Public Health England

Protecting and improving the nation's health

Central and North West London NHS

NHS Foundation Trust

Neurosyphilis: diagnostic challenges

Helen Fifer

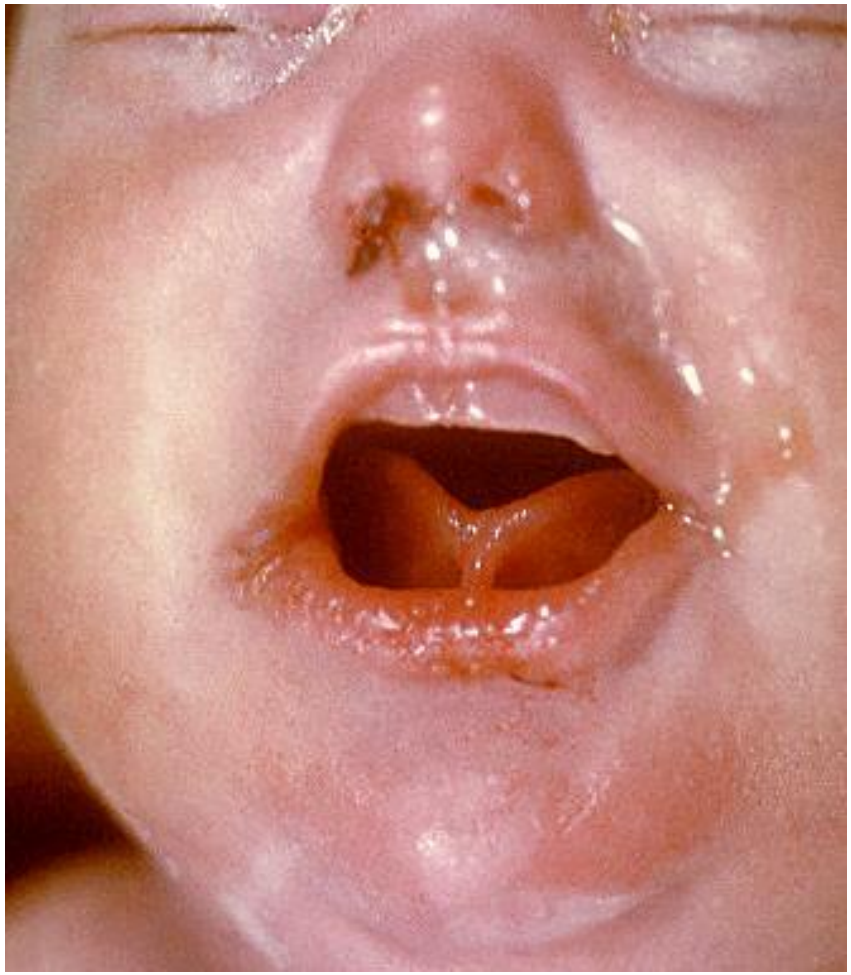
Patrick French

Syphilis

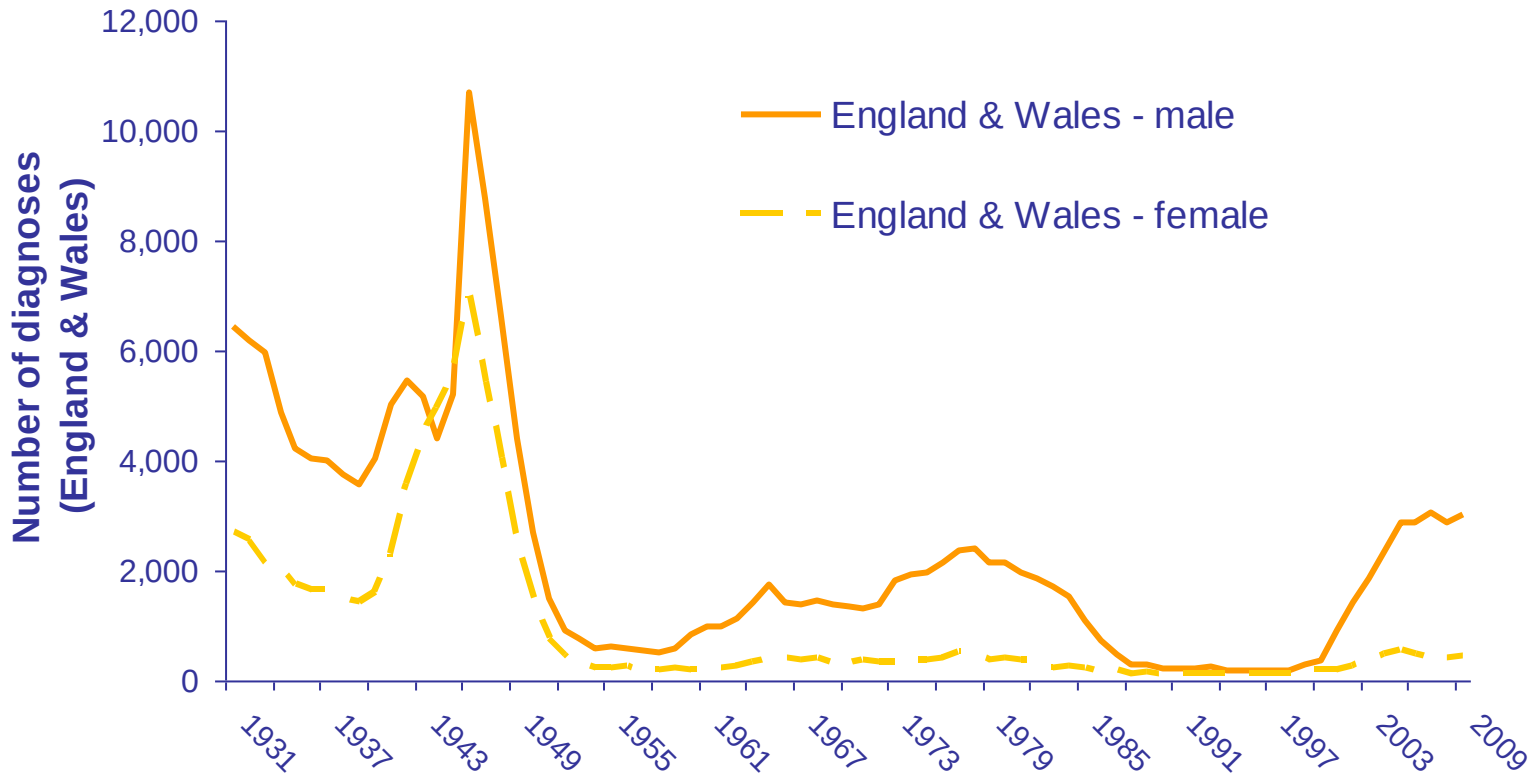
