C.trachomatis, PID, and Epithelial Ovarian Cancer

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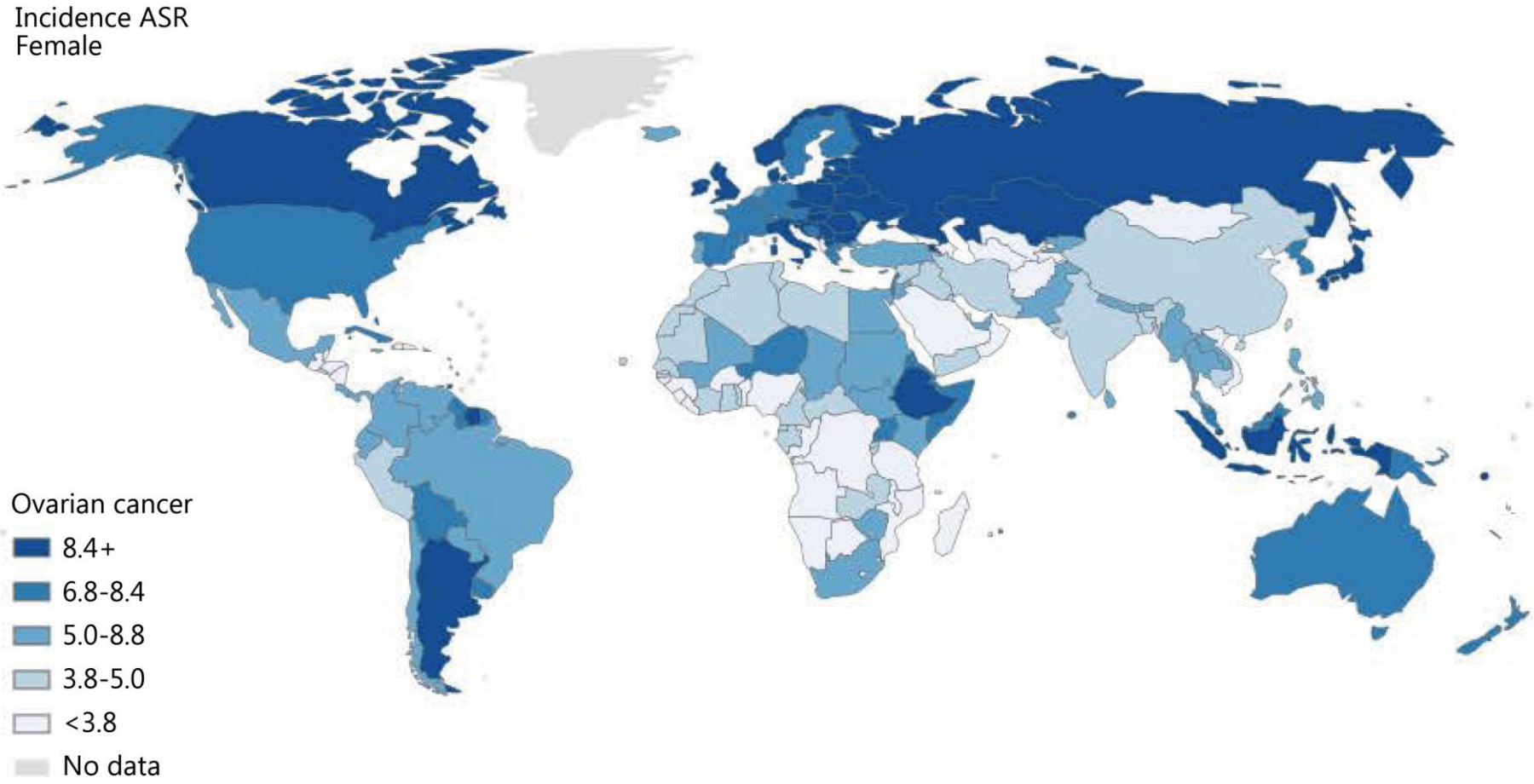
Declaration of conflicts of interest:

I have no conflicts of interest to declare

SVENSK FÖRENING FÖR OBSTETRIK & GYNEKOLOGI
Swedish Society of Obstetrics and Gynecology

Global incidence of ovarian cancer



Source: GLOBOCAN 2012 (IARC)

Extraovarian origin of epithelial ovarian cancer: Shifting the paradigm

- Fallopian tube epithelium implants on the ovary: Source of epithelial ovarian carcinoma
  - Type I tumors
    - Low-grade carcinomas developing from precursor lesions
  - Type II tumors
    - High-grade carcinomas, aggressive, grow rapidly, chromosomally unstable
- Etiologic implications
- Prevention
  - New approaches to prophylaxis

Kurman and Shih: Hum Pathol 2011;42:918

Etiology of epithelial ovarian cancer

- Involvement of the fallopian tube in the pathogenesis
  - Potential role of chronic inflammation
  - Inflammatory stimuli may contribute to inititation and progression of epithelial ovarian cancer

Shan and Liu: Cell Cycle 2009

Etiology of ovarian cancer: Historical aspects

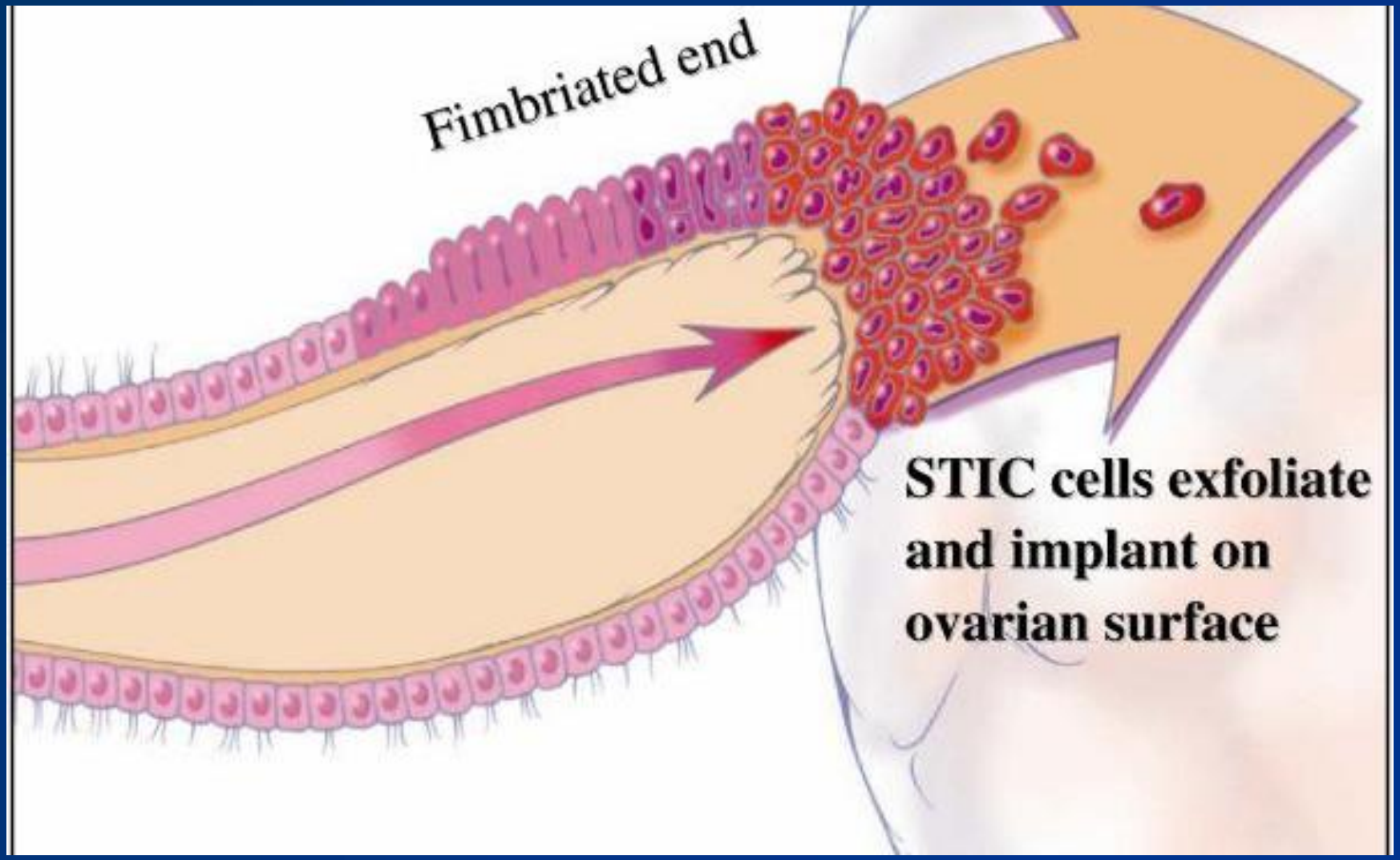
- Talc use
- History of endometriosis
- NSAID use
- History of PID
- Hysterectomy and tubal ligation protect

Wu et al: Int J Cancer 2009;124:1409;
Cramer: Obstet Gynecol 1999;94:160;
Merritt et al: Int J Cancer 2008;122:170

Infection, inflammation and carcinogenesis

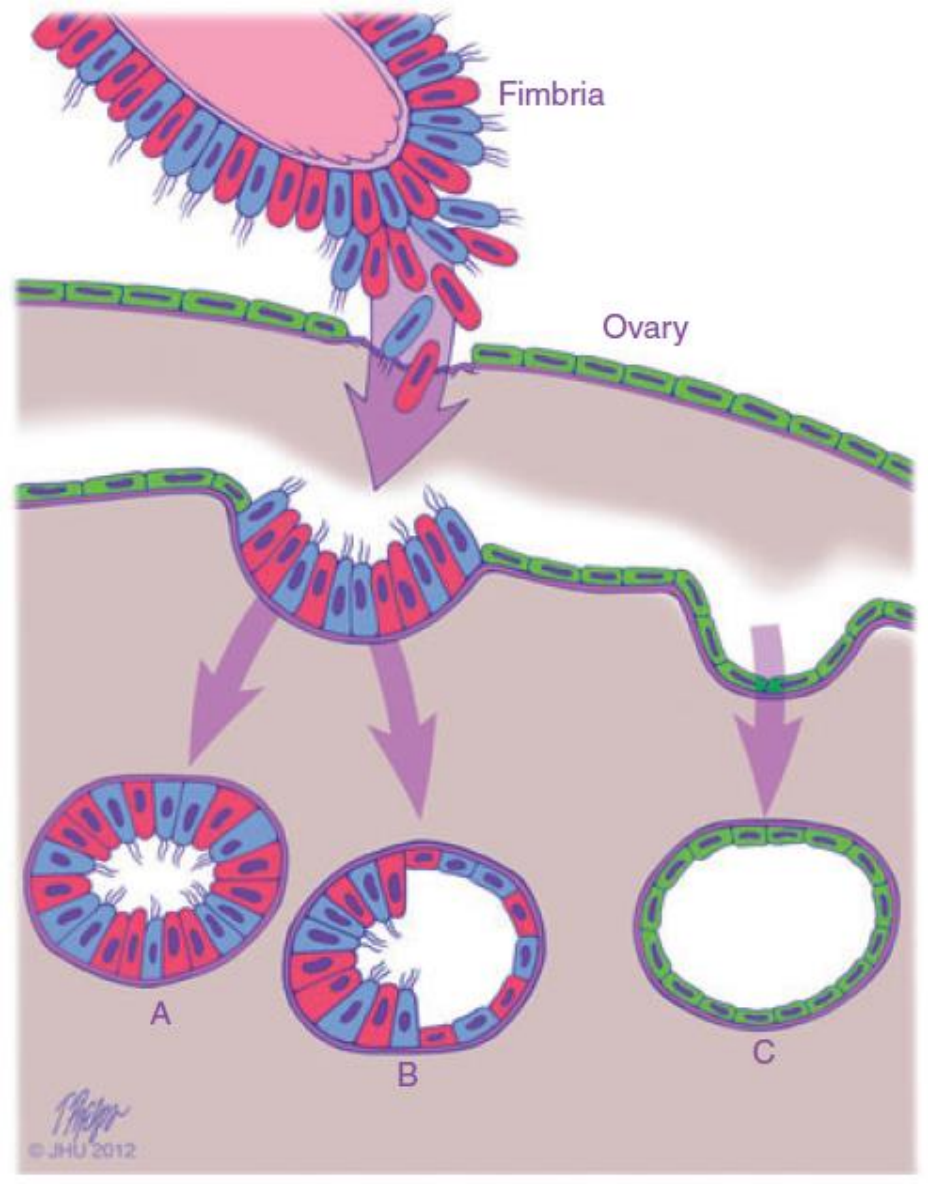
- Helicobacter pylori
- Human papillomavirus
- Hepatitis B virus
- Hepatitis C virus
- EBV

Spread of serous tubal intraepithelial carcinoma (STIC) from the fimbria to the ovarian surface



