# Syphilis
## New spread of an old disease

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VENEREAL DISEASE
COVERS THE EARTH
Learn to protect
yourself NOW

# 1. Epidemiology

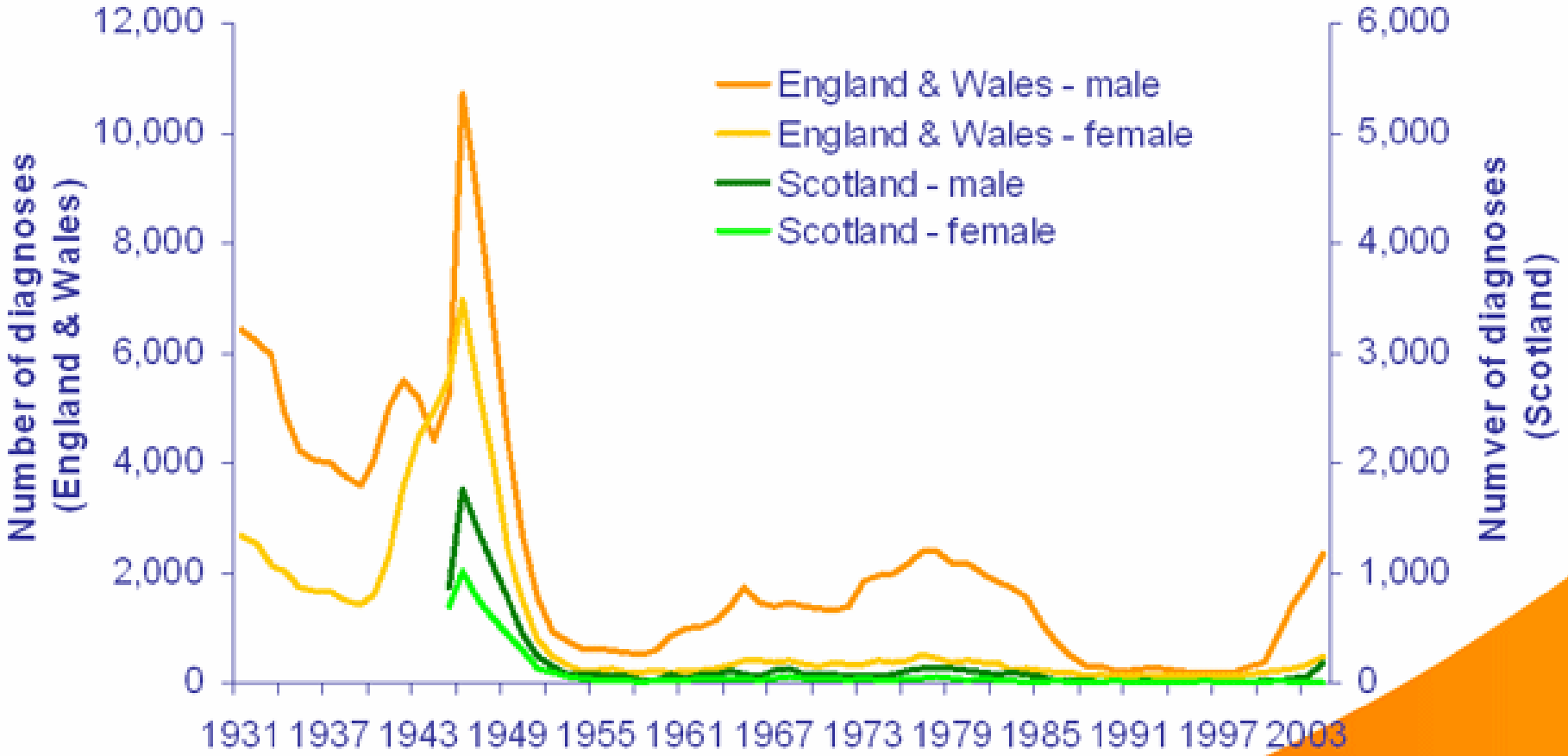
- 3 waves of syphilis in 20th century:

1. Post-world war II:
   - mainly heterosexual
   - Decline with use of penicillin

2. 1980-1991:
   - mixed population (MSM, hetero, drug use (crack)
   - Decline in AIDS-era (safer sex, AIDS-related mortality (cf *Chesson, STD 2003*)
   - 1997: lowest incidence since 1941 (<1/100.000)

