# Cystitis: often simple, but not always.

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# Urinary tract infections (UTI)

- "… and finally the patient died from a Gram negative sepsis due to a UTI…"

*Intensive Care reality*

- (phone call) " Yes doctor, there we go again, I have a new cystitis. Would it be possible to deliver me a prescription for an antimicrobial..."

*GP reality*

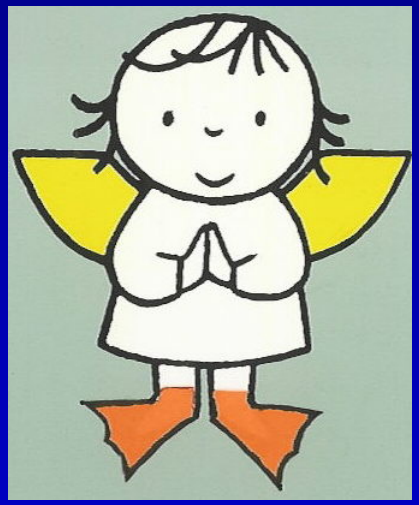
➔ **Cystitis prevalence :+/- 40 pro mille in women**

To treat “simple” infections qualitatively is one of the major goals of general practice.

Clinical microbiologists can help us substantially by collaborating in our research.

# Clinical microbiologists for or against general practitioners?

- Clinical microbiologist



- General Practitioner

# Clinical microbiologists for/against general practitioners?

- The gold standard: “Kass or Stamm”?
- Can (directly available) diagnostic test substantially improve the diagnostic accuracy in GP?
- How to rule out *Chlamydia trachomatis* infections?
- A multitude of possible treatment options?
- Reliability of the resistance data  for empirical treatment in GP?

# The gold standard

"Kass is dead."

Friedrich Nietzsche

# The “gold standard”

- 100.000 cfu/ml by Kass (1956), Brumfit, Bolan
- 10.000 cfu/ml by Gallagher ( already in 1965!), Smith, Baerheim, Schultz, Leibovici
- 1.000 cfu/ml by Osterberg, Johnson, Echols, IDSA, Rubin, Pfau, Pfaller, Gupta
- 100 cfu/ml by Stamm (1980), Hooton, Reid, Elder
- variable cut-off point in function of several criteria (Gram + vs - ; symptoms or not ; pyuria or not)

# The “gold standard”

- Symptoms without bacteriuria
- Bacteriuria without symptoms
- Symptoms and bacteriuria without pyuria
- Symptoms and pyuria without bacteriuria

# The “gold standard”

“Kass is dead”

**But we don’t have a successor yet...**

**PLEASE LET US LOOK FOR THE NEW STANDARD !**

# Can tests substantially improve the diagnostic accuracy?

…knowing that the prior probability for a cystitis in adult women with dysuria and no vaginal discharge is greater than 80% in GP!

# The ideal diagnostic test in GP :

- Perfect detection (*confirmator*) of UTI and (*excluder*) discrimination between uncomplicated UTI and (1) complicated UTI or (2) STD or (3) vaginitis
- Identification + quantification of uropathogens + antimicrobial sensitivity determination in UTI
- Immediately available result
- Technically simple (in all settings)
- Cheap for the community, the patient and GP

# That ideal diagnostic test is not available

- Culture: delay ++, gold standard discussion, $$
- Dipslide: delay +, gold standard discussion
- Urinary sediment: WBC proxy for infection, technical problems ++
- Direct microscopy: WBC proxy for infection, difficult to learn
- Nitrite test: false negatives ++
- LE-test: WBC proxy for infection, false pos. ++

BUT…

DO WE REALLY NEED A DIAGNOSTIC TEST??

Does confirmation of infection matter to the patient?

# Cystitis as a self-limiting disease

- **Overlooking a cystitis is not a real problem:**
  Evolution in women with proven cystitis
  after 3 and 7 days placebo treatment versus 3 days of Nitrofurantoin (NF):

| | Placebo | | Nitrofurant. | |
|---|---|---|---|---|
| | Bact | Symp | Bact | Symp |
| Cured after 3 days | **20%** | **44%** | 81% | 80% |
| Cured after 7 days | **41%** | **54%** | 74% | 88% |

*Christiaens et al BJGP 2002;52:729-34.*

# Symptomatic improvement with AB-treatment in women without infection

- **Diagnosis not important for prognosis (?):** Treatment of women with dysuria but negative LE-test (94% negative culture) for 5 days with TMP (versus placebo) gives substantial effect:
  - Median time for resolution of symptoms: TMP 3 days, placebo 5 days
  - At day 7: dysuria in 10% of TMP group, 41% in Placebo ➔ NNT 4

*D. Richards BMJ 2005;331:143-5*

# Treat on symptoms?

- Simple and quick
- Short courses few side effects
- Short courses few costs
- Short courses few resistance induction (?)

- What about risks?

# How to rule out *Chlamydia trachomatis* infections?

- Chlamydia infection gives *dysuria* in circa 30% (??) of the cases
- Chlamydia causes *leukocyturia*
- Chlamydia is sensitive to several drugs used in cystitis (but needs longer treatment)

- ?? PCR on urine in young women with dysuria??

➔ more data needed

# How to treat cystitis?

- A broad range of possible antimicrobials have proven efficacity
- Worldwide high resistance against aminopenicillins in uropathogens (also in ambulatory care)
- We need to reserve the potent fluorochinolones as fall back option for complicated infections
- We lack RCT's with trimethoprim and certainly with nitrofurantoin (antimicrobials used exclusively in UTI)

➔ More resources needed for trials with old/cheap drugs

# How long to treat?

- **3 days versus 5 days or more:**
  Cochrane review: Duration of antibacterial treatment for uncomplicated urinary tract infection in women (Milo G, Katchman E, Paul M, Christiaens T, Barheim A, Leibovici L)
  - **Same symptomatic effect**
  - **Slightly better bacteriological result for longer treament**

**→ 3 days is enough**

# How to treat?
# The empirical choice

- Untill direct desk-top resistance determination is available (??)
  - all treatment is empirical treatment
  - supposing knowledge on pathogens and their bacteriological sensitivity…

Bacteriologists are apparently convinced that worrying resistance-data will **prevent** clinicians to use too much broad-spectrum antimicrobial agents.

But often the effect is the opposite: the growing resistance pushes GP's to use **more** broad-spectrum agents for fear that their patients will not be cured in case of resistant bacteria.

# Antimicrobial susceptibility of uropathogens in ambulatory care in Belgium

- Distribution and susceptibility
- Comparison of 1996-2005 data
- Comparison between GP data and lab data
- « cystitis filter »

# method

- 97 GP's contacted, 80 participated
- Region of Ghent
- November 2004 – March 2006
- Every woman ≥ 18 yrs with symptoms of cystitis
- Dipslide inoculated in surgery