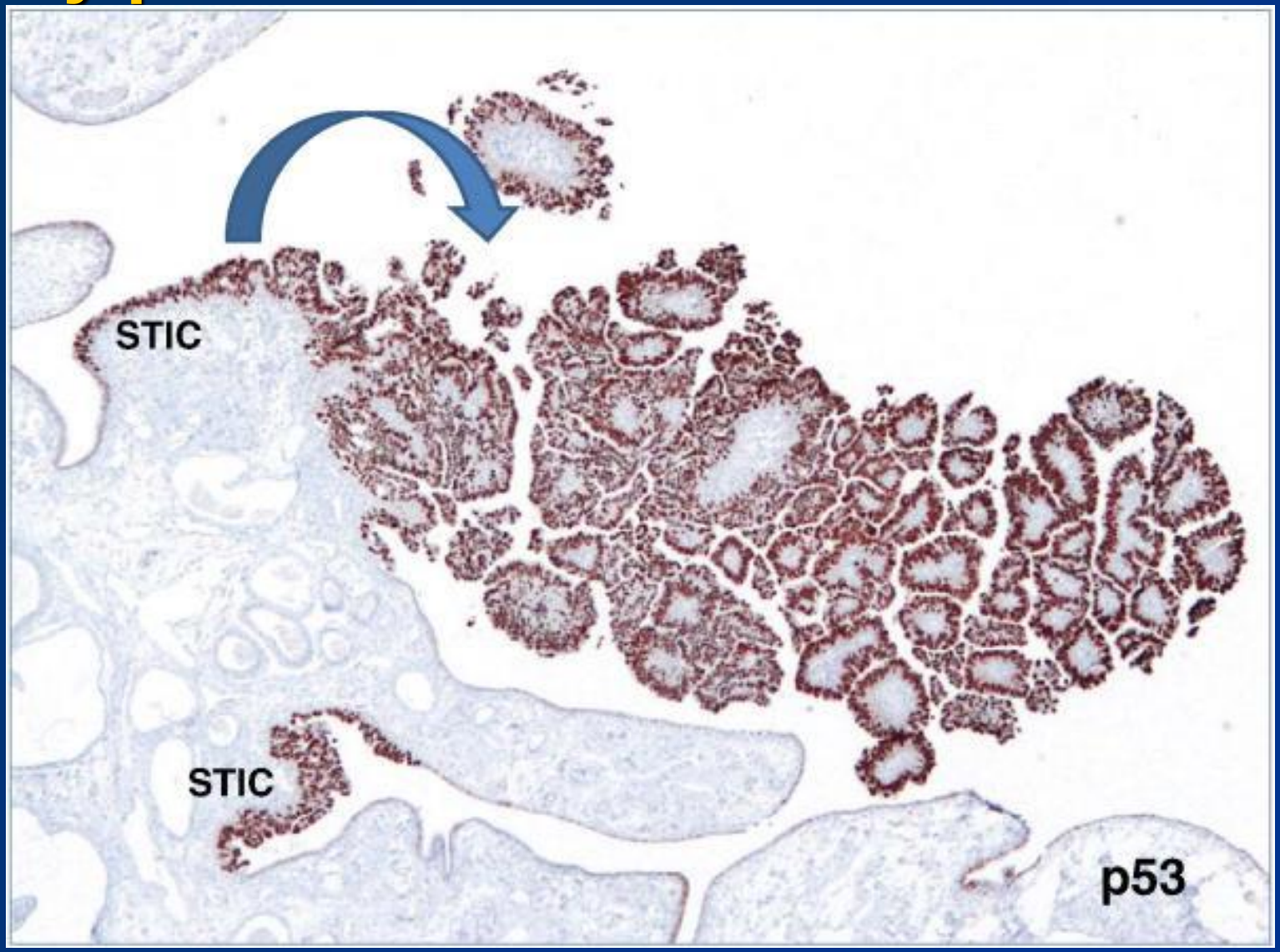
Kurman and Shih: Hum Pathol 2011;42:918

Development of a cortical inclusion cyst from tubal epithelium



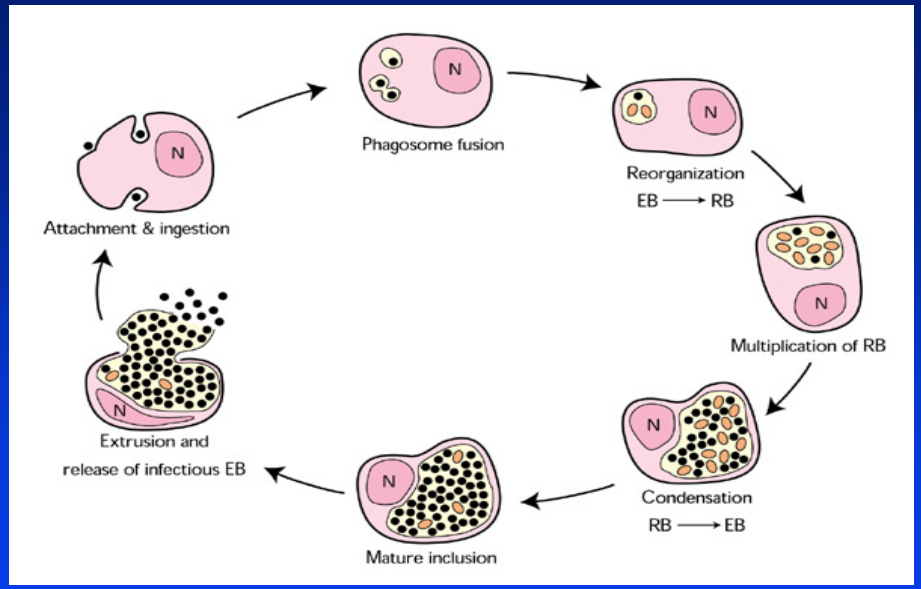
Kurman and Shih: Hum Pathol 2011;42:918; Am J Surg Pathol 2010;34:433

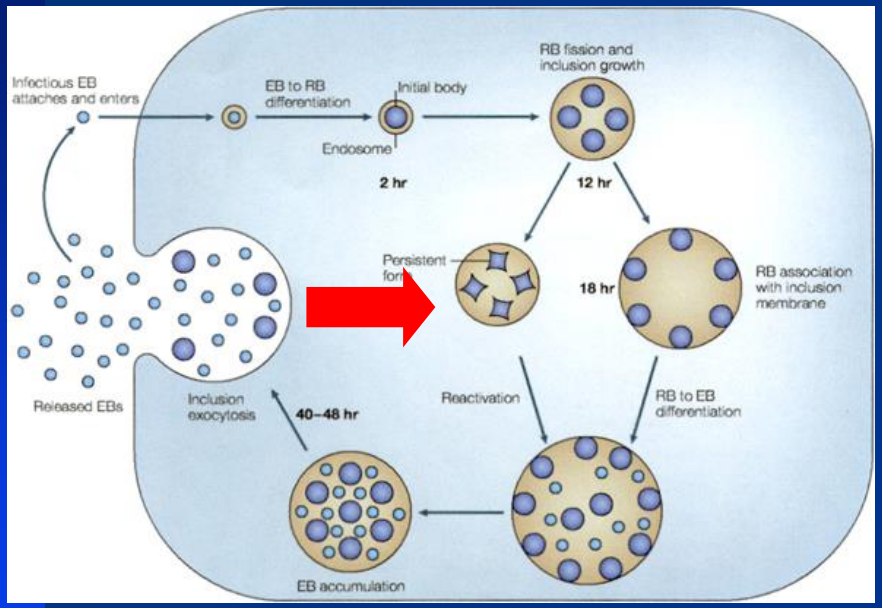
Fimbria with STIC and associated high-grade serous carcinoma demonstrated by p53 immunostain

