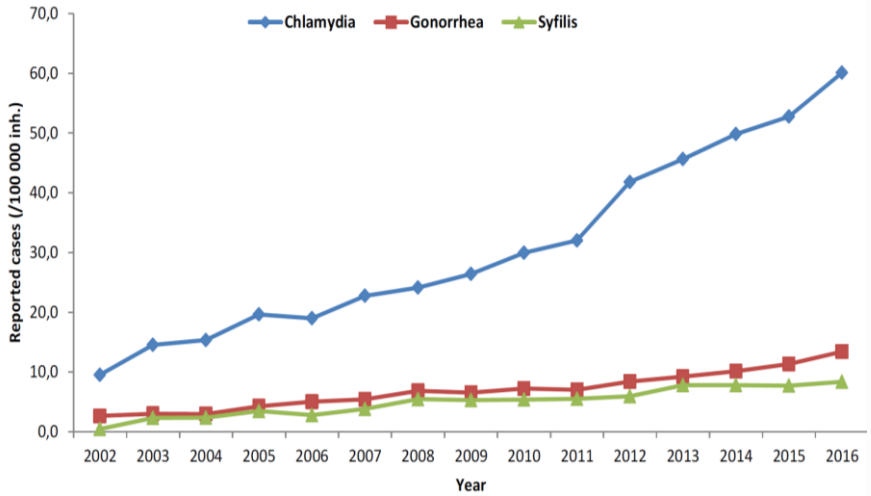
New diagnostic tests for sexually transmitted infections

Jens Van Praet
30/11/2018

Introduction



- Data from our national microbiological labs suggest STIs are an important clinical issue
- Correlation with clinical data is crucial to document real clinical burden
- Figures are focusing on the ‘big three’

STI: sexually transmitted disease

Surveillance report of STI’s Sciensiano, 2018

The ideal STI test

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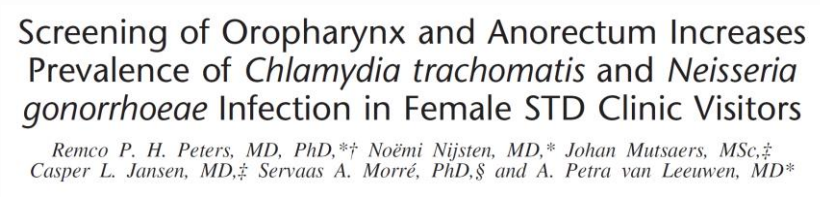
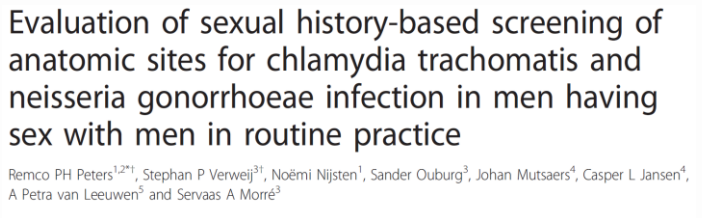
- Detects multiple STIs simultaneously with a high sensitivity and specificity
- Has a rapid turn-over and low cost
- Rapports presence of human cells in test sample
- Permits sexual history-based screening of multiple anatomic sites



Screening of Oropharynx and Anorectum Increases Prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infection in Female STD Clinic Visitors

Remco P. H. Peters, MD, PhD,† Noëmi Nijsten, MD,* Johan Mutsaers, MSc,‡ Casper L. Jansen, MD,‡ Servaas A. Morré, PhD,§ and A. Petra van Leeuwen, MD**



Evaluation of sexual history-based screening of anatomic sites for chlamydia trachomatis and neisseria gonorrhoeae infection in men having sex with men in routine practice

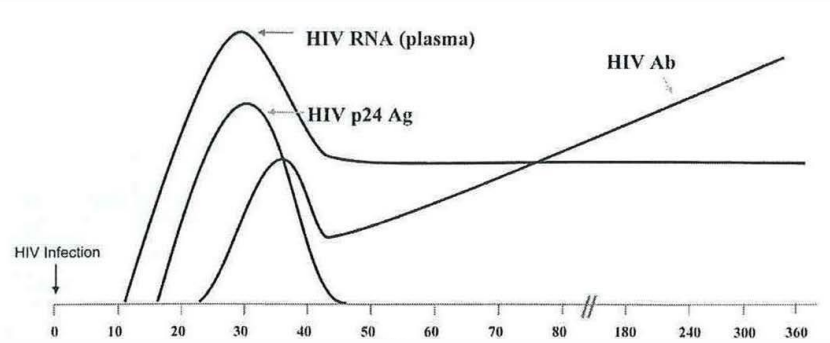
Remco PH Peters[1,2*†], Stephan P Verweij[3†], Noëmi Nijsten[1], Sander Ouburg[3], Johan Mutsaers[4], Casper L Jansen[4], A Petra van Leeuwen[5] and Servaas A Morré[3]

