	56 (43%)	33 (25%)
Gastrointestinal disorders	57 (44%)	31 (24%)

- Solithromycin n'est pas non inférieure à CFT+AZTh
- La solithromycin ne peut pas être recommandée en 1<sup>ère</sup> intention pour traiter les infections gonococciques
- Ce n'est pas un pb de résistance
- Pb de diffusion de la solithromycin





# Gepoditacine et infections gonococciques

- Taylor et al, CID 2018
- Gepoditacine est un inhibiteur de la topoisomérase II, interaction avec GyrA et ParcA
- Essai de phase 2, 2 doses de gepodtacine (1500 et 3000 mg en une PU)
- 69 participants
  - Souches uro-génitales 100%
  - 2 pharyngées et 3 rectales
- Culture négative 66/69 infections UG, soit 96%
- 3 échecs, dans 3 cas il s'agissait de souches résistantes avec une CMI > 1 microg
- La cure microbiologique était obtenue dans 1 cas de gono pharyngée et dans les 3 localisations rectales
- De cette étude, on a un taux de réponse >95% avec la gepoditacine qui peut être recommandée pour le traitement des urétrites à gono non compliquées



# Ceftriaxone has been shown to have no comparable challenger

- Ceftriaxone is better than 240 mg of gentamycin, especially for pharyngeal infection (Ross JDC. Lancet 2019)
- Ceftriaxone is better than zoliflodacin at 2 or 3 gr, again for pharyngeal infection (Taylor SN. NEJM 2018)
- Ceftriaxone is better than solithromycin for all sites (Chen MY. Lancet 2019)
- Ceftriaxone is better than gepoditacin for urethral infections (Taylor SN. Clin Infect Dis 2019)



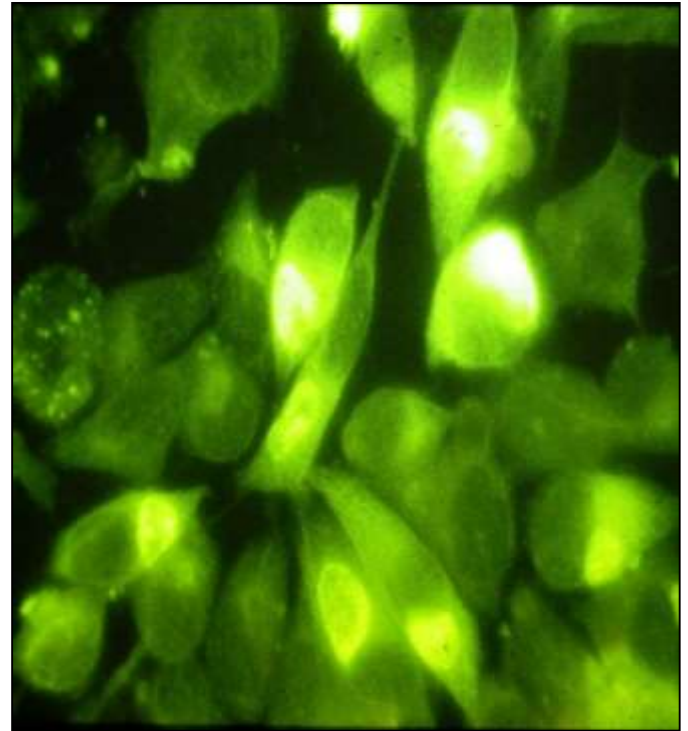
# Recommendations for treatment of gonococcal infections

- **Septicemia:** ceftriaxone 1 gr iv or im for 7 to 10 days
- **Prostatitis:** ceftriaxone 1 gr iv or im for 7 to 10 days
- **Anorectal gonococcal infection:** as urethral gonococcal infection
- **Epididymitis:** ceftriaxone 500 mg im associated with doxy 100 mg x 2 for 10 days
- **In HIV + patients:** same treatment
- **In pregnant women:** gentamycin, ciprofloxacin cannot be considered in case of allergy to ceftriaxone



# *Chlamydia trachomatis* (CT)

- **Sexual transmission**
  - direct contact
  - genito –genital, -oral, - anal.
- **Incubation is variable :**
  - some days to some months,
  - mean 10-15 days
- **Asymptomatic in most cases**
  - 70% in women, 50% in men
- Culture is difficult and no more used
- Diagnostic is based on molecular amplification techniques (PCR and others...)
- Serotype D to K are those implicated in urethritis and cervicitis