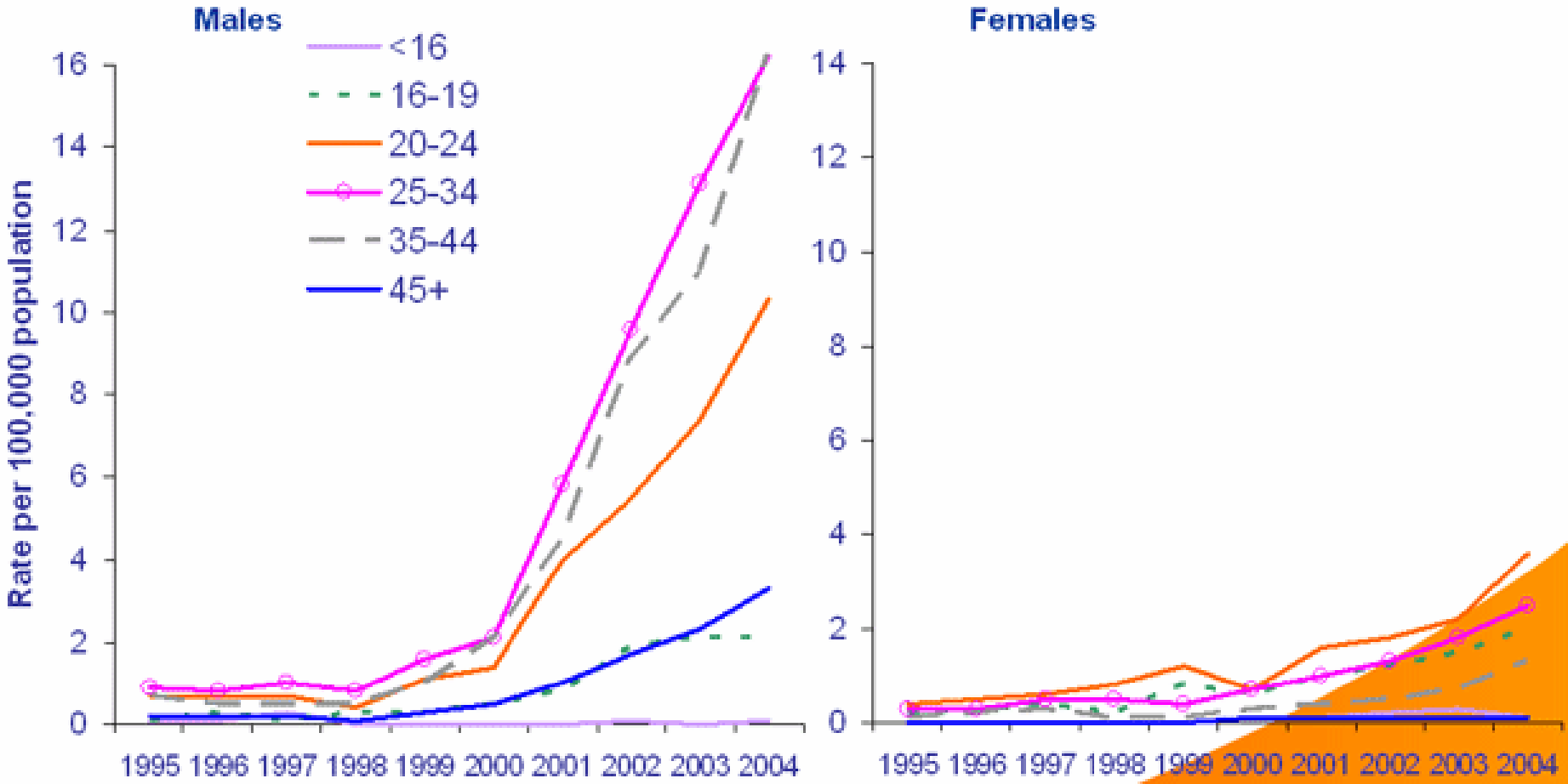

She may be..
a bag of
TROUBLE
SYPHILIS - GONORRHEA

# Numbers of diagnoses of syphilis (primary, secondary and early latent) by sex, GUM clinics, England, Wales and Scotland*: 1931 - 2004




* Equivalent Scottish data are not available prior to 1945. As N. Ireland data from the time period 1931 to 2000 are incomplete they have been excluded.
Data source: KC60 statutory returns and ISD(D)5 data.

# Rates of diagnoses of infectious syphilis (primary & secondary) by sex and age group, GUM clinics, United Kingdom: 1995 - 2004




Data source: KC60 statutory returns and ISD(D)5 data.

**UK**
London 2001-2004:
**1910** cases (1276 MSM)
Risk:
MSM: risk x 25, HIV+ 53%, white 89%, oral sex 44%
Hetero: risk 3-6%, HIV+ 7%, black 40%, CSW 15

**Denmark**
Copenhagen 2002-2003
**136** cases (50)
HIV+ 37%
Age 20-39 y

**Ireland**
2000-2003
**887** cases
MSM 83.6 %
20% HIV+
Risk: Sex abroad (Europe)

**Holland**
From 1999
Amsterdam en big cities
75% MSM
20% HIV+
Risk: many partners, oral sex

**Germany**
Baseline 1,3/100.000
MSM 100/100.000
HIV+ 1000/100.000

!! 23 cases congenital syphilis (immigrants E-Europe

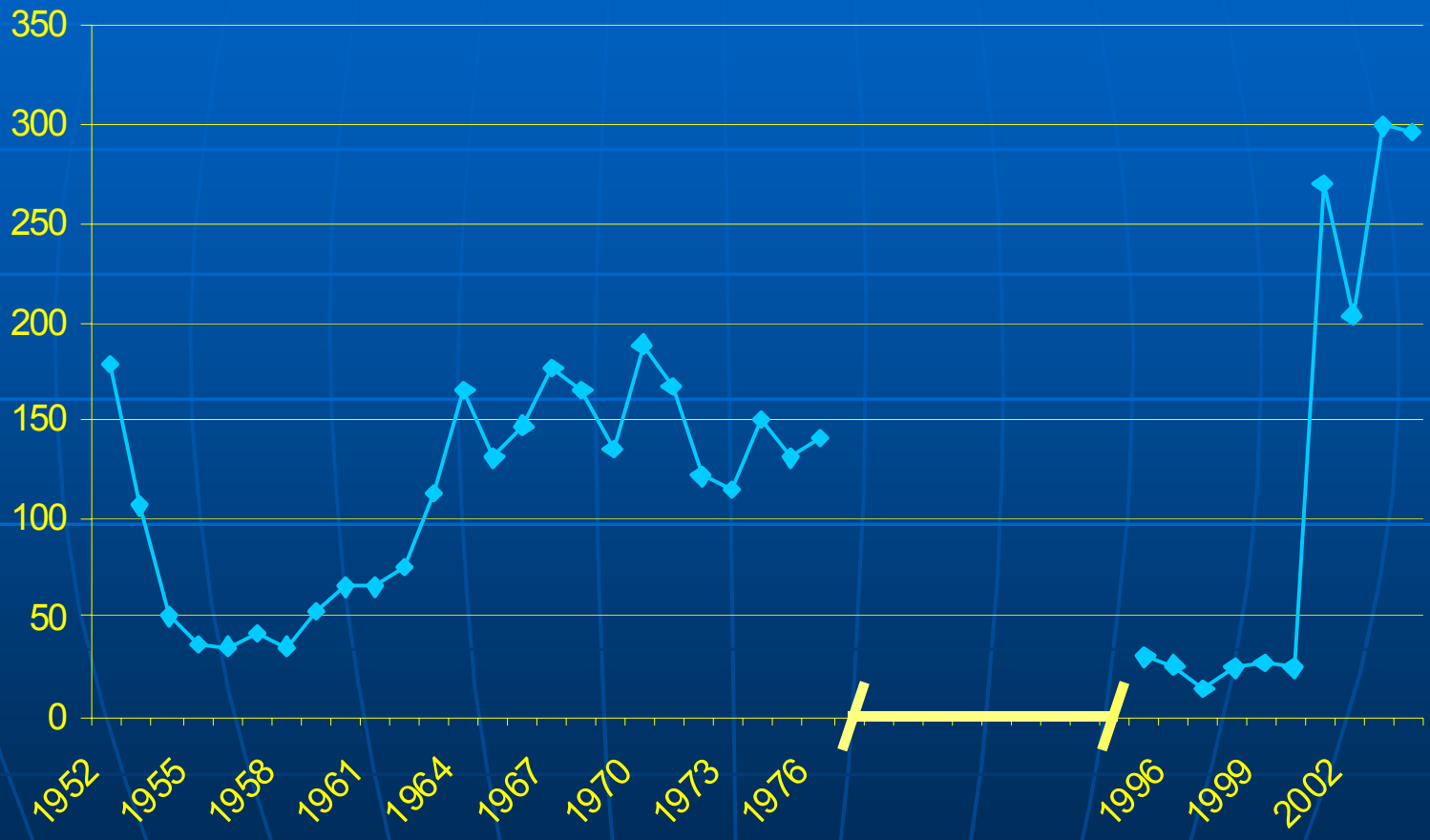
**France**
2000-2003, Paris region
**1089** cases
HIV+ 49%
MSM 80%

