Recurrent UTI in Adult Women: Contemporary Management & Future Prospects

Chris Harding

What is the definition of recurrent UTI (rUTI)?

- No universally accepted definition
- Most commonly used is “2 in 6 months or 3 in a year”

Schoof and Hill 2005
Hooton and Stamm 2006

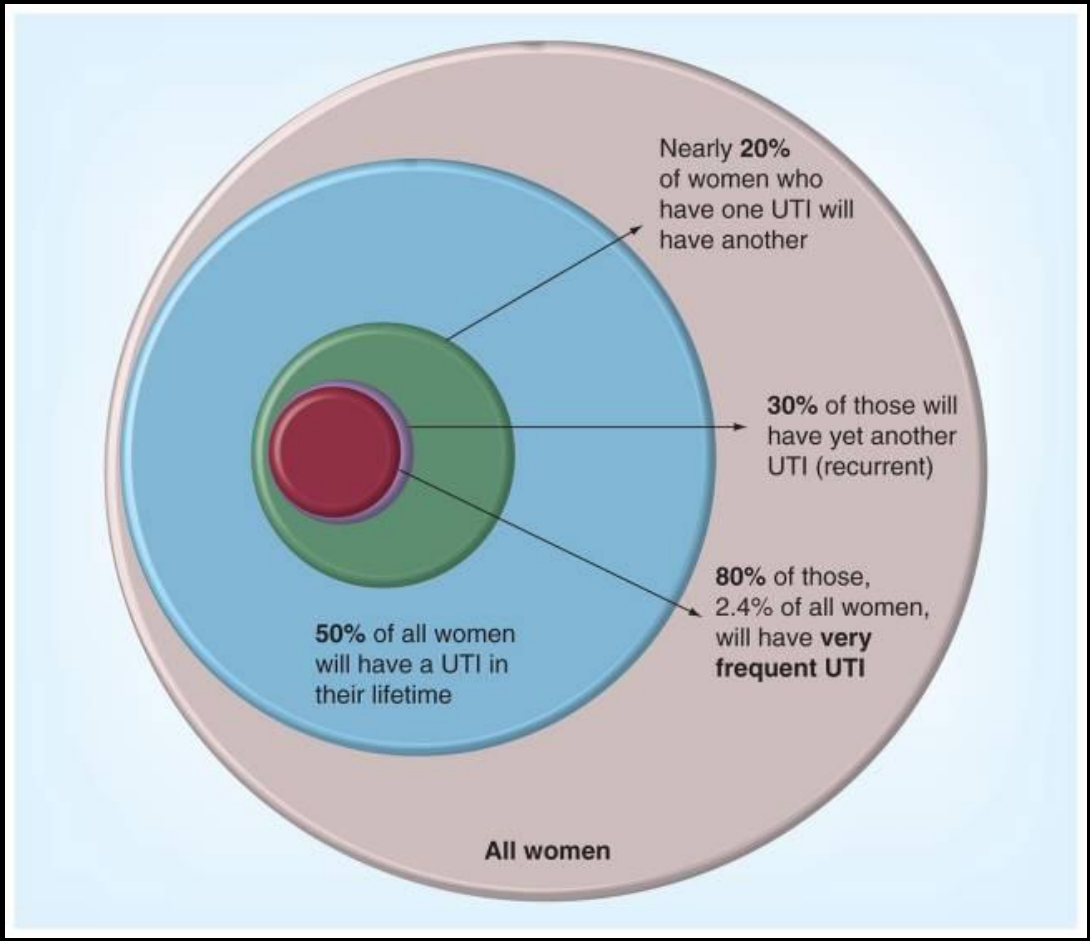
- Estimated 20-50% of young women with UTI will have another within a year

Mabeck *et al* Postgrad Med J 1972.
Brumbaugh and Mobley Expert Rev Vaccines. 2012.

- Finnish study showed older (>55yrs) more likely to have recurrence in first year (53% vs 36%)

Ikaheimo Clin Infect Dis 1996

Common Problem



Expert Rev Vaccines. 2012; 11(6): 663–676.

Antibiotic Resistance in Cystitis

ECO.SENS – 2003/11 N.-Europe, Canada	NAUTICA – 2006 USA, Canada	ARESC – 2008 Europe, Brazil
SRGA standard	CLSI standard	CLSI standard
Ampicillin – 26/28%	Ampicillin – 38%	Ampicillin – 51%
TMP/SMX – 13/17%	TMP/SMX – 21%	TMP/SMX – 29%
Nalidixic acid – 4/10% Ciprofloxacin – 1/4%	Nalidixic acid – n.d. Ciprofloxacin – 5%	Nalidixic acid – 18% Ciprofloxacin – 8%
Nitrofurantoin – 1/0.3% Mecillinam – 2/1% Fosfomycin – 0.4/1%	Nitrofurantoin – 1% Mecillinam – n.d. Fosfomycin – n.d.	Nitrofurantoin – 5% Mecillinam – 3% Fosfomycin – 1%

GG Zhanel et al. Int J Antimicrob Agents. 2005; 26(5):380-8.
KG Naber et al. Eur Urol. 2008; 54(5):1164-75.
G Kahlmeter et al. Int J Antimicrob Agents. 2012; 39(1):45-51.

Global Risks 2014
Ninth Edition

WORLD ECONOMIC FORUM
COMMITTED TO IMPROVING THE STATE OF THE WORLD

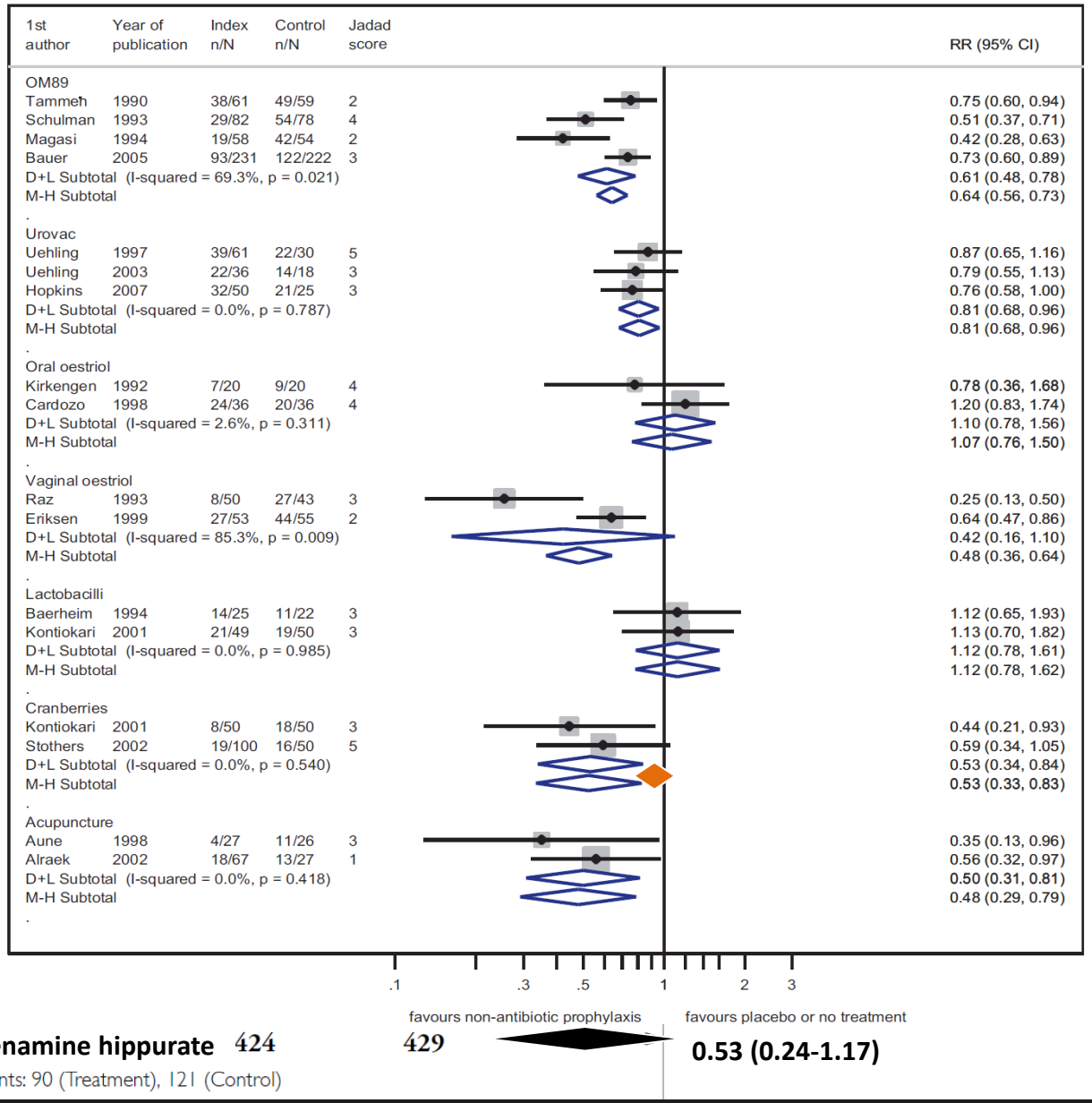
Societal Risks

Contemporary Management

Contemporary Management

- Non-antibiotic (and non-invasive)
  - Cranberry Products
  - Topical Oestrogens
  - Methenamine Hippurate
  - Vaccines
- Antibiotics
  - Prophylactic Antibiotics
  - Self Start Therapy
- Intravesical agents

Non-antibiotic prophylaxis



Outcome
= Clinical UTI
during prophylaxis

Beerepoot et al
J Urol 2013; 190: 1981-1989

Jepson RG. *Cochrane Database of Systematic Reviews* 2012, Issue 10. Art. No.: CD001321.