- Epidemiology
- Natural history
- Diagnostics
- Neurosyphilis cases

Why is syphilis important worldwide?

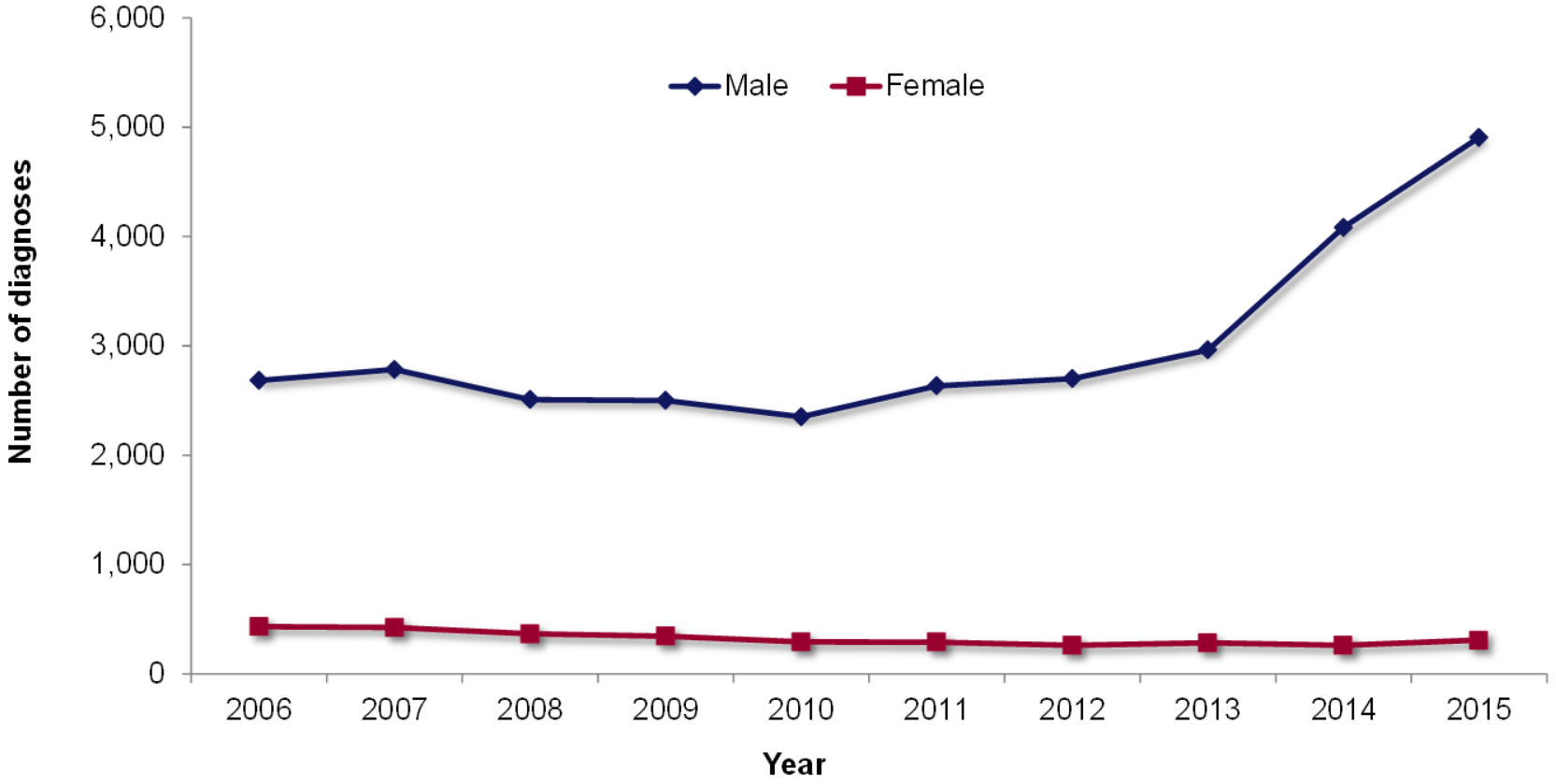
- 10-12 million new infections per year
- 4-5x increased risk HIV transmission
- 1 million pregnancies affected per year