**Chech republic**
1999-2002
4-5,6/100.000
Big cities

!! 59% immigrants former USSR (Ukraine, Moldova…)

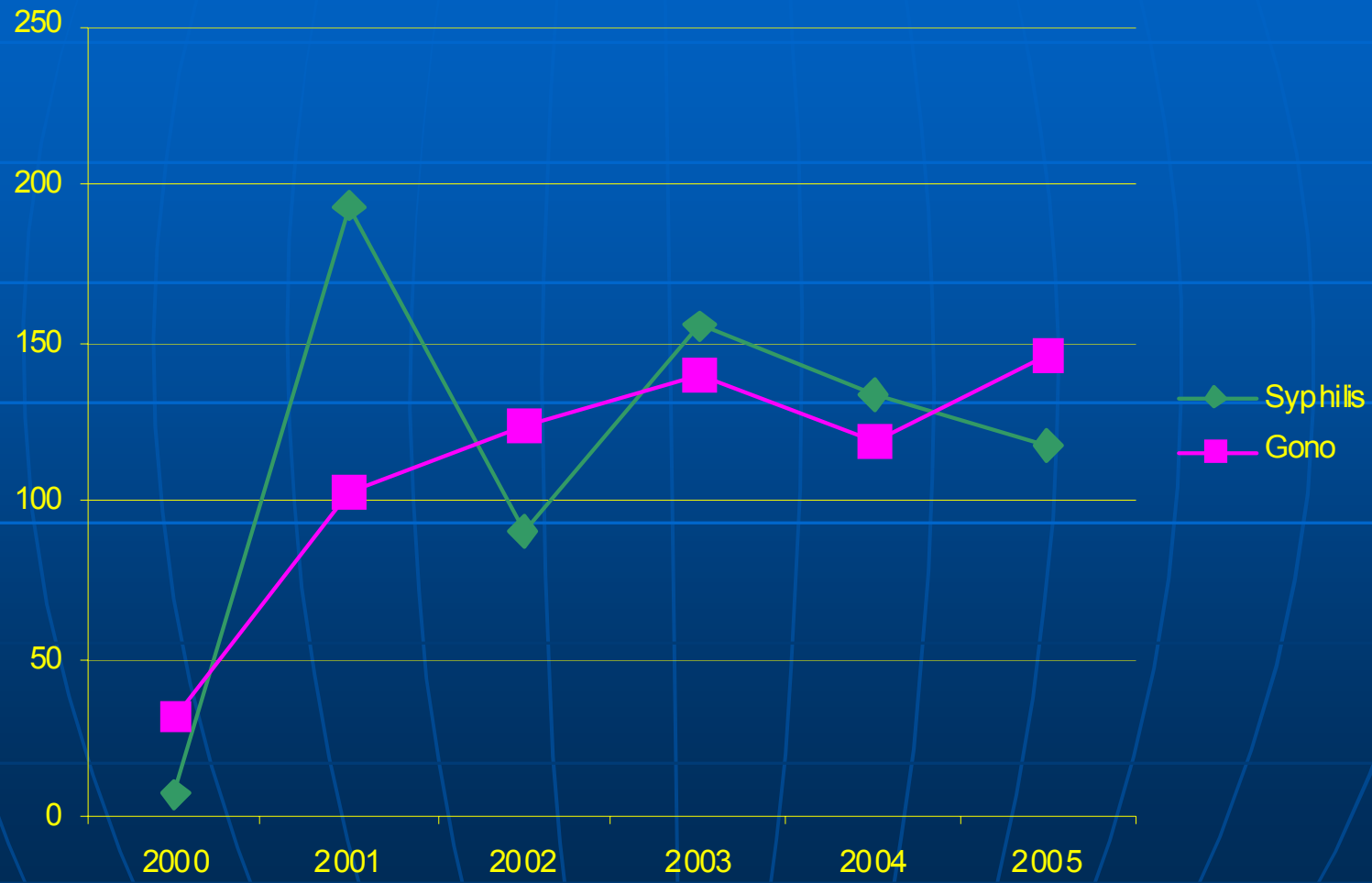
*Eurosurveillance 2004*

# Primary and secundary syphilis cases, mandatory notification, Belgium, 1952-2004



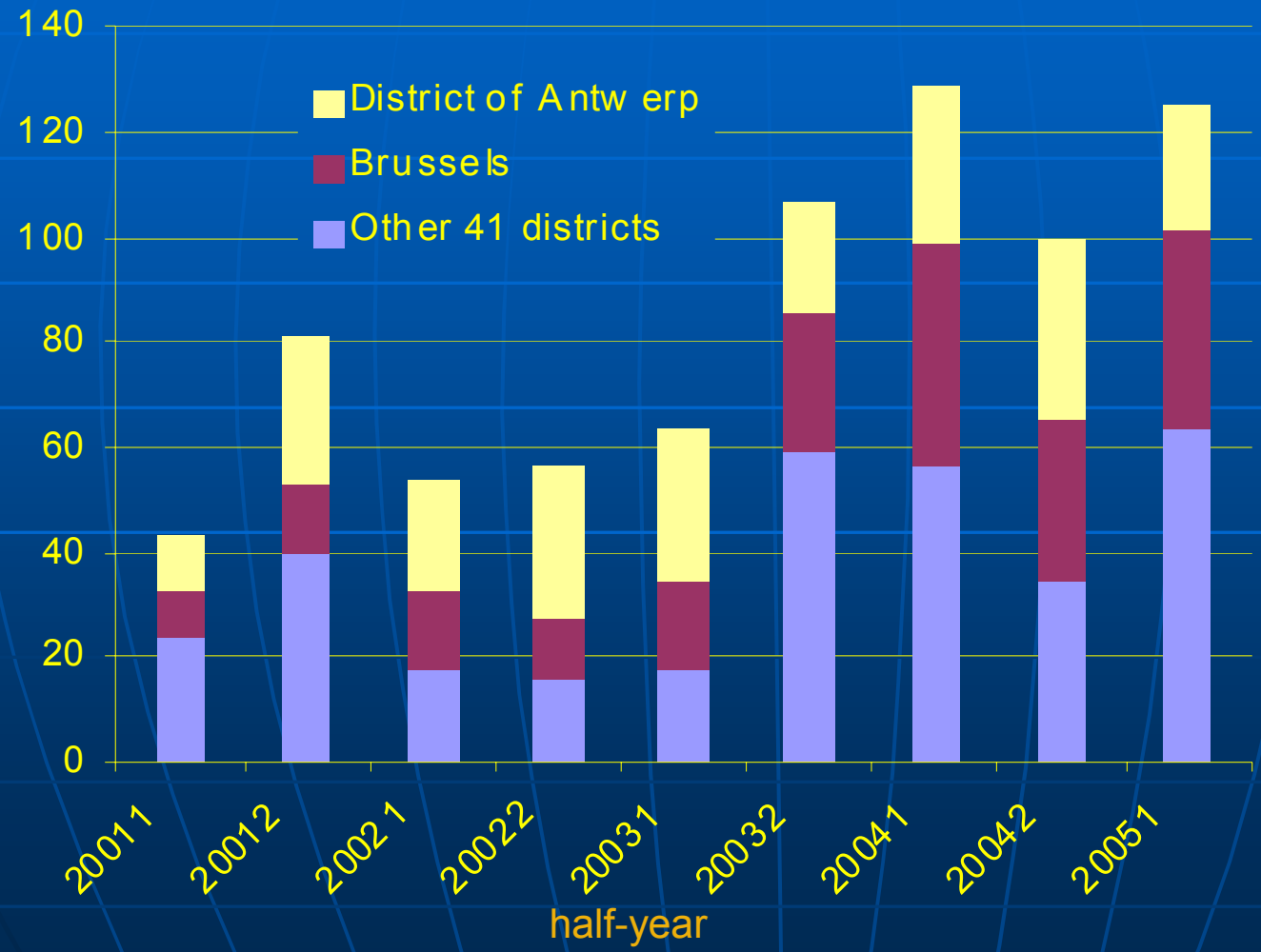

Data sources: Ministery of Public Health, Flemish Community, French Community, Brussels (COCOM)

# Notifications of syphilis and gonorrhea, Antwerp Province, Flemish Community, 2001 - 2005




Data : Dr K. Deschrijver, Health Inspectorate, Antwep

