

URINARY TRACT INFECTIONS

AN UPDATE ON MODERN CLINICAL PRACTICE

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INTRODUCTION

Urinary Tract Infections (UTIs) are the most common bacterial infectious disease worldwide

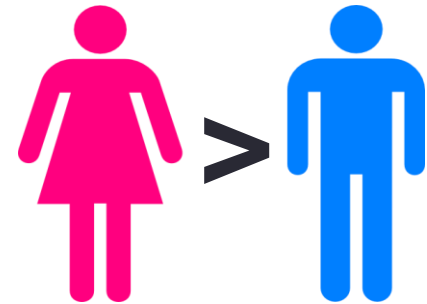
Affects disproportionately more women than men

Symptoms: Irritation, urgency, frequency, dysuria

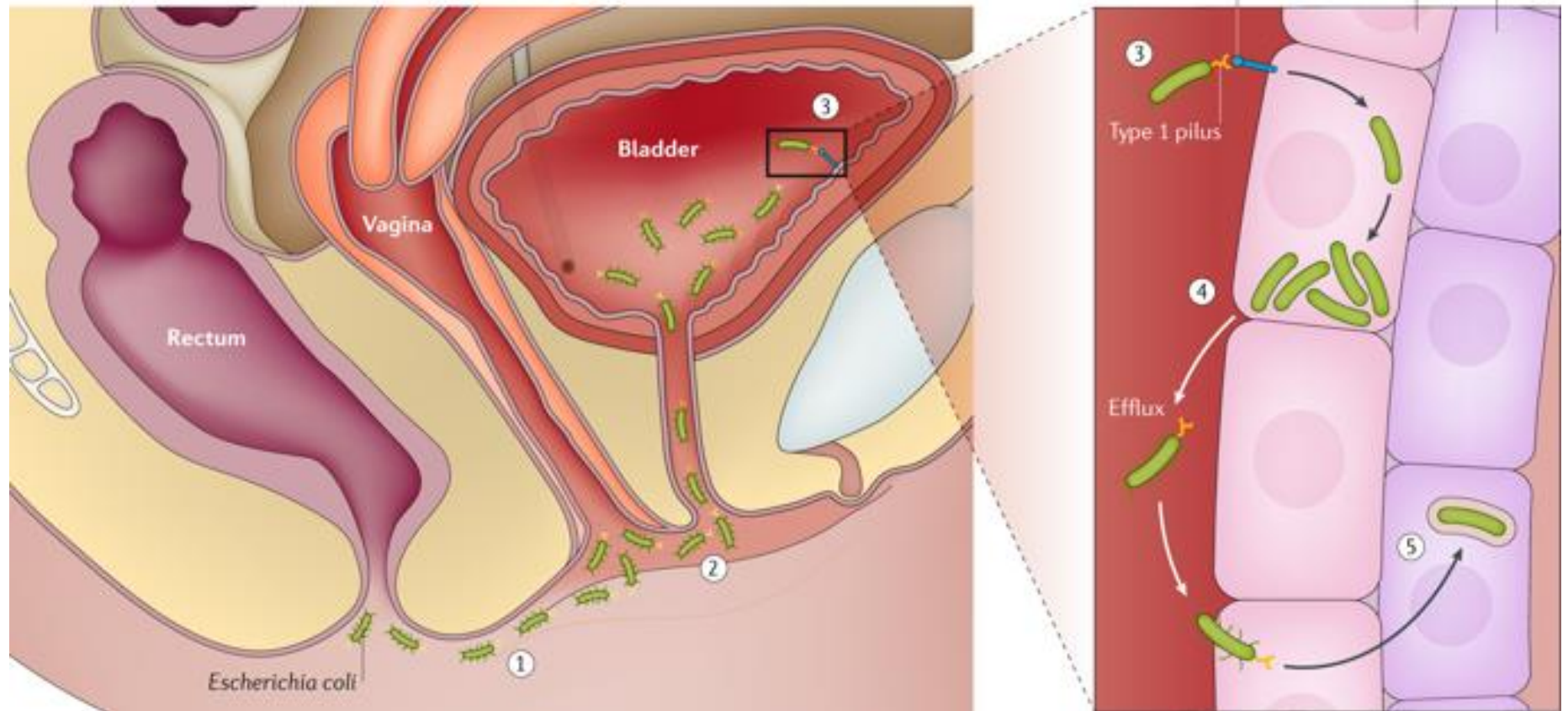
National Institute of Clinical Excellence (NICE) defines UTIs as “the presence of bacteria in the urine with a combination of clinical features indicating an infection of the urinary tract.”