- Microbiological lab (CRI,Ghent) for comparison

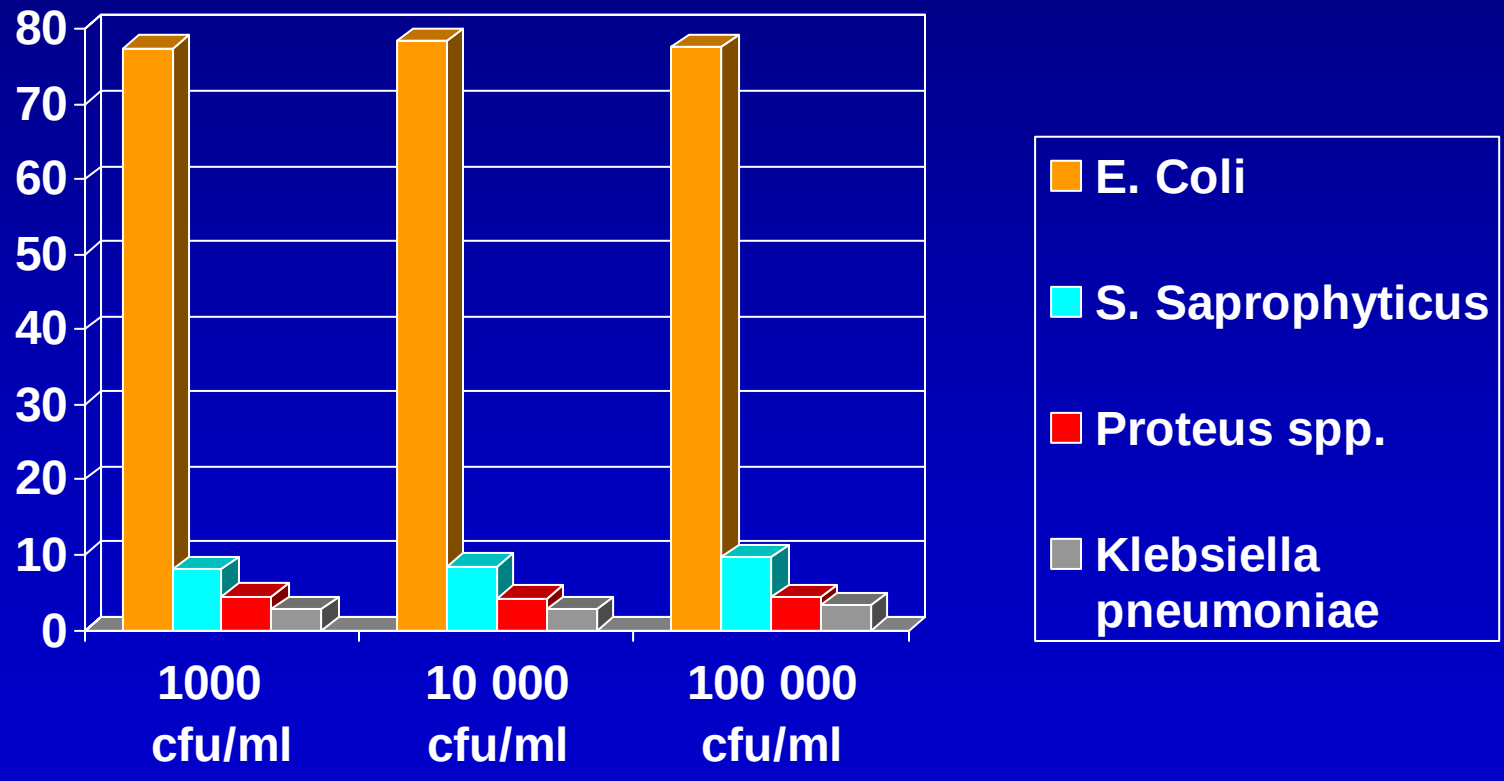
# Inclusion / exclusion

- Inclusion: dysuria and/or urgency and/or frequency
- Exclusion:
  - Pregnancy
  - Symptoms > days
  - Temp ≥ 38 °C
  - Nephrological/urological problems
  - DM
  - Gynaecological complaints

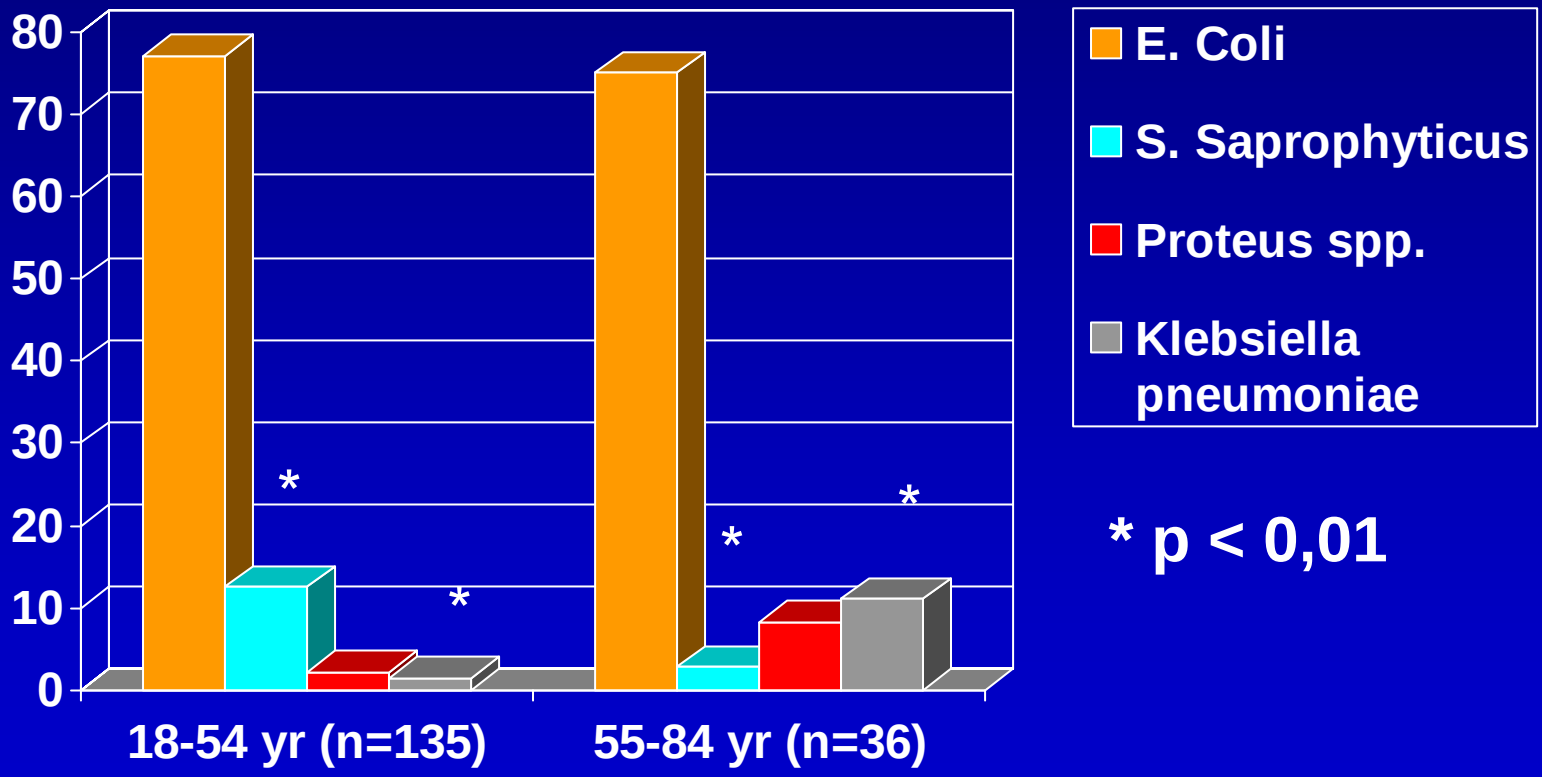
## results

- 300 samples
- Mean age 39 (18-84)
- 63% pos culture (100 000 cfu/ml)