# Geographic distribution of syphilis cases, Sentinel Network of Laboratories, Belgium, 2001 - 2005




IPH - 2005

# Sources of information

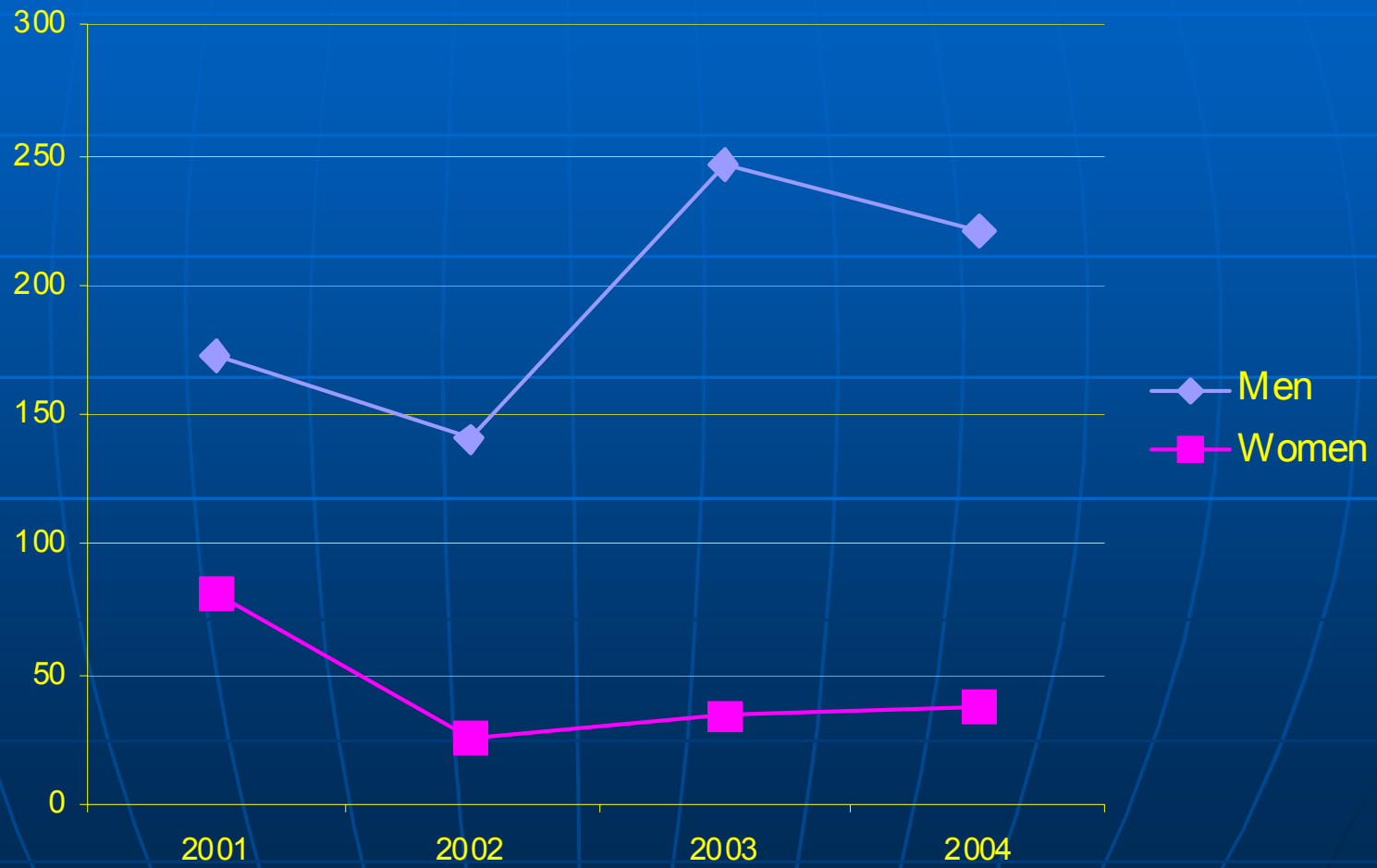
- 3 complimentary systems:
  - **Mandatory notification**
    - Via Health Inspectorate (per province)
    - Depends on (underreporting) clinicians
  - **Sentinel Laboratory Network**
    - 56% of all labs for clinical microbiology in Belgium
    - Case definition VDRL/RPR > 1:4 and positive TPHA/FTA
  - **Sentinel Network of Clinicians**
    - Mixed GP's, STDclinics, specialists…
    - Notification period sept-march

