Causes of genital ulceration – viruses and others

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Outline

- Definition
- Causes
- Epidemiology
- Diagnosis

Definition of genital ulcer

A defect in the epithelium of the genital skin or mucous membrane

Causes

- Sexually transmitted infections (STIs)
- Non-STI infections
- Dermatological conditions
- Dermatological manifestations of systemic illnesses
- Malignancy
- Trauma

Sexually transmitted viral infections

- HSV types 2 & 1
- HIV seroconversion
- CMV

Herpes of the penis

Herpes of the cervix

Sexually transmitted bacterial infections

- Syphilis
  - Primary chancre
  - Mucous patches

Sexually transmitted bacterial infections

- Tropical infections
  - LGV
  - Chancroid
  - Donovanosis

Parasitic STIs

Scabies - anywhere on the genitals

Non-STI infections

- Candida
- Herpes zoster
- Bacterial infection of STI-related ulcer
- Pyogenic

Dermatological conditions

- Erythema Multiforme
- Aphthous ulcers
- Fixed Drug eruptions
- Pemphigus
- Pemphigoid
- Lichen Sclerosus
- Erosive Lichen Planus

Behçets Syndrome

- Ulcers - painful, persistent, punched out
- Rash - papulopustular or acneform, erythema nodosum
- Uveitis, retinal vasculitis, optic atrophy, glaucoma
- Musculoskeletal, CNS, GIT manifestations

Crohn's Disease

- Extension of intestinal disease
- Perineal, perianal and vulval ulcers, fissures or abscesses

Estimated global incidence of ulcerative STIs

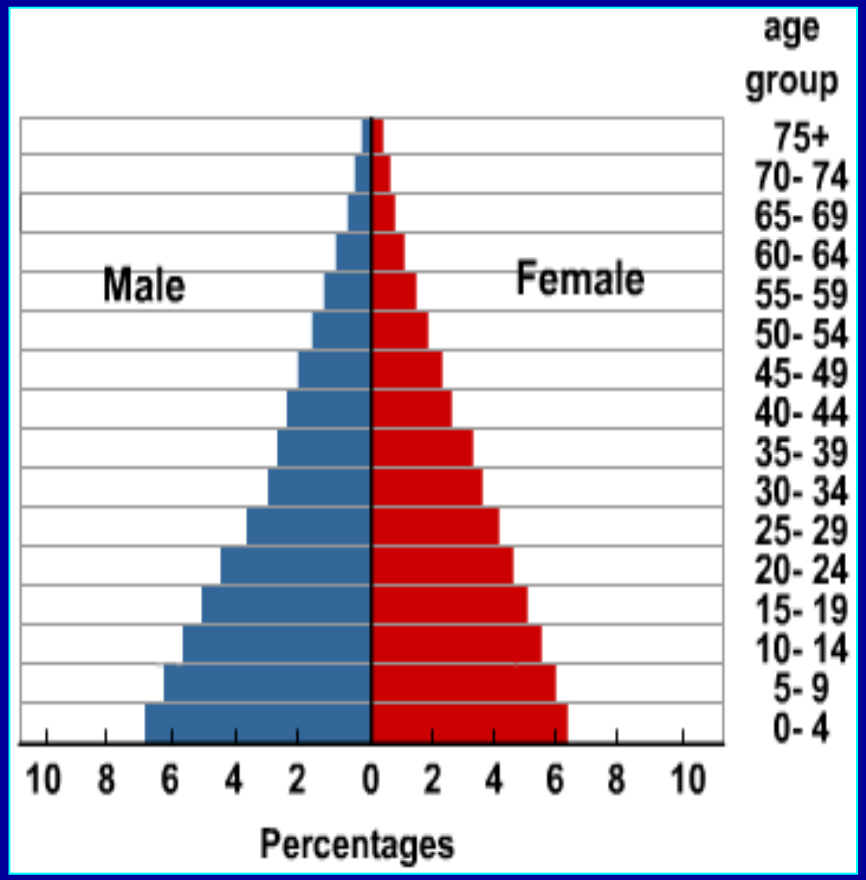
- Syphilis 35 million
- HSV 50 million
- Chancroid 2 million