Cranberry Products

- Postulated to acidify urine and reduce bacterial adhesion/prevent fimbrial expression
- Some evidence that rUTIs reduced but optimum dose /duration unclear.
- Original Cochrane review (2008) identified *some benefit*

  BUT

  Meta-analyses in updated review (2012) showed that compared with placebo, water or non-treatment,

  "cranberry products did not significantly reduce the occurrence of symptomatic UTI overall" (RR 0.86, 95% CI 0.71 to 1.04)

Topical Oestrogens

- Falling oestrogen levels lead to a change in vaginal flora and pH
- Local oestrogen can reverse this without SE of systemic oestrogen

Esposito *et al.* Gynaecological Endocrinology 1991

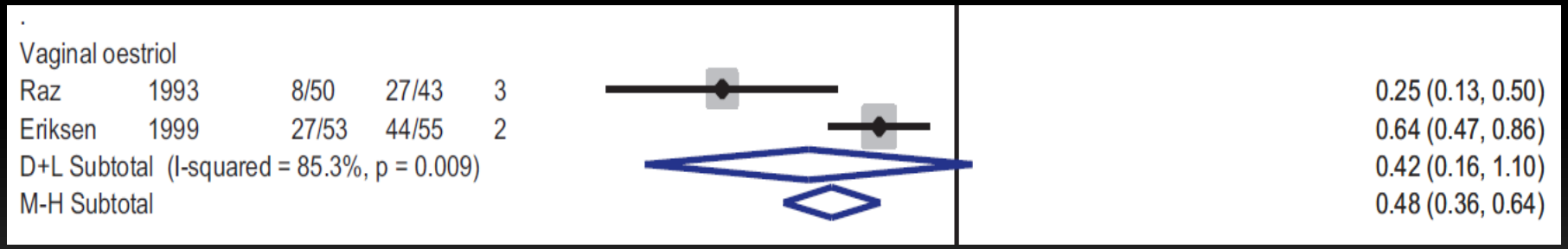
- Oestrogen may also enhance innate immune mechanisms against urinary tract infection

Lüthje *et al.* Science Translational Medicine 2013

- Systematic review found no reduction in UTIs with oral oestrogen but showed vaginal preparations superior to placebo

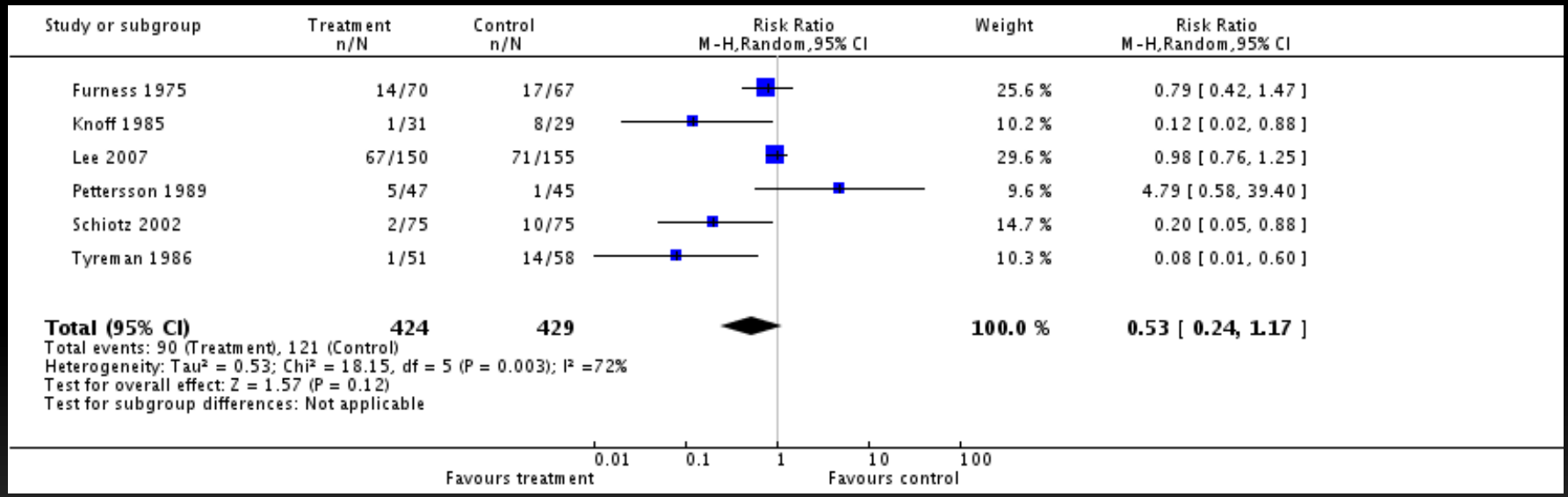
  (RR 0.25/0.64)

Perrotta *et al.* Cochrane Database 2008



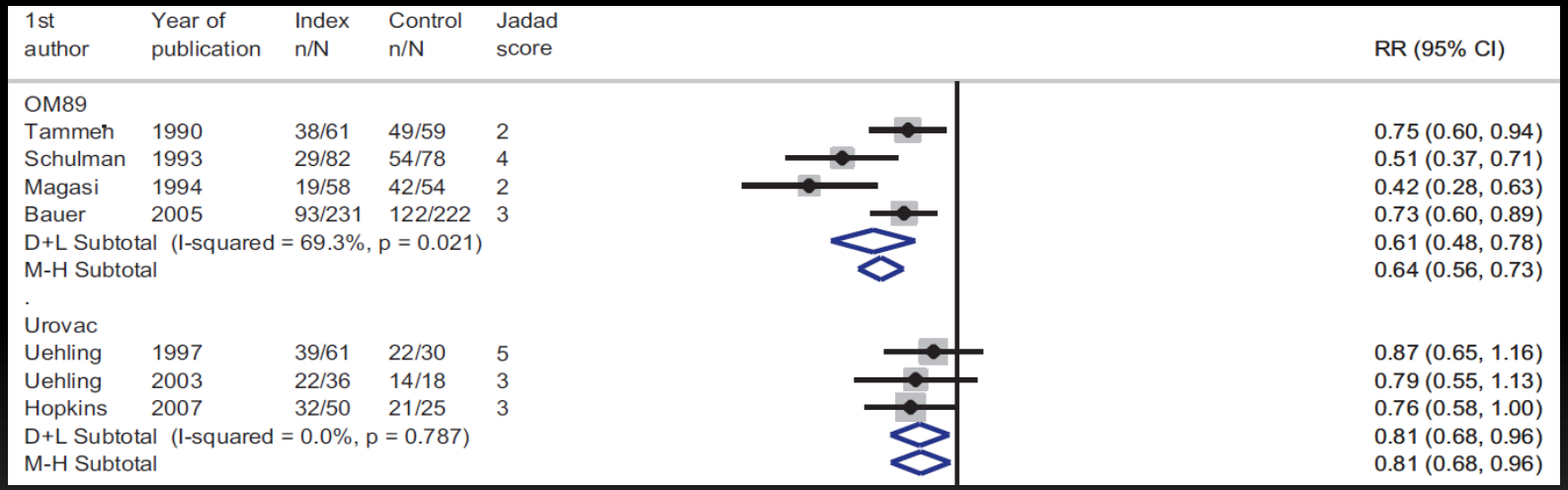
Methenamine Hippurate

- Methenamine has antibacterial properties - hydrolysed to formaldehyde in acid urine
- Systematic review highlighted heterogeneity of data *but* ***so*me studies report reduction in symptomatic UTIs (RR 0.24)**
- ? Ineffective in pts with neuropathic bladder / abnormal renal tract.
- **"There is a need for further large well-conducted RCTs to clarify…"**



Vaccines

- Uro Vaxom® (OM-89) is only one recommended by EAU guidelines EAU Guidelines Urological Infections 2015
- Oral administration of immunologically active bacterial lysates of 18 *E coli* strains . Better than placebo in several RCTs.
- The vaginal vaccine Urovac® slightly reduced UTI recurrence and increased time to re-infection.
- New agent, UROMUNE® (under the tongue spray) currently undergoing multi-centre trials in Spain.