- Third wave:
  - 1999-present:
    - predominance MSM 30-50 y
    - Oral sex
    - 50% HIV prevalence
    - Internet/methamphetamine/Viagra
    - Quick and simultaneous spread US, Canada, Europe

# Belgium

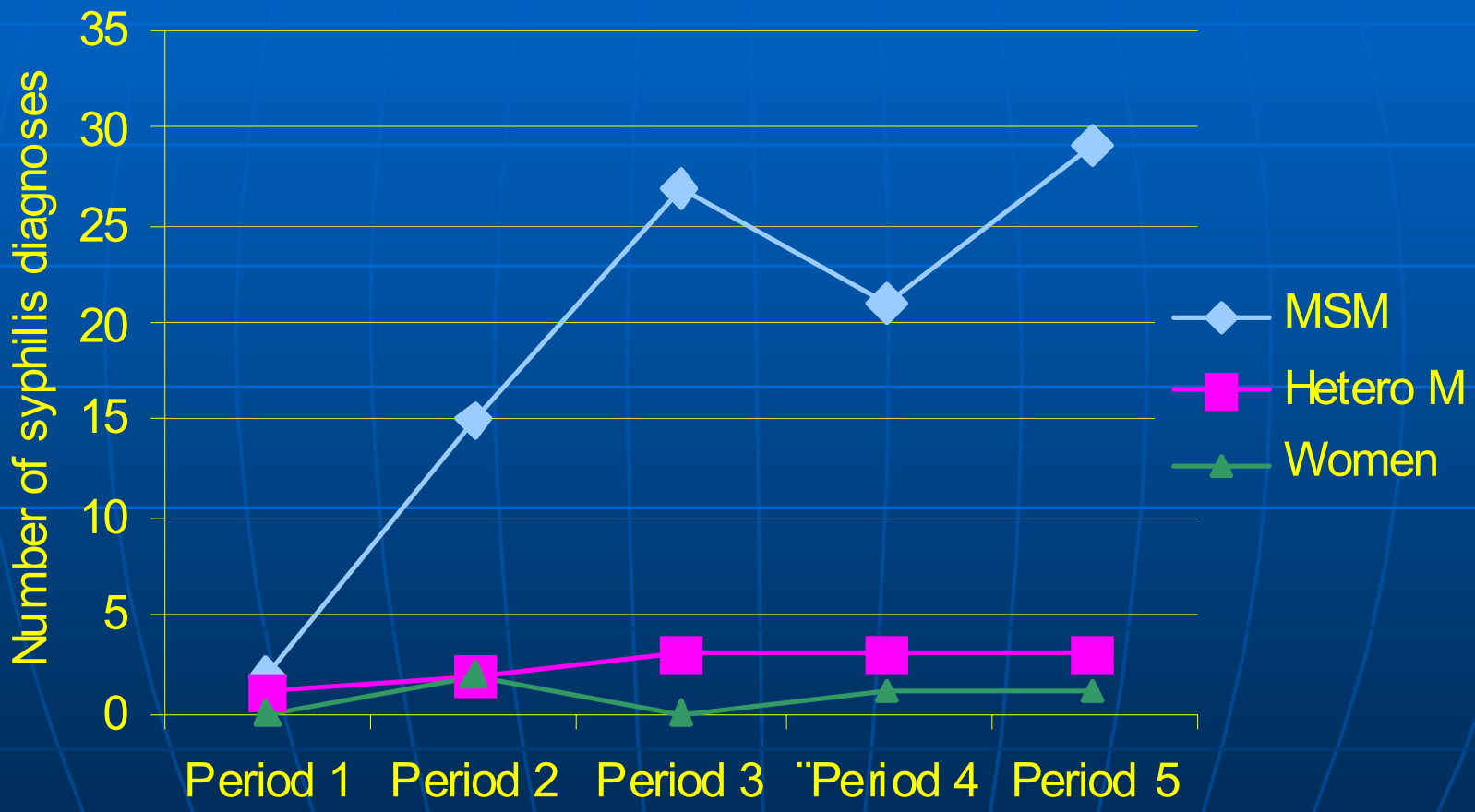
- 2000-2004:
  - Evolution from 30 cases/y to 300 cases/y
  - 1st Q 2001: 51 cases (32 Antwerp)
    - Predominance Antwerp, Brussels
  - 79.9% MSM
  - Average age 39 y
  - HIV+ 50,5%
    - 24% newly diagnosed
    - **76% known HIV+**