# CT in men-urethritis (20-40% of all urethritis)

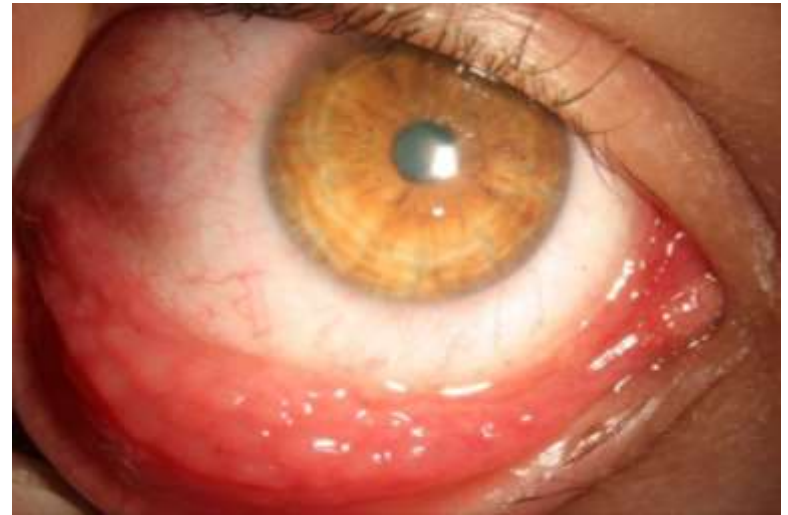
- Symptomatic forms are rare
- Discharge is present in less than 50% of cases
  - most often moderate, translucent, the morning gout
  - sometimes urethral symptoms without discharge
    - intracanal itch or tingle
    - dysuria
    - pollakiuria
- Anorectal and pharyngeal infection are possible with these serotypes but most often it is asymptomatic: should we treat ?





# CT infections complications in men

- Orchi and/or epididymitis is the most frequent complication,
  - CT is the cause of more than 50% of orchi-epididymitis before 40 years of age
- Prostatitis
  - Discussed, controversial data
  - Serology interest ?
- Extra-genital localizations
  - Kerato-conjunctivitis (with follicles, mostly autoinoculation)
  - Arthritis (specific not those reactionals)
  - Pharyngal infection with or without symptom (most often asymptomatic)
  - Rectitis due to chlamydia (non L serotype, so non LGV), most often asymptomatic



# Oculo-uretrosynovial syndrome (the so called Fiessinger-Leroy-Reiter sd)

CT is one of the cause of reactional arthrititis occurring after an urethritis most often in young men (sex ration M/W = 50/1) associating:

- Bilateral conjunctivitis
- Joints involvement: polyarthrititis (or oligoarthrititis) involving symetrically the knees, ankles associated with an axial involvement is frequently
- Entesopathies with talalgia, tenosynovitis
- Skin and mucosal lesions
  - circinate balanitis balanite circinée,
  - psoriasiforms lesions of the skin
  - plantar vidal-Jacquet papules
- HLAB27 is frequent





Oculo-uretrosynovial syndrome

Man of 26 y

on PrEP

Circinate **balanitis**

Severe and disbling

oligoarthritis

HLA B27

Requiring treatment associating

etanercept and betamethasone

dipropionate



# CT in women-cervicitis

- Cervicitis: is the most frequent manifestation of CT infection in women
- sometimes symptomatic
  - Yellow or white leucorrhea,
  - cystalgia,
  - uretral syndrom,
  - dyspareunia
- In 50 to 90 % of cases, completely asymptomatic +++
- Risk of transmission during pregnancy
  - pneumopathies
  - kerato-conjunctivitis in the new borns



# CT infection complications in women

- Salpingitis is the most important complication:
  - Preceded by an endometritis
  - Most often subacute or chronic
  - Delay for the diagnostic which is difficult:
    - Non specific abdominal pains
    - During menstruation
  - Pain during the vaginal touch
  - Wheelbase of the vaginal dead
- *CT* is responsible:
  - 50 % of all salpingitis in young women
  - 70% of all tubal sterility



# CT infection complications in women

- Perihepatitis
- Bartholinitis (rare)
- Post-partum endometritis
- Neo-natal infections
  - conjunctivitis
  - pneumopathies