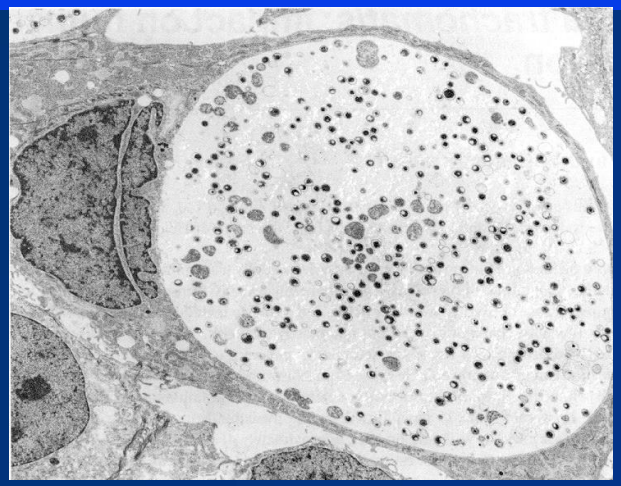


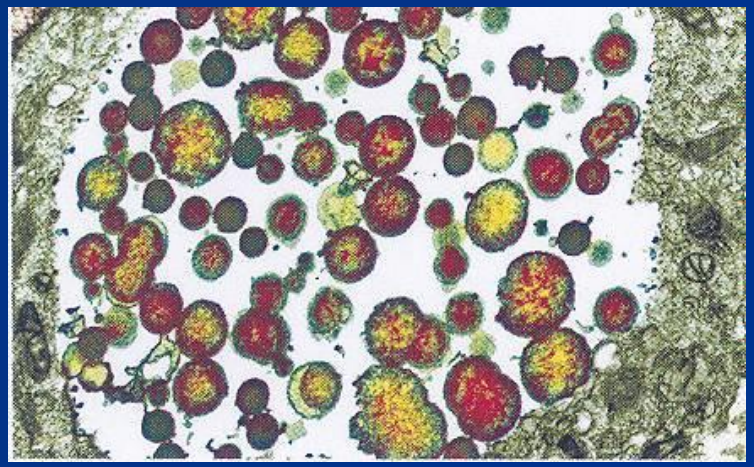
Kurman and Shih: Hum Pathol 2011;42:918

Chlamydia trachomatis-The Ultimate Intracellular Micro-organism



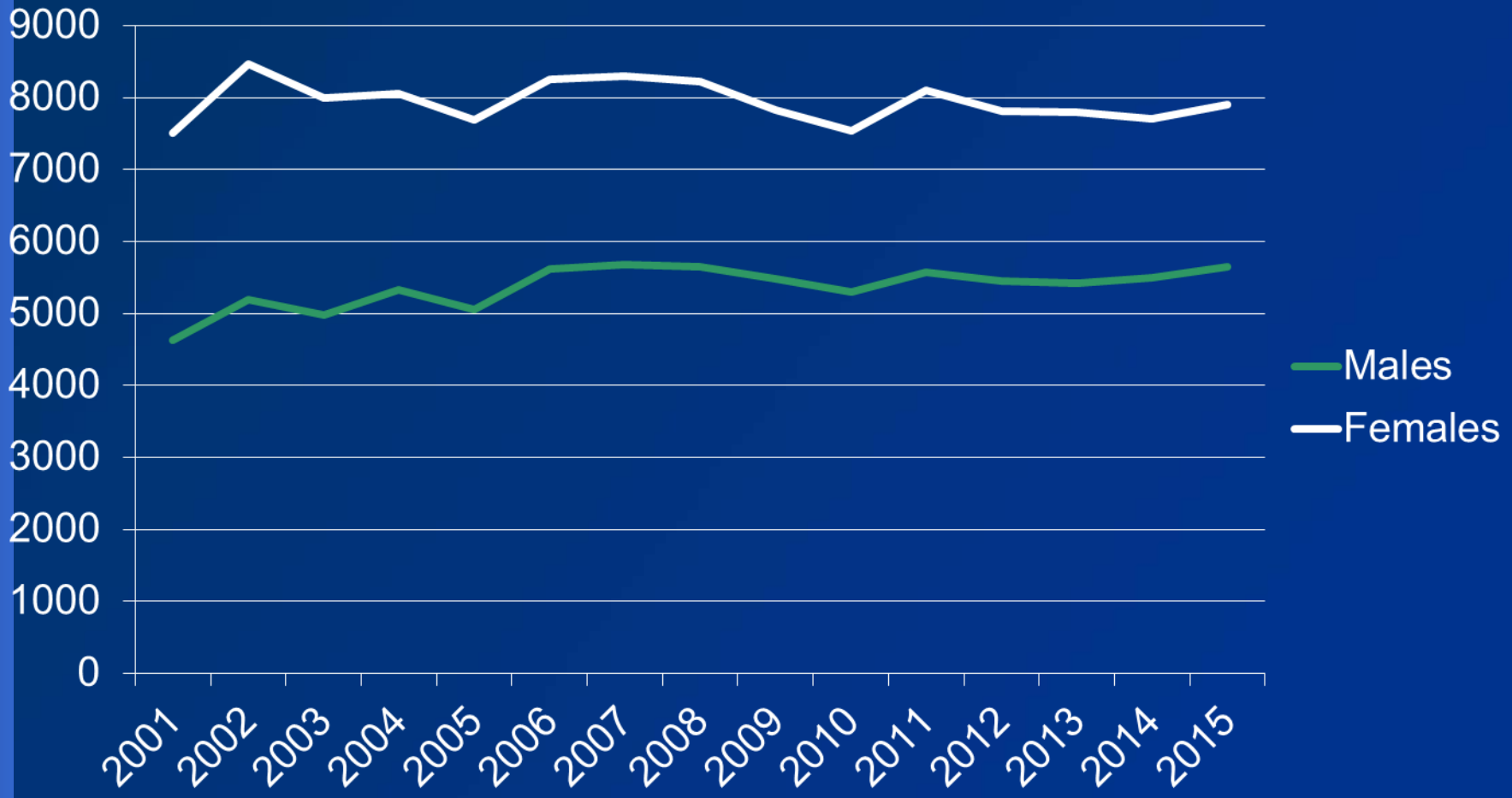






Brunham RC, Rey-Ladino: Nature Reviews 2005;5:149

Reported Chlamydia trachomatis infections in Finland 2001-2015



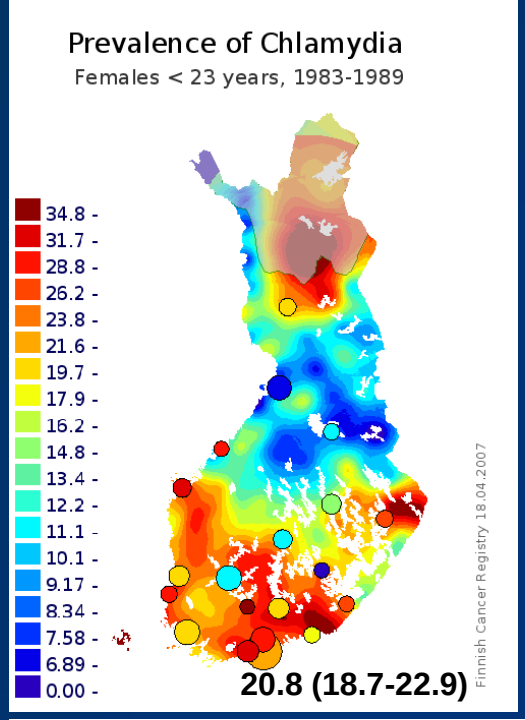
Hiltunen-Back E: THL 2015

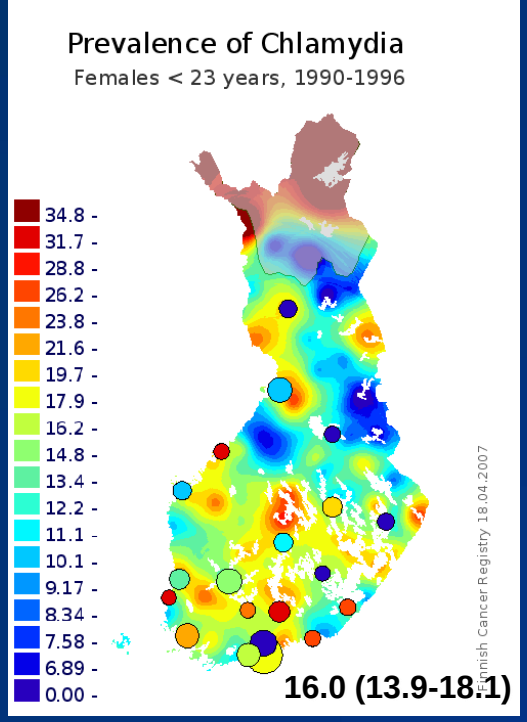
C.trachomatis seroprevalence atlas 1983-2003 of Finland

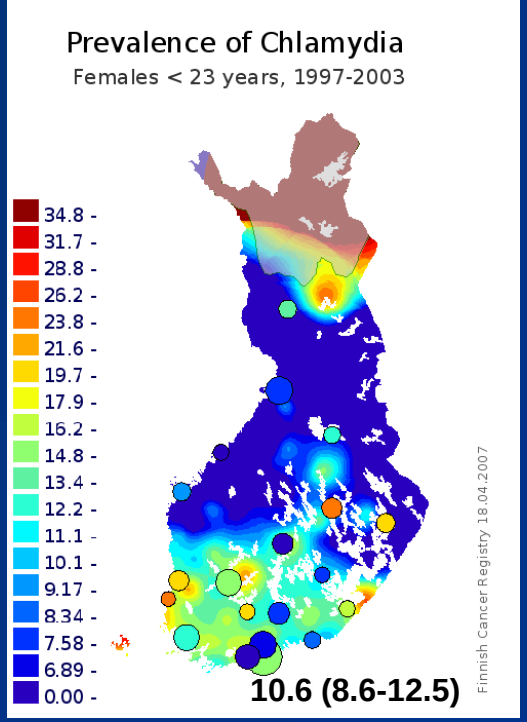
- Finnish Maternity Cohort serum bank (1983-2008)
  - Random sample
  - Serum IgG antibodies (MOMP peptide EIA)
  - Age categories
    - <23 years
    - 23-28 years
  - Seropositivity trends over time
  - Spatio-temporal maps developed