Huge financial cost

- Most common presentation to primary care in UK and USA
- 50% women experience in lifetime



Pathophysiology of UTI in Women



Recurrent UTIs

- **Recurrent UTIs** = “three or more episodes of UTI during a twelve month period or two or more within 6 months”
- **Two types:**
 - Persistent (95%) – same organism
 - New – different organism
- Often requires **continuous low dose antibiotic prophylaxis, estrogen replacement, probiotics etc**
- Rising **resistance** triggered **WHO Global Action Plan**



World Health
Organization

Diagnosis

- Urine dipstick
 - **Leucocytes**: white cells in urine, neutrophils produce leucocyte esterase which reacts with dipstick
 - Sensitivity 50-70%
 - **Nitrites**: Gram negative bacteria converts urinary nitrates to nitrites
 - 92-100% specificity in literature to presence of infection
 - Sensitivity between 35-85% in literature – many bacteria unable to convert nitrates to nitrites
 - **Blood**: Present in severe infection from lining inflammation
 - False positives from malignancy, stones, renal disease, dehydration
- **MC&S** – gold standard for diagnosis
 - $>10^5$ /ml is deemed diagnostic for a UTI
 - Between 10^2 and 10^4 associated with infection
- **Asymptomatic positive MC&S** –20% of menopausal women

Imaging

- Indicated in:
 - Failure to respond to treatment
 - Recurrent infections
 - Critically ill patient
 - Suspicion of functional/structural abnormalities
- USS KUB – first line
 - Detects hydronephrosis, parenchymal abnormalities, peri-nephritic collections, ureteral dilatation, bladder wall abnormalities, calculi (user dependent, smaller ones often missed)
 - Requires full bladder to visualise lining and assess bladder contents
 - Measures post void residual

Imaging

- CT-Urogram – contrast study, with delayed phase to allow contrast opacification of ureter
 - Detects ureteric lesions/cause for hydronephrosis
 - Can also detect drainage and indirectly assess for PUJ-O
- CT – KUB – non contrast low resolution (often low dose) scan to detect stones
 - Can detect other intraabdominal issues (diverticulitis, AAA, appendicitis, masses, but poorer sensitivity)

Antibiotics

- Utilise according to local guidelines and previous sensitivities

Options to use in clinic

- **Trimethoprim** – resistance rates up to 70% in areas of UK
- **Nitrofurantoin** – warn of risk of lung fibrosis and hepatotoxicity from long term use, needs adequate renal function for use
- **Penicillin** – Also rising resistance rates (50% in areas of UK to amoxicillin)
- **Fluroquinolones** – especially good for prostatitis/epididymitis/orchitis. However warn patient of risk of tendon rupture with prolonged use
- **Cephalosporin** – similar MOA as penicillin, but less susceptible to B-Lactamases
- **Fosfomycin** – given as a STAT oral megadose

- **Aminoglycosides** – *gentamicin can be given IV or IM. Be aware of ototoxicity and nephrotoxicity with use.*

Preventive Measures

- Conservative
- Cranberry
- Hiprex
- D-Mannose
- Oestrogen
- Herbal

Conservative

- **Increase fluid intake** – advise to drink 2 - 3 litres per day overall.
 - In patients who drink less than 1.5L per day, advise an additional 1.5 litres to their usual fluid intake per day
- **Sexual hygiene** – increased coital frequency, sexual partners, use of diaphragms and spermicide increase risk of UTI.
 - Advise pre coital genital washing, post coital micturition, wiping front to back.
- **Personal hygiene** – advise care when shaving or using products around the genital-urinary region, regular underwear changes and avoid tight fitting undergarments.
- **Voiding** – advise techniques to reduce amount of residual urine in bladder post void, including double voiding, pelvic floor exercises and pelvic tilting
- **Weight loss** – higher risk of UTI and pyelonephritis if BMI over 30

Cranberry

Cranberry (*Vaccinium Macrocarpon*) – juices, tablets, capsules

- Active ingredient = **Proanthocyanidins (PAC)** within cranberry bind to bacterial P-Fimbriae – inhibiting adherence to bladder epithelial cells