# Diagnostic is based on DNA amplification techniques, in most cases the techniques permit amplification of CT and NG

- **In asymptomatic men**
  - On first urine steam
  - Obtained at least 1h (1h30, 2 h ?) after the last micturition
  - If needed because of sexual risk PCR can be done on an anorectal and/or a throat swab
- **In symptomatic men**
  - On first urine steam or on the purulent or the translucent discharge
  - Obtained at least 1h (1h30, 2 h ?) after the last micturition
  - In case of anorectal or pharyngal symptoms on a swab for each site
- **In asymptomatic women**
  - On vaginal self-sampling
  - If needed because of sexual risk PCR can be done on an anorectal and/or a throat swab
- **In symptomatic women**
  - On the purulent or the translucent discharge
    - At the cervix
    - and ideally on a periuretral sample (not in practice)
  - In case of anorectal or pharyngal symptoms on a swab for each site



# *Chlamydia trachomatis*



- New recommendations for uncomplicated infections
- To limit the diffusion of resistance to macrolides and especially of resistance of *M genitalium* to azithromycin, the 1st line is back to doxycycline 100 mg twice a day for 7 days
- Alternative treatment remains azithromycine but at 1g MD then 500 mg per day for 2 days





# *Mycoplasma genitalium*

- Man
  - NGU 20%
  - Persistent NGU 40%
  - Prostatitis +/-
  - epididymitis +/-
  - Proctitis ?
- woman
  - Cervicitis
  - PIS ?
  - Preterm birth
  - Miscarriages ?
  - Tubal infertility ?

70% of all MG + are asymptomatics +++  
High prevalence in patients under PrEP 10% with a high level  
of resistance (AZTh 69%, FIQ 15%)  
3 studies in ClinicalTrials.gov with 2 RCT

*ClinicalTrials.gov*



# *Mycoplasma genitalium* treatment ?

- No screening if no symptoms +++
- Privilege doxycycline to azithromycin for the treatment of chlamydial infection to prevent the diffusion of resistance of MG strains to azithromycin
- **For a symptomatic MG infection:**
  - First line recommendation:
    - Doxy 100 mg twice a day 7 days
    - Then azithromycin 1 gr once then 500 mg per day for 2 days
  - In case of clinical failure or in case of documented resistance to azithromycin
    - Moxifloxacin 400 mg per day for 10 days
  - 3<sup>rd</sup> line ???
    - Doxy 100 mg twice a day for 14 days
    - Pristinamycin 1gX4 per day for 10 days...(tolerance ??)
    - Doxy 100 mg twice a day for 7 days then pristinamycin 1gX4 per day
    - Minocycline 100 mg twice a day for 7 days (not convinced)

# Urethritis with discharge



**1st visit**

- sampling the discharge:
  - Gram or methylen blue on a slide
  - look also for trichomonas
  - Swab for culture of NG
- PCR CT/NG on the FUS
- Screening for other STDs (HIV, HBV, S)
- Conseling, partners, use of condom...



If risk factors  
(MSM)  
PCR CT/NG  
Pharynx  
Anorectal

gram is pos

Treat NG and CT

gram is neg

treat CT

**2<sup>nd</sup> visit (D7)**

- Check the clinical response
- Check the results of the exams
- Check the results of other tests
- If symptoms are still present
  - Look fo MG



# Screening for STDs in heterosexual?

- Check regularly, rhythm depends of the risk ?
  - HIV serology (speak about POC, autotest...)
  - HBV serology
  - HCV, only if there is a risk identified on the questionnaire
  - Elisa for syphilis
- Duplex PCR CT and NG (now they are inseparable)
  - FUS in men
  - Vaginal self sampling in women ( pharyngal and anal +/-)
- Check for vaccination ++
  - Hepatitis B
  - Gardasil 9
  - And others also...
- Speak about prevention, use of condom, PrEP for HIV
- Socialisation and psychologisation...



# Screening for STDs in MSM?

- Check regularly, rythm depends of the risk ?
  - HIV serology (speak and eventually use POC, autotest)
  - HBV, HAV serologies
  - HCV, only if there is a risk identified on the questionnaire
  - Elisa for syphilis at least once a year
- Duplex PCR CT and NG (now they are inseparable)
  - FUS, anal and pharyngal (rythm ?)
  - Check for vaccination ++
  - Hepatitis B, A
  - Gardasil 9
  - Meningococcus (to prevent meningococcus and gonococcal infections)
  - And others also...
- Speak about prevention, use of condom, PrEP for HIV
- Socialisation and psychologisation...