Diagnoses of early syphilis GUM clinics, England & Wales 1931–2012



Number of syphilis (primary, secondary & early latent) diagnoses by gender: England, 2006–2015

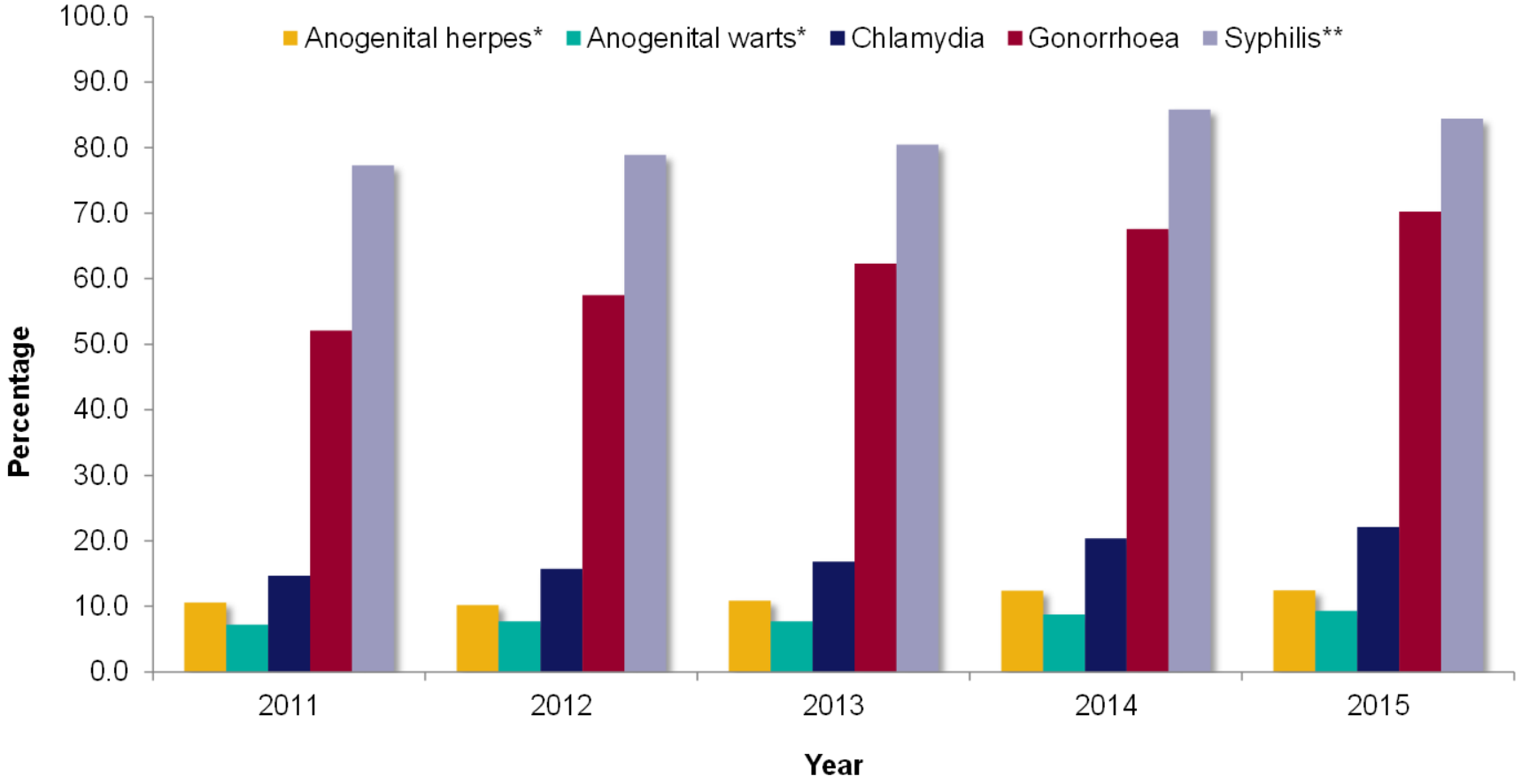


- Data from routine GUM service returns
- Data type: service data

Number of syphilis (primary, secondary & early latent) diagnoses by sexual risk: England, 2011–2015

