UROPATHOGENS AND SUSCEPTIBILITY IN WOMEN WITH UNCOMPLICATED UTI IN PRIMARY CARE

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UROPATHOGENS AND SUSCEPTIBILITY IN WOMEN WITH UNCOMPLICATED UTI IN PRIMARY CARE

BAPCOC
Belgian Antibiotic Policy Coordination Committee

Uropathogen distribution and antimicrobial susceptibility in women with uncomplicated cystitis in Belgium, a high antibiotics prescribing country:

20 year surveillance

Heytens Stefan, De Sutter An, Christiaens Thierry,
Boelens Jerina, Claeys Geert,

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Three of a kind:

- **Wich bacteria are found** in Belgian women with uncomplicated urinary tract infections in primary health care, and what is their susceptibility pattern anno 95-96?

  Christiaens T, Heytens S, Verschraegen G, De Meyere M, De Maeseneer J. **Acta Clinica Belgica** 1998.

- **Evolution of bacterial susceptibility pattern of *E. coli*** in uncomplicated urinary tract infections in a country with high antibiotic consumption : a comparison of two surveys with a 10 year interval. (2005-2006)

  De Backer D, Christiaens T, Heytens S, De Sutter A, Stobberingh E, Verschraegen G. **Journal of Antimicrobial Chemotherapy** 2008; 62, 364-368.

- **Uropathogen distribution and antimicrobial susceptibility** in uncomplicated cystitis in Belgium, a high antibiotics prescribing country: 20 years surveillance. (2014 -2015)

  European journal of clinical microbiology and infectious diseases 2016

1995 - 2005 - 2015

UROPATHOGENS AND SUSCEPTIBILITY IN WOMEN WITH CYSTITIS AND PREVALENCE OF ESBL PRODUCING BACTERIA IN PRIMARY CARE. (2014 -2015)

STUDY DESIGN

In- / exclusion criteria

INCLUSION

- Adult non pregnant women with dysuria or urinary frequency or urgency

EXCLUSION

- Signs of complicated UTI
- Symptoms > 7 days
- Temp > 38°C
- Prominent gynaecologic complaints
- Known nephrologic or urologic problems
- Diabetes
- Immunocompromizing condition (leukemia, immunosuppressants)
- Frequent episodes of UTI (> 3/year of > 2 in last 6 months)

In- / exclusion criteria

1) 1995
2) 2005
3) 2015

Comparison

1995 – 2005 - 2015

Characteristics
1995 – 2005 – 2015

	1995	2005	2015
Study duration	19	17	20
N	279	299	256
Pos rate ($\geq 10^5$ CFU/mL)	59%	65%	63.7%
Pos rate (EFU 2000)	NA	71.2%	79.3%
Breakpoints susceptibility	NCCLS 1994	CLSI 2004	EUCAST 2014
Premenopausal: 18-55 y Postmenopausal: > 55 y	279 0	222 (83%) 45 (17%)	188 (73.4%) 68 (26.6%)
Mean age • Premenopausal • Postmenopausal	34 34 0	39 33 68	42.6 34 67

Distribution of uropathogens in culture positive samples. All age groups included.

	1995 n=176	2005 n=213	2015 n = 212
E. coli	78.4 %	80.3 %	81.6 %
S. saprophyticus	9,1 %	8.5 %	8 %
Enterococcus faecalis	2.3 %	0.7 %	5.2 %
Proteus spp.	4 %	4.2 %	0 %
Klebsiella pneumoniae	0 %	2.8 %	3.3 %
Other gram –	2.8 %	2.8 %	1 %
Other Gram +	2.3 %	0.7 %	1 %

Susceptibility pattern (%) 1995 - 2005

	E. coli	
	1995 n=138	2005 n=170
Ampicillin	73.2 %	62.9 %
TMP-SMX	83.3 %	84.7 %
Nitrofurantoin	99.3 %	99.4 %
Ofloxacin/levofloxacin	99.3	98.8 %
Fosfomycin	-	98.8 %

Resistance rate of *E. coli* for cotrimoxazole %

ARESC (Naber 2008)

Austria	29
brazil	45.4
France	12.2
Germany	25.9
Hungary	40.3
Italy	28.8
Poland	20.0
Russia	30.5
Spain	33.7
The Netherlands	20.6

ARESC: *Antimicrobial Resistance Epidemiology Survey on Cystitis*

HIGH RESISTANCE RATES AGAINST TMP-SMX?