# Distribution of uropathogens in general practice

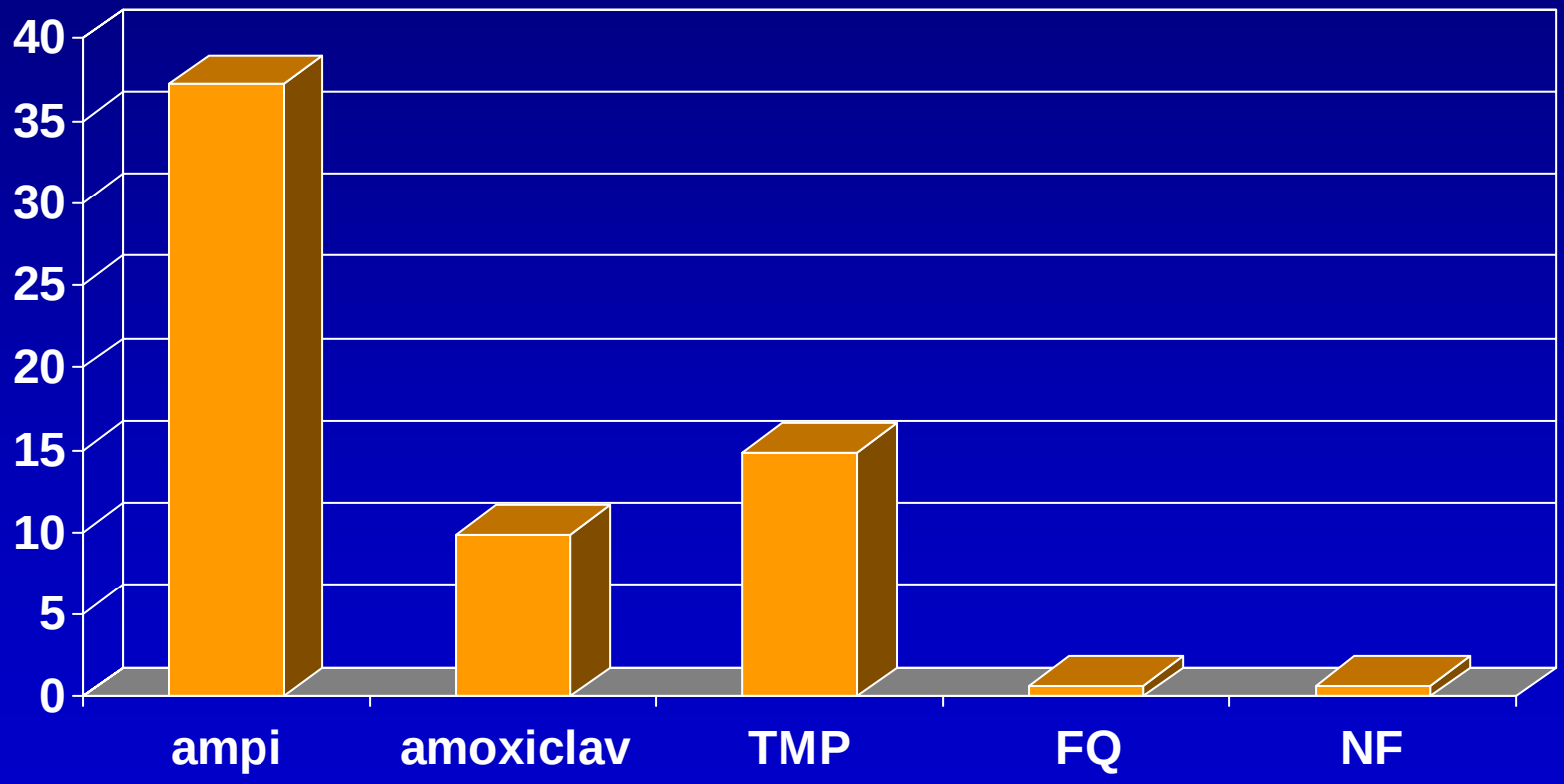


# Distribution of uropathogens for two age groups in general practice




* p < 0,01

# *E. Coli* resistance for all ages in general practice

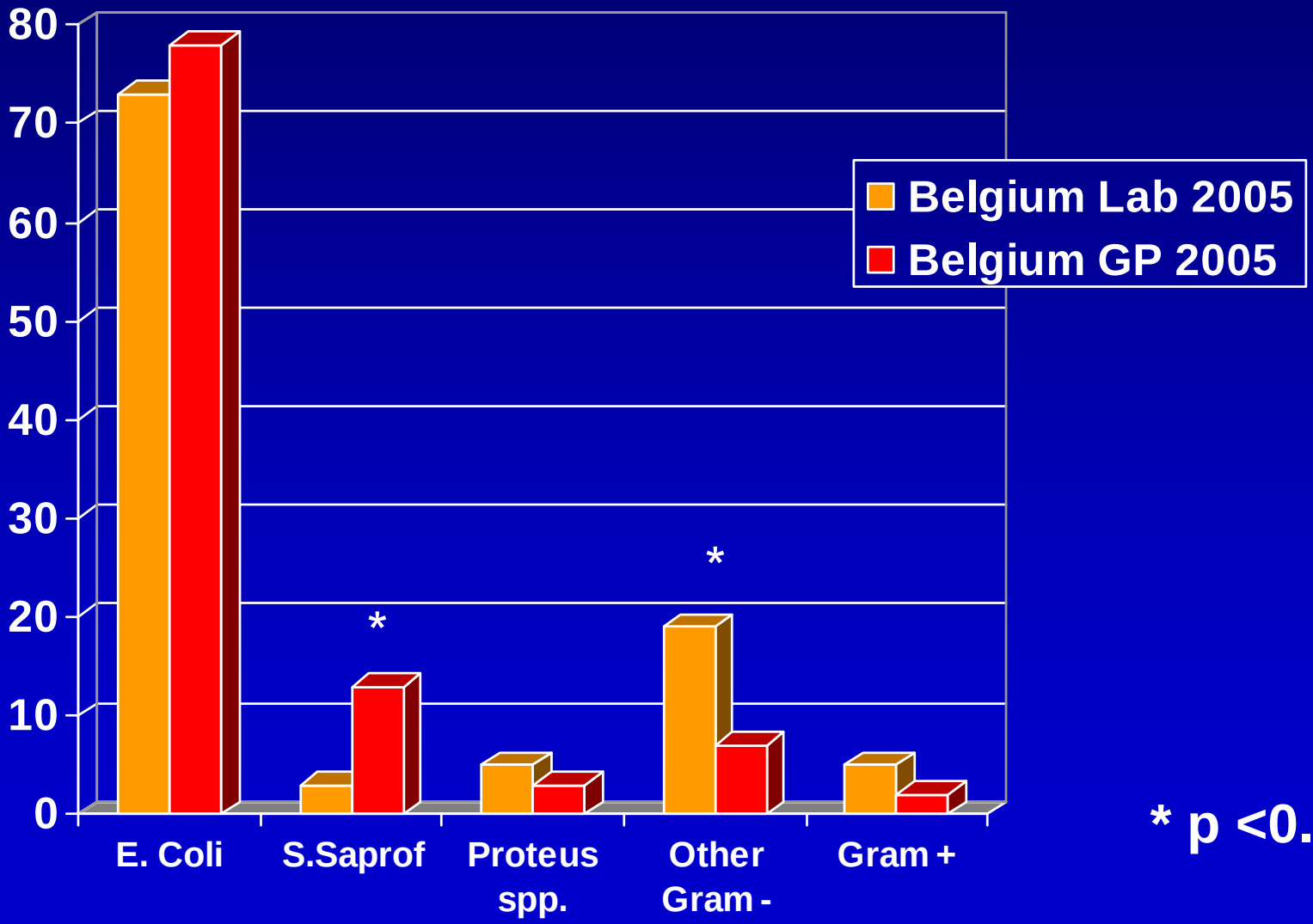


# Comparison GP 2005 with GP 1996
# Comparison GP 2005 with Lab 2005

selection GP samples:

- 18 – 54 yr
- No recurrent UTI's past year
- No UTI past 3 months

# Reliability of data for empirical treatment in GP: uropathogen distribution in GP and Lab

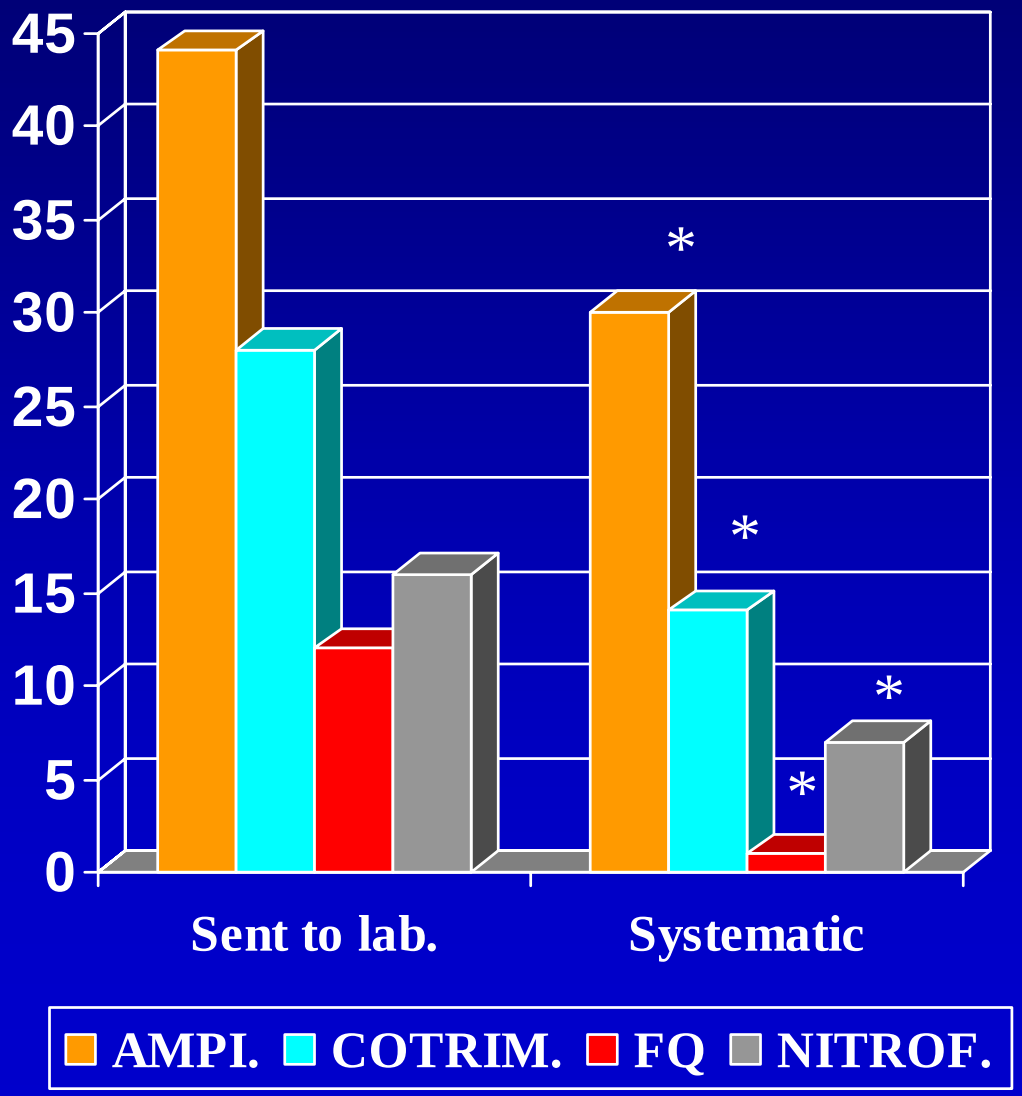



* p <0.01

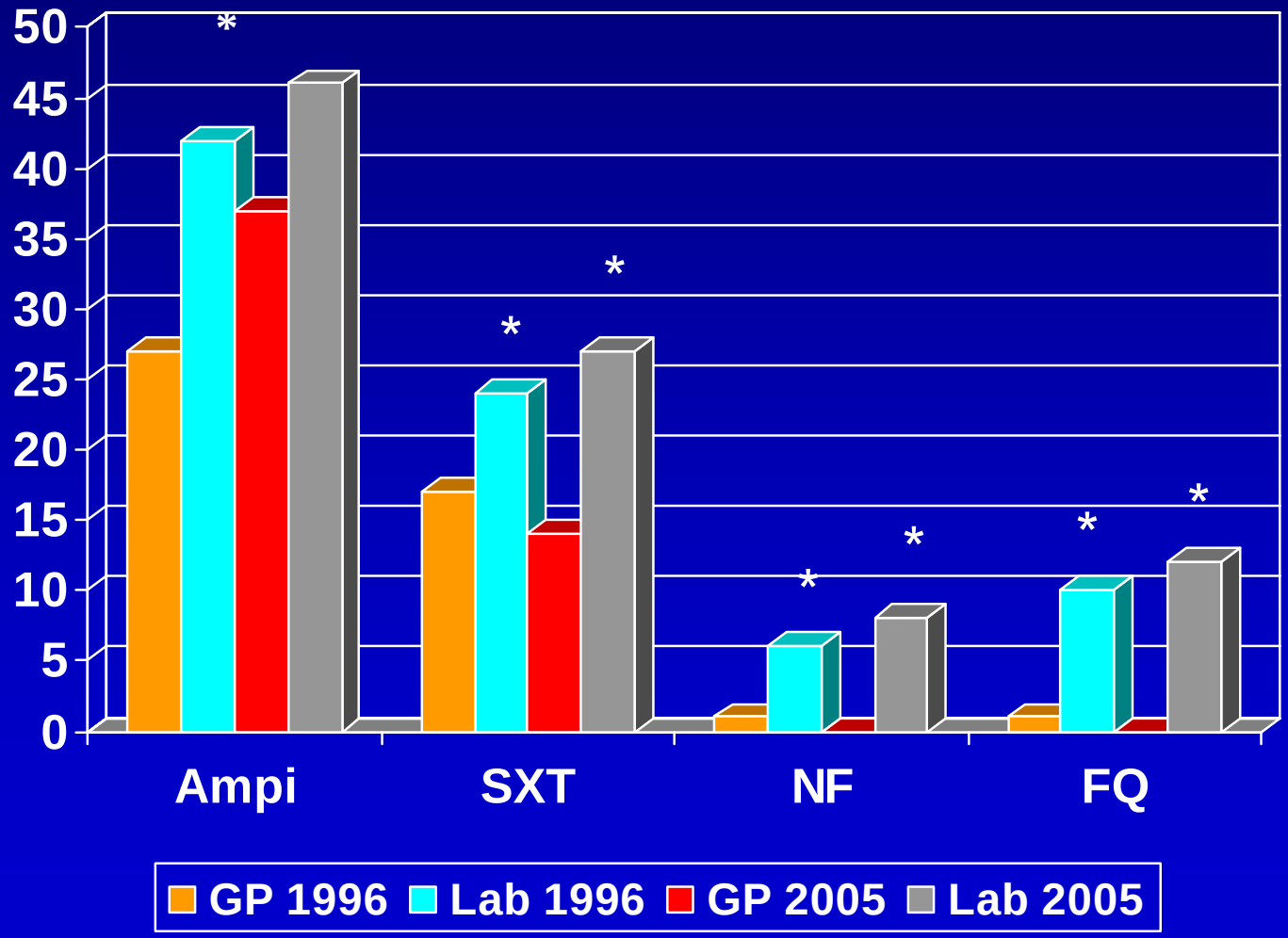
# Overestimation of resistance in GP by using data from microbiological lab (Belgium 1996)

*E. coli* resistance in ambulatory practice in Belgium : in samples sent to bact. lab. versus **systematically** in all women with symptoms (1996)