- Data from routine GUM service returns
- Data type: service data

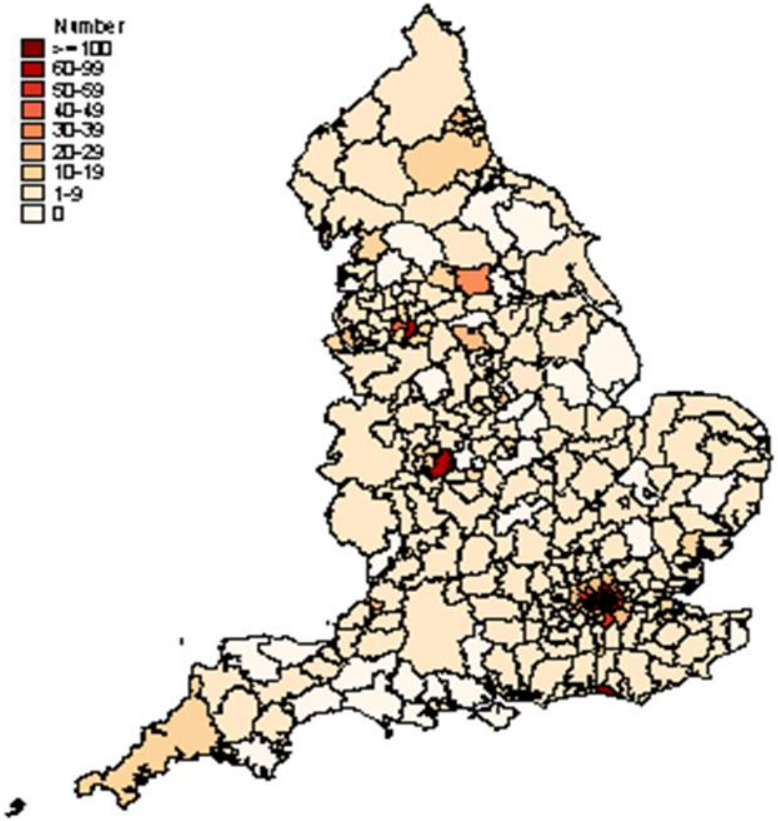
Percentage of all STI diagnoses in men which were among MSM: England, 2011-2015



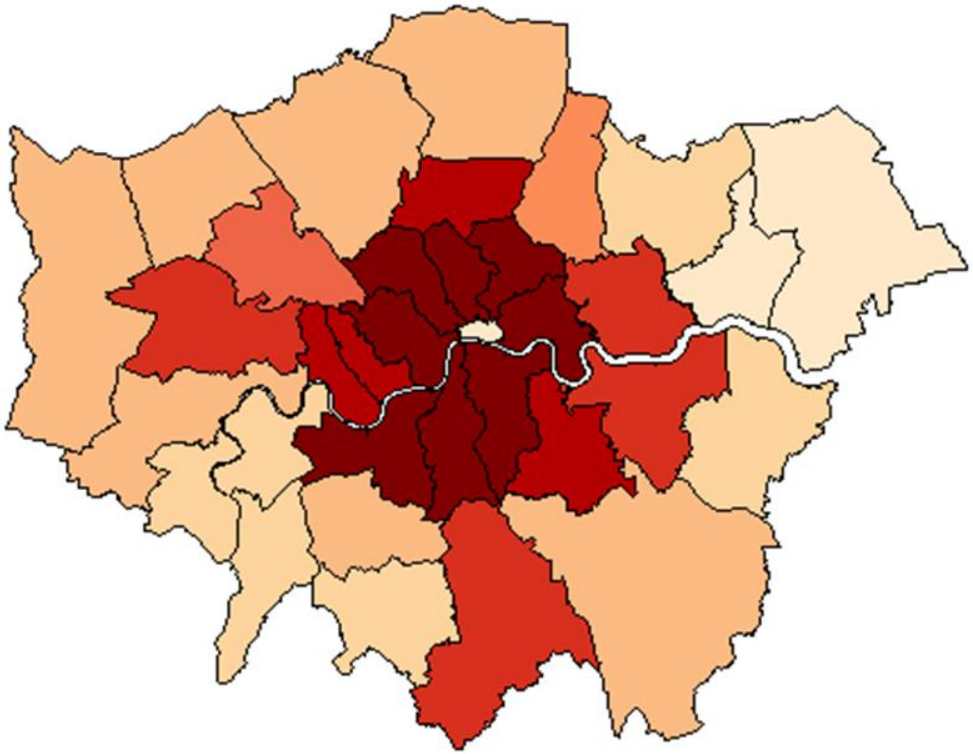
- Data from routine GUM service returns
- * First episode; **Includes diagnoses of primary, secondary & early latent syphilis
- Chlamydia data from 2012 onwards are not comparable to data from previous years (please see 'Notes' slide for more details)
- Data type: service data