2012 Cochrane – 4473 participants

NO significant difference found vs placebo, water etc

However cohort included complex patients (eg spinal cord injury, elderly, children etc)

2008 Cochrane review - 10 trials overall found a relative risk reduction of 0.65 (95% CI 0.46 to 0.90)

Did NOT include “complex” patients

Note: *quality of data lacking due to no standardization in type of cranberry product used and dosage*

All trials had high dropout rates



Hiprex

Methenamine Hippurate (Hiprex)

- Renal excretion of methanamine salts undergoes hydrolysis and formation of formaldehyde – bactericidal
- Hippuric acid acidifies urine, promotes hydrolysis of methanamine and has bacterial static effect in itself

2012 Cochrane – 2023 participants

Relative risk reduction of 0.24 in patients **ONLY** if no underlying anatomical abnormalities within renal tract.

Potentially more effective with Ascorbic acid (vitamin C) – further acidifies urine

1g BD (TDS if presence of indwelling catheter)



D-Mannose

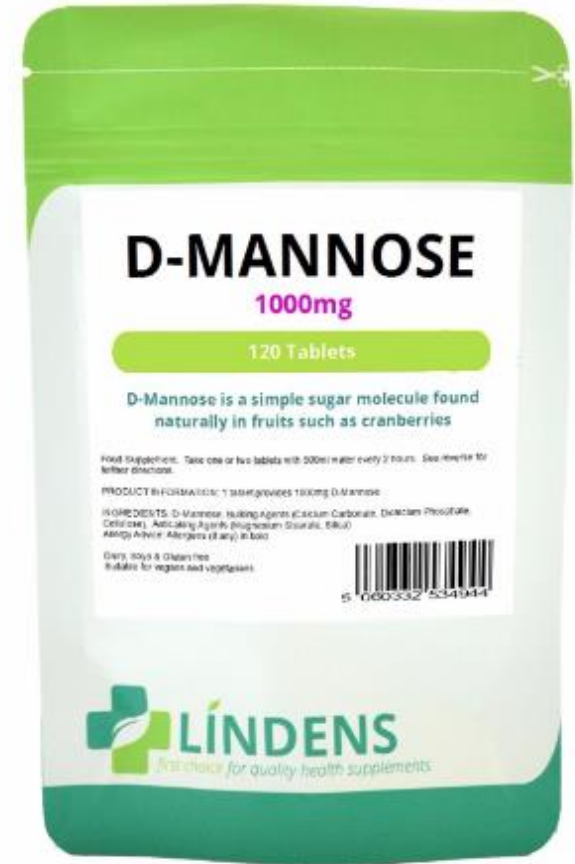
Natural sugar within human metabolism, inhibits adherence of bacteria to urothelial cells via inactivation of surface fimbriae

2014 RCT – 308 participants

2g dissolved in 200mls water daily significantly better vs nitrofurantoin prophylaxis and placebo