* p<0.01



# Resistance of *E.coli.* (%) against 4 antibiotics in 1996 and 2005: GP and microbiological lab




GP vs Lab
* p<0.01

GP vs GP
NS

# Reliability of data for empirical treatment in GP: why these differences?

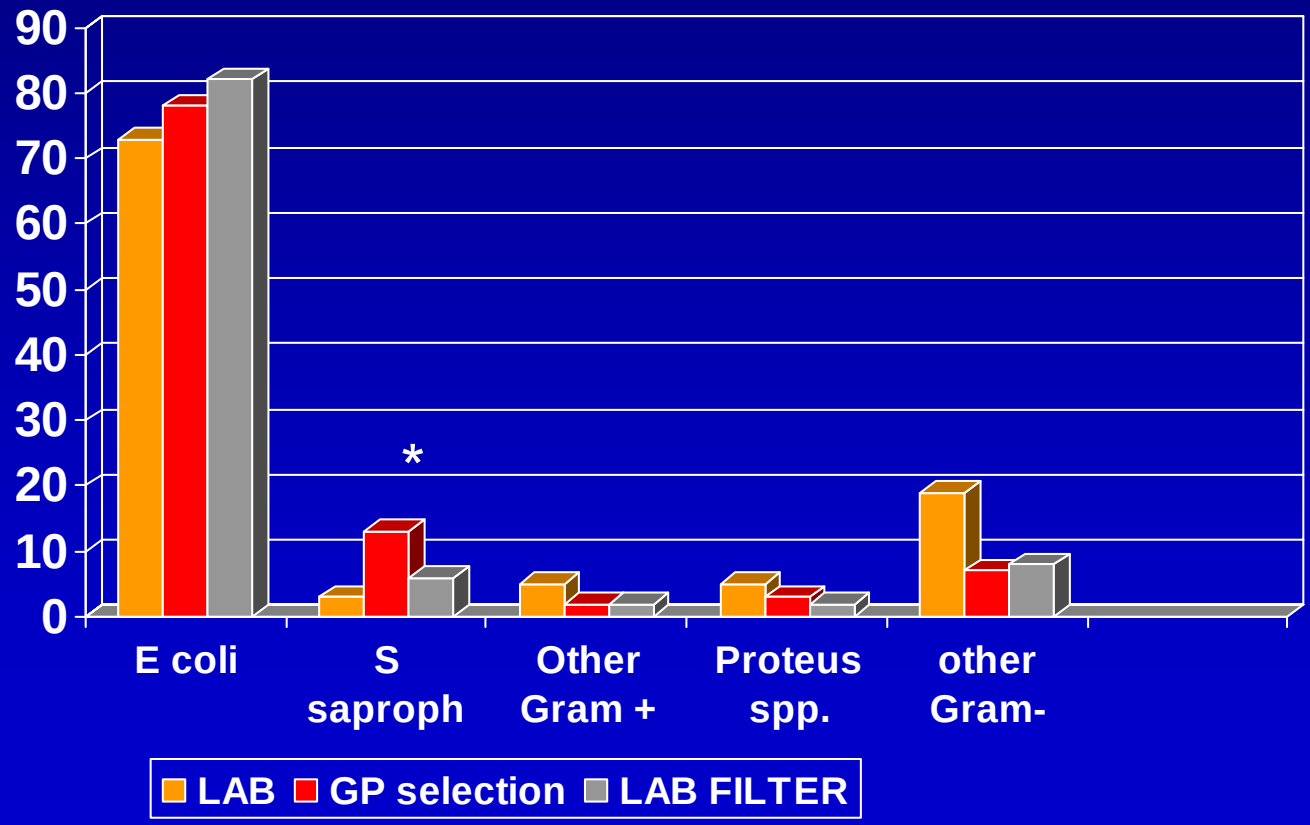
- GP do not send urinary samples to the microbiological laboratory without suspicion of complicated infection ( low *S.saprophyticus* rate)
- GP repetitively send samples in known complicated UTI ( more “other Gram negatives” AND high resistance rates)

**➔HOW TO MAKE THIS READILY ACCESSIBLE RESISTANCE DATA MORE RELIABLE??**

**➔ looking for a “Cystitis filter”**

# The “cystitis filter” : effect on uropathogen distribution

FILTER➔ **only lab data from women, 18-55y and only one sample/year (2005)**




Filter vs GP:

NS

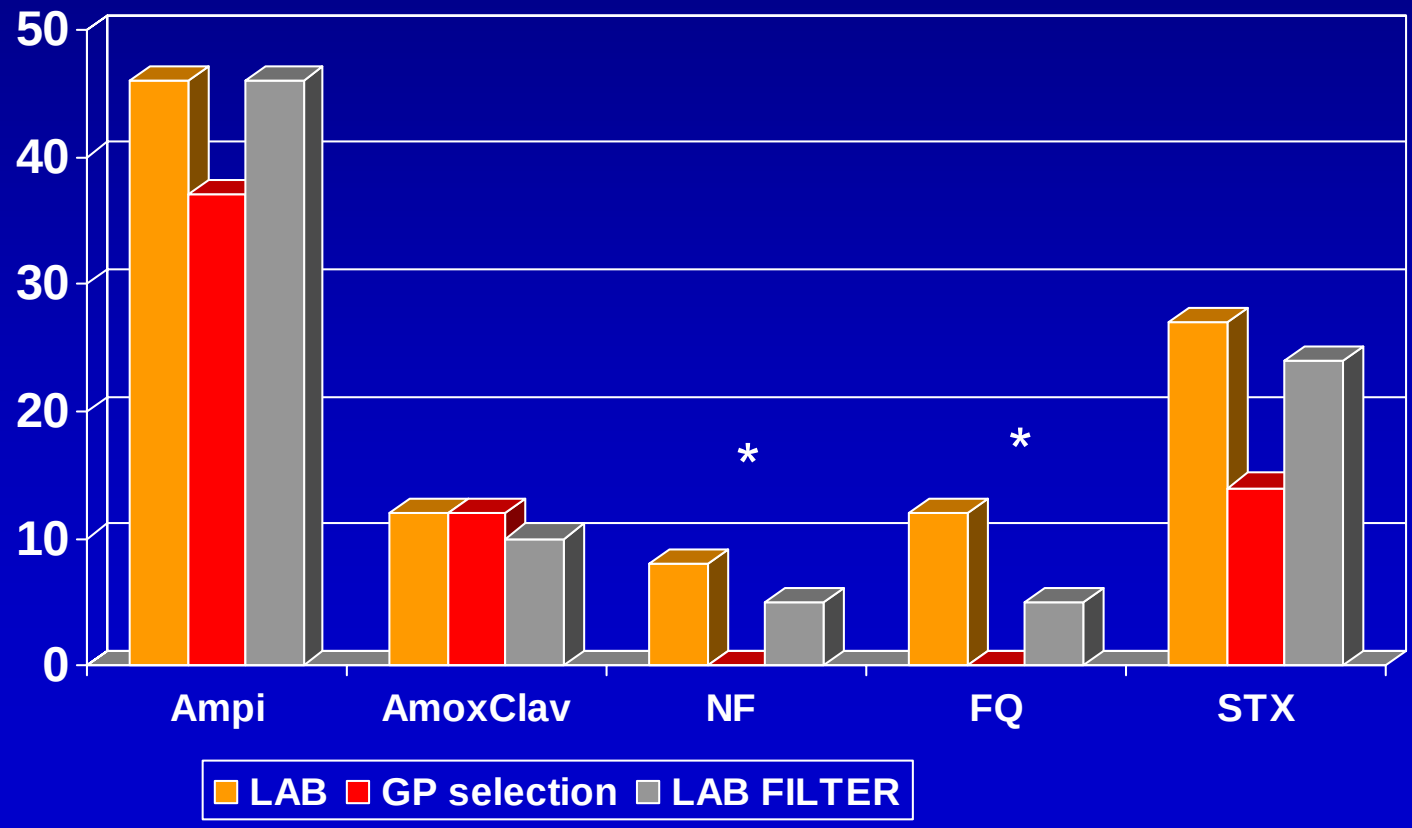
except

S.sapr

$p < 0.05$

# The “cystitis filter” : effect on *E. coli* resistance

FILTER➔ **only lab data from women, 18-55y and only one sample/year (2005)**




Filter vs GP: NS except NF FQ $p<0.05$

To treat “simple” infections qualitatively is one of the major goals of general practice, clinical microbiologists can help us heavily by collaborating in our research.