Number of syphilis (primary, secondary & early latent) diagnoses among MSM by LA of residence: England, 2015

England

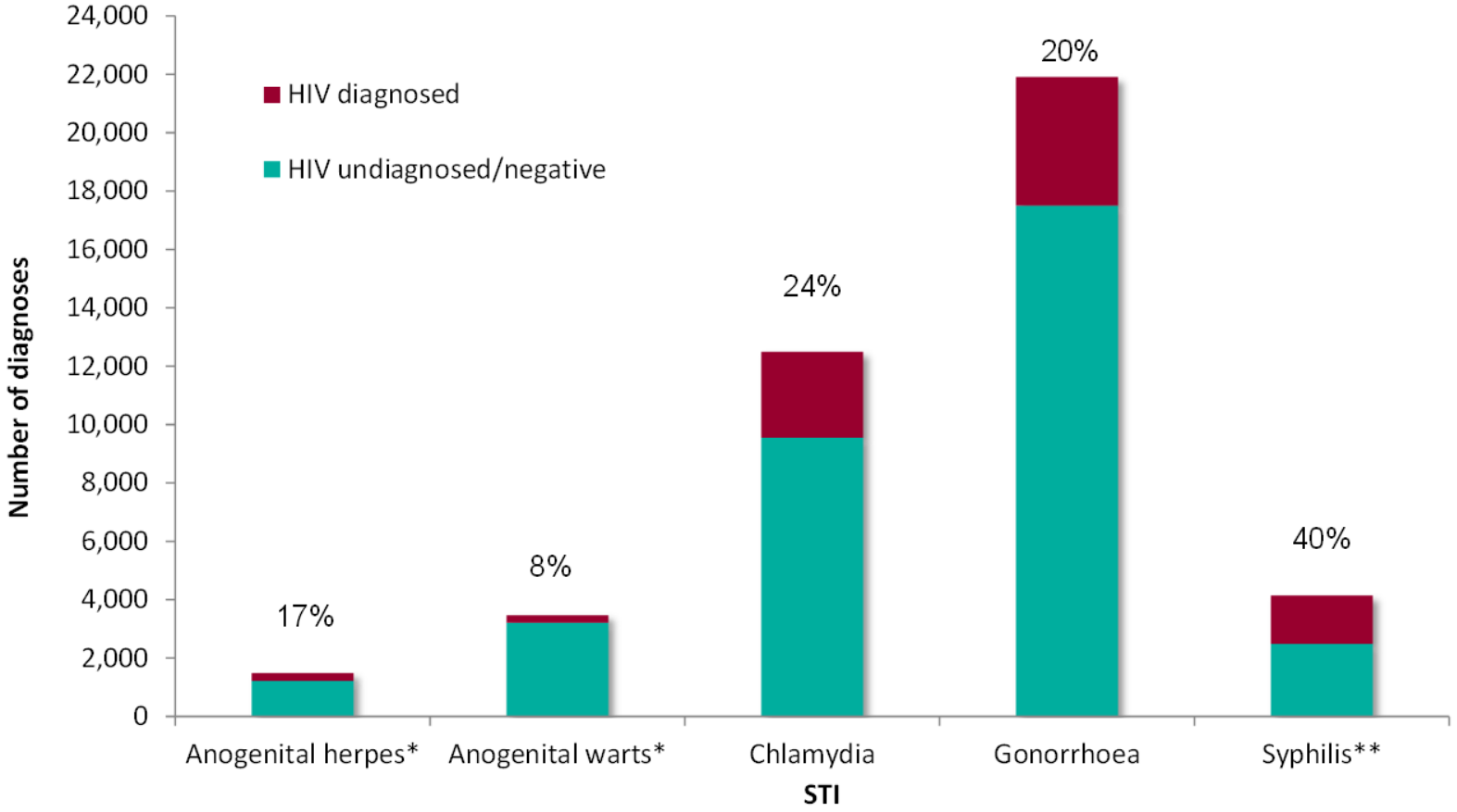


London



- Data from routine GUM service returns
- Data type: residence data

Number of STI diagnoses among MSM by HIV status: England, 2015



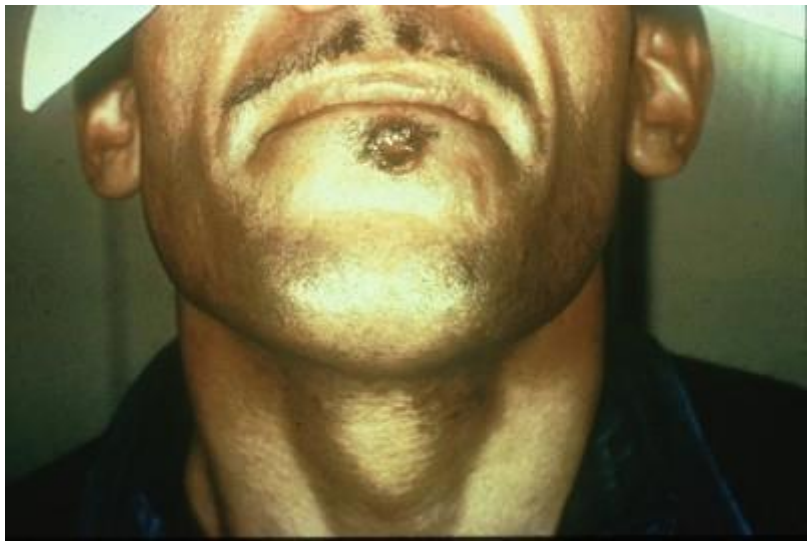
- Data from routine GUM service returns
- * First episode; ** Includes diagnoses of primary, secondary & early latent syphilis
- HIV diagnosed includes those who were diagnosed with HIV more than 6 weeks prior to their STI infection