Prophylactic Antibiotics

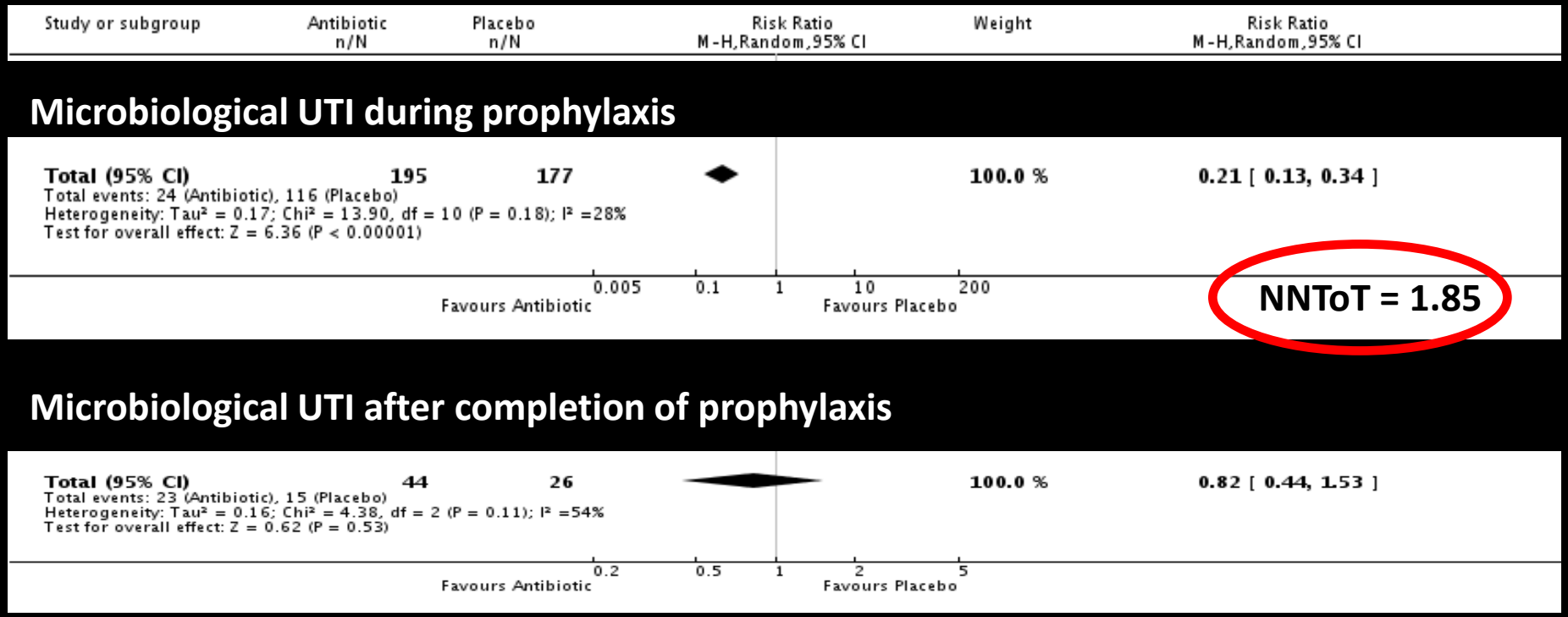
- Long term prophylaxis can range from 4 mths to 5 yrs!!
- 95% will remain UTI free but 50% relapse following cessation

  Nicolle *et al.* Am J Med 2002
- Cochrane review of RCT's - RR 0.21 for single recurrence (NNT 1.85) but RR after prophylaxis 0.82

  Albert *et al*. Cochrane Database 2004
- Single randomised study found prophylactic nitrofurantoin superior to oestrogen

  Raz *et al.* Clin Infect Dis 2003

Antibiotic prophylaxis



Albert *et al* . Cochrane Database Syst Rev. 2004;(3):CD001209

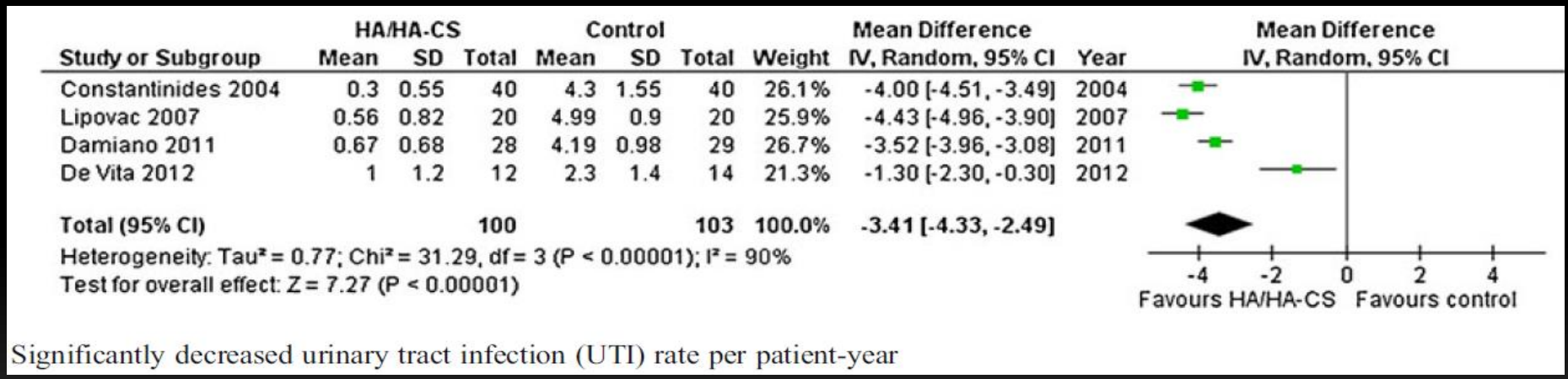
Self Start Antibiotics

- 85-95% of women with previous UTI can self diagnose successfully Gupta *et al.* Ann Intern Med 2001
- Clinical and Microbiological cure rates > 90%
- Best used in motivated women with previous culture confirmed cystitis Hooton NEJM 2012
- Advantages are less antimicrobial exposure and high patient satisfaction rates
- Post coital antibiotics reserved for group where it has been identified as the dominant risk factor.

Intravesical Treatments

- Glycosaminoglycan hyaluronic acid (HA) and chondroitin sulphate (CS) used to enhance protective function of urothelium. GAG layer damage / deficiency may be aetiological in rUTI.
- Agents available: Cystistat® (HA), Hyacyst® (HA), Gepan® (CS), iAluril® (HA &CS)
- Systematic review demonstrates ↓cystitis recurrence, UTI recurrence, and Pelvic Pain & Urgency/Frequency (PUF) total score.

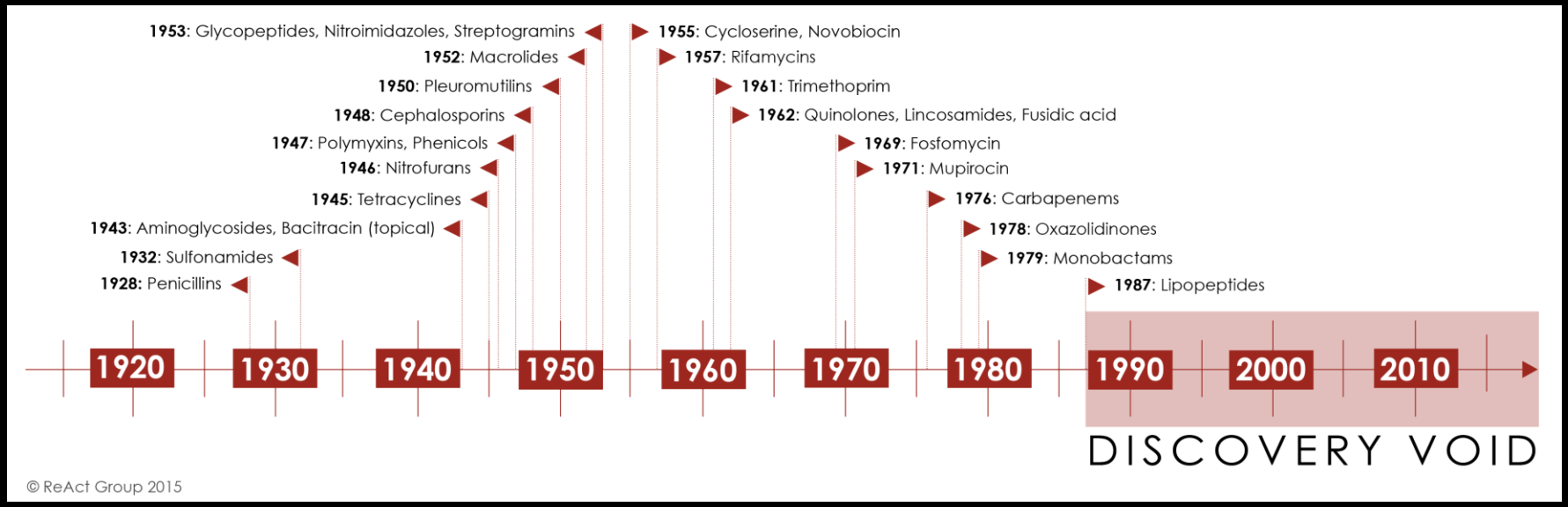
  De Vita *et al.* Int Urogynecol J. 2013.
- Study limitations include the small no. of pts and possible bias. **"Further studies needed to validate this promising treatment..."**



Significantly decreased urinary tract infection (UTI) rate per patient-year

Future Prospects

New Antibiotics?