# Clinical microbiologists WITH general practitioners : combining forces

- Participate in our search for an appropriate gold standard for cystitis (and the relation symptoms/bacteriuria/ pyuria)
- Collaborate critically in “treat on symptoms” pragmatic trials
- Optimalise Chlamydia diagnosis in GP
- Stimulate therapeutic trials with *old* drugs
- Join us in our search for local, easily available **and** reliable resistance data in uropathogens

# Clinical microbiologists WITH general practitioners: what you may expect from us

- A pragmatic scientific approach
- Patient relevant research
- Stimulating and critical discussions (a lot of them)

# Acknowledging my research partners

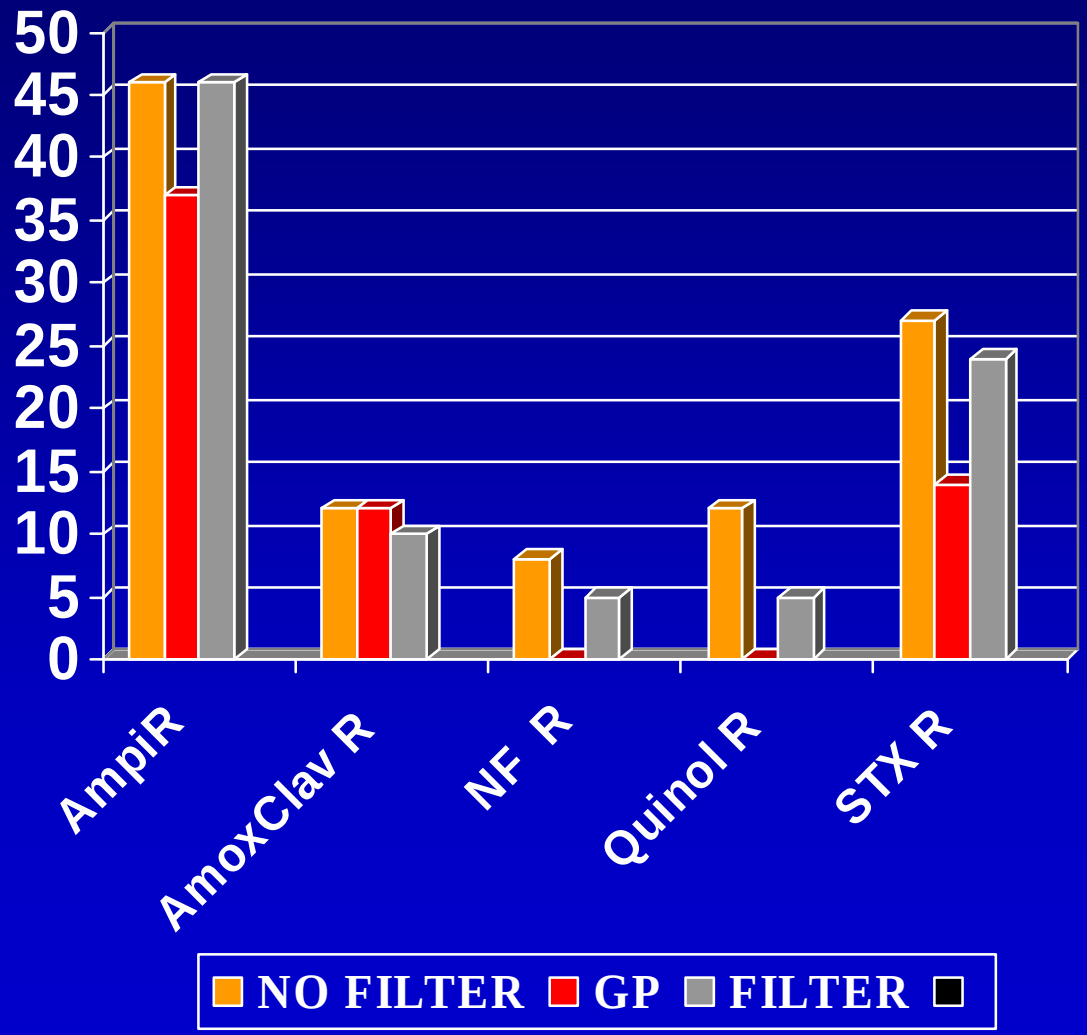
Prof Gerda Verschraegen
Prof  Ellen Stobberingh
Dr Guy De Groote