Belgium guideline: TMP as first choice

Can we still recommend TMP?

HIGH RESISTANCE AGAINST TMP-SMX?

Naber et al (2011)

- Recommendation **country-specific**
- Threshold: resistance rate: **20%**

Gupta et al (2011):

- TMP-SMX remains a highly effective treatment
- Threshold: resistance rate < 20%

Susceptibility pattern (%) 1995 - 2005

	E. coli	
	1995 (n=138)	2005 (n=170)
Ampicillin	73.2 %	62.9 %
TMP-SMX	**83.3 %**	**84.7 %**
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Fosfomycin	-	98.8 %

Can we still recommend TMP ?

YES WE CAN

Can we still recommend TMP ?

BUT….

Susceptibility pattern (%)
1995 – 2005 – 2015

	E. coli		
	1995 n=138	2005 n=170	**2015** **N=173**
Ampicillin	73.2 %	62.9 %	**55.5 %**
TMP-SMX / TMP*	83.3 %	84.7 %	**76.3 %**
Nitrofurantoin	99.3 %	99.4 %	**99.4 %**
Ofloxacin/ levofloxacin	99.3	98.8 %	**94.2 %**
Fosfomycin	-	98.8 %	**100 %**

*TMP not tested in 1995

Susceptibility pattern (%) 1995 - 2005

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*TMP not tested in 1995

TMP resistance ↗

- TMP-SMX: <1% of total DDD

(RIZIV data 2013)*

- Frequent use in industrial animal production**

* RIZIV: Belgian Disease and Disability Institution

** Persoons et al (2012)

HIGH RESISTANCE RATES AGAINST TMP-SMX

Can we still recommend TMP ?

HIGH RESISTANCE RATES AGAINST TMP-SMX

Can we still recommend TMP ?

20% threshold?

TMP-SMX RESISTANCE – CURE RATE

TMP/SMX resistance rates	Expected bateriologic eradication rate	Expected clinical succes rate
0%	93%	**95%**
10%	89%	**92%**
20%	84%	**88%**
30%	80%	**85%**

Gupta et al. Ann Intern Med. 2001; 135:9-12; 41-50

Pharmacokinetics

- Breakpoints?
- $C_{urine} = 10 \times C_{serum}$
- Urinary breakpoints?

TMP?

- Clinical relevance: 20% vs 30% resistance rate

  Cure rate: **88%** vs **85%**

- Urinary breakpoints ≠ systemic breakpoints ?

- Well known,
- inexpensive,
- few side effects

Uncomplicated UTI in women 20 year surveillance

- Bacterial distribution remained stable
- No change in Susceptibility of *E. coli* (exc TMP)
- Nitrofurantoin, fosfomycin = first choice
- TMP?

WOMEN WITH SYMPTOMS OF A UTI

BUT A NEGATIVE CULTURE.

case

- 35 y female patient
- Dysuria, frequency
- No other signs or symptoms
- Dipstick: Nitrite: - ; LE: -

- Treatment?

case

- 35 y female patient
- Dysuria, frequency
- No other signs or symptoms
- Dipstick: Nitrite: - ; LE: -
- Culture: < 10^3 CFU/mL;
- Lab report: negative culture

- Treatment?

SYMPTOMATIC WOMEN AND NEGATIVE CULTURE

Women with typical symptoms of cystitis

SYMPTOMATIC WOMEN AND NEGATIVE CULTURE

Women with typical symptoms of cystitis

=> 25 – 30% negative culture

SYMPTOMATIC WOMEN AND NEGATIVE CULTURE

WOMEN WITH URINARY COMPLAINTS BUT A NEGATIVE CULTURE?

What do they have?

SYMPTOMATIC WOMEN AND NEGATIVE CULTURE

WOMEN WITH URINARY COMPLAINTS BUT A NEGATIVE CULTURE?

What do they have?

An infection?

Do culture negative women have an infection?

1. **Cut off rate**

Do culture negative women have an infection?

1. **Cut off rate: Kass: 10^5 !**

Do culture negative women have an infection?