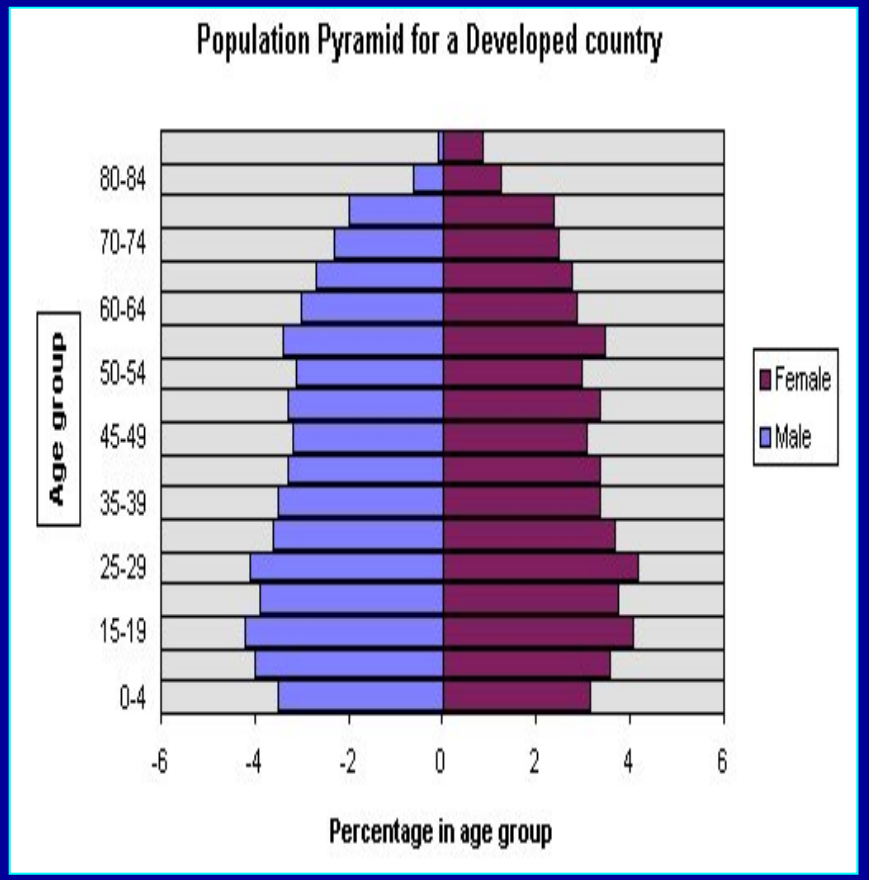
Over 90% in the developing world

Ulcerative STIs & geography

- Demographics
- In resource poor countries:
  - Lack of diagnostic and treatment facilities
  - Higher prevalence of STIs
  - Lower levels of education
  - Lack of health promotion activities
  - Poverty
  - Commercial sex work