- Data type: service data

Natural history of syphilis

Incubation period 2-3 weeks

Primary syphilis – an ulcer or ulcers

Heals after 3-4 weeks



Secondary syphilis – generalised infection – rash, enlarged lymph nodes 6- 12wks

Latent syphilis

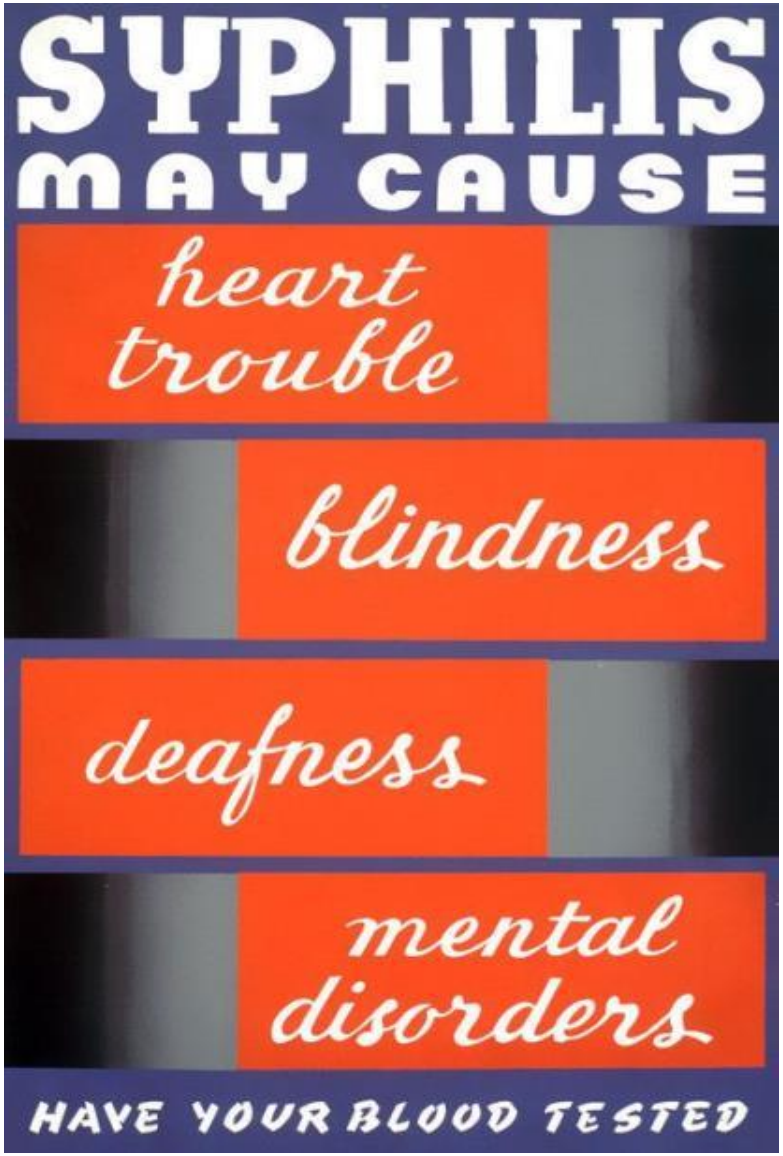
positive serology but no symptoms or signs of syphilis

Early < 2 years Late > 2 years

Tertiary syphilis

- 1/3 patients with untreated latent syphilis develop tertiary syphilis after 20-40 years
  - 15% gummas
  - 10% cardiovascular
  - 7% symptomatic late neurosyphilis