- Rapports resistance of relevant pathogens
- Detects emerging (potential) STI as *M. genitalium*, *U. urealyticum* and *M. hominis*
- Is available at my local institution/nearby lab

STI: sexually transmitted disease

Diagnostic tools for STI: old stuff

- (Culture)
  - Relevant to determine antimicrobial resistance
- Serology
  - Cornerstone for diagnosis of syphilis, HIV and viral hepatitis
  - ‘Windows phase’
  - Historic sample needed for proper interpretation
- Combotest (antigen/antibody) for viruses
  - Enhanced sensitivity as test becomes positive during viremia
  - Available for HIV and HCV



Diagnostic tools for STI: better stuff

- Nuclear acid amplication tests (NAATs)
  - Available since the 90's for chlamydia and gonorrhoea
  - Different detection techniques, including PCR, SDA, LCR and TMA
  - More sensitive than culture, especially for extra-genital sites
  - Also more sensitive (20-35%) than other non-culture direct tests, including EIA, DAT and nucleic acid hybridization tests
  - Permits less invasive collection of specimens (first-voided urine and vaginal swabs)
  - Feasible transport conditions

EIA: enzyme immunoassay DAT: direct fluorescent antibody test
PCR: polymerase chain reaction SDA: strand displacement amplification
LCR: Ligase Chain Reaction TMA: transcription-mediated amplification

Papp JR et al, 2014

NAAT: PCR principle

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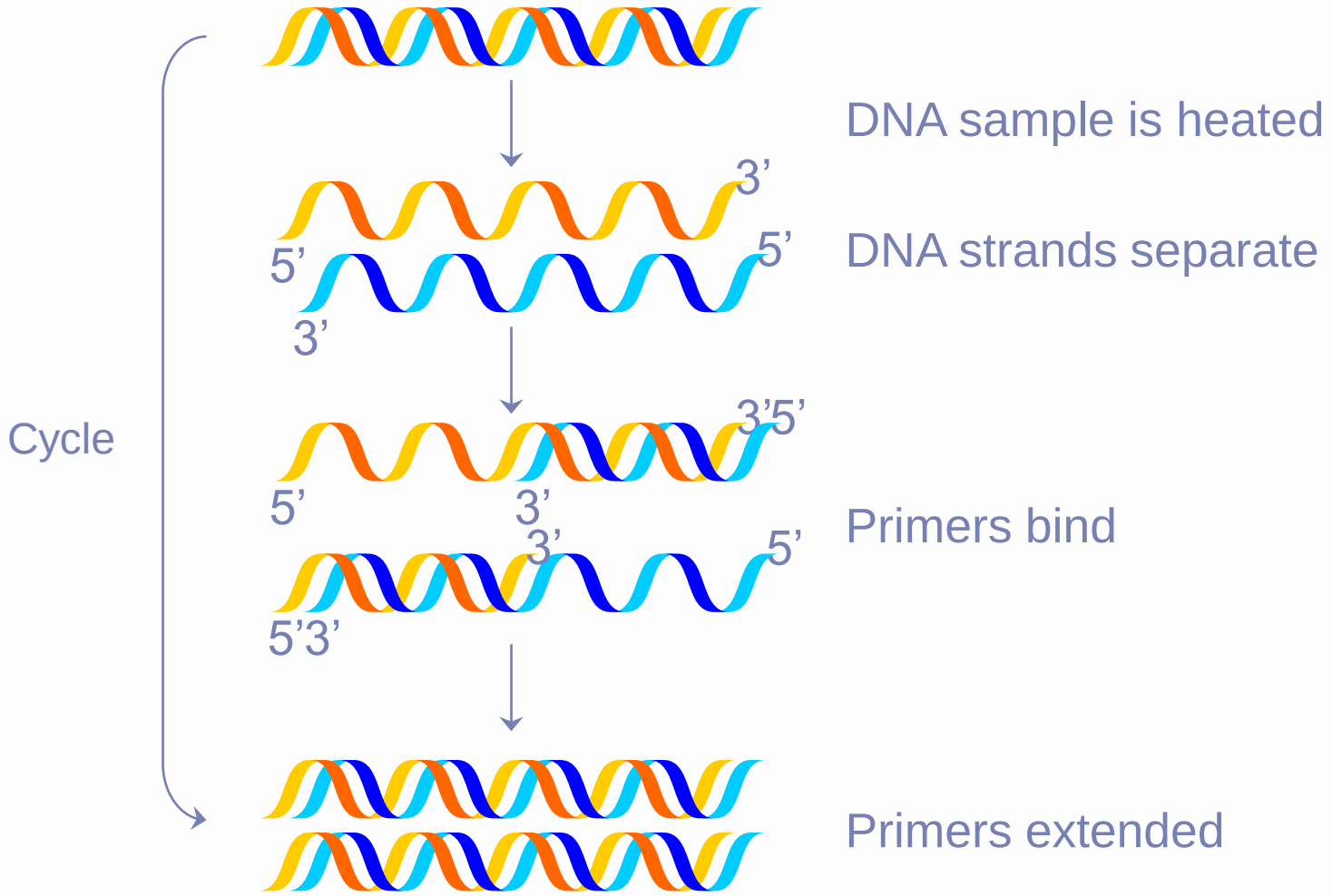
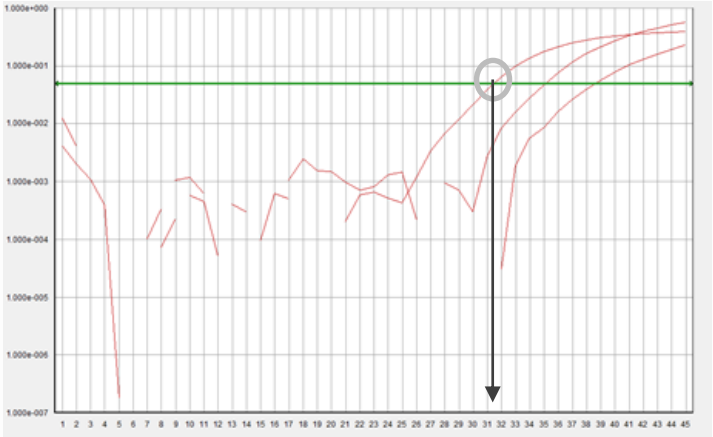