Lyytikäinen E, et al: Sex Transm Infect 2008;84:19

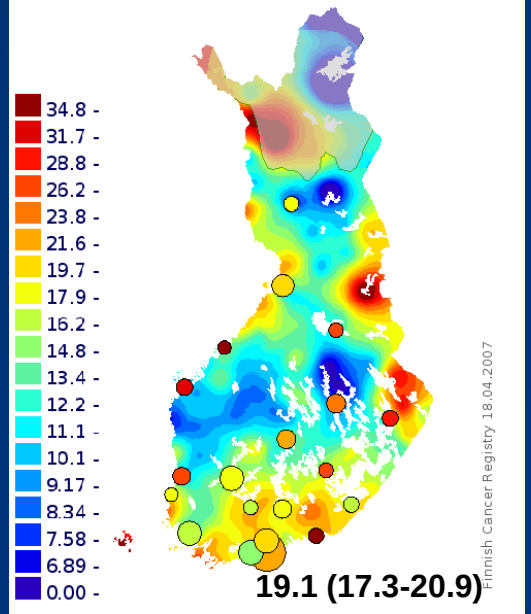
Age <23

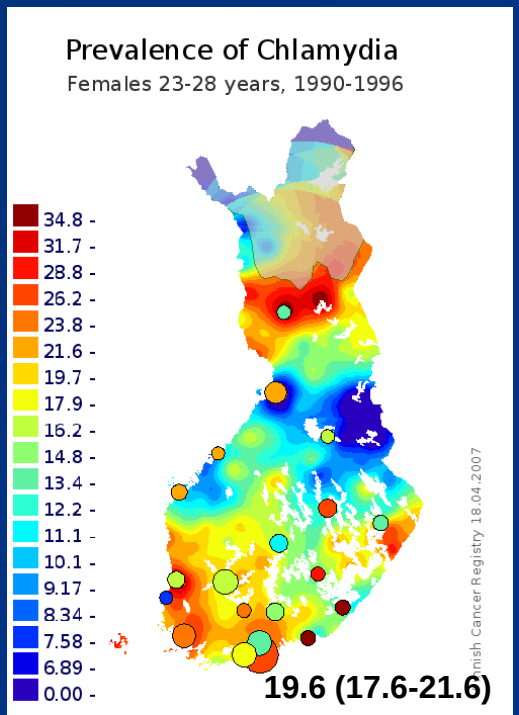


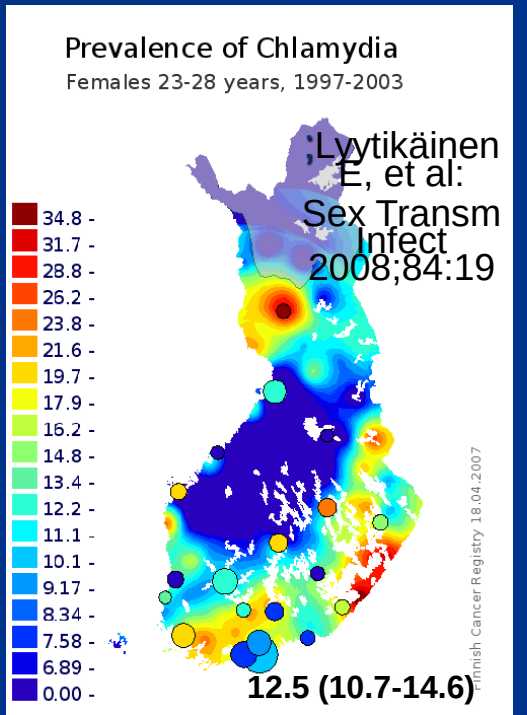




Age 23-28

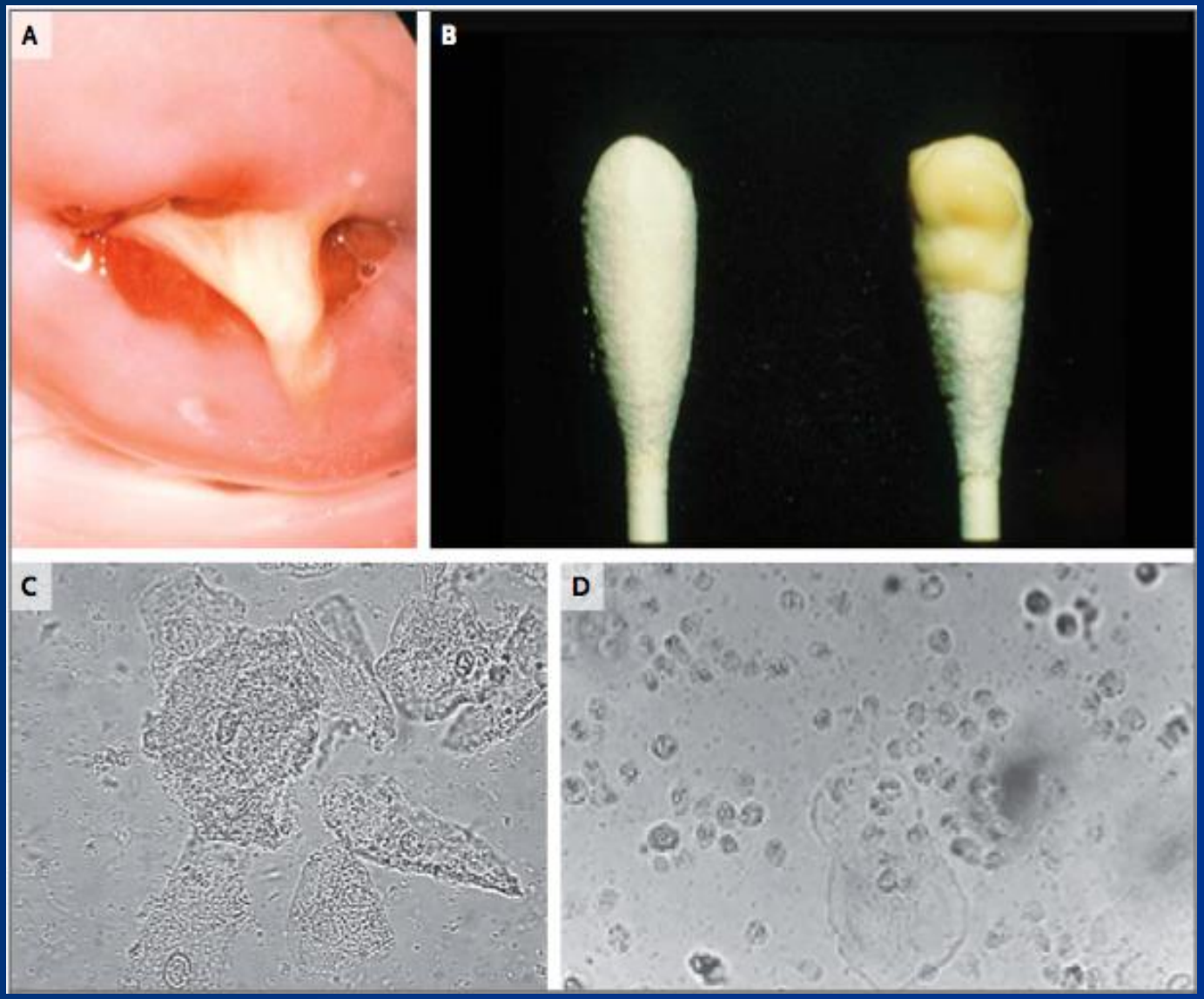






;Lyytikäinen E, et al: Sex Transm Infect 2008;84:19

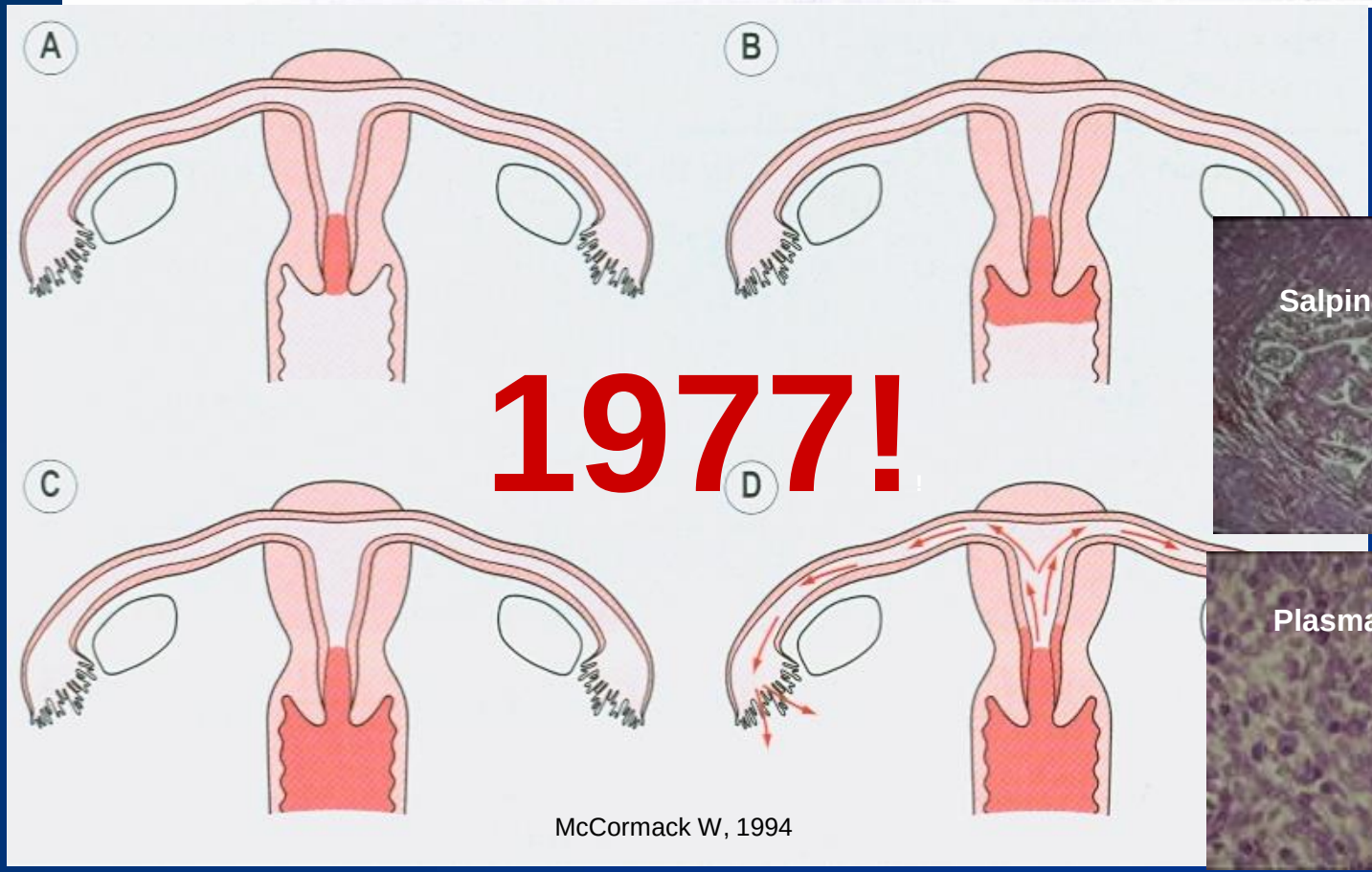
C.trachomatis causes mucopurulent cervicitis



CHLAMYDIA TRACHOMATIS INFECTION IN PATIENTS WITH ACUTE SALPINGITIS

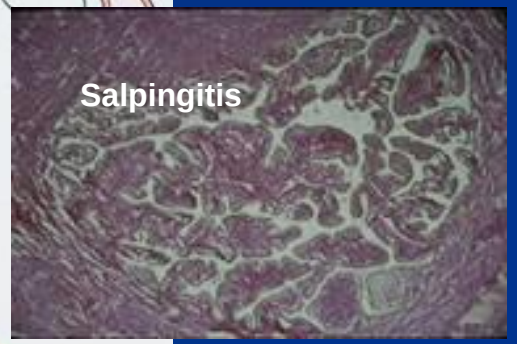
PER-ANDERS MÅRDH, M.D., TORVALD RIPA, M.D., LARS SVENSSON, M.D., AND LARS WESTRÖM, M.D.

Abstract We examined the prevalence of *Chlamydia trachomatis* in the cervix and the fallopian tubes of patients with acute salpingitis. Cycloheximide-treated McCoy cells were used as the growth medium. For purposes of comparison, women with infections confined to the lower genital tract and women without signs of genital infections were also studied. *C. trachomatis* was isolated from the cervix in 19 of 53 patients with acute salpingitis, in one of 18 lower-genital-tract infections and in none of 12 without signs of genital infection. *C. trachomatis* was recovered from six of the 20 valid specimens from the fallopian tubes of the patients with acute salpingitis. Our results indicate that chlamydia is a common etiologic agent in acute salpingitis. (N Engl J Med 296:1377-1379, 1977)



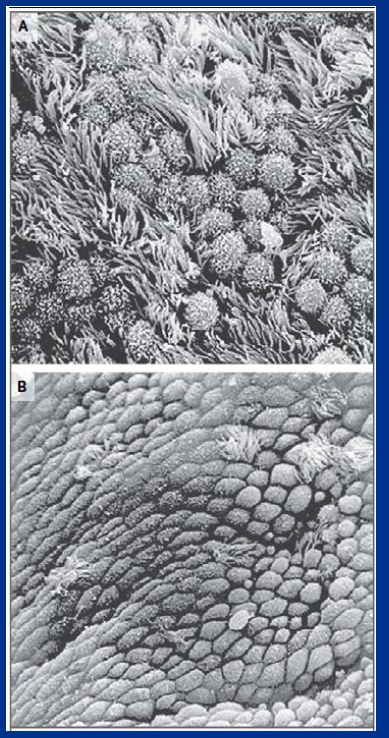
1977!

McCormack W, 1994



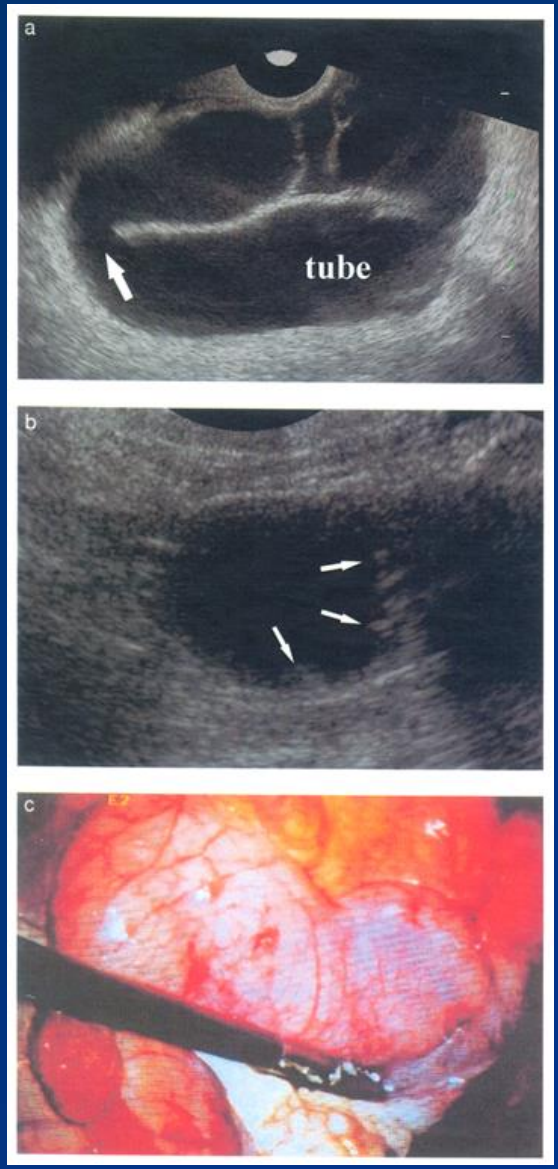
C.trachomatis and reproductive health

- C. trachomatis
  - Strikingly high rates
- Pelvic infection; PID
  - Decreasing rates in high income countries
- Tubal factor infertility (TFI)
  - PID attributable proportion of all infertility
  - Low income countries
- Adverse pregnancy outcome
  - Ectopic pregnancy



Brunham RC, et AL:
nejm 2015;372:21

Transvaginal sonographic findings of sactosalpinx and chronic salpingitis



Incomplete septa

”Beads-on-a-string” sign

Laparoscopy confirms sactosalpinx

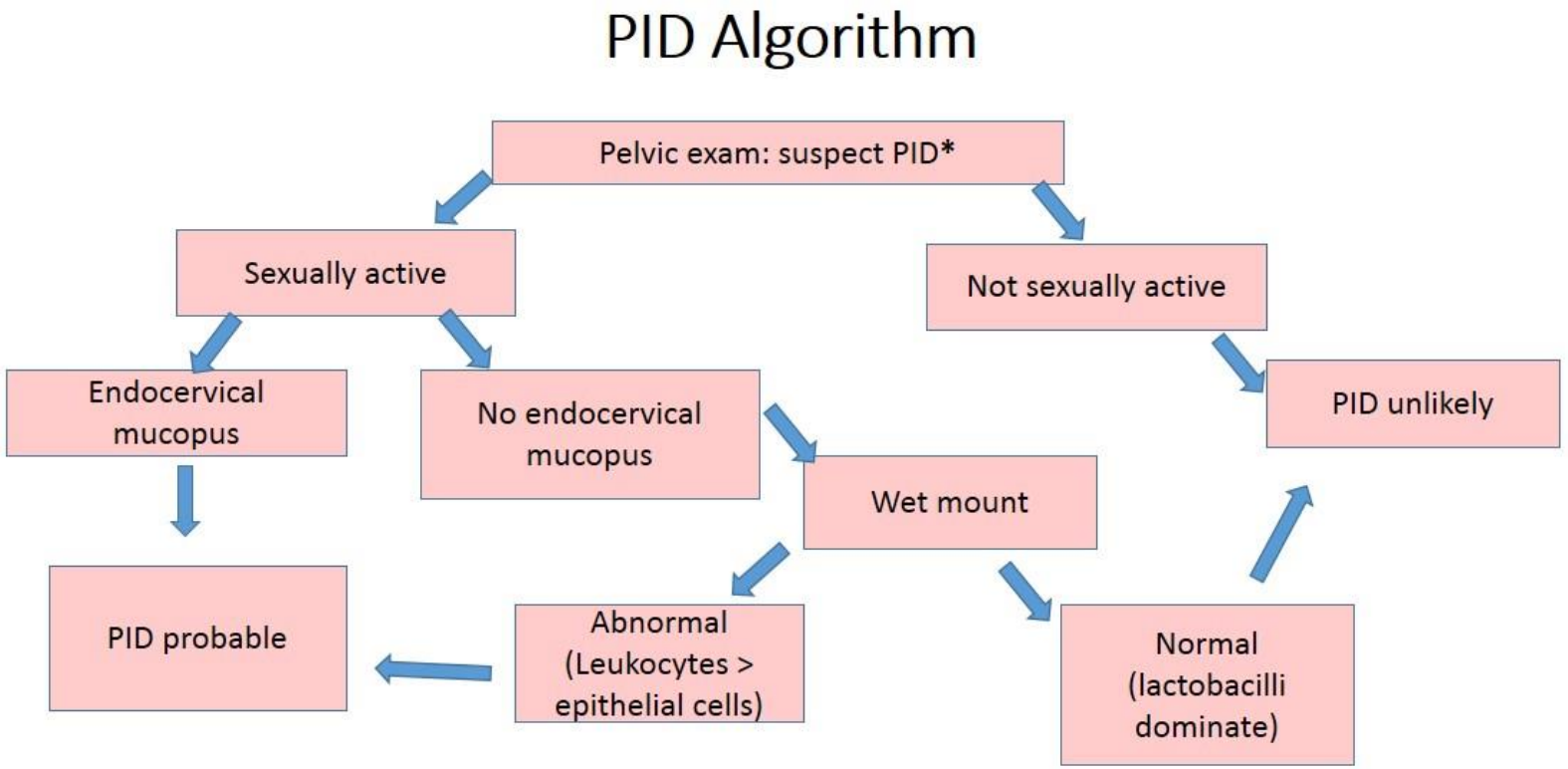
Molander P, et al: Ultrasound Obstet Gynecol 2001;17:233