However still lacking more high quality placebo controlled RCTs

Note: *can be sold and given in combination with cranberry supplements!*



Oestrogen

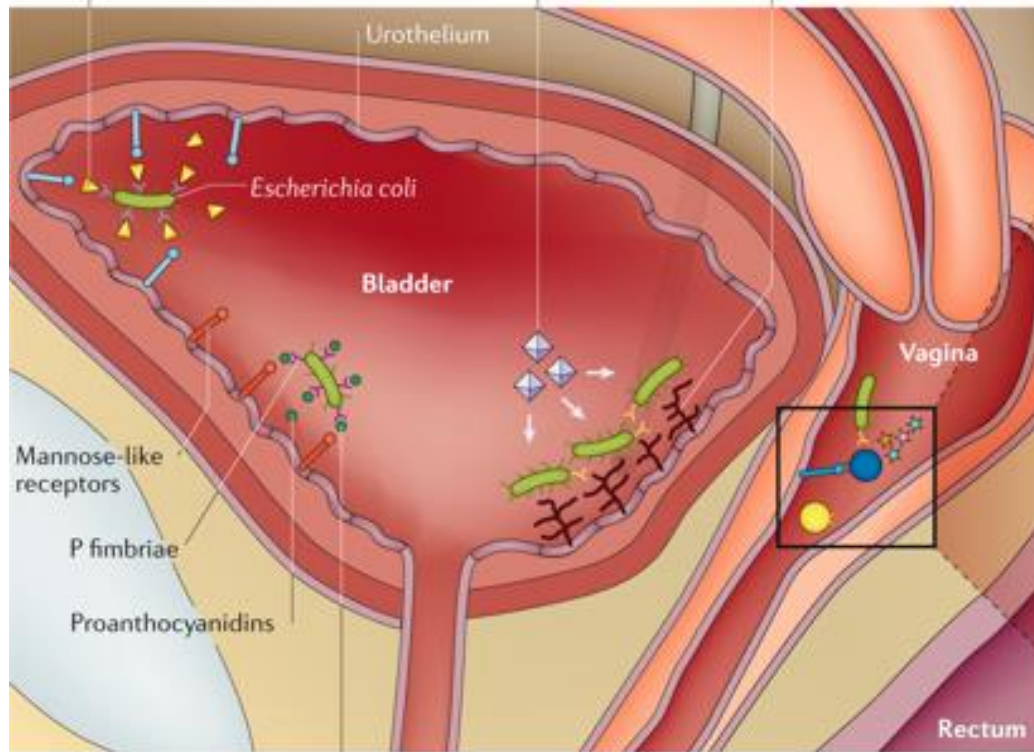
- Loss of protective acidic vaginal environment and *lactobacilli* after menopause due to low oestrogen levels
- Vaginal oestrogen: Cochrane study involving 3345 women.
 - When comparing vaginal oestrogen and placebo, reported vaginal oestrogen was effective at preventing recurrent UTIs
 - Risk reduction of between 0.25 (95% CI 0.13 to 0.50) and 0.64 (95% CI 0.47 to 0.86)
- Example: Vagifem 1 tablet daily for 2 weeks, then 1 tablet twice a week – administered vaginally

D-Mannose preventing *Escherichia coli* binding to urothelial receptors

Formaldehyde produced from methenamine hippurate prevents further bacterial growth

Glycosaminoglycan layer replacement preventing bacterial adherence

Lactobacilli preventing binding of *Escherichia coli* to vaginal epithelial adhesion receptors

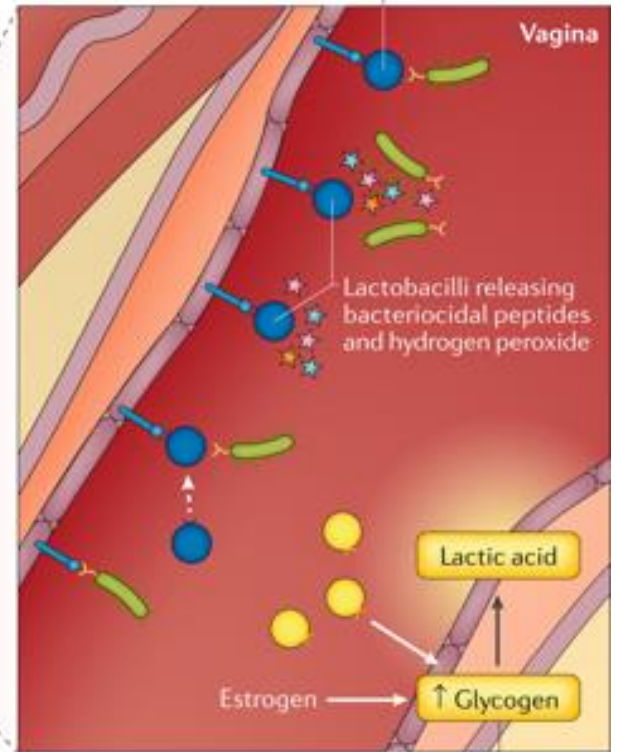


Mannose-like receptors

P fimbriae

Proanthocyanidins

Proanthocyanidins from cranberry preventing *Escherichia coli* binding to urothelial receptors



Estrogen causing increased glycogen storage and conversion of glycogen to lactic acid by lactobacilli