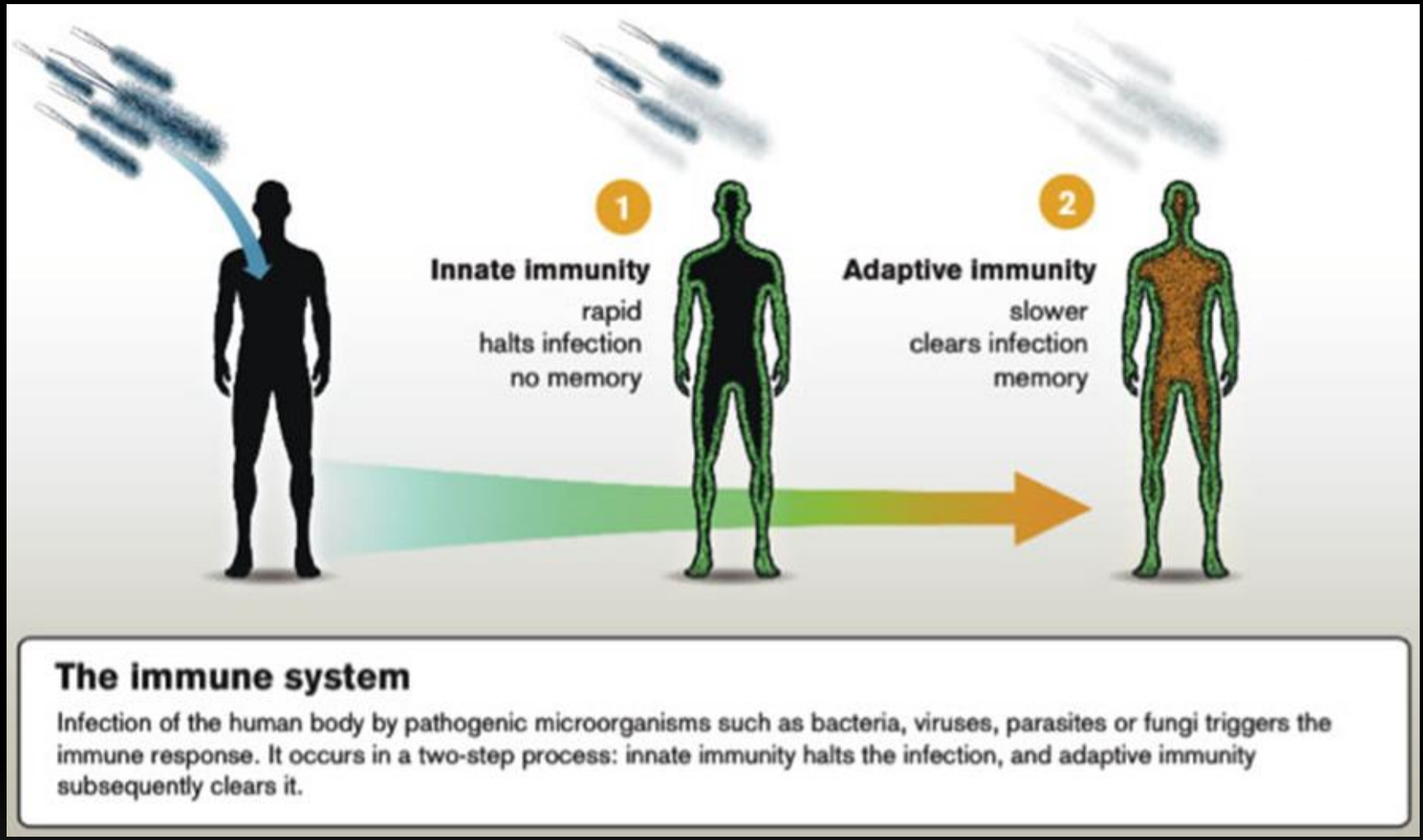


Unlikely….

Future Prospects

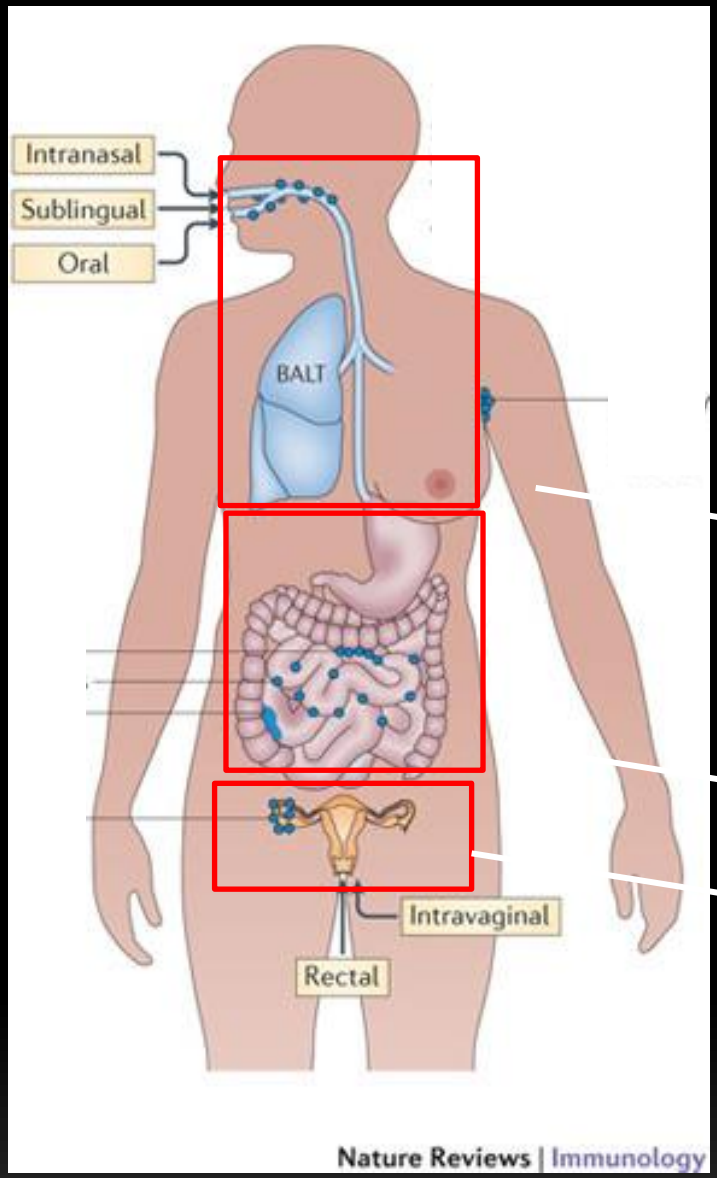
- Vaccination
  - Mucosal multivalent bacterial vaccine
  - Virulence factor vaccines
- Bacterial Adhesion Inhibitors
- Immune Modulation
  - Boosting bacterial expulsion
  - Exogenous enhancement of innate immunity
- Natural flora modulation
  - Probiotics
  - Gastrointestinal decolonisation
- Acupuncture