Pretty Inadequate Diagnosis

P oorly
I nvestigated
D iagnosis

P hysician
I n
D istress

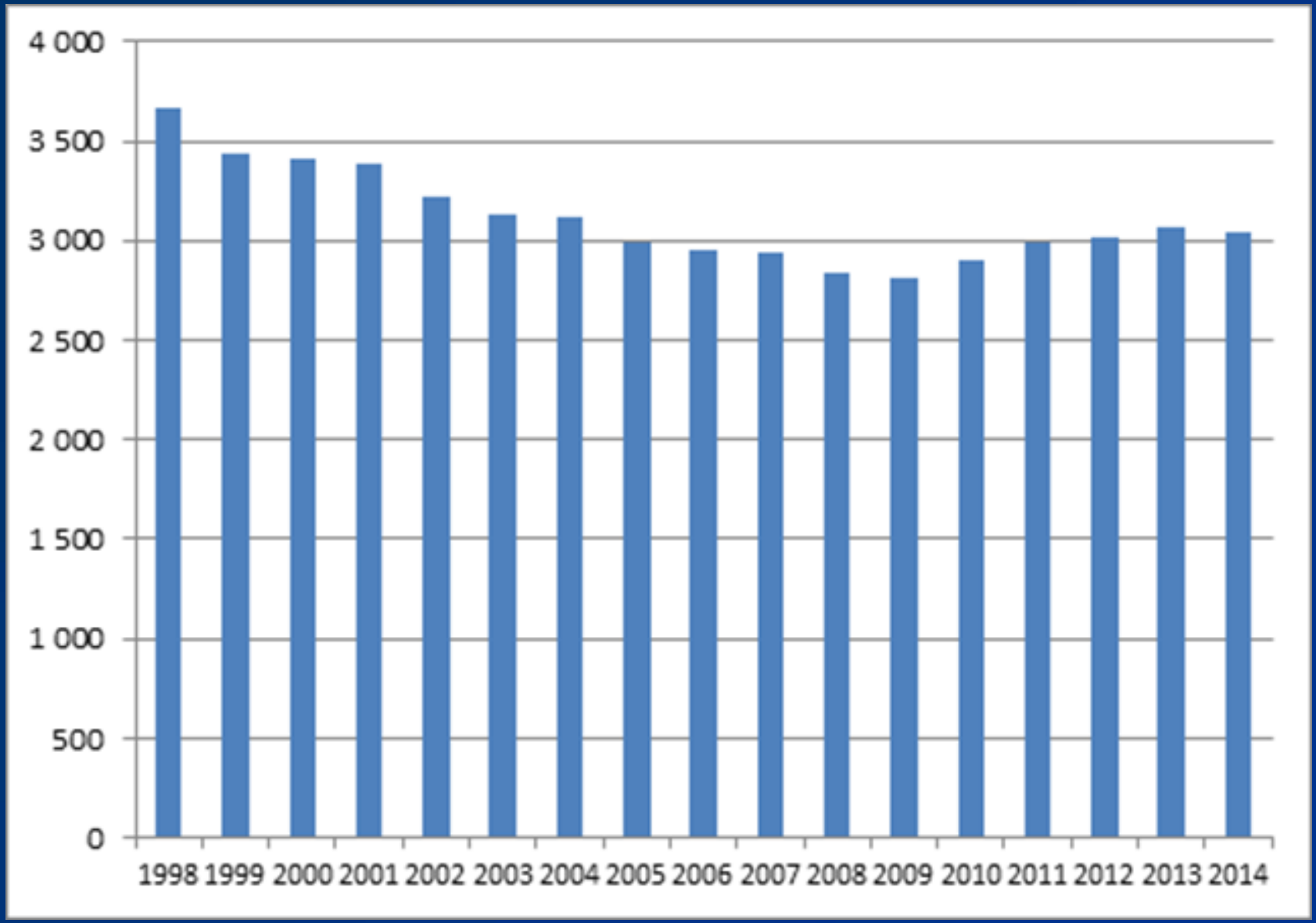
Clinical algorithm for the clinical diagnosis of PID



*Cervical motion tenderness, uterine tenderness or adnexal tenderness

Brunham RC, Gottlieb S, Paavonen J: NEJM 2015;372:21

PID rate in Finland 1998-2014



Gissler M: HDR, THL, Finland

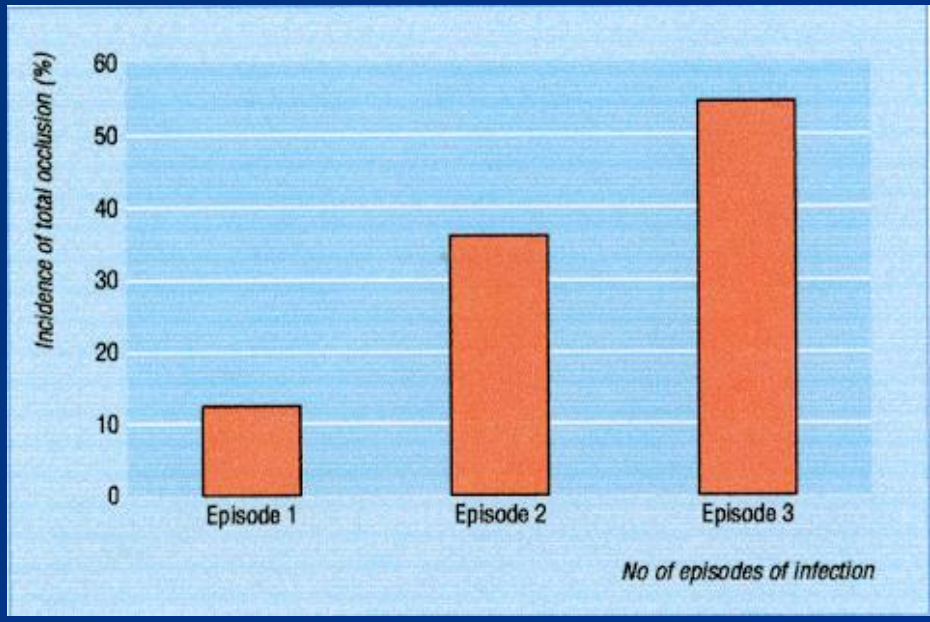
PID today: A retrospective study

- 392 women with PID, Department of Obstetrics and Gynecology, University Hospital, Helsinki
- 2015-2016
- 43 (11%) positive for C.trachomatis
- 3 (0.8%) positive for N.gonorrhoeae
- Young age and repeat C.trachomatis infection risk factors for chlamydial PID
- History of endometriosis a risk factor for severe PID, often requiring surgical intervention

Rantsi et al: Submitted for publicaiton

Reproductive morbidity following PID

	RR
Ectopic pregnancy	6x
Tubal factor infertility	14x
Chronic abdominal pain	10x
Risk for hysterectomy	8x



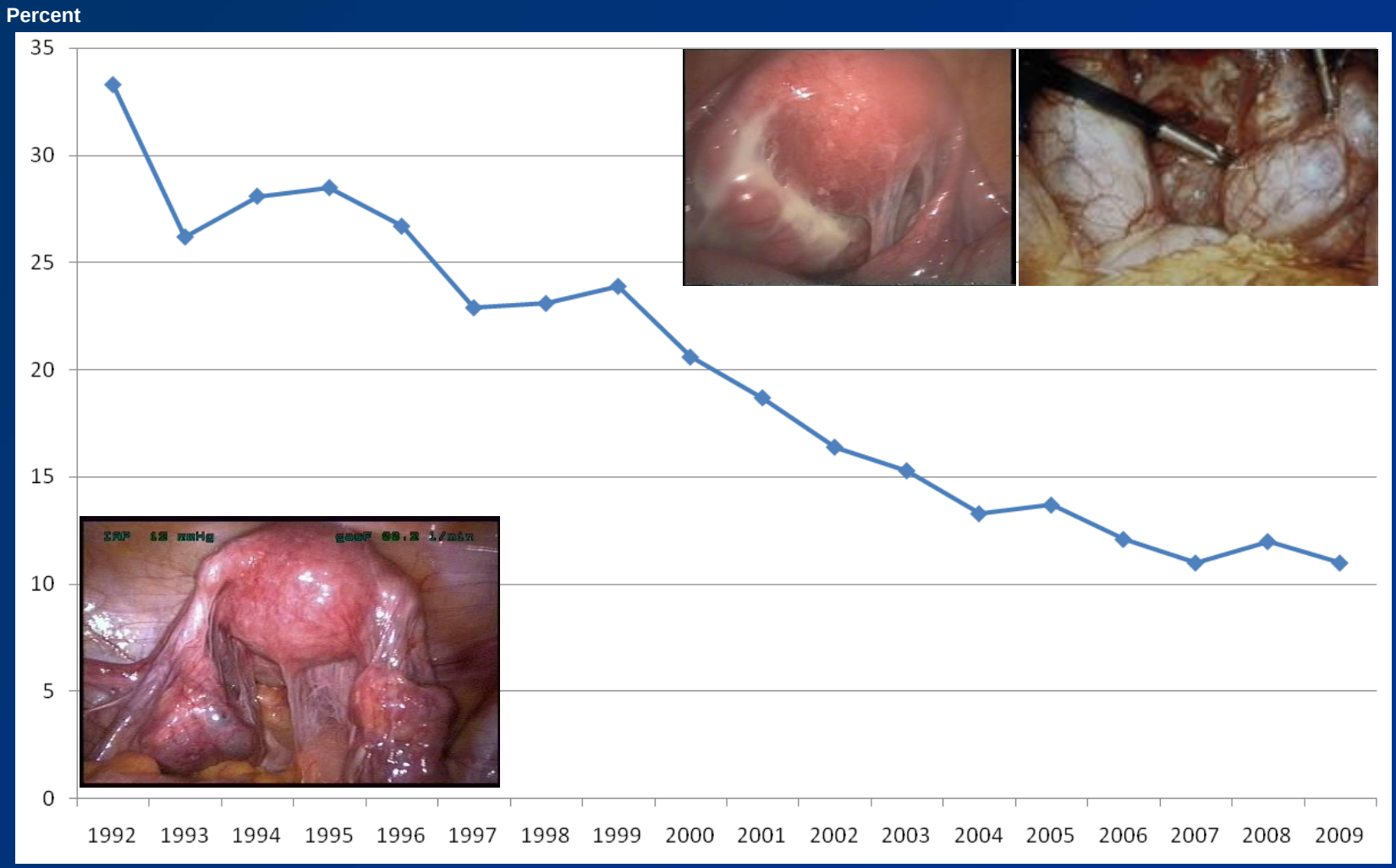
Weström L: Am J Obstet Gynecol 1980;138:880; Am J Obstet Gynecol 1975;121:707;
Paavonen J: Am J Obstet Gynecol 1980;138:957;Cates, Wasserheit: Am J Obstet Gynecol 1991;164:1771;
Weström L: Am J Obstet Gynecol 1975;121:707; Weström: Sex Transm Dis 1994;21:S32;
Buchan et al: Br J Obstet Gynecol 1993;100:558; RR=Relative risk

PID complication rates have been overestimated

- Previous estimates have been based on
  - Selected high risk populations
  - Case-control studies
  - Potential for major bias
- Revised estimates are based on population registry networks
  - Hospital discharge registries
  - General practice registries
  - Validity can be assessed
  - Less bias

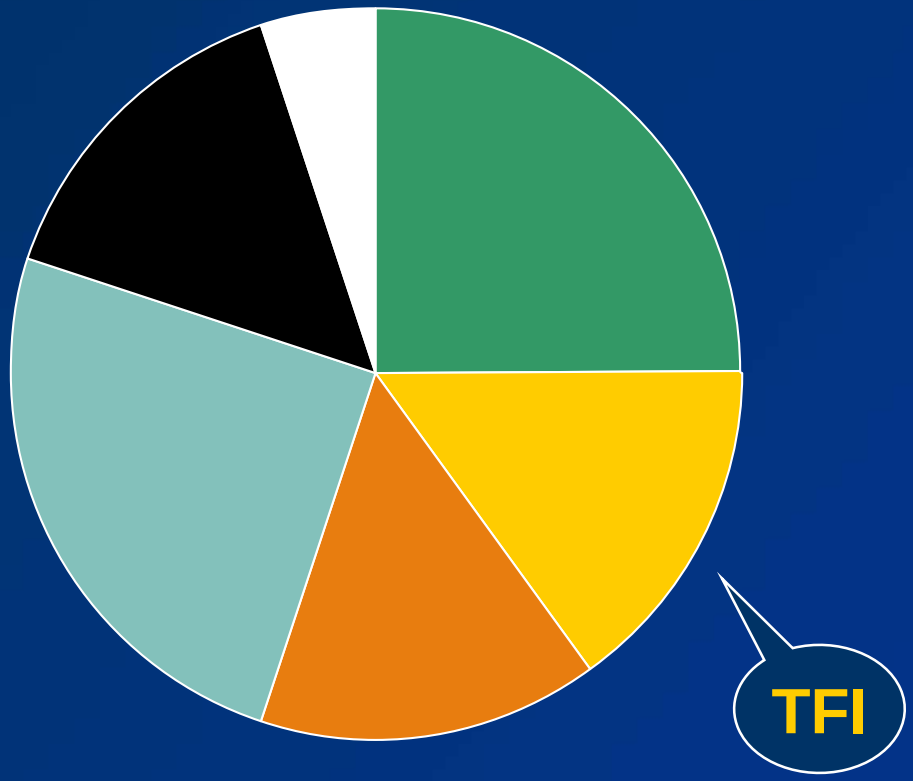
van Valkengoed IGM, et al: Int J Epidemiol 2004;33:416

Proportion of tubal factor infertility of all infertility 1992-2009



THL, 2011

Causes of subfertility: Infertility Clinic, University Hospital, Helsinki



Tiitinen A, unpublished

C.trachomatis and mutagenesis

- C.trachomatis induces double-strand breaks in host cells
- C.trachomatis inhibits repair of DNA breaks by interfering with protein phosphatase 2A signaling
- This may lead to mutagenesis and loss of cellular homeostasis

Mi et al: mBio 2018

Past chlamydial infection was not associated with fallopian tube carcinoma

- 79 cases with primary fallopian tube carcinoma 1985-2000
- Two controls per case
- IgG antibodies to C.trachomatis
  - No difference between cases and controls
- Conclusion: Chlamydial infection seems not to play role in the etiopathogenesis of fallopian tube carcinoma