Diagnostic tools for STI: new stuff

- Micro-array rtPCR
  - ‘In-house’
  - Semi-quantification through rtPCR (C_t value)
  - Tests a battery of STI
  - Resistance testing by detecting resistance-mediating mutations



Courtesy of M. Reynders

rtPCR: real-time PCR C_t: threshold value

Diagnostic testing: rtPCR

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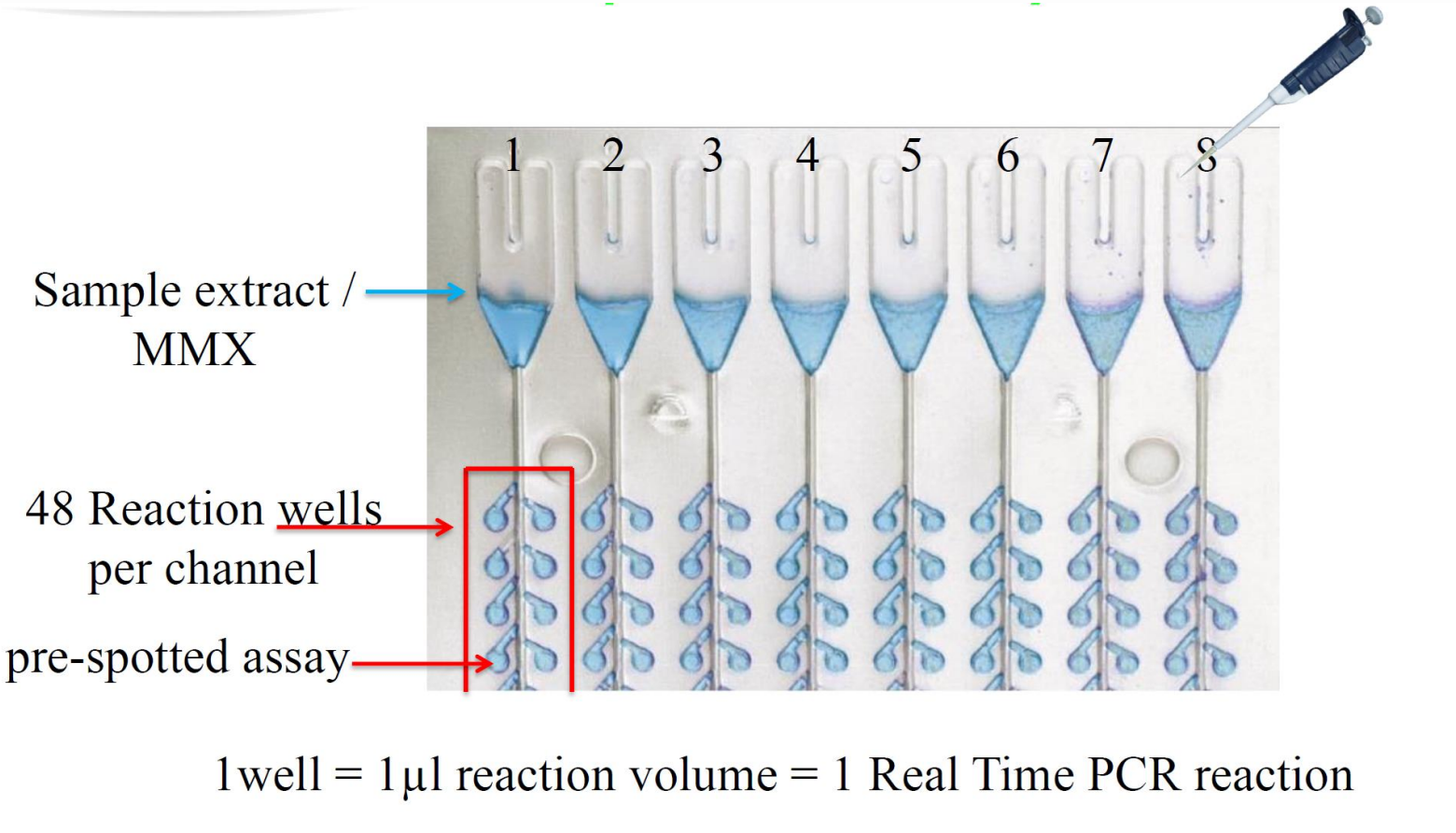
The micro-array Taqman® amplification card allows performing multiple rtPCR



Courtesy of M. Reynders

Multiplex testing for STI

- STI TAC AZ Sint-Jan detects 13 potential pathogens allowing a syndromic approach
  - Adenovirus, CMV, HSV-1 and HSV-2
  - *Chlamydia trachomatis, Mycoplasma genitalium, Mycoplasma hominis, Haemophilus ducreyi, Neisseria gonorrhoeae, Treponema pallidum, Ureaplasma parvum and Ureaplasma urealyticum*
  - *Trichomonas vaginalis*
  - Macrolide resistance-mediating mutations of *M. genitalium* (mutations in region V of the 23S rRNA gene (A2058G, A2059G, A2058T))