1. Cut off rate: Kass: 10^5

- 10^5 Kass (1956), Brumfit, Bolan
- 10^4 Callagher, Smith, Baerheim, Shultz, Leibovici
- 10^3 Osterberg, Johnson, Echols, Rubin, Pfau, Pfaller, Gupta
- 10^2 Stamm (1980), Hooton, Reid, Elder

Cystitis study

Positive urine samples

Threshold	N=256	%
$\geq 10^5$	163	63,7

European Federation for Urinalysis.
Aspeval, 2000.

Cystitis study

Positive urine samples

Threshold	N=256	%
$\geq 10^5$	163	63,7
$\geq 10^4$	193	75.4

European Federation for Urinalysis.
Aspeval, 2000.

Cystitis study

Positive urine samples

Threshold	N=256	%
$\geq 10^5$	163	63,7
$\geq 10^4$	193	75.4
$\geq 10^3$	206	80.9

European Federation for Urinalysis.
Aspeval, 2000.

Do culture negative women have an infection?

1. Cut off: 10^5 => 10^3 cfu/ml

Do culture negative women have an infection?

1. Cut off: 10^5 => 10^3 cfu/ml
2. **Richards et al (2005)**

Do culture negative women have an infection?

Richards et al 2005

Symptoms and neg culture

Do culture negative women have an infection?

Richards et al 2005

Symptoms and negative culture

300 mg TMP/d	placebo

P=0.002

Do culture negative women have an infection?

Richards et al 2005

Symptoms and negative culture

300 mg TMP/d	placebo
Median: 3 days	Median: 5 days

P=0.002

Do culture negative women have an infection?

1. Cut off: 10^5 => 10^3 cfu/ml
2. Richards et al (2005)
3. **Routine laboratory protocol**

Do culture negative women have an infection?

1. Cut off: 10^5 => 10^3 cfu/ml
2. Richards et al (2005)
3. **Routine laboratory protocol**
   - Micro-organisms that are not routinely cultured

     Chlamydia trachomatis, Mycoplasma genitalium
   - Fastidious growing bacteria
     - ❑*Gardnerella, Ureaplasma*
     - ❑Causative agents?

Do culture negative women have an infection?

1. Cut off: 10^5 => 10^3 cfu/ml
2. Richards et al (2005)
3. Routine laboratory procedure
4. **Intracellular *E. coli*** (Hunstad 2010)

Do culture negative women have an infection?

1. Cut off: 10^5 => 10^3 cfu/ml
2. Richards et al (2005)
3. Routine laboratory procedure
4. Intracellular *E. coli* (Hunstad 2010)
5. **'New' uropathogens**
   - *Aerococcus urinae*
   - *Actinobaculum schaalii*

SYMPTOMATIC WOMEN AND NEGATIVE CULTURE

Women with symptoms of cystitis

But a negative culture

Infection?

SYMPTOMATIC WOMEN AND NEGATIVE CULTURE

“Culture Negative Gap”

Do culture negative women have an infection?

PCR

- Cystitis study >> symptomatic group
- Healthy volunteers >> control group

Control group (n=86)

Exclusion criteria

- **Dysuria or other signs and symptoms of UTI**
- Frequent episodes of UTI (> 3/year of > 2 in last 6 months)
- Have received an antibiotic during the past 4 weeks
- Abnormal vaginal discharge or vaginal itch
- Prominent gynaecologic complaints
- Known nephrologic or urologic problems
- Diabetes or other chronic condition
- Immunocompromizing condition (leukemia, immunosuppressants)
- Pregnant women

Characteristics

Characteristic	Control group	Women with symptoms of UTI
Number of women	86	220
Mean age in years* (Standard deviation)	37.2 (11.481)	38.5 (13.839)
Range (years)	23-65	17-91
Recruitment	University of Ghent campus volunteers	Patients consulting their GP's practice
Culture	Fresh urine sample Laboratory work out	Fresh urine sample Dipslide

Legend: *: p = 0.440

E. Coli culture and qPCR results

	% of positives	
Group (number of women)	PCR	Culture
Symptomatic group (220)	95.9	80.9

E. Coli culture and qPCR results

	% of positives	
Group (number of women)	PCR	Culture
Symptomatic group (220)	95.9	80.9
Control group (86)	11.5	8.1