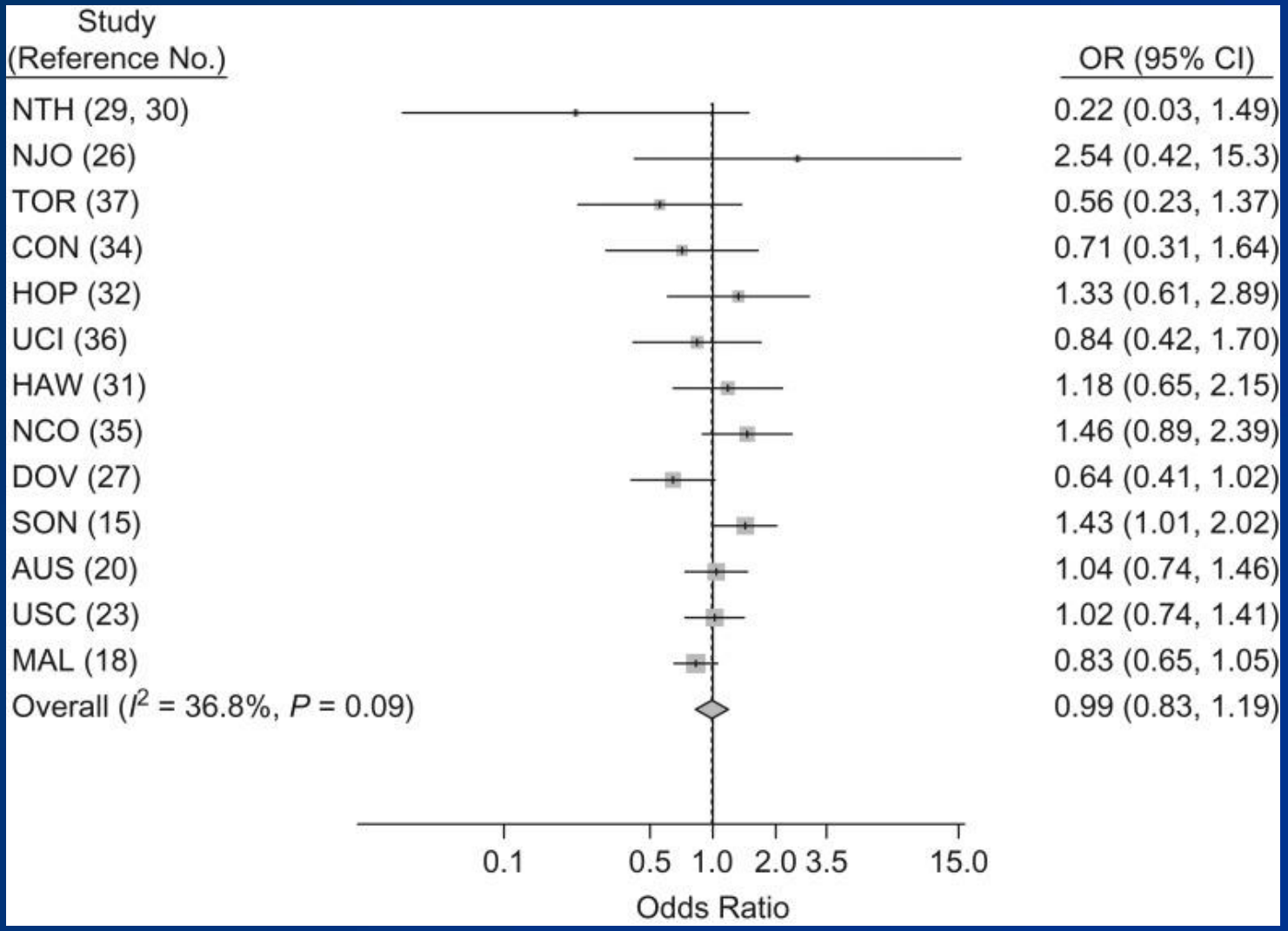
Riska et al: Eur J Cancer 2006;42:1835

C.trachomatis in relation to epithelial ovarian cancer

- C.trachomatis, M.genitalium, HPV, and polyomavirus not detectable in epithelial ovarian cancer tissue*
- Chlamydial HSP-1 IgG antibodies associated with type II ovarian cancer, and M.genitalium IgG antibodies associated with borderline ovarian tumors **
- C.trachomatis DNA in 8/48 (17%) women with invasive ovarian cancer ; overexpression of chlamydial HSP60 was higher in invasive compared with non-invasive ovarian tissue (58% vs. 28%)****
- Chlamydia plasmid-encoded Pgp3 associated with increased risk for ovarian cancer (OR 1.63; 95% CI 1.2-2.22) in 2 independent populations***

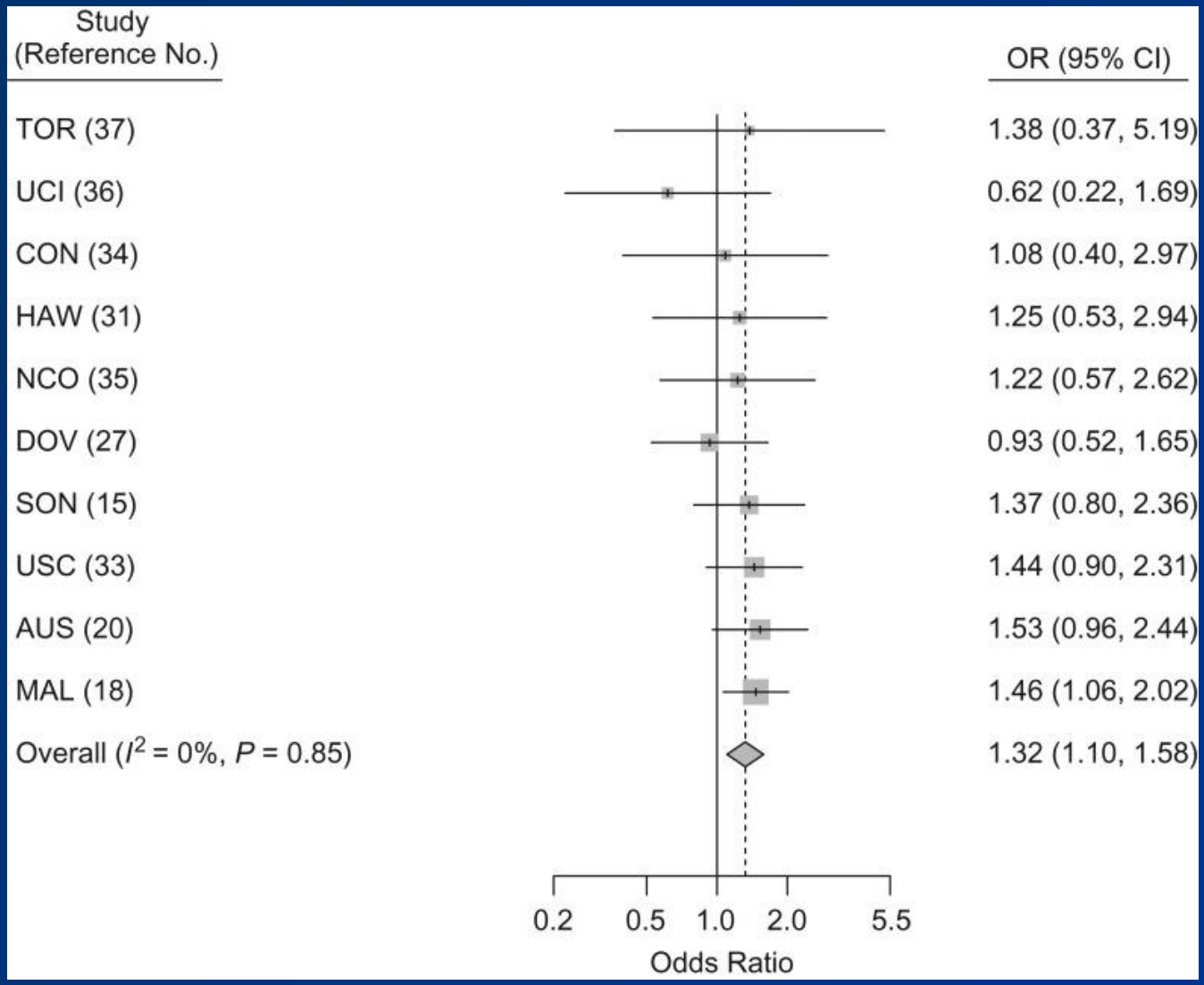
***Idahl et al: AJOG 2010; **Idahl et al: Infect Dis Obstet Gynecol 2011; ***Trabert et al: JNCI 2019; ****Jonsson et al: Translational Oncol 2018**

Association between PID and the risk of ovarian cancer: 13 case-control studies 1989-2009



Rasmussen et al: Am J Epidemiol 2016

Association between PID and the risk of borderline ovarian tumors: 13 case-control studies 1989-2009



Rasmussen et al: Am J Epidemiol 2016

Risk of ovarian cancer in women with PID: A population-based study

- Asian women aged 13-65
- Health registries
- 67,936 women with PID; 135,872 controls
- 3 year follow-up
- 90 cases with ovarian cancer
- Adjusted hazard ratio 1.92 (95% CI 1.27-2.92) in women with PID vs. controls
  - Number of PID episodes
  - Age <35 years

Lin et al: Lancet Oncol 2011;12:900

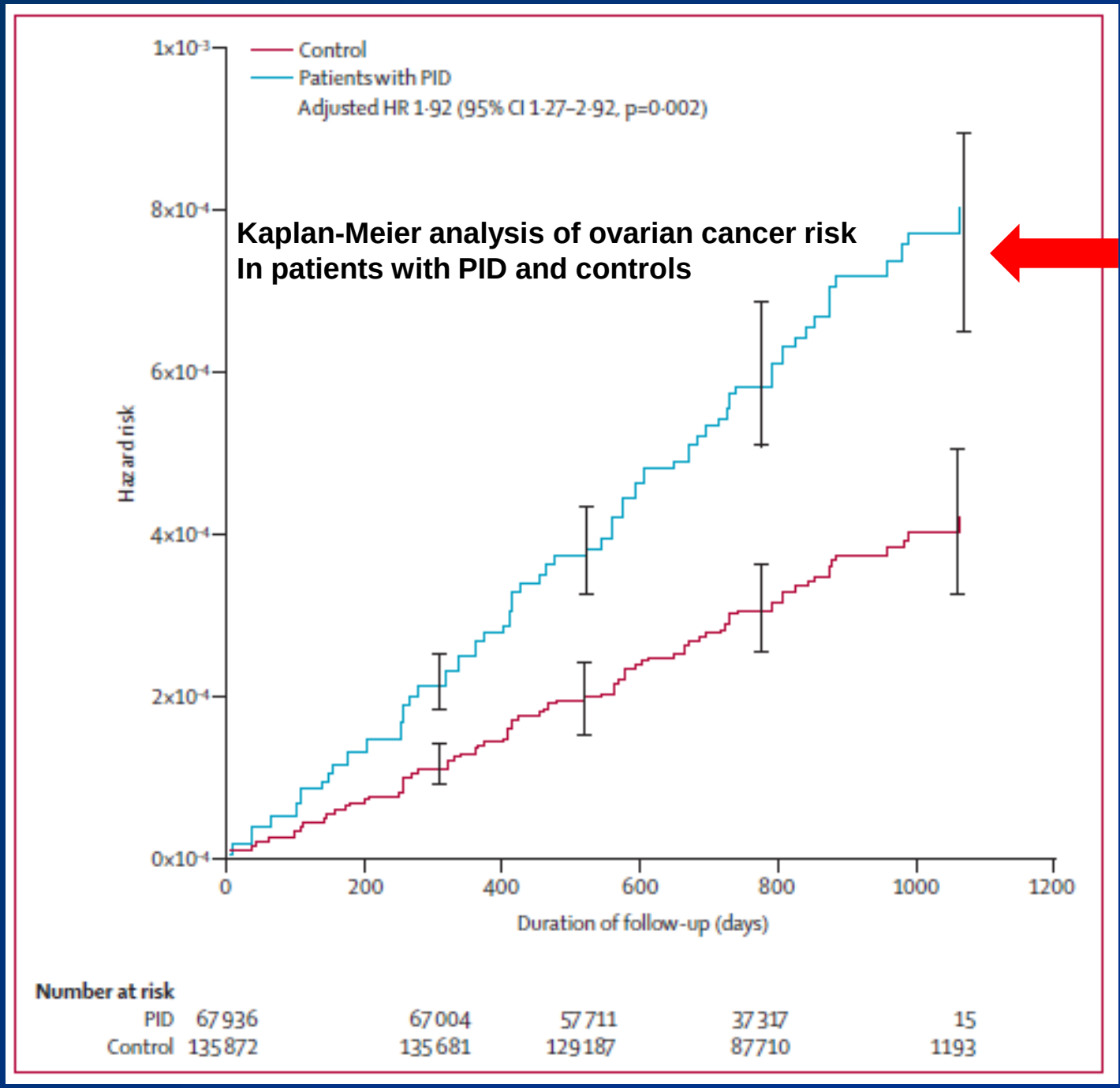
Risk of ovarian cancer in women with PID: A population-based study

	Patients with PID (n=67 936)	Controls (n=135 872)
Number of patients with ovarian cancer*	42	48
Incidence per 10 000 person-years	2·78	1·44
Crude HR (95% CI)	1·93 (1·27–2·91)	1·00
Adjusted HR† (95% CI)	1·92 (1·27–2·92)	1·00

PID=pelvic inflammatory disease. HR=hazard ratio. *Within 3 years of follow-up. †Adjusted for age, monthly income, degree of urbanisation, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and endometriosis.