Population pyramids





Ulcerative STIs developing and developed world

Developing

- HSV ++
- Syphilis +
- Chancroid +/-

Developed

- HSV +
- Syphilis +/-*

* Mainly in MSM

Ulcerative STIs in Australia

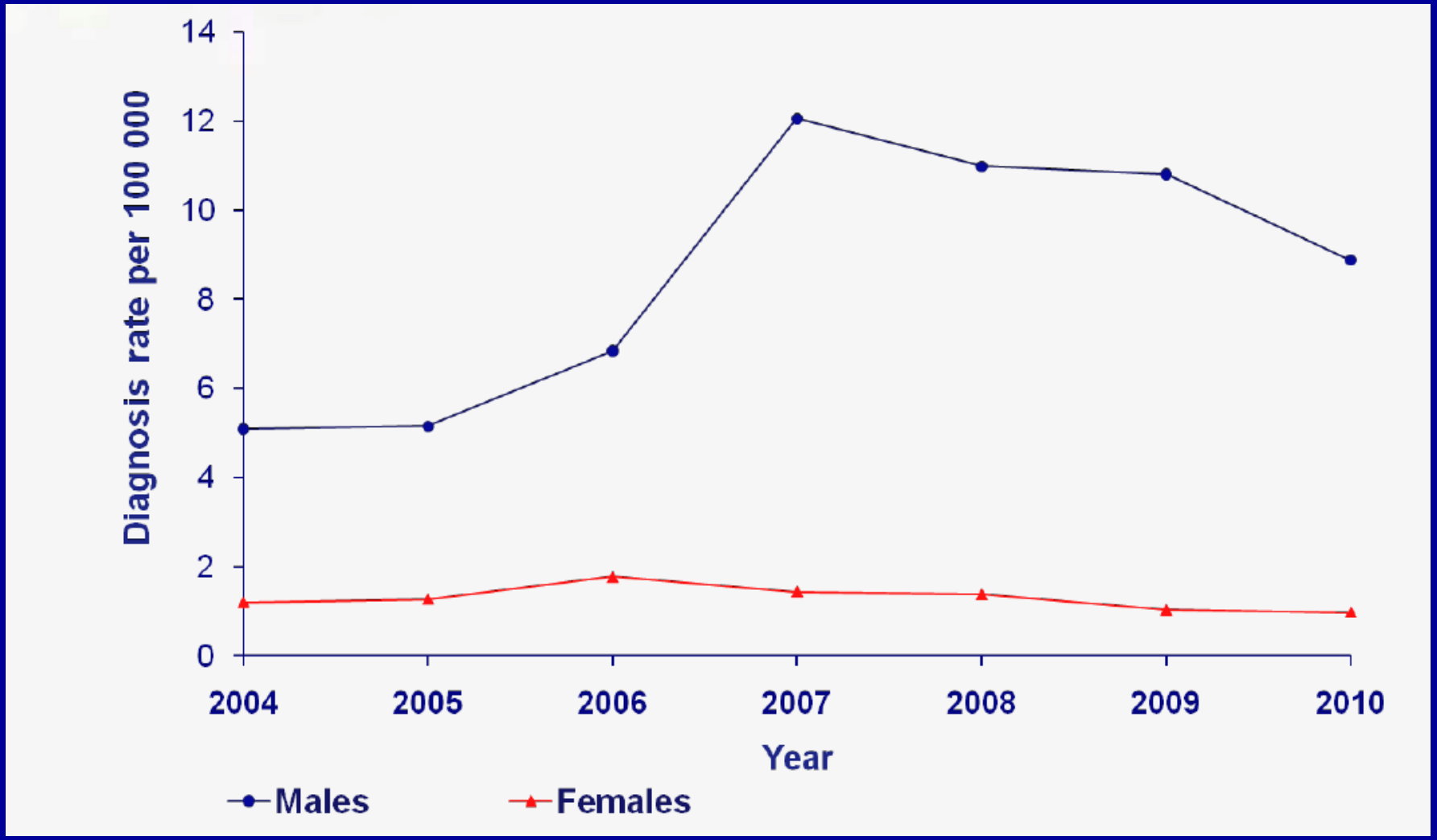
Notifiable

- Syphilis
- Tropical STIs

Not Notifiable

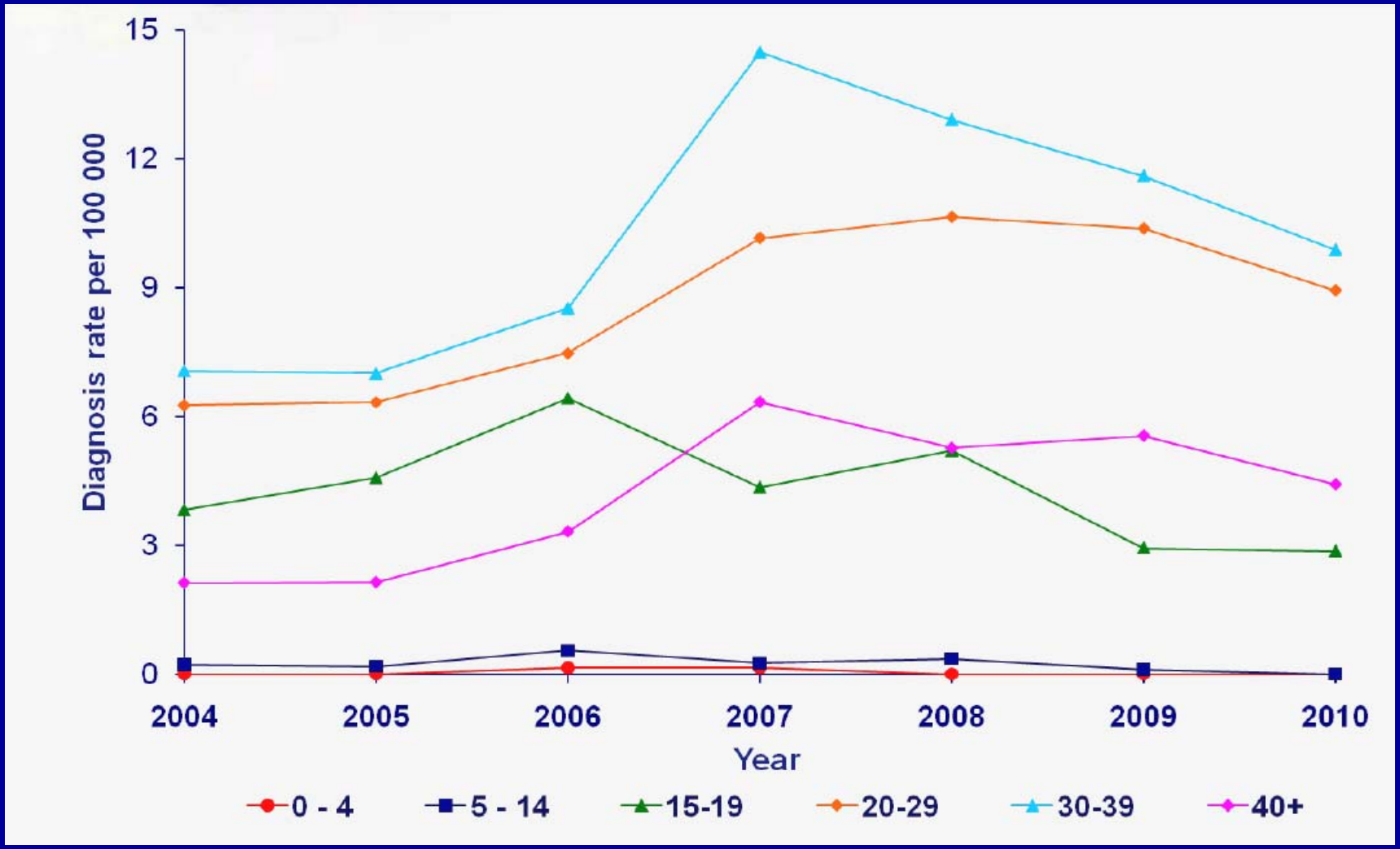
- HSV