Control group (n = 86): Correspondence between *E. coli* qPCR and culture

qPCR E. coli (geqs/ml)	Culture E. coli (CFU/ml)
10^7	10^6
10^6	10^6
10^5	10^6
10^5	10^5
10^4	10^4
10^4	Negative
10^4	Negative
10^4	Negative
10^4	Negative
10^6	$<10^3$
0	$<10^3$

Positive PCR rate for different organisms in symptomatic group (n= 220)

	number	%
Escherichia coli	211	95.9
Staphylococcus saprophyticus	16	7.3
Actinobaculum schaalii	20	9.1
Trichomonas vaginalis	1	0.5
Mycoplasma genitalium	1	0.5
Neisseria gonorrhoeae	0	0
Chlamydia trachomatis	0	0

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Mycoplasma genitalium	1	0.5
Neisseria gonorrhoeae	0	0
Chlamydia trachomatis	0	0

Positive sample rate according to detection technique.

Symptomatic group

Used technique	Positive urine samples	
	n	%
Culture of *E. coli*	147	67,7
Culture of any uropathogen	177	80.9
qPCR for *E. coli*	211	95.9
Culture of any uropathogen and *E. coli* qPCR	216	98.2

E. coli qPCR

- Positive in 95.9% of symptomatic women
- Remained negative in control group
- Yet postitive in asymptomatic bacteriuria

“Closing the negative gap”

All women with typical urinary symptoms have an *E. coli* infection

What do women with symptoms of cystitis but a negative urine culture have? PCR based quantification of *Escherichia coli* indicates that they have an infection after all.

Heytens S, De Sutter A, Coorevits L, Cools P, Boelens J, Vaneechoutte Mario, Christiaens T, Van Simaey L, Claeys G.

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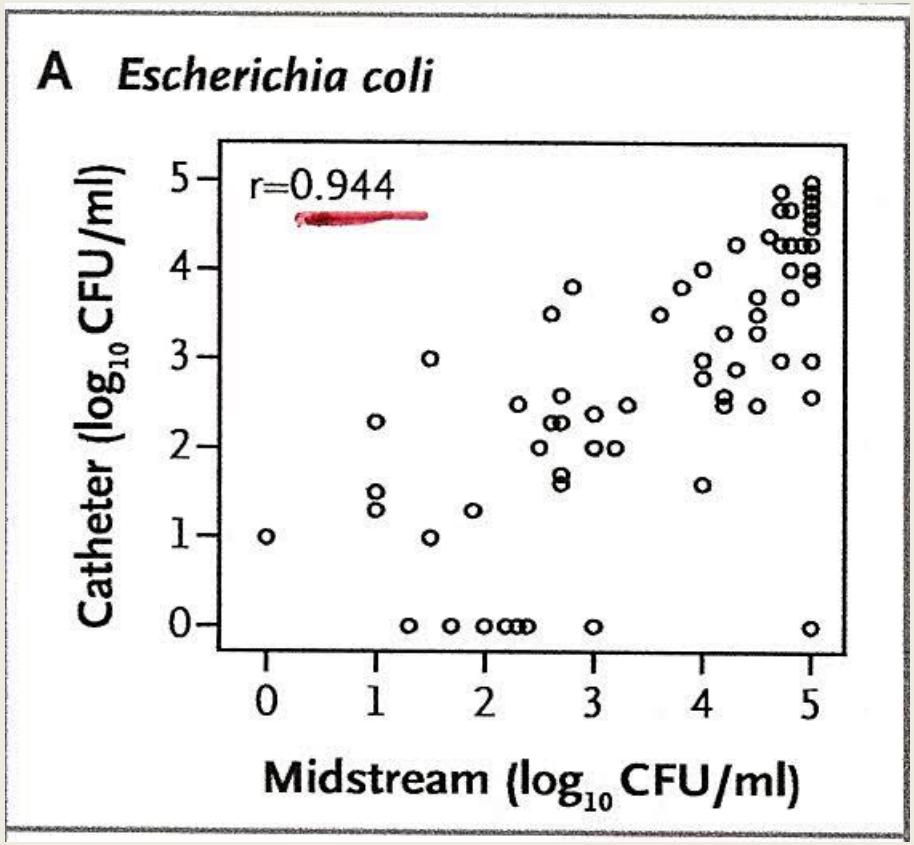
END

Syplementary slides

Do culture negative women have an infection?