Table 2: Incidence and crude and adjusted risks of ovarian cancer

Lin et al: Lancet Oncol 2011;12:900



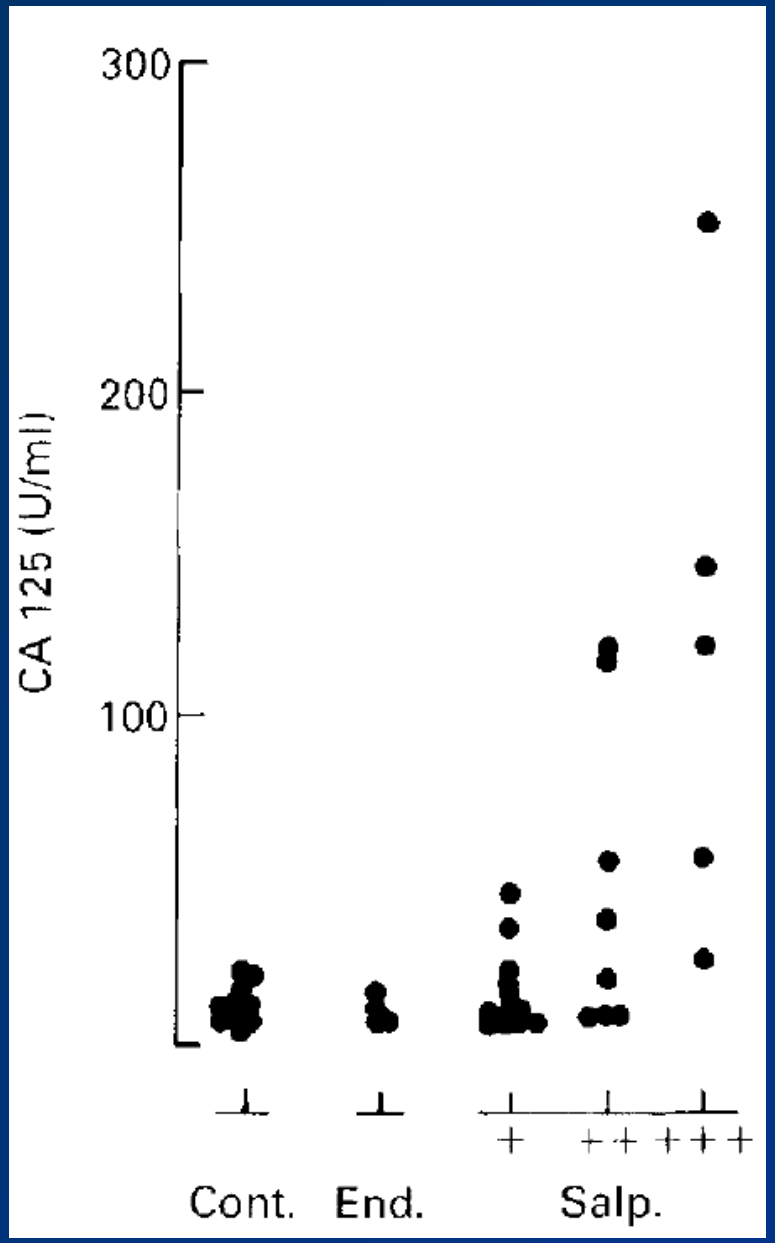
Lin et al: Lancet Oncol 2011;12:900

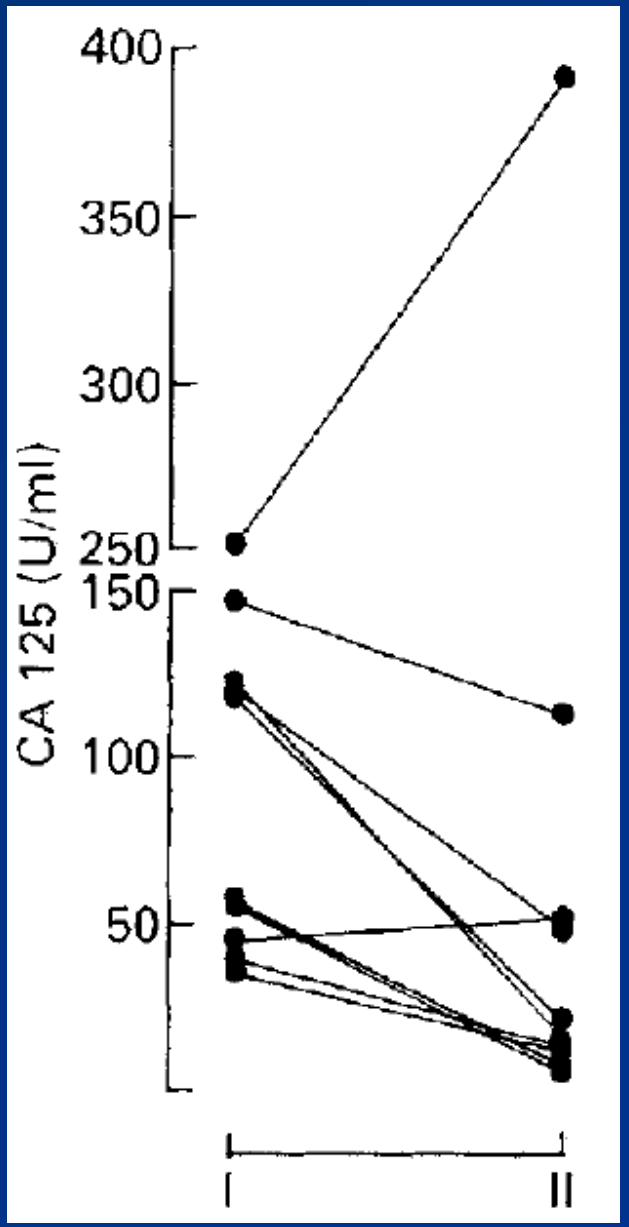
Research gap

- Need of a noninvasive biomarker
  - Identify women with UGT infection at risk for chronic disease
  - Identify proteins specific for UGT tissue
  - Identify host markers of increased susceptibility to ovarian cancer
  - Identify an optimal biomarker combination