New antibiotic – free Preventatives

- Instillations
- Immuno-modulators (Vaccines)
- Vaginal Lasers

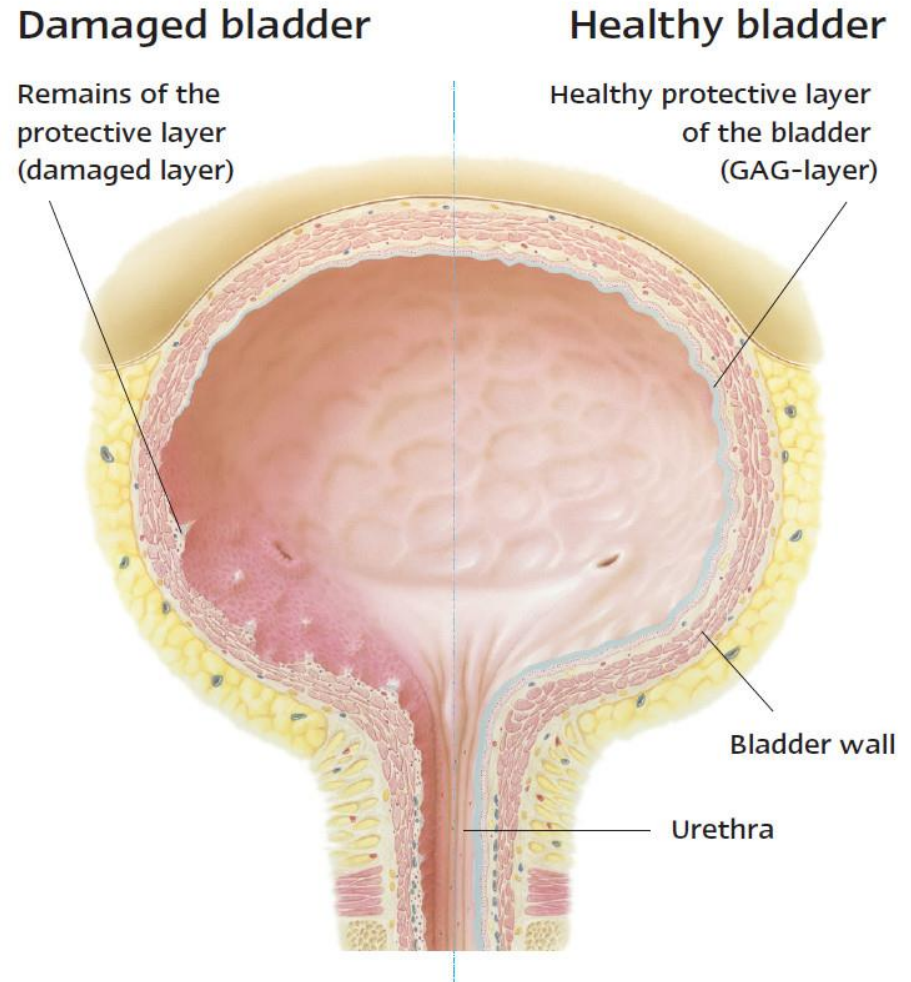
Intravesical instillation

Intact bladder epithelium and glycosaminoglycan (GAG) layer prevents bacterial adherence

Loss of this layer increases risk of rUTIs

Instillation of **Hyaluronic Acid** or **Chondroitin Sulphate** via catheter restores this layer

- Administered in outpatient clinic
- **Negatives:** Catheter related issues, invasive, requires clinic attendance