# Notifications of syphilis cases per sex, Flemish Community, Belgium, 2001 - 2004




Data : Dr G. Top, Flemish Community

# Syphilis cases per sex and sexual orientation, Sentinel Network of Clinicians, Belgium, Oct.-Jan. periods, 2000 - 2005



# Risk factors

*(Simms 2005, Righarts 2004, Peterman 2005)*

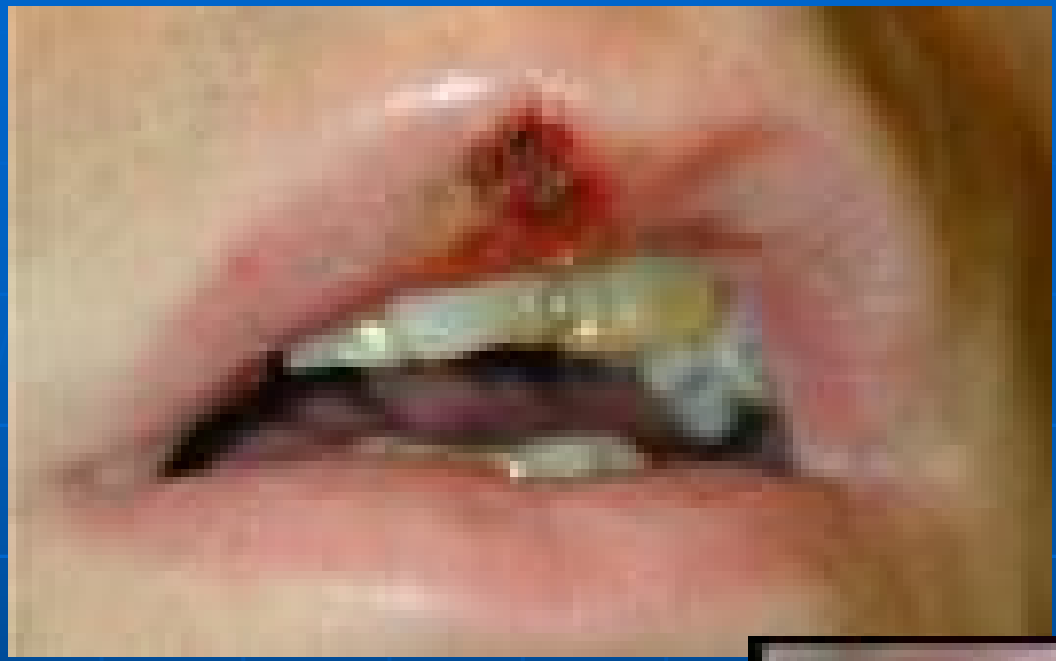
- MSM
  - Many partners
  - Anonymous partners and venues
  - Internet, chatrooms
  - Mobile population
- Oral sex
- HIV+ status

# Syphilis and oral sex

- HIV-prevention:

shift from anal to (unprotected) oral sex

- Not safe for other STD's (gonorrhea, syphilis)
- If STD: few clinical symptoms, often untreated
- Many sexual contacts /short time



# Syphilis and HIV

- **Syphilis increases vulnerability to HIV** (*Piot & Laga 1989*, *Chesson AIDS 1999*)
  - Disruption of epithelial/mucosal barriers
  - Local inflammation and recruitment of CD4 cells

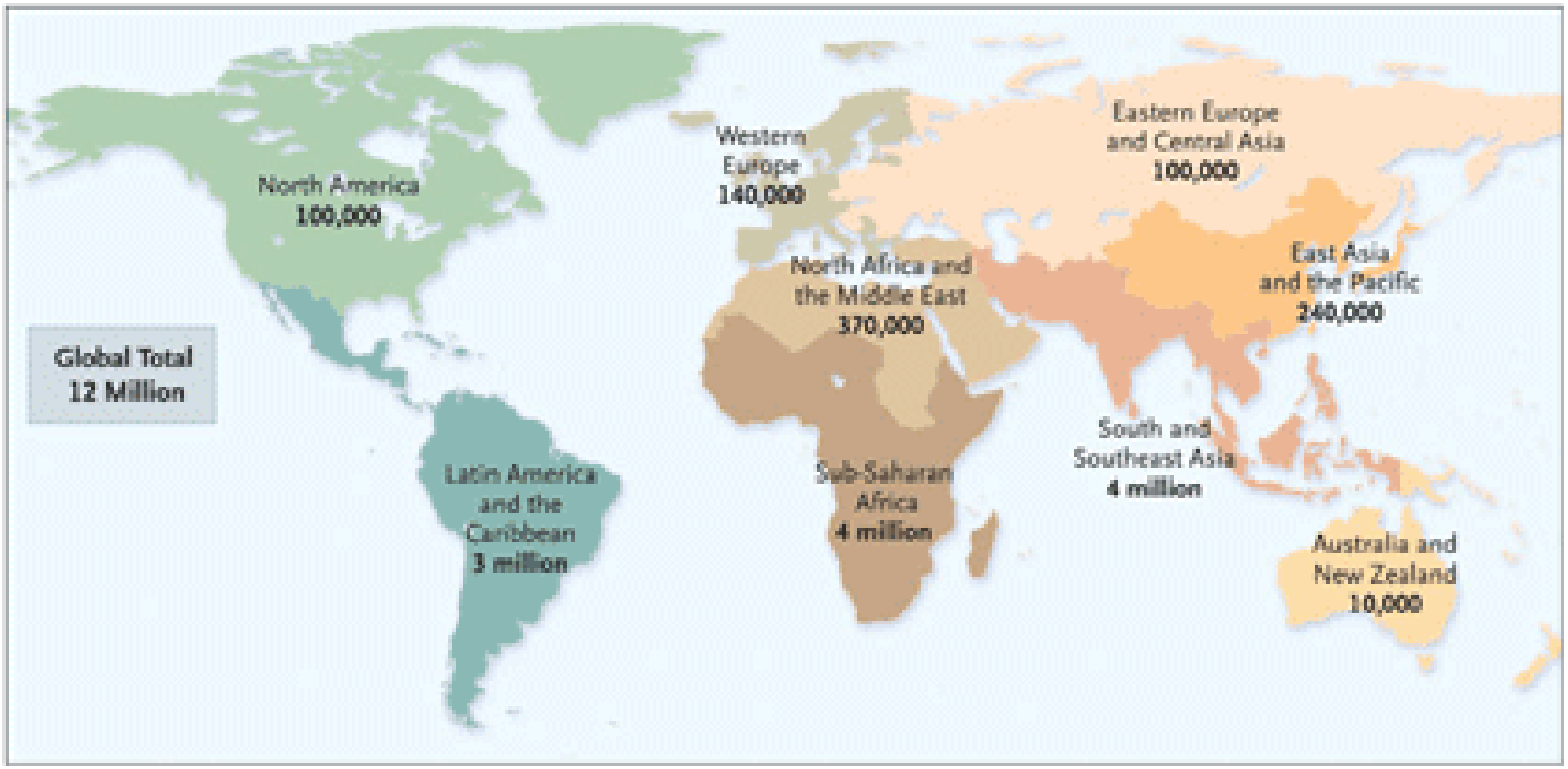
- **Syphilis increases infectivity of HIV+ people** *(Buchacz 2004, (Sadiq 2005)*
  - Increase of HIV-VL in semen and blood