Infectious syphilis by year and sex



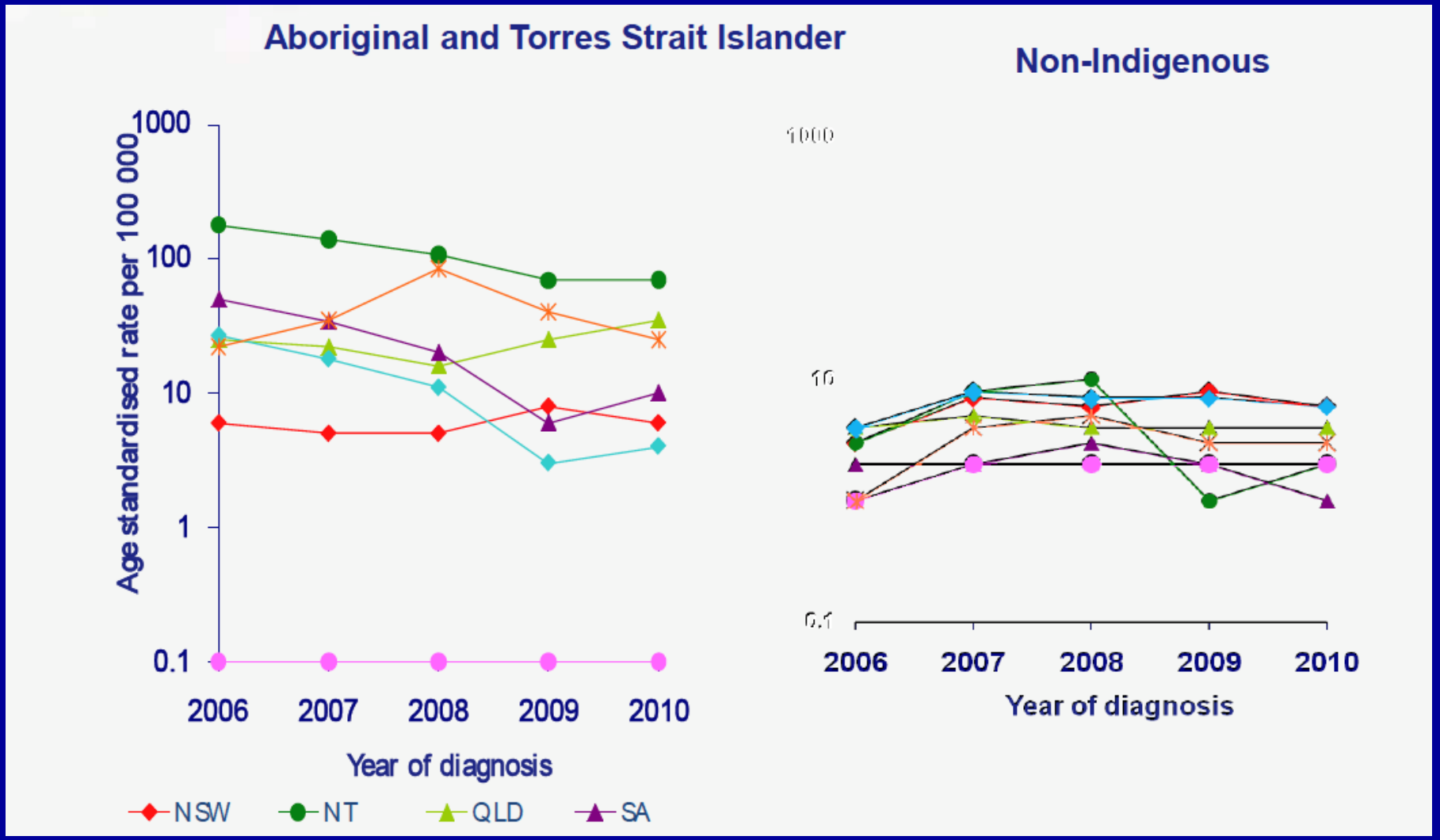
Source: National Notifiable Diseases Surveillance System

Infectious syphilis by year and age group



Source: National Notifiable Diseases Surveillance System

Infectious syphilis by Aboriginal and Torres Strait Islander status, State/Territory and year



Source: State/Territory health authorities

Herpes in Australia

- Limited data, largely derived from sexual health clinics and small research surveys

HSV-2 Seroprevalence in selected populations in Australia

• Blood donors	14%
• Pregnant women	11-14%
• STD clinic attendees	35-65%
• Homosexual men HIV pos	61%
• Homosexual men HIV neg	20%
• NSW Prisoners Male	21%
• NSW Prisoners Female	58%