J Chr Dis 1955 2(3):311-44



Neurosyphilis

- Wide dissemination including CNS invasion in primary syphilis
- CSF abnormalities suggestive of asymptomatic neurosyphilis in 20-30% of patients with early syphilis but ?clinical relevance (*NEJM* 1997;337:307-14)
- Many patients will clear CSF *T pallidum* without therapy; no indicators for development of symptomatic neurosyphilis
- Neurological manifestation may occur **anytime** from 2 months – 20 years +
- Commonest presentations in UK are uveitis and otosyphilis as part of early infection
- Also causes CVA (meningovascular), dorsal column loss (tabes dorsalis) and cognitive decline (general paresis)

Syphilis diagnostics

- Spirochaete *Treponema pallidum* subsp *pallidum*
- Cannot survive and multiply outside the mammalian host i.e. cannot culture
- Demonstration of *T pallidum* from lesions or infected lymph nodes (dark ground or PCR)
- Diagnosis mainly depends on detecting the host antibody response; treponemal and non-treponemal tests
- Neurosyphilis diagnosis challenging as no single test is both sensitive and specific

Syphilis serology: treponemal tests

- Total antibody enzyme immunoassay (EIA)
- Treponema pallidum particle agglutination assay (TPPA)
- Treponema pallidum haemagglutination assay (TPHA)
- Fluorescent treponemal antibody absorbed assay (FTA-abs)

- Specific tests, remain positive for life
- None can distinguish between the treponematoses e.g. yaws, pinta
- Syphilis IgM EIA: decreases after treatment and disappears in 3-12 months. Sensitivity varies.

UK Standards for Microbiological Investigations: Syphilis Serology. 2016 *PHE*. V44

Syphilis serology: non-treponemal tests

- Detect IgG and IgM antilipoidal antibodies released by cells damaged by treponemal or non-treponemal infection
- Rapid plasma regain (RPR)
- Venereal Disease Research Laboratory (VDRL)
- Information about the ‘activity’ of the disease, useful for monitoring treatment
- RPR titre >1:16 indicates active infection
- Serum RPR titre >1:16 significantly associated with neurosyphilis (11x HIV-negative, 6x HIV-positive) regardless of stage of syphilis (*JID* 2004; 189:369-76)

CSF tests

- WCC >5 cells/μL (HIV -) or >20 cells/μL (HIV +). Non-specific and poor sensitivity
- Raised protein >0.45 g/l
- TPPA: high sensitivity, poor specificity (passive transfer serum antibodies, blood-CSF barrier dysfunction)
- Negative TPPA “rules out” neurosyphilis?
- CSF TPPA titre > 1:320 (*Int J STD AIDS* 2000; 11: 224-34)
- RPR or VDRL: “gold standard” high specificity but poor sensitivity (20-50%)
- Positive RPR “rules in” neurosyphilis

Case 1

- 84yr woman
- Worsening memory for 6 years
- Born in Dominica, moved to UK aged 26 years
- Referred by care of elderly consultant

- Total antibody +ve, TPPA +ve, RPR 1:1

- No focal neurology
- Mini-mental score – 19/30
- CT scan – mild white matter atrophy

Questions

- Is neurosyphilis likely?

- Should she have a lumbar puncture?

- Neurosyphilis very unlikely (slow onset, low RPR titre <1:4, not an atypical presentation of cognitive decline)

- Yaws (*T.pallidum* subsp *pertenue*) possible

- ? CSF examination
- ? Treat for neurosyphilis without LP

Acta Derm Venereol 2006;86(4):335-9.

CSF

- WCC <5 /µL
- RBC 0
- Protein / glucose normal
- TPPA positive 1:160
- RPR negative

- How would you interpret these results?

Case 1 treatment

- Not neurosyphilis
- Diagnosis: late latent syphilis or yaws
- Benzathine penicillin 2.4MIU IM x 3 doses 0,7,14 days
- UK Syphilis Guidelines 2015 BASHH

Int J STD AIDS 2016; 27(6):421-46

Case 2

- 41year old man
- Acute onset left hemiplegia
- MRI - Right MCA thrombosis

- Normotensive. No diabetes. Normal echocardiogram, carotids, autoantibodies.

- Syphilis serology
  - Total antibody EIA +ve
  - TPPA +ve >1:1280
  - RPR 1:32

CSF

- WBC 350/µL
- RBC 0
- Protein – 1.5g/L
- Glucose normal

- TPPA + ve 1:1280
- RPR negative

Case 2 treatment

- Steroid Cover – prednisolone 60mg day -1, 0, 1.