Importance of Innate Immunity



http://www.usbio.net/misc/nobel-prize-in-physiology-or-medicine-2011

Mucosal Immunisation

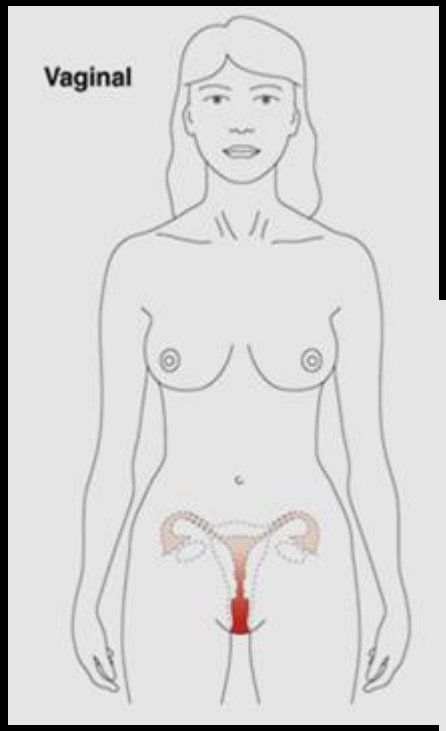


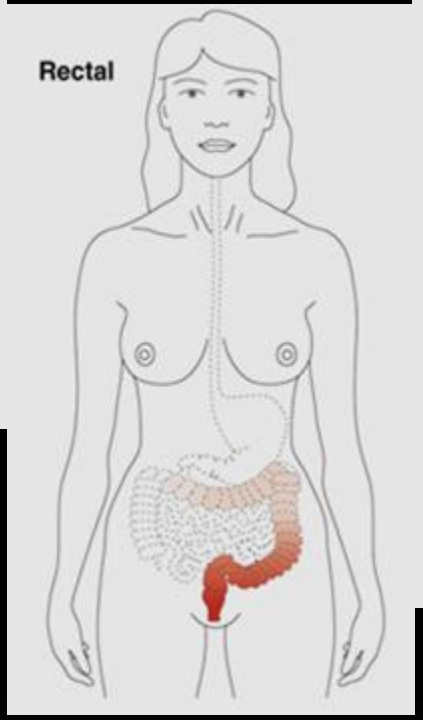
300 m^2

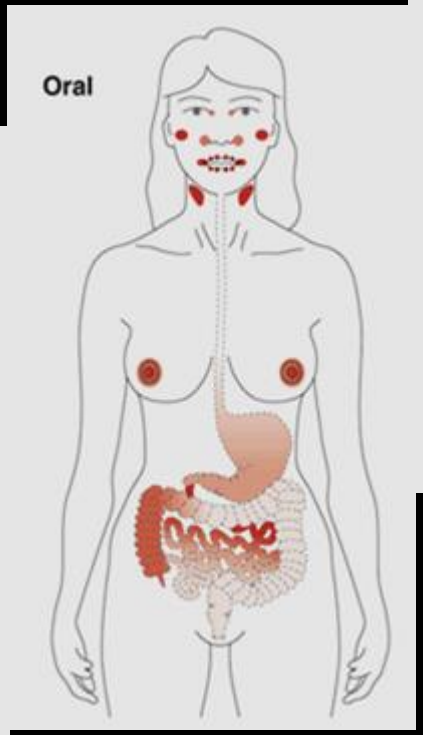
Respiratory

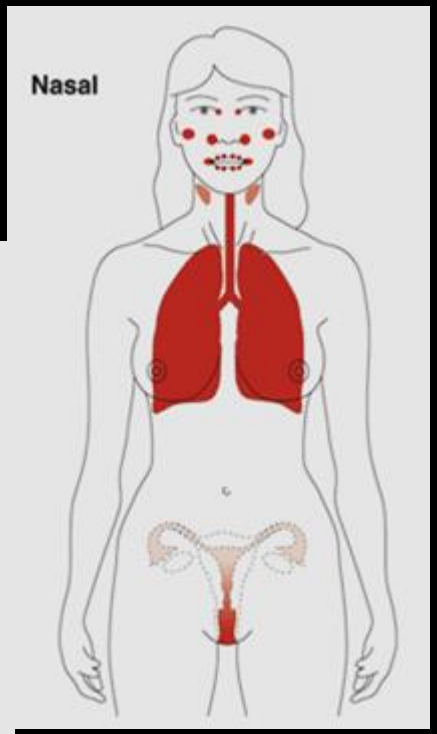
Digestive

Genitourinary





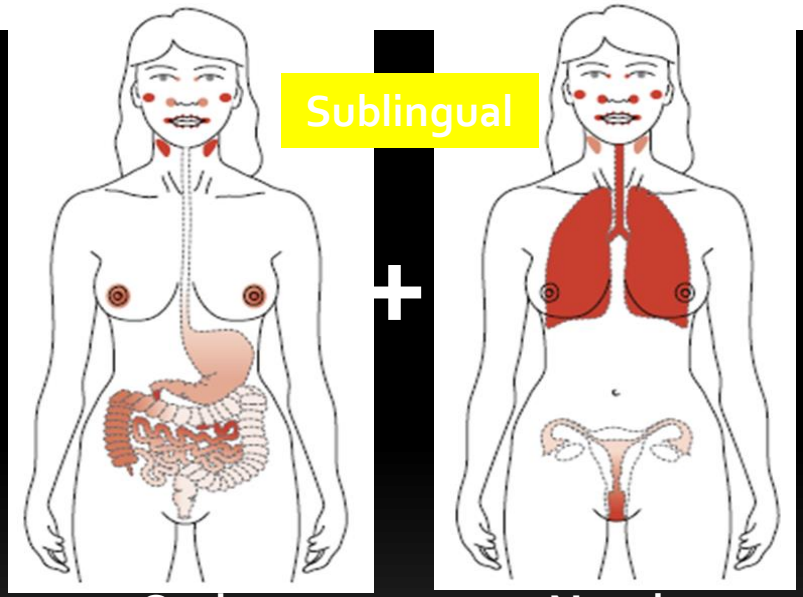




Holmgren et al. Nat Med 2005

Table 1. Comparative anatomic dissemination of the mucosal SIgA antibody response after different routes of immunization

	Sublingual	Nasal	Oral
Upper respiratory	+++	+++	-
Lower respiratory	+++	+ to +++	-
Stomach	+/+++	-	+/+++
Small intestine	+++	-	+++
Colon	?	-	±
Rectum	?	-	±
Genital tract	+++	++	-
Blood	++	+++	+



Çuburu et al. Vaccine, 2007
Czerkinsky et al. Human Vaccines, 2011

Uromune®
Multivalent Bacterial vaccine

A suspension of selected strains of 10^9 inactivated bacteria/mL, for mucosal oral/sublingual administration (spray).

- ***Escherichia coli***
- ***Klebsiella pneumoniae***
- ***Proteus vulgaris***
- ***Enterococcus faecalis***

Int Urogynecol J (2013) 24:127–134
DOI 10.1007/s00192-012-1853-5

ORIGINAL ARTICLE

Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics

M. F. Lorenzo-Gómez · B. Padilla-Fernández · F. J. García-Criado · J. A. Mirón-Canelo · A. Gil-Vicente · A. Nieto-Huertos · J. M. Silva-Abuin

Received: 11 April 2012 / Accepted: 3 June 2012 / Published online: 18 July 2012

Uromune® - 15month Trial

- Observational retrospective study
- 319 patients with prophylactic treatment:
- Uromune: 159 patients treated during 3 months (group A)
- SMX/TMP: 160 patients treated during 6 months (group B)
- Evaluation variables:
  - Number of UTIs before the treatment.
  - Number of episodes of UTI after the initiation of treatment.
  - Number of positives urocultures (UC+).
- Data collection:
  - Before the treatment's beginning.
  - After 3, 9 and 15 months of treatment's initiation.

Uromune® - Patients' Epidemiological Data (before treatment)

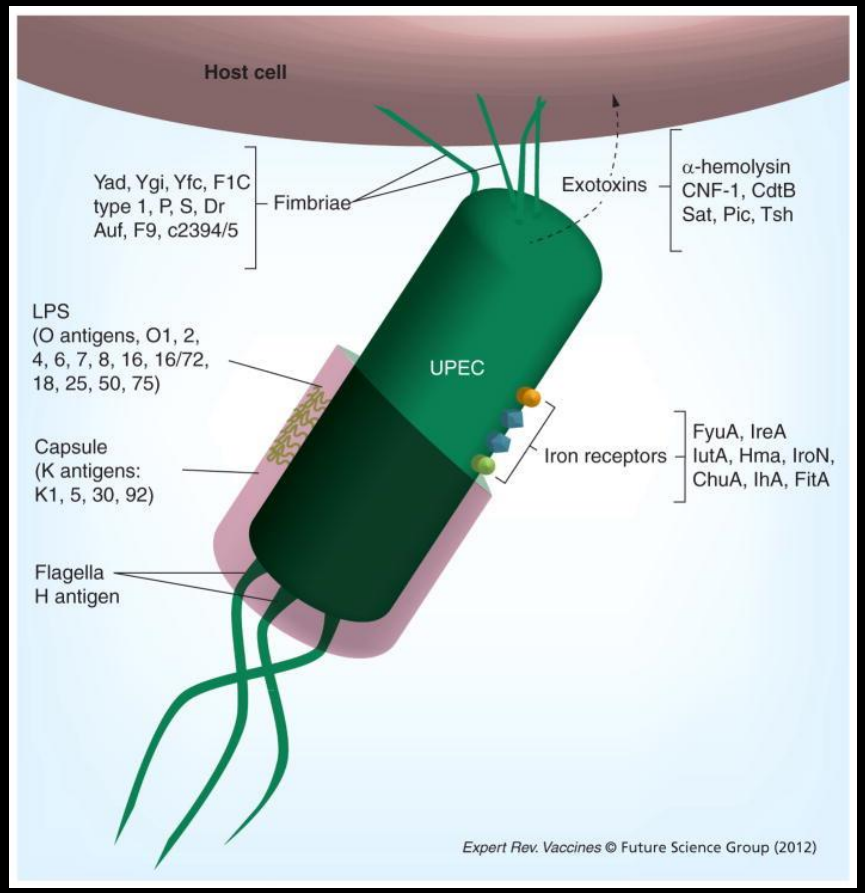
	A (Uromune)	B (SMX/TMP)	*P*
Age (years)	47.7	48.1	0.8536
Range of age	16-85	16-87	
Months of evolution	56.7	59.2	0.7641
Average of UTI in 6M	3.2	3.1	0.2789
Average of UC+ in 6M	2.4	2.2	0.6392
Average of UTI/month	0.53	0.51	0.6408
Average of UC+/month	0.41	0.36	0.2788

Uromune® - Trial Results

- Average number of episodes of UTI/month.