# Syphilis and HIV

- **Does the actual syphilis-epidemic lead to more HIV-infections?**
  - Through oral sex??
  - Rather through occasional UAI (common risk factor)
  - ?? 1000 HIV cases/y extra through syphilis (mathematical) (*Chesson AIDS 1999)*

# Estimated Annual Number of New Cases of Syphilis among Adults.

*Hook, NEJM 2004*



# 2. Clinical presentation

- Primary (2-3 w after contact)
- Secondary (3-6 w)
- Early latent (< 1 y)
  - Early neurosyphilis
- Late latent (> 1 y or unknown)
- Tertiary (7-30 y)

# Syphilis and HIV

1. Is the clinical course different?
2. Is the diagnosis different?
3. Is treatment response different?
4. Should therapy be different?

# 1. Different clinical course?

- Late ’80:
  - alarming case studies of quickly progressive, therapy-resistant, complicated syphilis *(eg. Johns 1987)*

# ‘Clinical course is different…’

- More **secondary syphilis** +/- persistent chancres *(Hutchinson 1994, retrograde 309 syphilis.)*
- More **ulcerative lesions** *(Schöfer, GASG 1996, retrograde 11368 HIV+)*
- More **neurosyphilis**…?

(Neurologic symptoms + VDRL/TPHA + CSF-VDRL)

- **1-3%** of all HIV+
- **9-23%** all HIV + syphilis

*(Katz 1989, Holtom 1992, Berger 1991, Mallessa 1996, Bordon 1995)*

- *Historical pre-HIV: 5-10% after 7-30y)*

# ‘Clinical course not (very) different…’

- *Rompalo 2000* (Prospective 541 syphilis (18.7% HIV+)
  - More multiple ulcers, condylomata lata in HIV+
  - No difference in neurological symptoms
  - No difference in treatment response

- *Rolfs 1997* (101 HIV+ syphilis, focus on neurosyphilis)
  - More lymphocytic pleiocytosis in HIV+
  - No difference in outcome

- *Nnoruka 2005* (Nigeria, 31 HIV + syphilis)
  - No cases of neurosyphilis

# Early neurosyphilis

- Pre-penicillin era:
  - Early syphilis:
    15-70% 'abnormal' CSF
    25% presence of *T.pallidum* in CSF (RIT)!
    **='Early asymptomatic neurosyphilis'**
    *(Moore 1922, Stokes 1934, Chesney 1934)*
  - Cleared by immunity
    (or asymptomatic latent presence?)
  - Without treatment: 5-10% progression to late neurosyphilis
  - With 'treatment': < 0.1% patients had symptoms
    *(Altshuler 1949, Perdrup 1981)*

# Early neurosyphilis

- Late ’80:
  - increasing incidence in **symptomatic** early neurosyphilis
  - 44% AIDS *(Katz 1989)*
    - Lack of clearance of *T. pallidum* from CSF?
    - Lack of control of latent *T. pallidum*?
    - Frequent reinfection?

# Early neurosyphilis

- Lukehart 1988, Rolfs 1997:
  - Isolation of *T. pallidum* (RIT) from CSF in early syphilis
  - HIV+ 29% = HIV- 30%
  - Clinical correlate?
    - Invasion or involvement?
    - But: HIV+ more failure after 1 x BP 2.4 MU
- Marra 2004:
  - Persistance of *T. pallidum* after conventional treatment if
    - CD4 <350 (OR 3.10)
    - RPR> 1:32 (OR 5.9)
    - if both : OR 18.9

# LP?

- All HIV+ with syphilis?
- All HIV+ with syphilis and CD4< 350 and/or RPR> = 1:32?
- All HIV + with latent syphilis?
- All HIV+ with latent syphilis and neurologic symptoms or treatment failure?

# CDC-guidelines update 2005

- Signs or symptoms of neurosyphilis
- Signs or symptoms of ophtalmic syphilis
- Evidence of active tertiary syphilis
- Treatment failure (< 4 x decrease VDRL/6 months)
- HIV and late latent syphilis/unknown duration

- Some experts recommend CSF examination in all patients with latent syphilis and VDRL≥ 32 or in HIV-infected if CD4 count ≤ 350

# ?

- Few prospective studies
- Small studies, few patients
- Lack of good comparator groups
- Lack of ‘gold standard’ for diagnosis
- Clinical correlate of lab findings…?
- Lack of longterm follow-up

- ***"He who knows syphilis, knows medicine"***

Sir William Osler

# 2. Different diagnostics?

- Organism:
  - No direct culture
  - Dark field microscopy (chancre)
  - (PCR)
  - Biopsy (Whartin-Starry)
  - (Rabbit Infectivity Test)
- Serology
  - Non-treponemal tests (VDRL, RPR)
  - Treponemal tests (TPHA, TPPA, FTA-abs)

- False negative RPR/VDRL *(Schöfer 1996, Nnoruka 2005)*
  - Prozone phenomenon (< 2% - 10%)
- False positive RPR/VDRL 2-3% *(Rompalo 1992, Holton 1992)*
- High titers RPR + TPHA *(Hutchinson 1991, Rolf 1996, Schöfer 1996)*
- Persisting RPR/VDRL after treatment (serofast)
  - Reinfection? Treatment failure?
- Seroreversion (VDRL + TPHA)

# 3. Different treatment response?

- 'No':
  - 1 year after treatment for early syphilis: no difference in relapse HIV+/HIV-

*(Gourevitch 1993, Hutchinson 1994)*

# ‘Yes’

- More serologic failure after treatment for early syphilis (benzathine penicilline 2.4 MU IM)
- Slower decline of RPR-titers

*(Rolfs 1997, Lukehart 1988, Malone 1994, Marra 1995, Telzak 1991, Gordon 1994, Smith 2004)*

- …but
  - Relapse of reinfection?
  - Clinical correlate of serologic failure?
  - Small studies

# 4. Should treatment be different?

- *'Treatment recommendations for syphilis have been based on expert opinion, case series, some clinical trials and 50 years of clinical experience.'* *(Pao 2002)*