WHY NOT SIMPLY USE EXISTING DATA?

Which bacteria and susceptibility pattern 1995-1996

Christiaens et al 1998

E. COLI SUSCEPTIBILITY IN PHC 1994-1995 Christiaens et al

	Ampicillin	TMP-SMX	Nitrofurantoin	fluoroquinol
OUR STUDY				
Regio Gent 1995-96 Christiaens e.a. (n=138)	**73%**	83%	99%	99%
REGIONAL LABORATORIES (outpatients)				
Hasselt 1994 (n=4140)	63%	80%	91%	95%
Leuven 1994 (n=2019)	64%	80%	93%	94%
Gent 1994 (n=1416)	58%	80%	94%	90%

E. COLI SUSCEPTIBILITY IN PHC 1994-1995 Christiaens et al 1998

	Ampicillin	TMP-SMX	Nitrofurantoin	fluoroquinol
OUR STUDY				
Regio Gent 1995-96 Christiaens e.a. (n=138)	**73%**	83%	99%	99%
REGIONAL LABORATORIES (outpatients)				
Hasselt 1994 (n=4140)	63%	80%	91%	95%
Leuven 1994 (n=2019)	64%	80%	93%	94%
Gent 1994 (n=1416)	58%	80%	94%	90%

Distribution of uropathogens in culture positive samples pre and post menopausal women 2015

	2015 18-55 y n = 153	2015 > 55 y n= 59
E. coli	78.4 %	89.8 %
S. saprophyticus	11.1 %	0 %
Enterococcus faecalis	5.2 %	5.1 %
Proteus spp.	0 %	0 %
Klebsiella pneumoniae	3.3 %	3.4 %
Other gram –	0.7 %	1.8 %
Other Gram +	1.4 %	0 %

Knottnerus 2013

1. Dysuria?
2. Vaginal irritation
3. Selfreporting

E. Coli qPCR negative: 10
Symptomatic group (n=220)

Organism	
E. coli	10^6
E. coli	10^3
S. saprophyticus	10^6
Pseudomonas Aeruginosa	10^4
S. agalactiae	10^5
S. agalactiae	10^4
CNS	10^3
Contaminated sample	10^3
Contaminated sample	10^3
No organism isolated	0