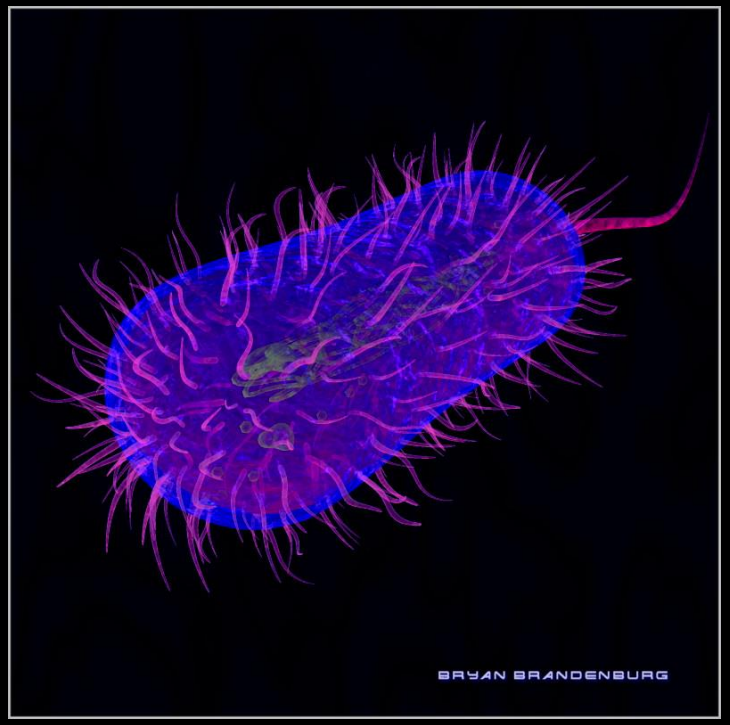
	Uromune	SMX/TMP	*P*
Pre	0.53	0.51	0.6408
0 to 3M	0.12	0.53	<0.0001
0 to 9M	0.08	0.41	<0.0001
0 to 15M	0.09	0.38	<0.0001
3 to 9M	0.06	0.35	<0.0001
3 to 15M	0.08	0.35	<0.0001
9 to 15M	0.10	0.34	<0.0001

Vaccination Against Virulence Factors

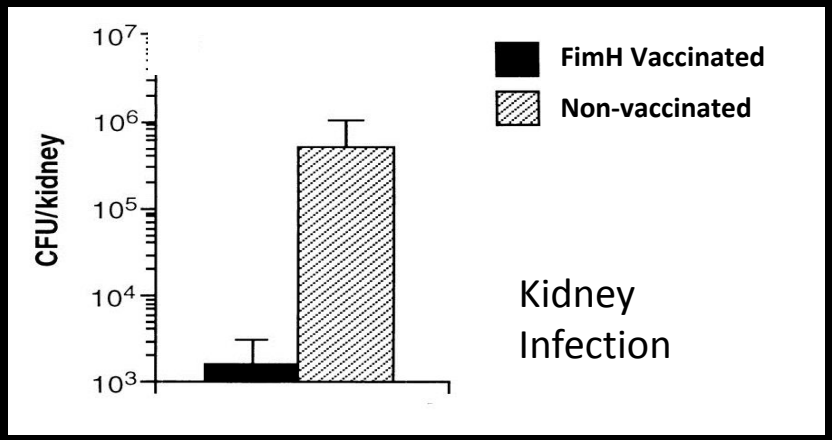


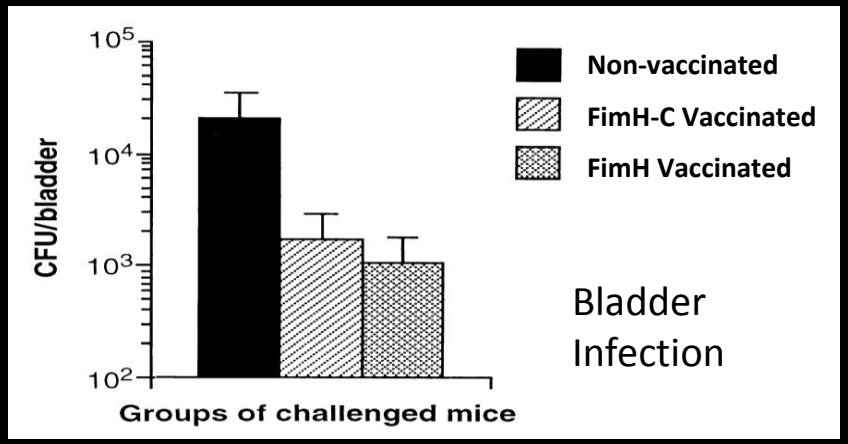
Fimbriae

- **Fimbriae or Pili** are Filamentous organelles expressed on the surface of gram-negative bacteria and mediate attachment to host tissues.
- First described by Duguid et al. in 1955
- Found on a variety of gram-negative bacteria including saprophytes, commensals and pathogens.
- Adhesin (FimH) binds to mannose oligosacchaarides attached to uroplakin on surface of urinary bladder epithelium



FimH Vaccine

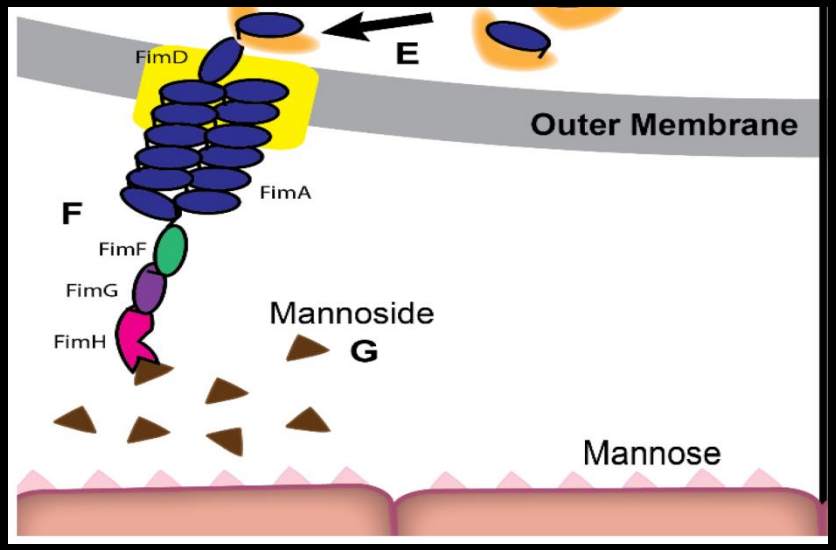




Solomon Langermann et al. Science 276:607-611

- Fimbrial adhesin FimH has been used as an effective vaccine antigen in mouse models.
- Less immmunogenicity and lack of safe & effective adjuvant has prevented use in humans.
- Several new safe and efficacious adjuvants for human use, which will faciitate use of FimH vaccines in clinical trials.