  - Controls: 18S, SHV control, Human Rnase Pgen, Hs04260458_s1
- Reporting is semiquantitatively (low/medium/high load), potentially discerning infection from asymptomatic carriership/shedding
- Oral swabs, vaginal swabs, first-voided urine or rectal swabs

Courtesy of M. Reynders

Syndromic approach of STI

- Acute urogenital symptoms
- Genital ulcer disease
- Anorectal symptoms
- Screening after risk contact(s)
- Pelvic inflammatory disease or Fitz-Hugh-Curtis syndrome
- Chorio-amnionitis and/or premature contractions
- Fertility problems
- Respiratory failure and/or sepsis of the neonate after chorio-amnionitis

Syndromic approach: acute urogenital symptoms

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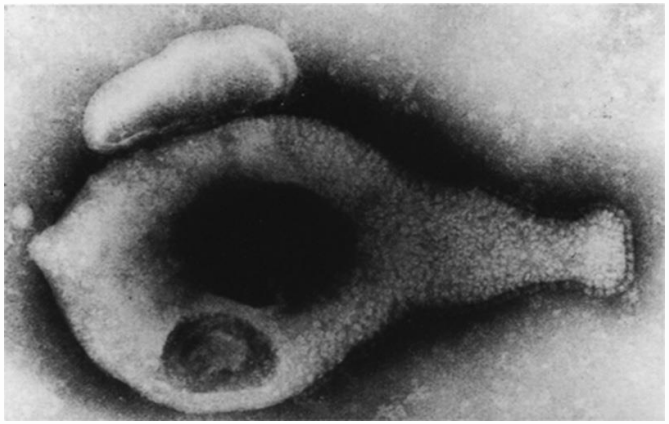
F.V., 35-year old male, MSM, HIV negative, presenting with persisting urethritis despite treatment with azythromycine 1 g and ceftriaxone 500 mg IM by his GP