# Actual treatment standards

- Early syphilis
  - 1 x 2.4 MU Benzathine penicillin IM
- Latent syphilis
  - 3 x 2.4 MU Benzathine penicillin IM
- Neurosyphilis
  - 10-14 d IV Benzylpenicillin

- Alternatives:
  - Procaine penicillin IM, ceftriaxone, azithromycin, doxycyclin

# New treatment for early syphilis?

- **BP 2.4 MU + amoxycilline/probenecid x 10 d**
  - No additional benefit *(Rolfs 1997)*
- **BP 2.4 MU versus azithromycin 1 x 2 g or 2 x 2 g**
  - Equal results, cave azithromycin resistance

  *(Hook 2001, Riedner 2005, Lukehart 2004)*

# New treatment for latent syphilis?

- **ceftriaxone 1-2 g IM 10-14 d versus 3 x BP 2.4**
  Equal response 77%, no additional benefit *(Dowell 1992)*

- **ceftriaxone versus IV Benzylpenicillin 10 d.**
  Equal response, small groups *(Marra 2000)*

- **ceftriaxone versus IM Procaine Penicillin/probenecid 10 d.**
  Equal response 70% *(Smith 2004)*

>>>Ceftriaxone:

- good alternative to usual schedule
- no therapeutical benefit
- Too costly for routine use

# Alternatives?

- ‘protective’ role of HAART?
- secondary prophylaxis?
- long term suppression therapy?

**‘One night with Venus and the rest of your life with mercury…’**

# Prevention: what? how?

- Traditional partner notification *(T.Parran, 1937)*
  - Treatment of identified partners and persons at risk
  - Heterosexual contact, identifiable sex partners (CSW), identifiable venues
  - Syphilis *(Hogben, STD 2005)*
    - 1996: **78%** identification of partners, **1.1** partners per index case
    - 2003: **14%** of partners located, **6.8** partners per case
      - Anonymous partners and locations

# Prevention: new ways?

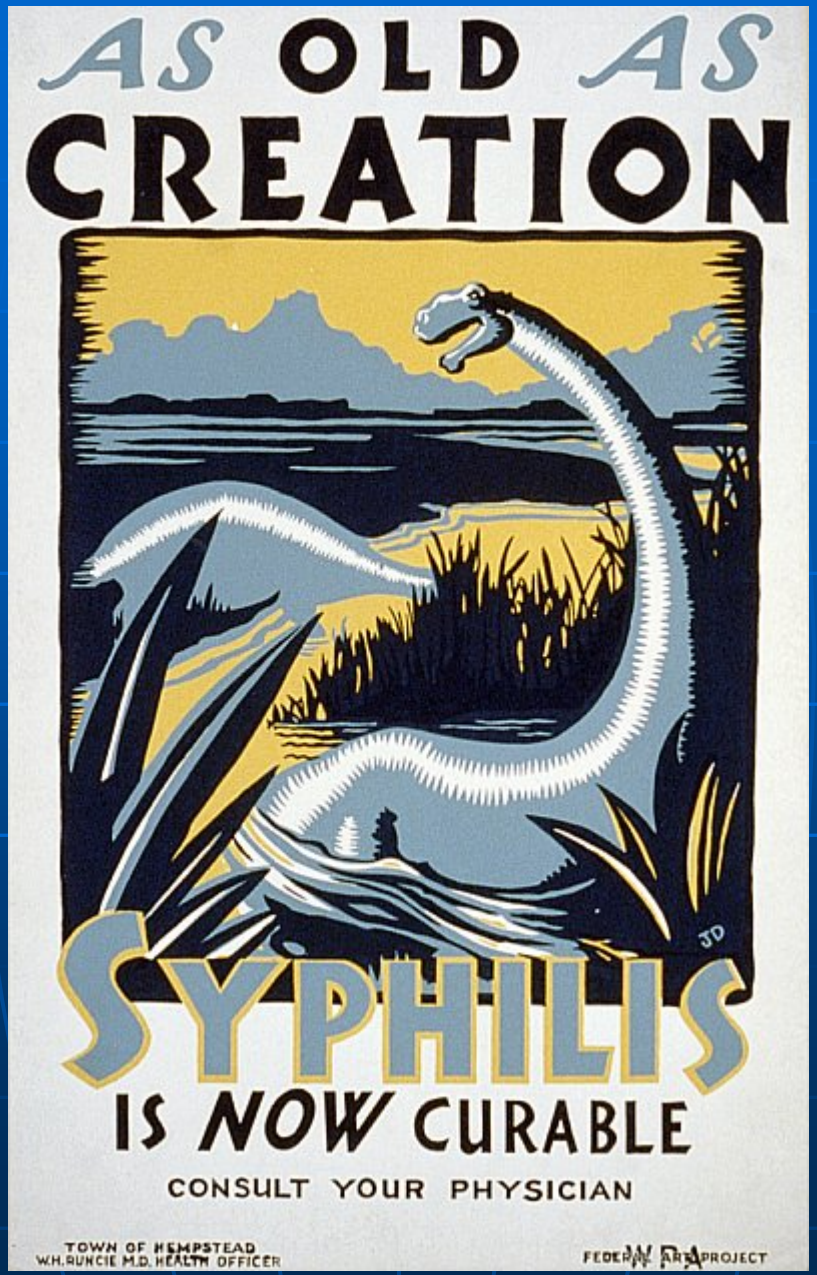
- Warning and counseling via internet
- Prevention at 'sexual marketplaces'
  - Quick (oral?) screening
  - Mass treatment (azithromycin?)?
  - Vaccination for syphilis…?
- Prevention campaigns tailored to specific target groups…
- Offer HIV-screening!
- Close clinical follow-up

# Conclusions (1)

- Since 1999-2000 multiple local epidemics of syphilis in Western world
- Mainly MSM, HIV+, oral sex, unsafe sex
- ? Increasing HIV prevalence in this population?

# Conclusions (2)

- Syphilis and HIV
  - More secondary syphilis + chancres
  - More aberrant serology
  - More neurosyphilis?
- Treatment: penicillin (ceftriaxone, azithro)
- Prevention essential but difficult


AS OLD AS
CREATION
SYPHILIS
IS NOW CURABLE
CONSULT YOUR PHYSICIAN
TOWN OF HEMPSTEAD
W.H. RUNCIE M.D. HEALTH OFFICER
FEDERAL ART PROJECT

# Thanks to…

- André Sasse (IPH)
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