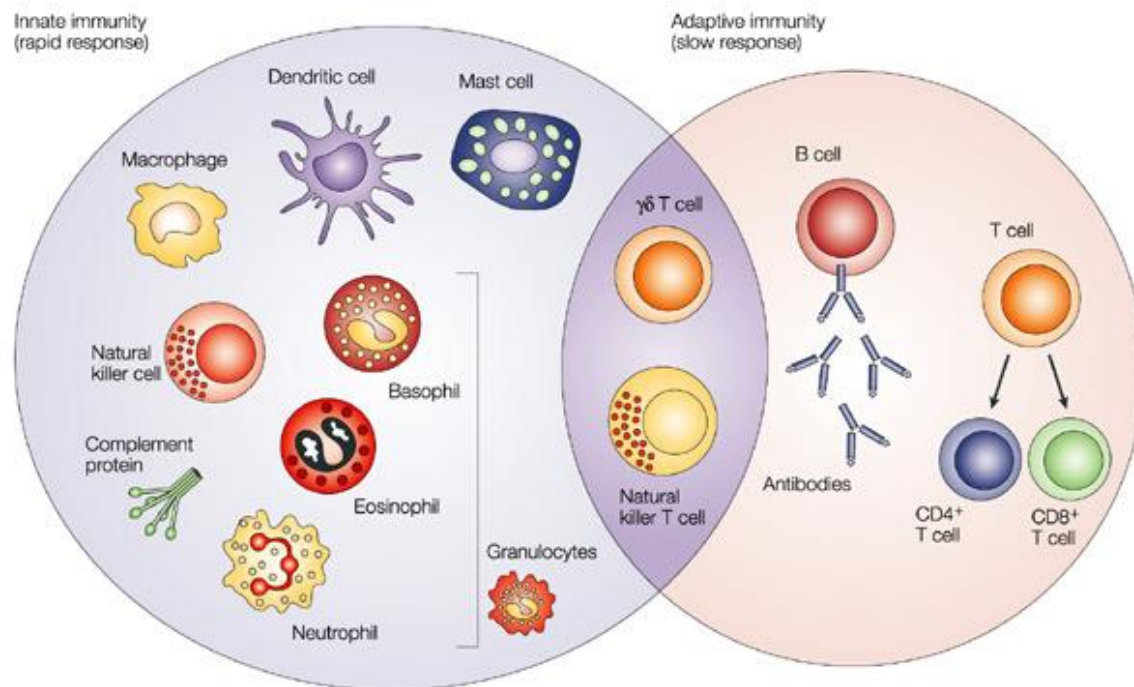
HA and CS – 2016 European Study

276 women – multi-centre across Europe

- Compared against low dose antibiotic prophylaxis
- **Reduced UTI recurrence risk by 49% over 12 month**
- Increasing number of instillations associated with better odds ratio at preventing recurrence
- *Only large study available to data which compared installation to antibiotic prophylaxis (current gold standard)*

Vaccines - Immunomodulation

- Utilise the most common strains of uropathogens, both surface antigen or inactivated whole bacterium, to induce a host immune response to prevent recurrent infections.



Vaccine options

- **UroVaxom®**
 - oral tablet
 - bacterial extracts from 18 strains of *Escherichia coli*
 - daily for 90 days.
 - use has been reported in the literature since 1990 and was found in the systematic review to reduce UTI recurrence rates the most (risk ratio [RR] 0.67, 95% CI 0.57–0.78). *BJU Int* 2019; 123: 753– 68

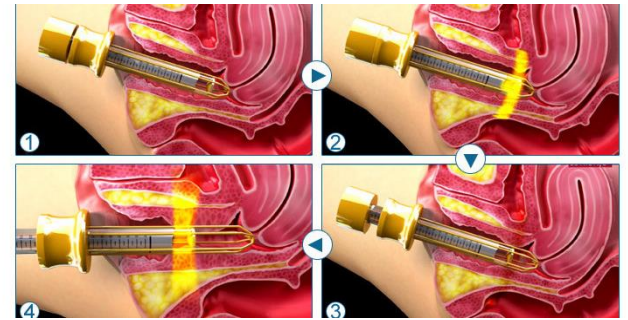
- **Urovac®**
 - 10 inactivated uropathogen strains including six *E. coli* strains and one *Proteus mirabilis*, *Morganella morganii*, *Enterococcus faecalis* and *Klebsiella pneumoniae*.
 - weekly vaginal suppository for three doses, followed by three booster doses at 6, 10 and 14 weeks.
 - effectively reduce UTI recurrence rates (RR 0.75, 95% CI 0.63–0.89).

Another vaccine option

- **Uromune®** (Syner-Med (PP) Ltd UK, Inmunotek S.L. Spain)
 - sublingual vaccine
 - Composed of inactivated *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Enterococcus faecalis*,
 - two large retrospective Spanish studies to decrease UTI recurrence by up to 90% when compared to antibiotic prophylaxis [SM J Clin Med 2016; 2: 1018].
 - A prospective UK observational study found after 3 months of daily administration, 78% of women developed no further UTIs in the 12-month follow-up period. BJU Int 2018; 121: 289– 92.
 - One international multicentre phase III RCT is currently underway, due to report in 2019/2020.

Vaginal Laser Therapy

- Fractional CO2 or YAG lasers
- Vulvovaginal **atrophy** and urinary **incontinence**
- **MOA:** controlled injury to the epithelium to stimulate tissue repair and remodelling.
- Similar pathway to **Estrogen replacement** therapy
- Early evidence of use in recurrent UTIs in **Post meno-pausal women**
- Benefit previous **breast cancer history** and cannot tolerate oestrogen



Thank you

Any Questions?