SOA-screening dmv real-time PCR op micro-array card

Chlamydia trachomatis [U]	Niet detecteerbaar.
Neisseria gonorrhoeae [U]	Niet detecteerbaar.
Trichomonas vaginalis [U]	Niet detecteerbaar.
Mycoplasma genitalium [U]	**Sterk positief.**
Significante aanwezigheid van M. genitalium in het monster, suggestief voor actieve infectie of uitgesproken kolonisatie. Te toetsen aan kliniek en voorgeschiedenis.	
Macrolide resistent	
Mycoplasma hominis [U]	Niet detecteerbaar.
Ureaplasma urealyticum [U]	Niet detecteerbaar.
Ureaplasma parvum [U]	Niet detecteerbaar.
Treponema pallidum [U]	Niet detecteerbaar.
Herpes simplex virus type 1 [U]	Niet detecteerbaar.
Herpes simplex virus type 2 [U]	Niet detecteerbaar.
Cytomegaal virus [U]	Niet detecteerbaar.
Adenovirus [U]	Niet detecteerbaar.
Haemophilus ducreyi [U]	Niet detecteerbaar.

Symptoms resolved after moxifloxacine 400 mg dd during 10 days, test of cure was negative

M. genitalium: key features



- First identified in 1981 as a cause of nongonococcal urethritis
- In the 90's NAATs were introduced in research labs
- Moderate to strong association with PID and cervicitis in women, but frequently asymptomatic
- Infection raises risk for HIV infection
- First choice treatment is azithromycin (500 mg on d1, followed by 250 mg dd during 4d)
- Mutations in region V of the 23S rRNA gene confer resistance to macrolides
  - Moxifloxacin 400 mg dd during 10d

Tully JG *et al*, 1981
Manhart LE, 2013

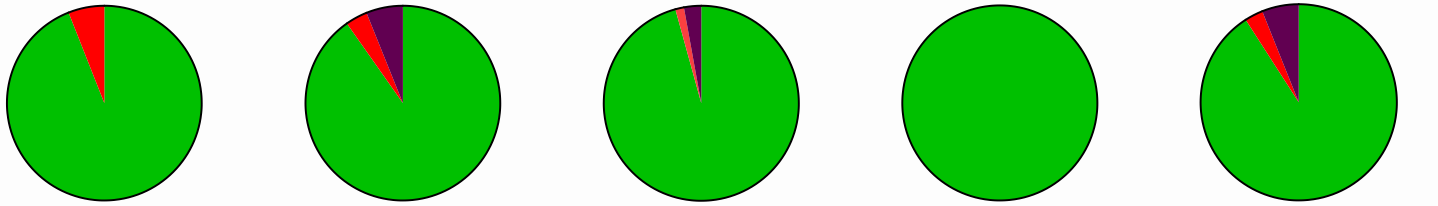
NAAT: nucleic acid amplification test, PID: pelvic inflammatory disease

Syndromic approach: screening after risk contacts

- Attestation of Truvada® for PrEP denotes:

  ‘ik verbind mij ertoe de volgende andere aangeraden testen uit te voeren/je m’engage à effectuer les autres tests recommandés suivants: ‘HIV, syphilis, gonorrhea, chlamydia, hepatitis C, others…’
- Patients starting on PrEP were screened by means of oral and rectal swabs, and collection of first-voided urine
- Urine, self-collected oral and rectal swabs were pooled from month 3
- In total 12% of screenings were positive for *M. genitalium* (first year)
- 43% of the strains were resistant for macrolides

Negative
Wild-type
Macrolide-R



PrEP: pre-exposure prophylaxis

Take home messages

- Serology and NAAT are not the ideal STI tests
- Micro-array rtPCR allows syndromic approach of STI
- Commercial STI field is growing
- AMR testing is possible by detecting resistance-mediating mutations
- *M. genitalium* is frequently detected in patients taking PrEP
- Prospective clinico-microbiological studies will learn us more on management of *Ureaplasma spp.* and *Mycoplasma spp.* in different clinical contexts

NAAT: nuclear acid amplication tests, STI: sexually transmitted disease, PrEP: pre-exposure prophylaxis
AMR: antimicrobial resistance