Prof Thierry Christiaens
Dr Stefan Heytens

# THANK YOU!

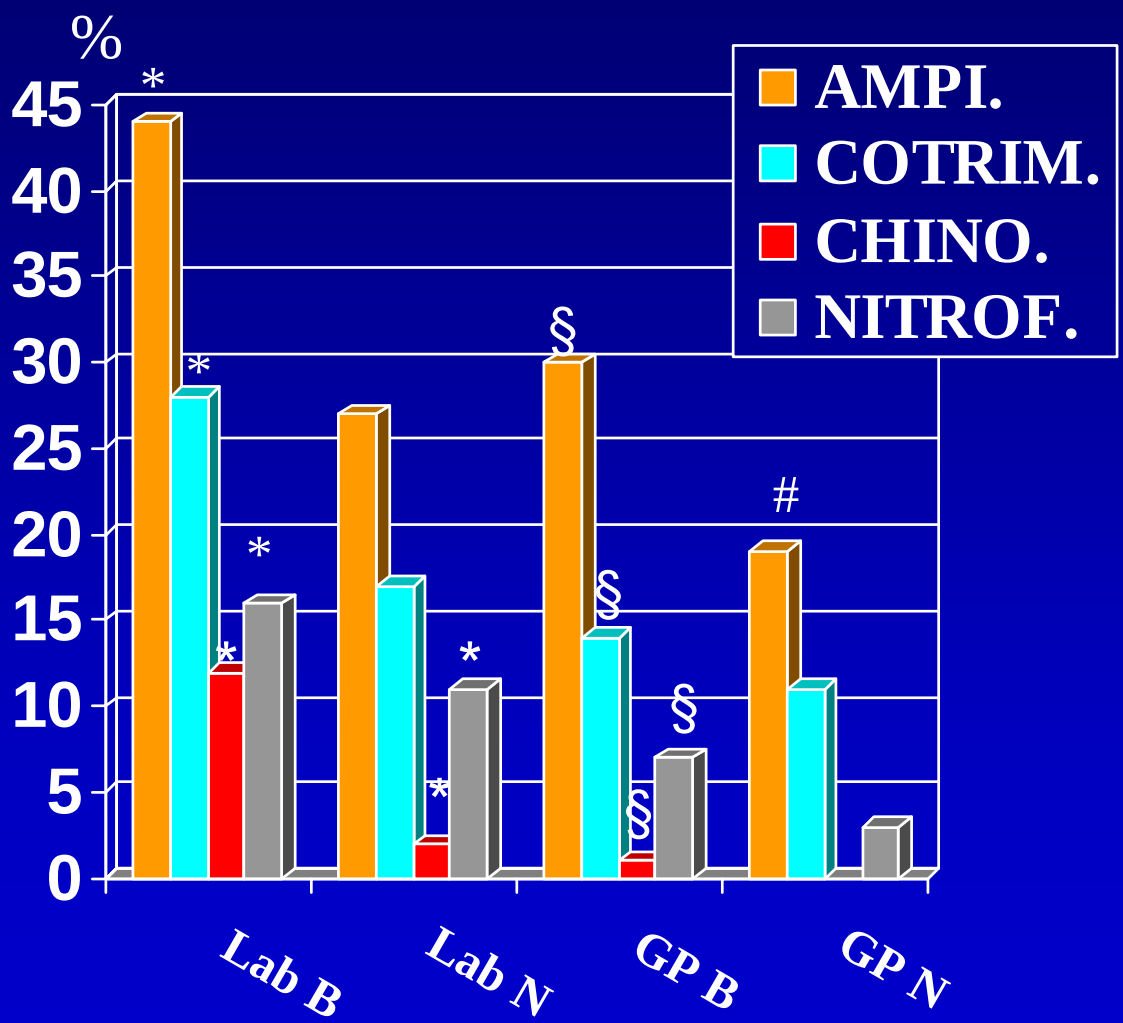
# The “cystitis filter”1

- Only women
- 15-55y
- Only one sample/year

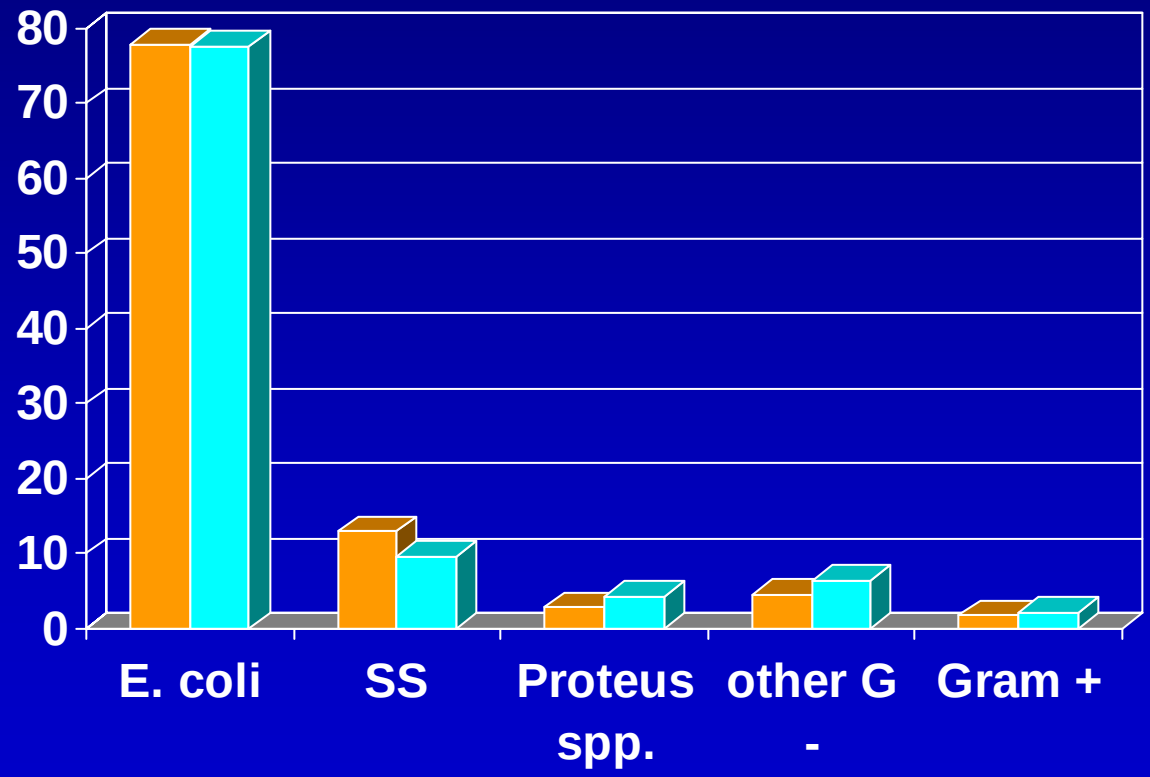


# Overestimation of resistance in GP by using data from microbiological lab: Belgium/Norway

- Resistance in uropathogens in ambulatory practice in Belgium and Norway : sent to laboratory versus systematic
- GP vs Lab
  * p<0.0001
  Lab N vs Lab B
  § p< 0.01
  GP B vs GP N
  # p<0.05