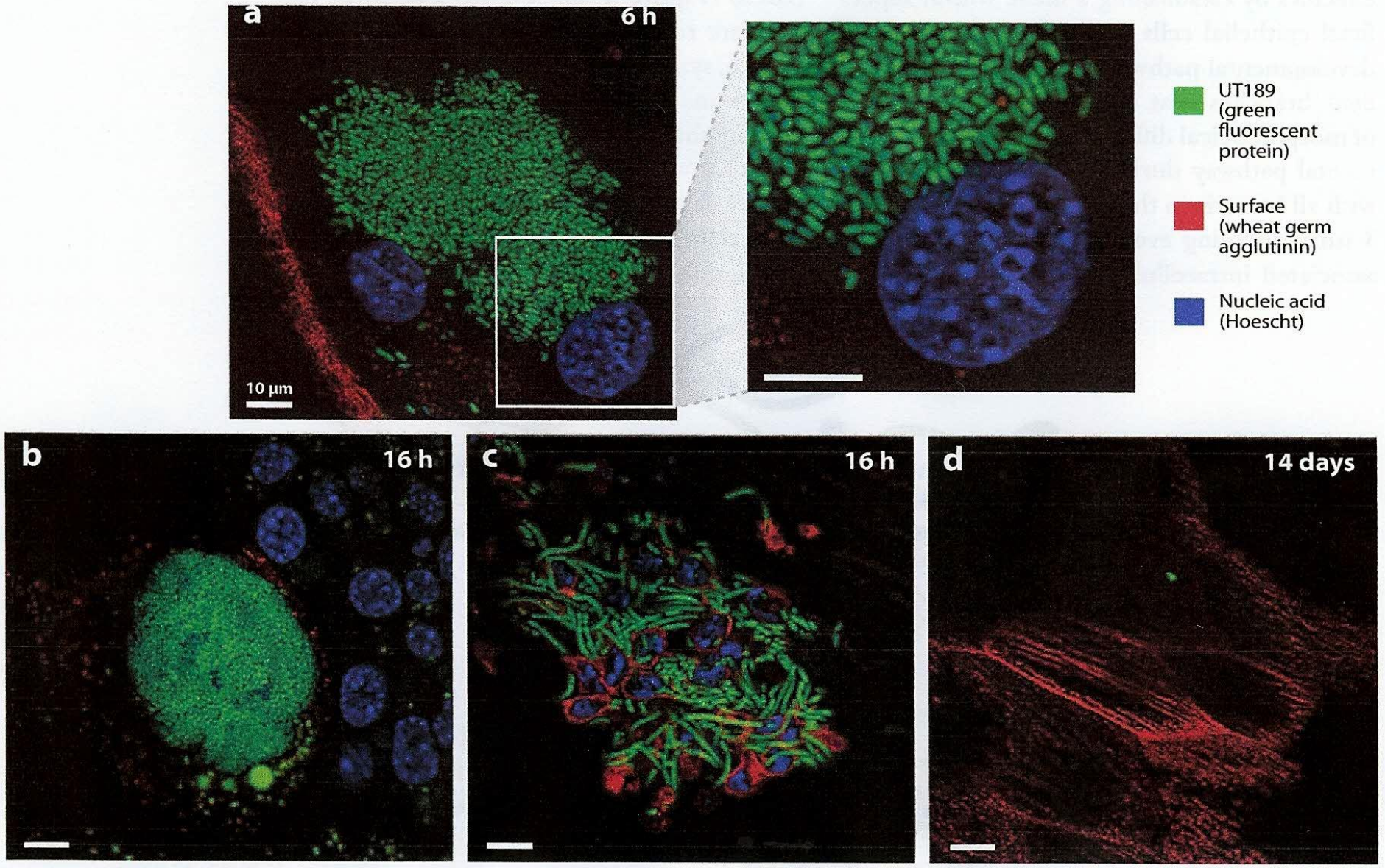
European Guideline for Urine analysis

- Primary pathogens:
  - *E. coli* and *S. saprophyticus*
  - **≥ 10^3 CFU/mL**
- Secondary pathogens:
  - Other Gram negative rods en Enterococcus spp
  - **≥ 10^4 CFU/mL**

Culture negative: 43
Symptomatic group (n=220)

E. coli qPCR result	Number of culture negative samples
Negative	5
$< 10^3$	5
10^3	1
10^4	4
10^5	20
$\geq 10^6$	8

Intracellular *E. coli* (Hunstad 2010)



S. saprophyticus

- 16 *S.s* PCR positive

  Culture:

  - 9 *S. saprophyticus*
  - 6 *E. coli*
  - 1 *Klebsiella*

- 15 culture positive => 6 negative *S.s* PCR

Actinobaculum schaalii

- 20 qPCR positive

- Culture:
  - 10 *E. coli*
  - 2 *S. saprophyticus*
  - 1 *Enterobacter aerogenes*
  - 7 negative culture

E. coli qPCR results in culture positive samples symptomatic group

	Culture (cfu/ml of urine)*	N	qPCR E. coli positive	qPCR E. coli negative
Escherichia coli	10^2	3	0	0
	10^3	10	0	0
	10^4	21	11	0
	10^5	32	40	0
	$\geq 10^6$	83	93	0
		149	144	
Staphylococcus saprophyticus	10^4	2	2	0
	10^5	1	1	0
	10^6	12	11	1
Klebsiella pneumoniae	10^4	1	1	0
	10^6	4	4	0
Enterococcus faecalis	$\geq 10^5$	2	2	0

WHY NOT SIMPLY USE EXISTING DATA?

- Filter raw data of regional lab's

- Filter:
  - women
  - 18-55 year
  - 1 sample per patient per year
  - Only samples sent by GP's
  - (Not from patients in LTCF)
    => age restriction

Threshold of 20%

- Clinical studies
- In vitro studies
- Mathematical modelling

Pharmacokinetics

- Urinary breakpoints?
- $C_{urine} = 10 \times C_{serum}$
- PK/PD targets are not known
  - Dependent on time above MIC (%*T*/MIC)
  - Concentration-dependent (AUC/MIC)

END