Bacterial Adhesion Inhibitors



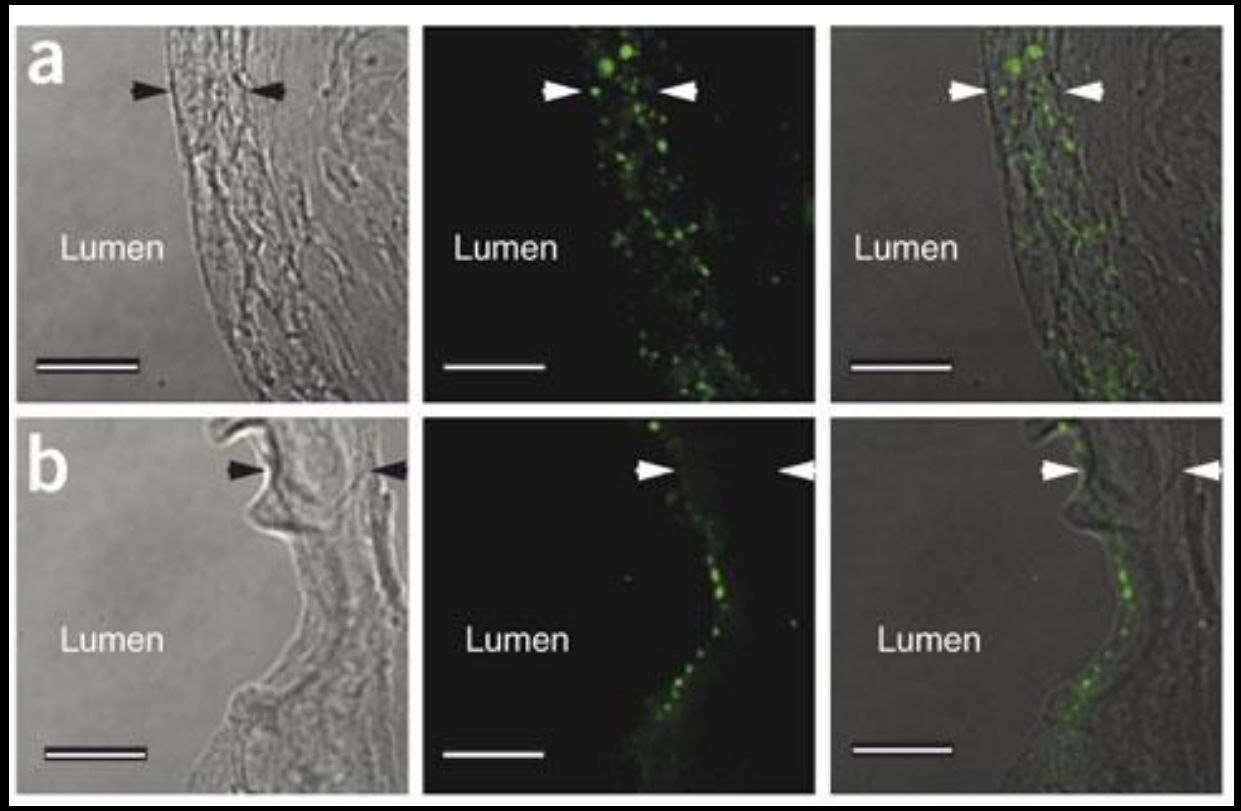
Spaulding and Hultgren Pathogens 2016; 5(1), 30.

- FimH-mediated cellular adhesion to mannosylated proteins is critical for uropathogenic E. coli (UPEC) to invade bladder epithelium.
- Small-molecule FimH bacterial adhesion antagonists, mannosides, have been developed and awaiting trials.

Immune Modulation: Boosting Bacterial Expulsion

- Expulsion of intracellular *E. coli* in urothelial cells can be greatly accelerated by increasing intracellular cAMP levels.
- Forskolin originates from the Asiatic herb Coleus forskohlii, used for centuries as an Ayurvedic medication to treat a various ailments, including 'painful micturition’
- In *E. coli* infected mice treated systemically or intravesically with forskolin after infection, up to 90% of the bacterial burden was reduced compared to controls.

cAMP Mediated Expulsion of *E. coli*

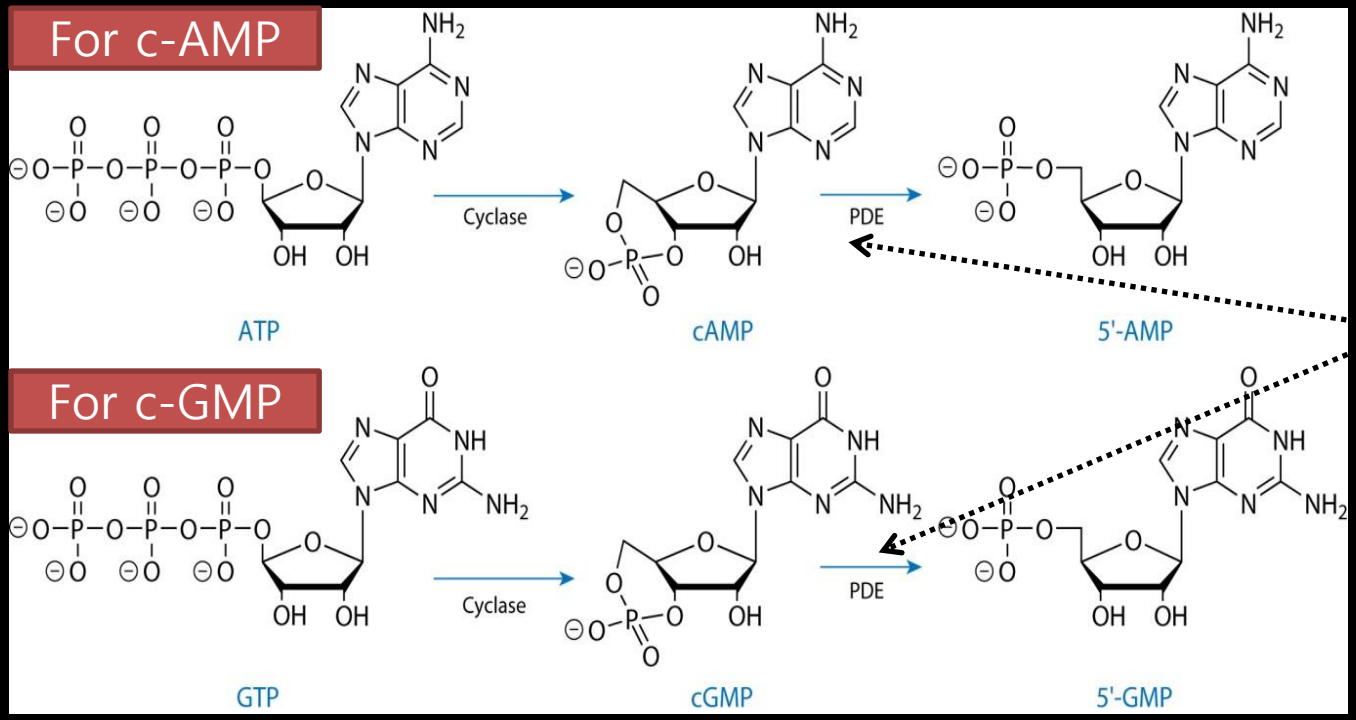


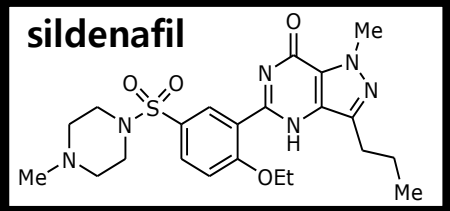
Without Forskolin

With Forskolin

Like Forskolin, Phosphodiesterase inhibitors can also increase intracellular cAMP levels….

PDEs & c-AMP and c-GMP

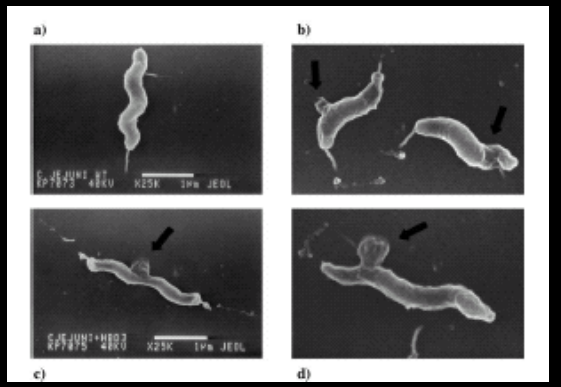




- Could we use Sildenafil or another PDE inhibitor in UTI?