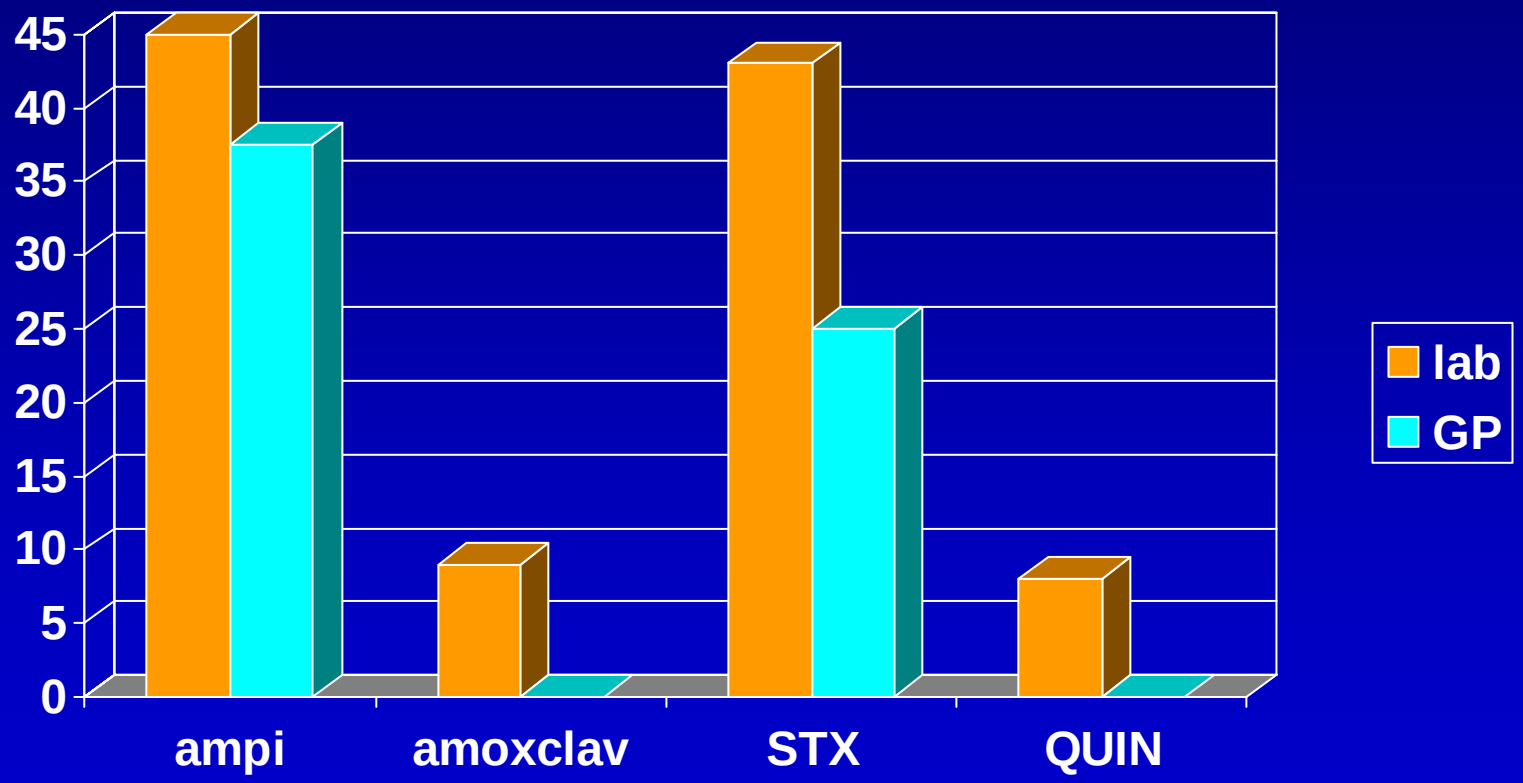


# Distribution of uropathogens: GP versus selection of GP samples

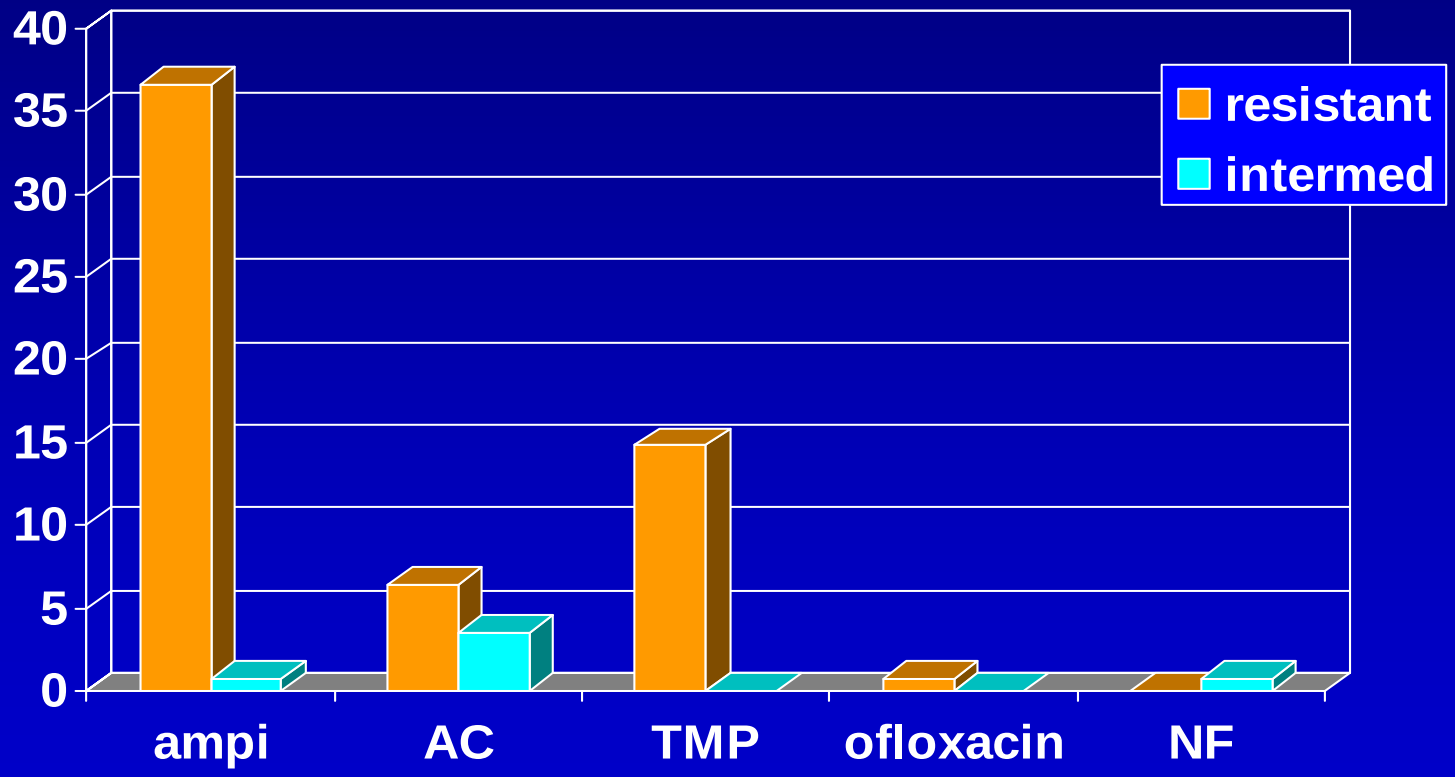



NS

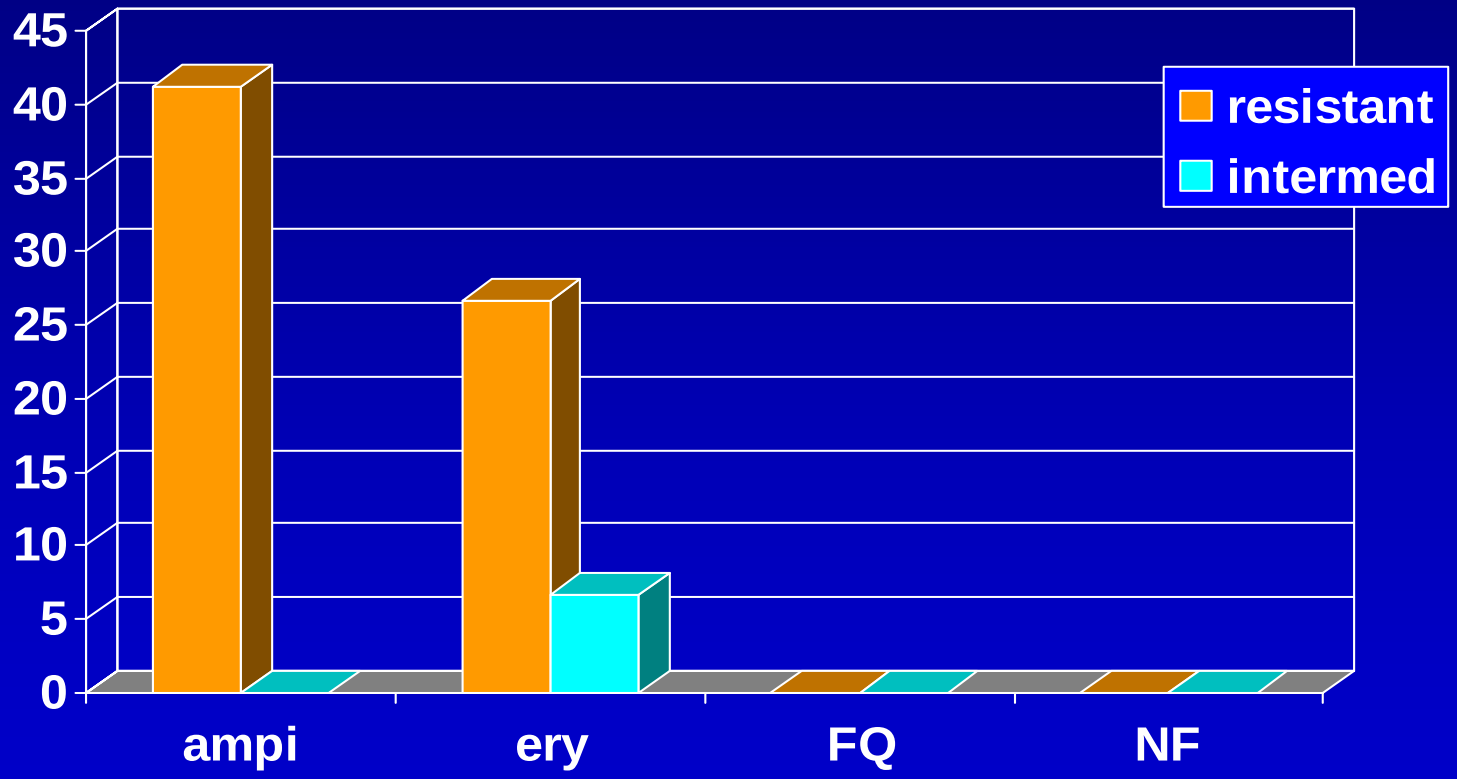
# *Proteus* resistance: lab vs GP



# *E. Coli* resistance for all ages in general practice



# *S. Saprophyticus* resistance for all ages in general practice



# *E. Coli* resistance for all ages in general practice