UGT=Upper genital tract

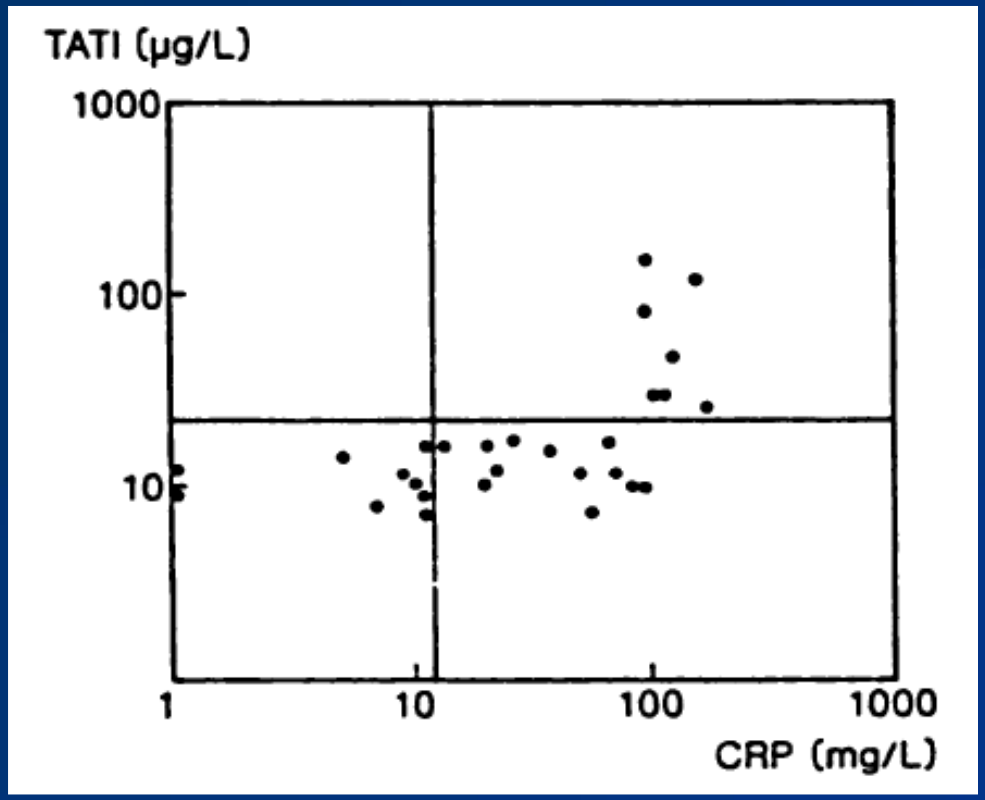
CA125 in pelvic inflammatory disease

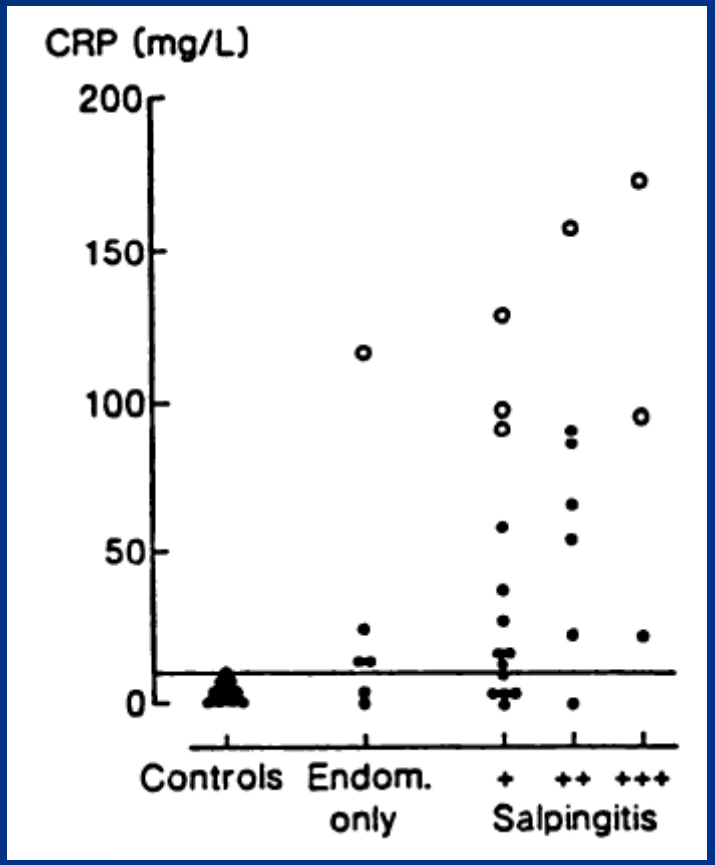




Paavonen et al: BJOG 1989

TATI in pelvic inflammatory disease





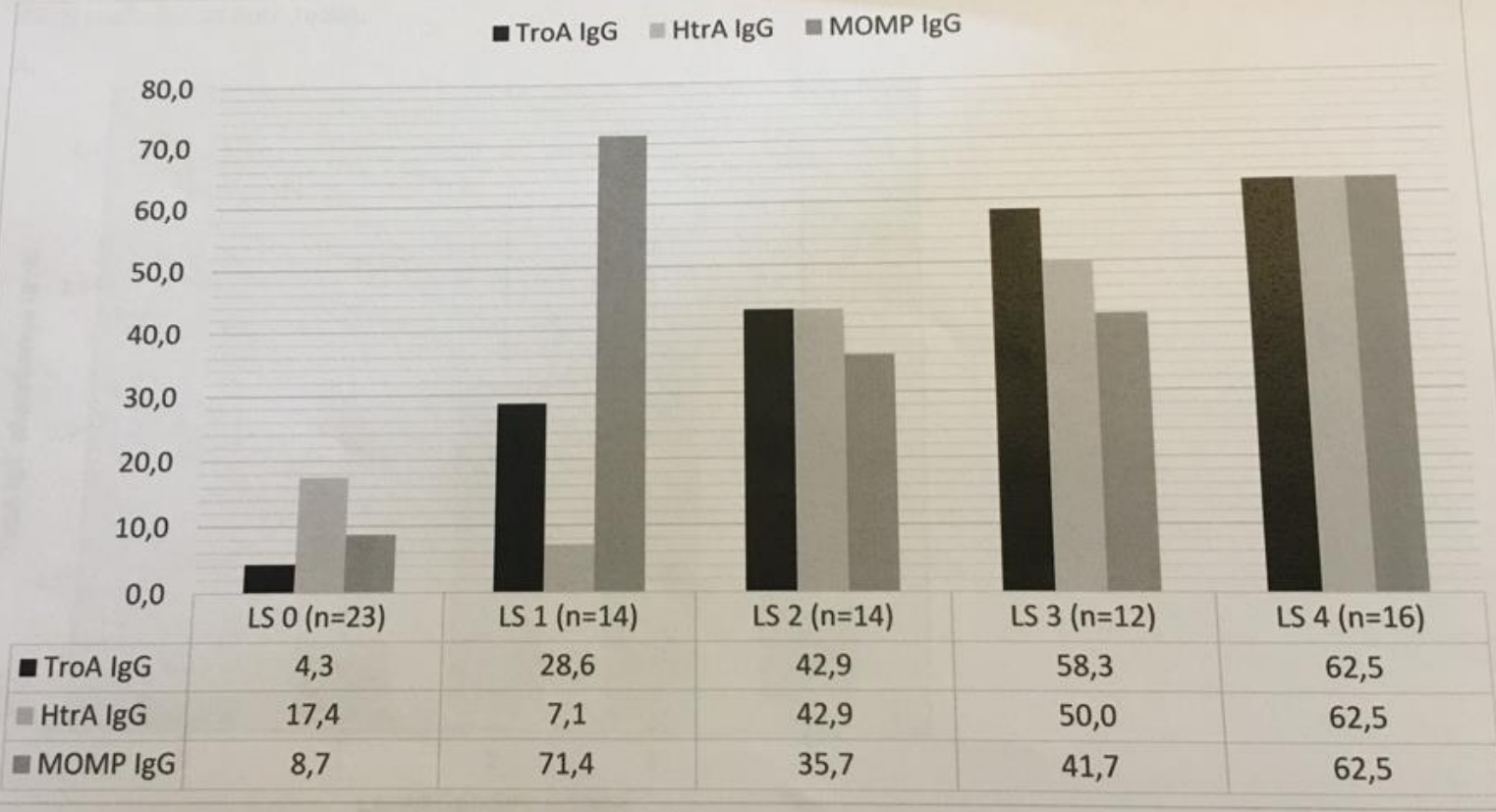
TATI=Tumor-associated trypsin inhibitor; Paavonen et al: Clin Chem 1989

C.trachomatis TroA, HtrA, MOMP IgG in TFI cases and controls

	TFI	Controls	p-value
	N=28	N=51	
▪TroA	17 (61%)	11 (21%)	.001
▪HtrA	16 (57%)	11 (21%)	.001
▪MOMP	15 (54%)	17 (33%)	.08

TFI=Tubal factor infertility; TroA and HtrA areproteins expressed during persistent infection; new biomarkers of chronic or persistent infection; MOMP=Major outer membrane protein
Rantsi et al: Micro-organisms (in press)

C.trachomatis TroA, HtrA, MOMP antibodies by the severity of TFI

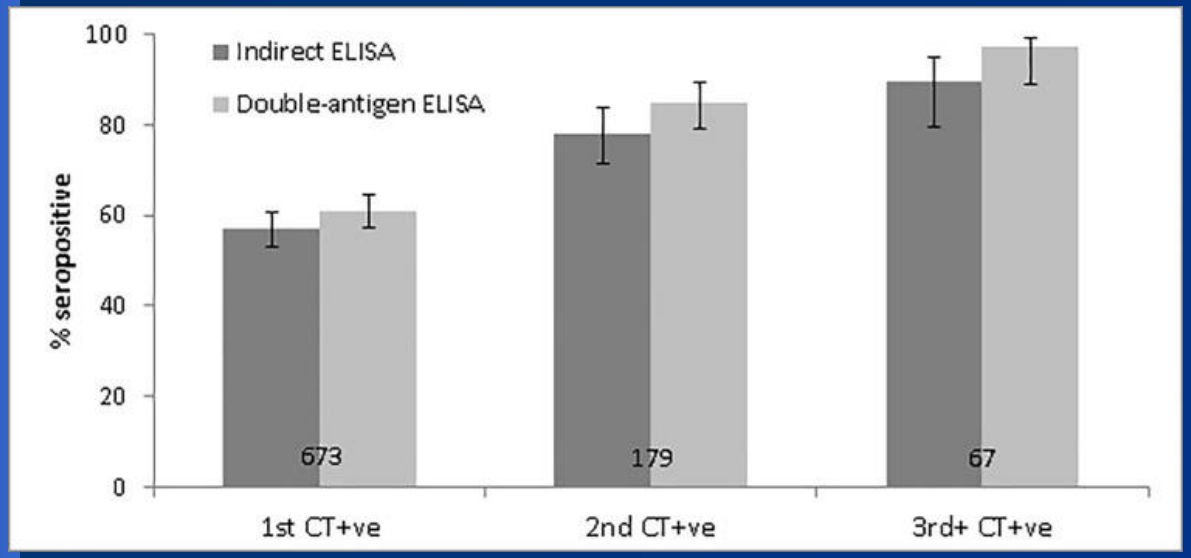


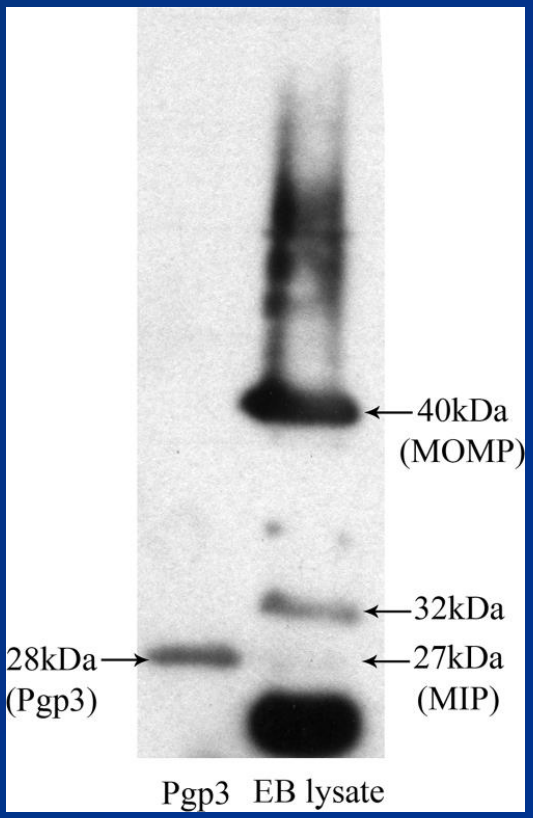
	LS 0 (n=23)	LS 1 (n=14)	LS 2 (n=14)	LS 3 (n=12)	LS 4 (n=16)
TroA IgG	4,3	28,6	42,9	58,3	62,5
HtrA IgG	17,4	7,1	42,9	50,0	62,5
MOMP IgG	8,7	71,4	35,7	41,7	62,5

TFI=Tubal factor infertility; TroA and HtrA are proteins expressed during persistent infection; MOMP=Major outer membrane protein
Rantsi et al: In press; LS=Laparoscopy score

Pgp3: a plasmid-encoded C.trachomatis specific protein

- Correlates with time since infection and number of episodes





Wills GS, et al: Clin Vacc Immunol 2009;
Blomquist PB, et al: PLOS One 2018

Vaccine against C.trachomatis

- Natural infection can induce partial immunity of short duration
  - Host immune response contributes to adverse sequelae
- Identification of vaccine target antigens is not easy
  - Single antigen or antigen cocktail?
- Vaccine against
  - Any infection?
  - PID?
  - TFI?

Hafner LM, et al: Vaccine 2013; in press; Brunham RC, Rappuoli R: Vaccine 2011;31:1892; Paavonen J: Ann Med 2012;44:18

C.trachomatis, PID, and ovarian cancer: Summary and conclusions

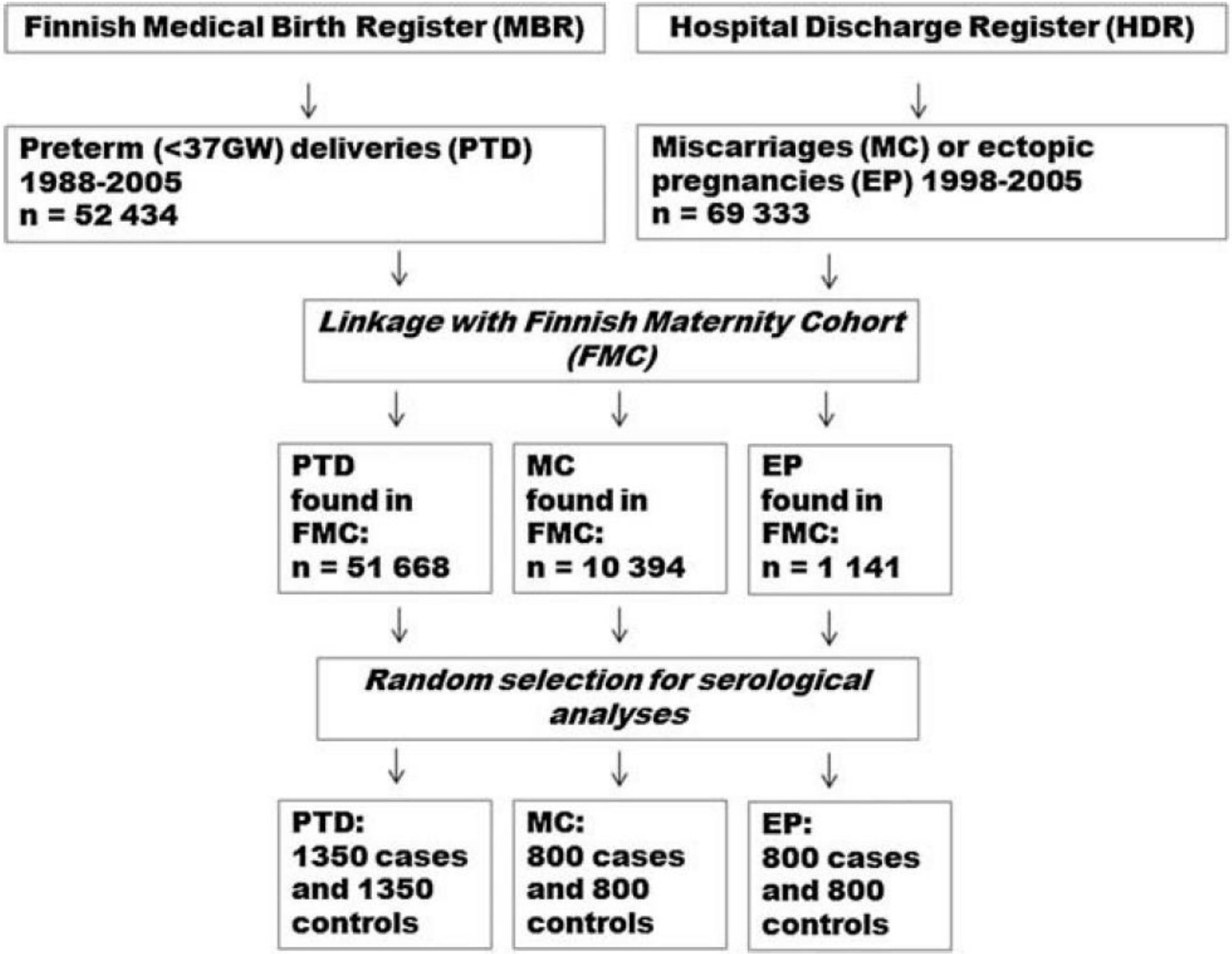
- Many epidemiologic and clinical research findings support the link
  - The link is relatively weak
- The exact pathogenetic mechanism is not known
  - Shifting the paradigm: The role of inflammation
  - Host immune response to C.trachomatis plays an important role
- PID as a potential marker for ovarian cancer risk
- Prevention of C.trachomatis infection may play a role in the prevention of epithelial ovarian cancer
  - Potential role of C.trachomatis vaccine
- Research gap: biomarker with high performance

Acknowledgements

Rantsi T, et al: PhD party Jan 2019, Helsinki:
Surcel H-M, Tiitinen A,Joki-Korpela P, Öhman H, Wikström H

Puolakkainen, M

Rantsi, T



PTD=Preterm delivery; MC=Miscarriage; EP=Ectopic pregnancy; Rantsi T, et al: Sex Transm Infect 2016;43:382

Population based study: Relative risk of ectopic pregnancy (EP) in women with C.trachomatis antibodies

Age at EP dg.	Cases N	Cases Seropos n (%)	Controls N	Controls Seropos n (%)	Crude OR (95% CI)	Adj.* OR (95% CI)
<20	14	1 (7)	14	2 (14)	0.5 (0.1-5.5)	
20-34	221	63 (30)	221	30 (14)	2.7 (1.6-4.4)	
≥35	75	24 (32)	75	13 (17)	2.0 (1.0-4.0)	
Total	**300**	**88 (29)**	**300**	**45 (15)**	**2.3 (1.5-3.5)**	**2.3 (1.5-3.5)**

*Adjusted for age at EP diagnosis; EP=Ectopic pregnancy

Rantsi T, et al: Sex Transm Infect 2016;43:382