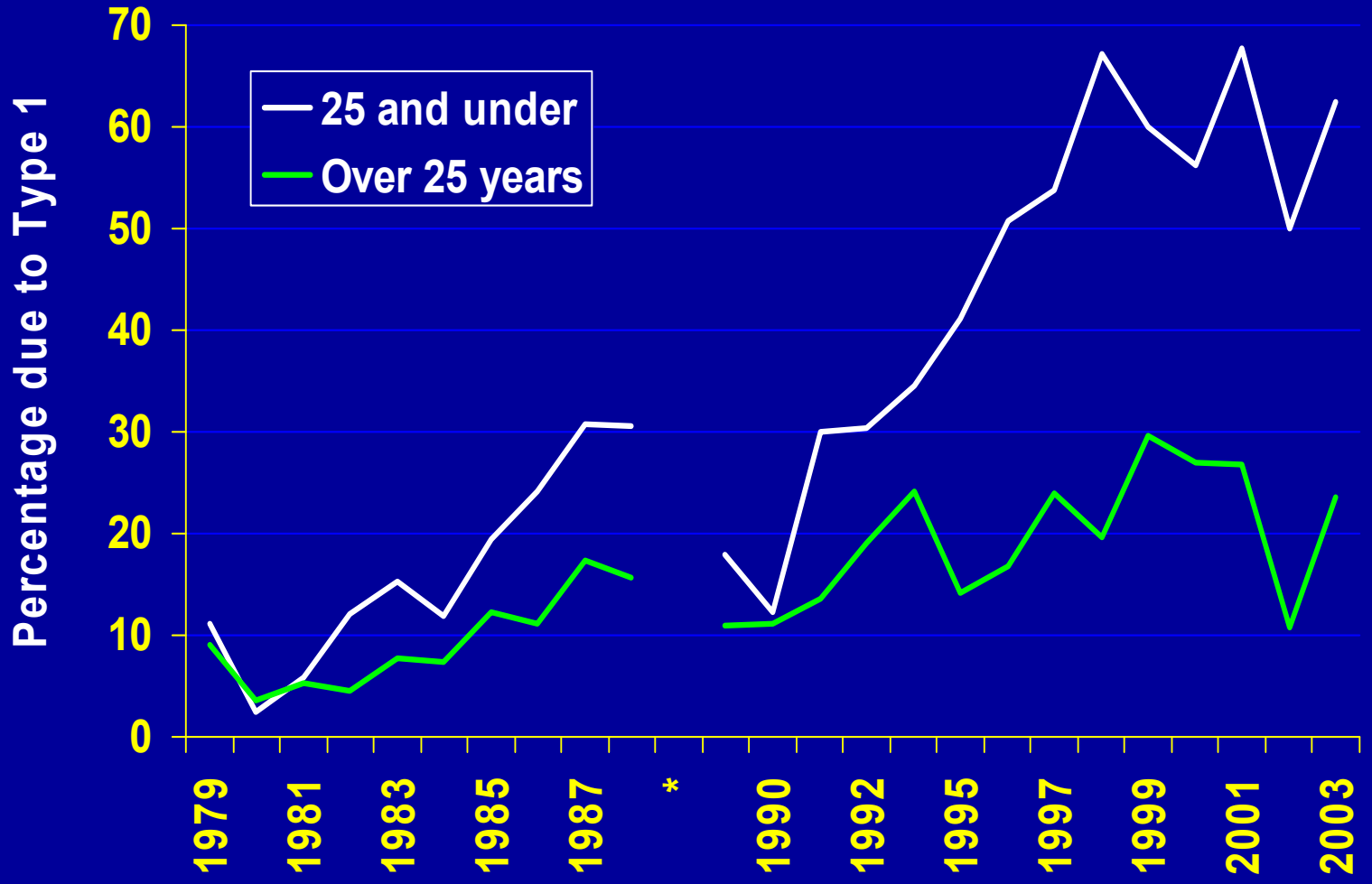
HSV seroprevalence in Australia - population-based survey

- HSV-2 12.1% (95% CI; 11.1 –13.1)
- HSV-1 75.7% (95% CI; 73.0-78.4)