- Parenteral penicillin – 14 days

- Benzylpenicillin 2.4 gm IV 4 hrly
- Or
- Procaine penicillin 2.4 MIU IM daily + probenecid 500mg QDS PO

- Full recovery

Int J STD AIDS 2016; 27(6):421-46

Case 2 follow up

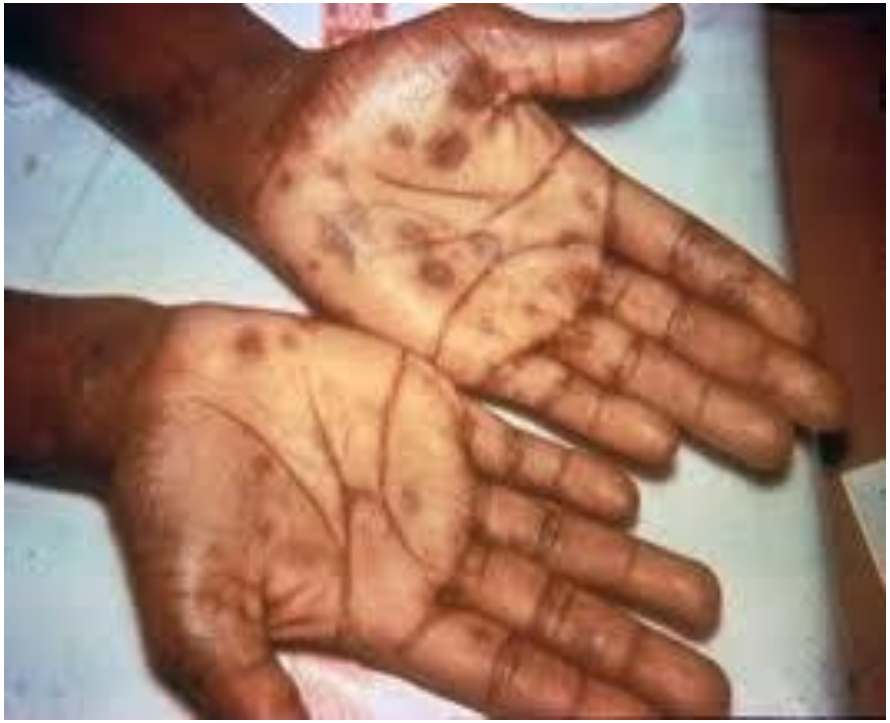
- Best parameter for treatment response is CSF WBC count
- Usually normal within 3 months
- Other markers much slower to normalise
- TPPA may remain positive indefinitely

Case 3

- 34year old HIV negative man

- Rapid onset blurred vision 4 days
- Generalised rash, fever
- Anterior uveitis

- Syphilis serology
  - Total antibody EIA +ve
  - TPPA +ve
  - RPR 1:64



- What is the likely diagnosis?
- What is the role of CSF examination?

Secondary syphilis and uveitis: treatment

- Parenteral penicillin with steroid cover
- Full recovery
- No CSF examination undertaken

- **HIV & Neurosyphilis** –
- CSF diagnosis > 5/µL if HIV neg but > 20/ µL if HIV positive

- If HIV positive & serum RPR >1:16 – 6 x risk of neurosyphilis
- If HIV positive & syphilis & CD4 < 350 – 3 x risk of neurosyphilis
- *JID* 2004; 189:369-76

Ocular syphilis

- Prevalence unknown but increasing reports of clusters of ocular syphilis: increased detection or true increase?
- Typing of *T pallidum* shows significant strain diversity globally, 14d most common type
- Possible neurotropic strain type 14d/f (*J Infect Dis* 2010; 202(9):1380–1388)
- Study of 14 patients with ocular syphilis in Seattle in 2015: 5 different *T pallidum* types i.e. no predominant strain (*STD* 2016; 43:8)

Future diagnostics for neurosyphilis

- Performance of tests depends on the criteria used for diagnosing neurosyphilis. Reference standard of CSF VDRL is not sensitive.
- PCR
  - Invasion by spirochaete = neurosyphilis?
  - Sensitivity 25 – 60%
  - Detected for up to 3 years post treatment (*J Clin Microbiol* 1991; 29:1976–84)
- VDRL vs RPR (sensitivity 66% vs 51%)
  - Diluted RPR antigen to improve antigen:antibody ratio, sensitivity 57% (*STD* 2012; 39(6): 453–457)

Future diagnostics for neurosyphilis

- TPPA index (intrathecal production of *T pallidum* specific antibodies)
  - Minimise effect of blood-CSF barrier dysfunction or high serum TPPA titres
  - Differentiate between intrathecal and peripheral antibody production
  - Determined using CSF:serum albumin, total IgG and TPPA titre
  - Specificity of 100% , sensitivity of 98% in one study of 60 HIV neg patients with symptomatic NS (*Int J STD AIDS* 2000; 11: 224-34)
- Biomarkers e.g. B cell chemokine CXCL13 (*STD* 2010; 37(5): 283–287)
  - Sensitivity 50%, specificity 90% (RPR positive) (*JCM* 2015; 53:1693-1696)

Summary

- Syphilis diagnoses increasing, particularly MSM, HIV +
- Neurosyphilis clinically diverse
- Laboratory diagnosis challenging, new tests needed

- Questions?