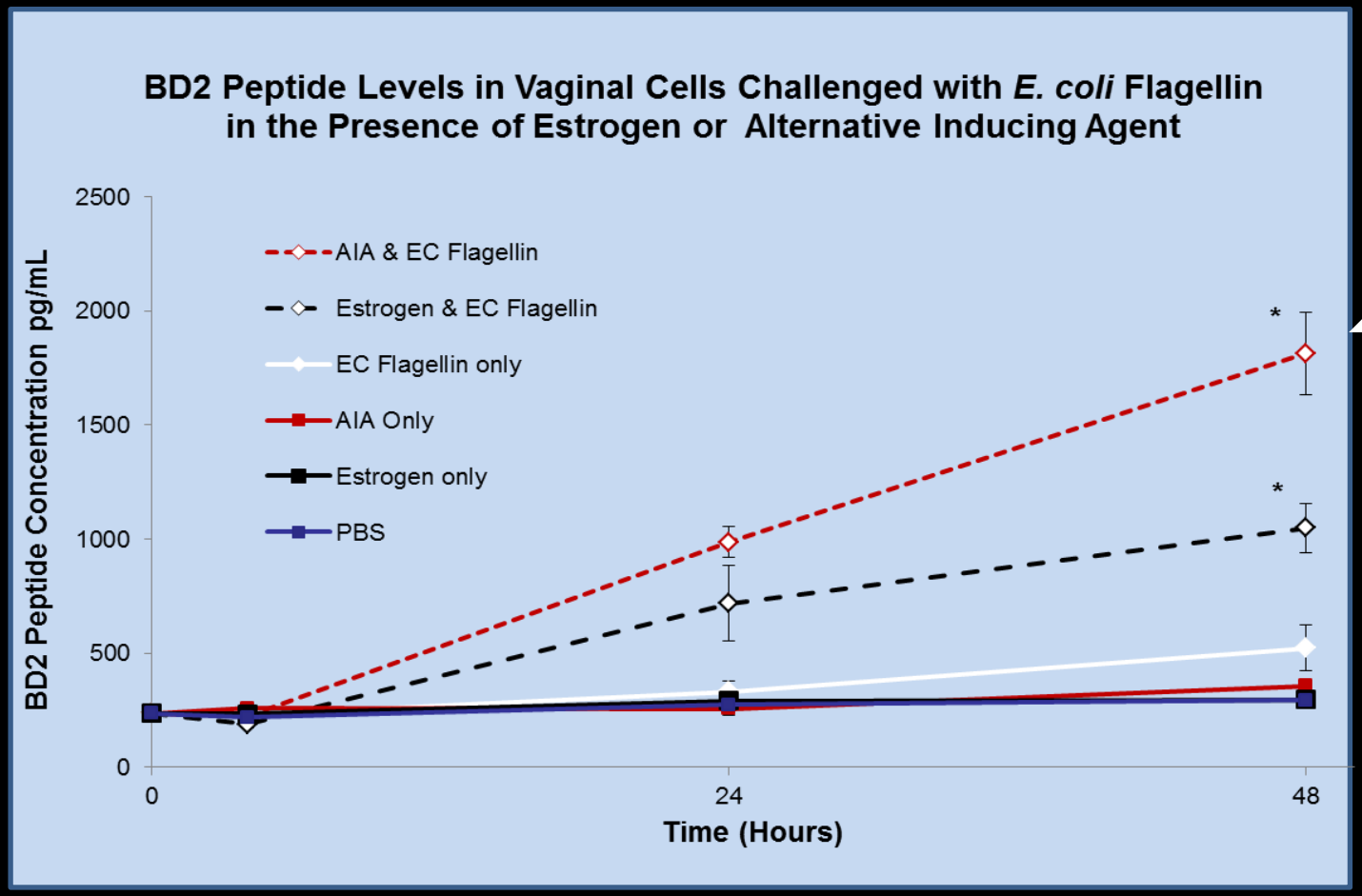
Immune Modulation: Exogenous Enhancement of Innate Immunity

- Innate immunity provides the immediate defences against infection and is the most important part of the body's response to UTI.
- Over the past 5-years, greater realisation that Estrogen enhances innate immunity. In particular, Estrogen enhances secretion of antimicrobial peptides (AMPs) in bladder and vaginal cells
- **Antimicrobial peptides are:**
  - Gene encoded 'natural antibiotics' secreted at epithelial surfaces.
  - Small, +ve charged (cationic) molecules
  - Broad spectrum (kill gram +ve & –ve bacteria, fungi & some viruses)
  - Target & disrupt microbial membranes



Membrane disruption in bacteria incubated with antimicrobial peptide

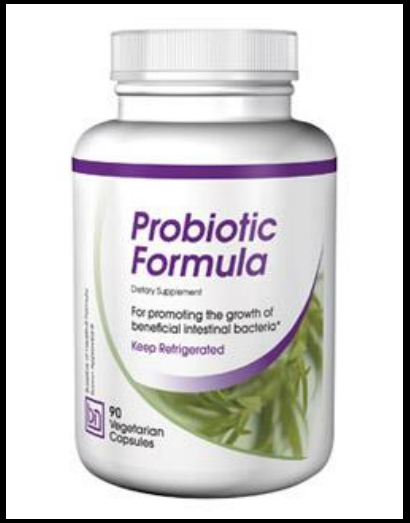
Exogenous Enhancement of Innate Immunity



In Newcastle University, Hyaluronic acid has been used to induce innate immune defences.

Probiotics

- Probiotic therapy and faecal transplant used successfully in treating severe *C.dificile* and pseudomembranous colitis.
- UTIs often preceded by presence of pathogenic microbiota in the vagina and urethra.
- Possible prevention strategy could be to normalise vaginal and urethral microflora by direct administration of probiotics
- Possibilities:
  - Innoculate asymtomatic bacteruria (ABU) strains of *E. coli* into bladder
  - Use commensal Lactobacilli in vagina to ‘out-colonise’ *E. coli*
  - Oral probiotics to displace pathogenic *E. coli* in gut



Probiotics

- Randomised study of 100 women with a history of recurrent UTI
  - All received antimicrobials for acute UTI.
  - Randomised to receive either Lactin-V or placebo daily for 5 days then once weekly for 10 wks.
  - Participants were followed up at 1 and 10 wks after intervention and for UTIs
  - Urine samples for culture and vaginal swabs for real-time quantitative 16S ribosomal RNA gene polymerase chain reaction for Lactobacillus

Probiotics

Results

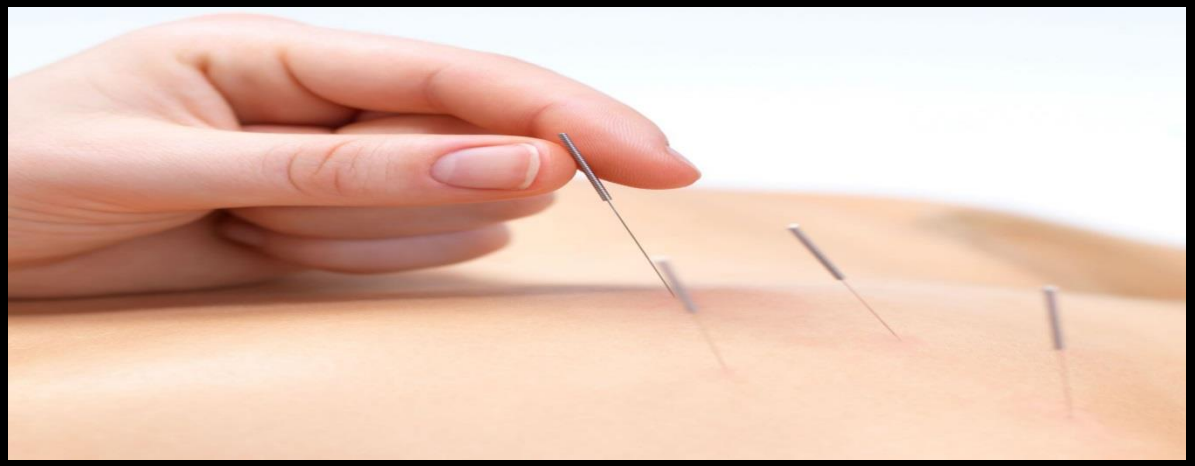
- Recurrent UTI occurred in 7/48 15% of women receiving Lactin-V vs 13/48 27% of women receiving placebo (relative risk [RR], .5; 95% confidence interval, .2–1.2).
- High-level vaginal colonisation with Lactobacillus was associated with significant reduction in rUTI (RR for Lactin-V, .07; RR for placebo, 1.1; $P < .01$).

Conclusion

- Authors concluded that “Lactin-V after treatment for cystitis is associated with a reduction in recurrent UTI.”
- EAU guidelines suggest that Lactobacillus may be used in rUTI where suitable preparations available

If all else fails, you could try….

Acupuncture



- In trial of acupuncture in female recurrent UTI, 67 pts received real acupuncture, sham acupuncture, or no treatment twice weekly for 4 weeks.
  - Real acupuncture - needles inserted to correct depth at known acupuncture points
  - Sham acupuncture - needles inserted superficially, outside known acupuncture points and without manipulation.
- **Real acupuncture significantly reduced UTI vs no treatment (RR 0.48, 95% CI 0.29–0.79).**
- Sham acupuncture comparable to no treatment.
- *Mechanism of action remains unclear* and larger well-designed double-blind randomized trials needed.

Alraek T, *et al.* Am. J. Public Health 2002, 92, 1609–1611.

Conclusions

- rUTI is prevalent in adult women.
- Non-antibiotic treatments preferable for recurrent UTI ***where possible…***
- Several treatment options exist for rUTI with varying levels of supporting evidence.
- Further RCTs are needed to evaluate these treatments.
- New non-antibiotics treatments on the horizon