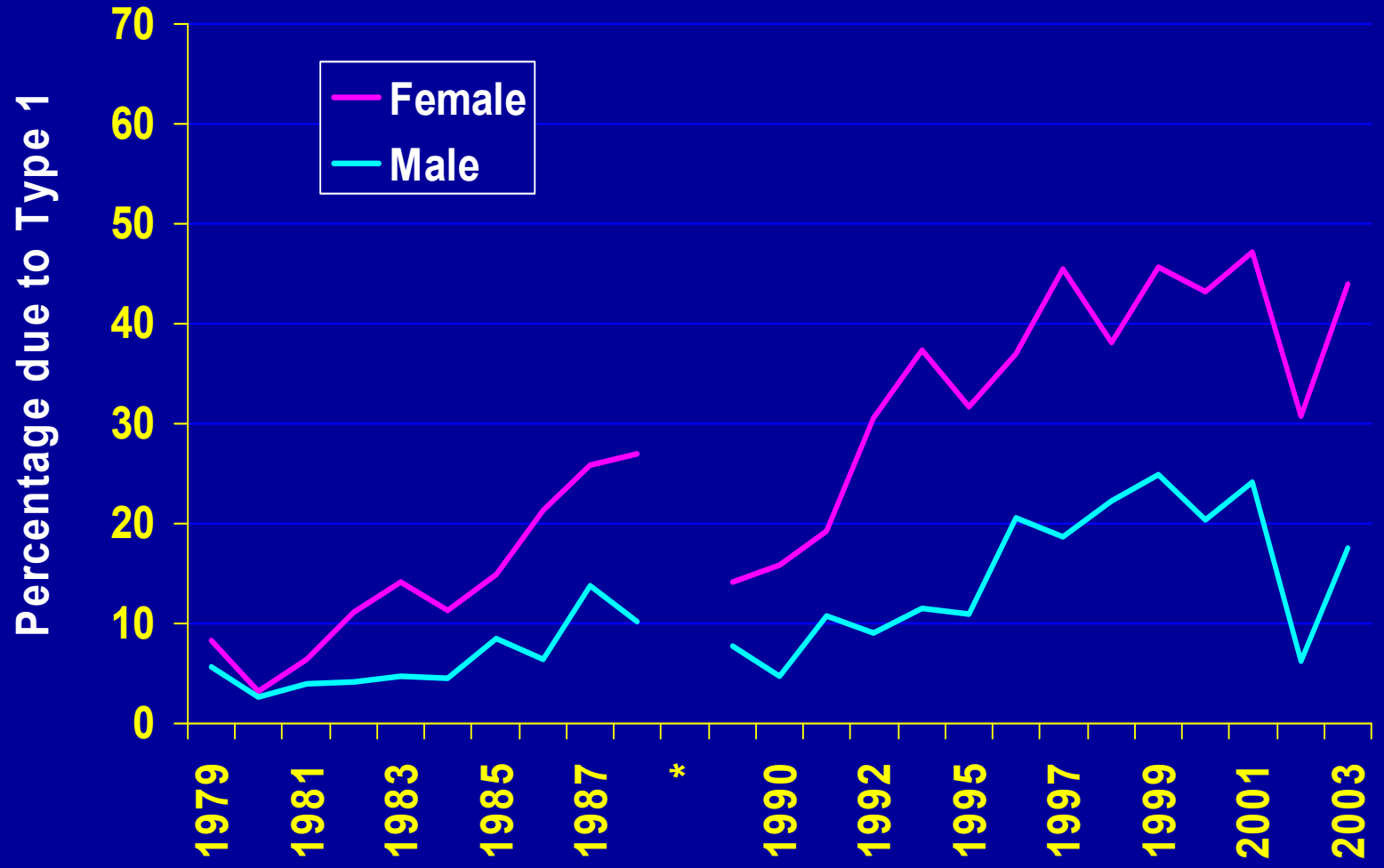
Risk factors for HSV-2 seropositivity

- Female gender
- Older age
- High lifetime number of sexual partners
- History of other STIs
- Young age at coitarche
- Inconsistent use of condoms
- Low socioeconomic status/limited education
- Ethnic origin

HSV-1 Genital Herpes



HSV-1 Genital Herpes (by sex)



HSV-2 and HIV co-infection

- HSV-2 has a high prevalence in areas where HIV is transmitted mainly via sexual intercourse
- HSV-2 is often acquired in early adolescence, before HIV
- The risk factors and behaviours for HSV-2 and HIV acquisition are similar

HSV-2 and HIV co-infection

- The calculated population-attributable risk percentage (PAR) of sexually acquired HIV varies according to the HSV-2 seroprevalence
- In the USA, where HSV-2 seroprevalence is 22%, the PAR is 19%
- In some areas in Africa where an HSV-2 seroprevalence is 80%, the PAR is over 50%

HSV-2 and HIV - biological plausibility

Enhanced HIV transmission

- Break in the skin/mucosa
- Increased HIV replication
- Activation of receptors
- Activation of CD4 lymphocytes and other target cells

Should we treat HSV-2 to reduce HIV transmission and acquisition?

- HSV-2 is associated with a doubling in risk of HIV acquisition
- The risk is independent of the occurrence of symptoms
- However, all the available observational data are subject to confounding by sexual behaviour
- RCT evidence was needed

HSV suppression to reduce HIV *acquisition*

- 821 “high risk” HIV-, HSV + Tanzanian women were randomised to acyclovir 400mg bd or placebo for 30 month. No effect on HIV incidence

Watson-Jones et al. NEJM. 358: 1560-71 2008

- 3172 HSV 2 – women from Africa and MSM from Peru and USA - randomised to receive acyclovir 400mg bd or matching placebo. No effect on HIV incidence

Celum C et al. Lancet 2008; 371: 2109-19

HSV suppression to reduce HIV *transmission*

- 3408 African, HIV serodiscordant, heterosexual couples, from 14 countries. Infected partner was HIV-1 +, HSV-2 +, CD4 count ≤250 and not on ART
- Infected partner randomised to acyclovir 400mg or placebo for 24 months
- 41 HIV-1 transmissions occurred in the acyclovir arm and 43 in the placebo arms (HR 0.92, 95% CI 0.60-1.41, p=0.70)

Celum et al. N Engl J Med 2010; 362: 427-39

Possible interpretations

- HSV-2 is not a risk factor - unlikely due to epidemiological evidence
- HSV in Africa responds less well to acyclovir
- Wrong drug and or dose
  - Acyclovir has poor bioavailability
  - Dose of 400mg bd is suboptimal
  - Valaciclovir and famciclovir have better bioavailability
- Underestimated of the frequency recurrences or reactivation
- Effect too small to be important

Herpes diagnostic tests

- NAATs
- Viral culture
- Serology

PCR for HSV

- More sensitive than culture
- Does not require live virus
- Now widely used in clinical practice

Interpretation of HSV type-specific serology

- A positive test indicates previous exposure to that virus
- Both HSV-1 and HSV-2 can cause genital and/or orolabial herpes
- Over time some individuals will loose antibody
- Tests may take up to 6 weeks to become positive

Syphilis serology

Treponemal tests

- TPHA and TPPA
- EIA
- FTA –Abs
- CIA
- WB -Western Blot

Non-Treponemal

- VDRL
- RPR
- GAST - Group Automated syphilis test
- Non-Treponemal EIA

Syphilis serology

- Screening – because of false positives:
  - In low prevalence populations use non-treponemal test
  - In high prevalence populations EIA

Syphilis PCR

- More sensitive and specific than dark field microscopy
- Can be used on ulcers and any other ‘wet’ lesion

LGV - diagnosis

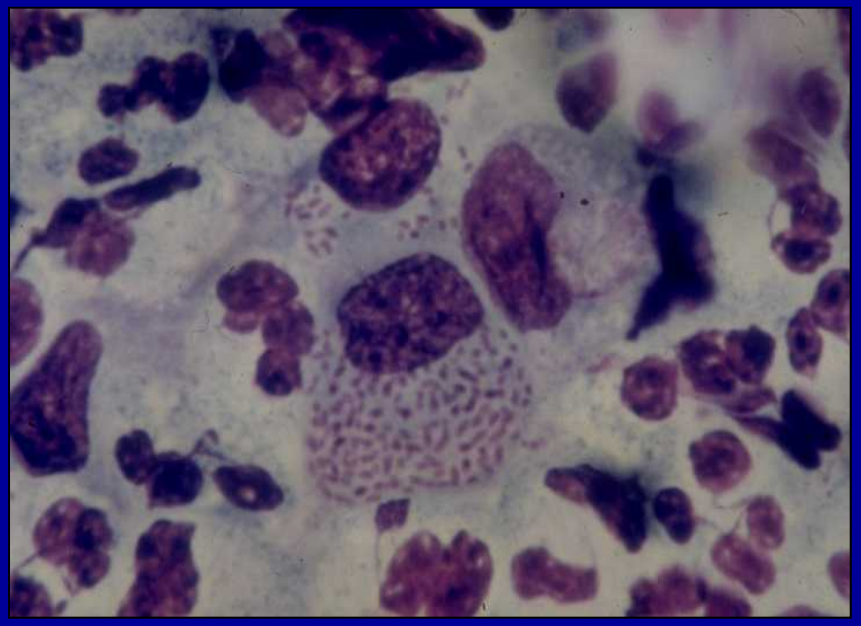
- General chlamydia PCR
- Followed by LGV specific PCR
- Serology

Chancroid – diagnostic tests

- PCR
- Serology

Donovanosis - diagnosis

- PCR



Investigations- both sexes if ulcers or vesicles are present

- PCR for HSV
- PCR for syphilis
- PCR for tropical infections (if appropriate)
- Serology for HIV and syphilis
- Tests to exclude other STIs