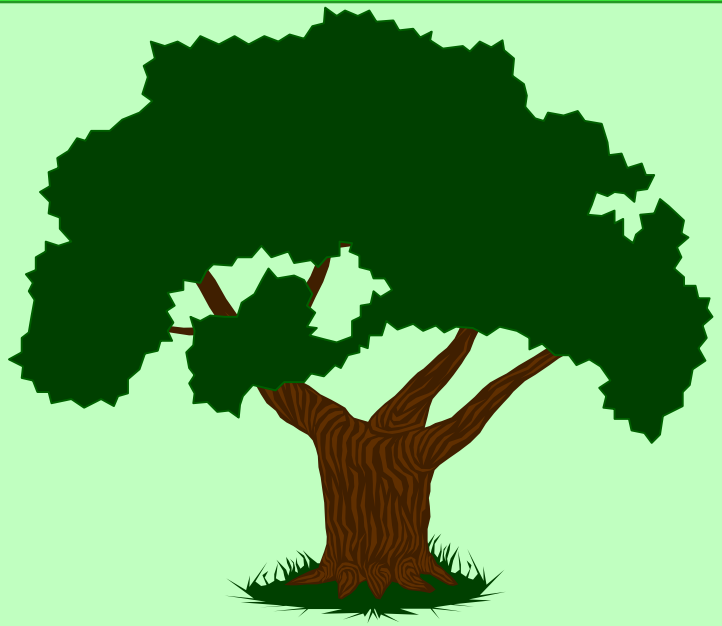
Natural or alternative therapies for infectious diseases



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INDONESIA
EAST TIMOR
PAPUA NEW GUINEA
Arafura Sea
Timor Sea
Gulf of Carpentaria
Pacific Ocean
Ashmore Islands
Cartier Island
Melville Is.
Bathurst Is.
Darwin
Groote Eylandt
Wellesley Islands
Great Barrier Reef
16° S
Indian Ocean
Derby
Broome
Northern Territory
Cairns
Karumba
Coral Sea
Port Hedland
Barrow Is.
Tennant Creek
Townsville
Queensland
Mackay
Alice Springs
Rockhampton
TROPIC OF CAPRICORN
24° S
Shark Bay
Carnarvon
Western Australia
Birdsville
South Australia
Brisbane
Gold Coast
Cunnamulla
Lismore
Geraldton
Lake Eyre
New South Wales
Perth
32° S
Port Augusta
Broken Hill
Newcastle
Great Australian Bight
Wollongong
Sydney
N
Esperance
Albany
Spencer Gulf
Kangaroo Island
Canberra
Victoria
Capital Territory
Melbourne
Adelaide
AUSTRALIA
40° S
Bass Strait
Flinders Island
King Island
Cape Barren Is.
Tasman Sea
Indian Ocean
Tasmania
Hobart
400 mi
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120° E
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Alternative therapies for infectious diseases

- *Probiotic therapy*

  Probiotic therapy uses a live microbial food supplement to beneficially affect the host.

- *Naturally-occurring antimicrobial agents*

  Phytomedicines (plant-based remedies in the form of teas, extracts and oils) are a multimillion dollar industry worldwide.

- *Bacteriophage therapy*

  Bacterial viruses that are making a comeback.

Probiotic therapy

- Uses supposedly non-pathogens
- Both bacteria and yeasts have been used

- vaginal candidiasis
- bacterial vaginosis
- urinary tract infections
- diarrhoeal diseases

How do probiotics work?

- Antagonism through production of inhibitory substances
- Competitive inhibition for sites/nutrients
- Immunomodulation of the host
- Inhibition of toxins

Filho-Lima *et al*. (2000) *J Appl Microbiol* 88: 365-370

Lactobacillus GG

- *Lactobacillus casei* var *rhamnosus*
- Extensively studied
- Reduces traveller's diarrhoea
- Reduces rotavirus diarrhoea
- Reduces the severity of diarrhoea in childcare centres
- Has lots of non-specific effects
- Available commercially

Urogenital tract infections

Lactobacilli

- Depleted lactobacilli may lead to:
  - Increased UTI
  - Bacterial vaginosis
  - *Candida* vaginitis
  - Post-antibiotic infections
- Lactobacilli susceptible to nonoxynol-9

Urogenital tract infections

Lactobacilli

- Possible mechanisms of control
  - Production of antimicrobial substances
  - Lactic acid production
  - Hydrogen peroxide production
  - Bacteriocin-like substances
  - Formation of a barrier population

Urogenital tract infections

Lactobacilli (*L.casei*, *L.crispatus*)

- Characteristics required as a probiotic
  - Ease of cultivation and non-pathogenicity
  - Adhesion
  - Population stability
- Preparations currently available
- Delivery systems need work

Diarrhoeal diseases

- *Clostridium difficile*-associated diarrhoea
- Can be difficult and expensive to treat
- Relapse rate around 20%
- Various probiotic treatment regimens
  - Oral *Lactobacillus* GG
  - Rectal administration of faecal enemas
  - Non-toxigenic *C.difficile*
  - *Enterococcus* SF68

Effect of LGG yoghurt on *Clostridium difficile*-associated diarrhoea

	Diarrhoea	No diarrhoea
Yoghurt	1 (No *C.difficile*)	15
No yoghurt	7 (2 *C.difficile*)	10

Fisher's exact test, P = 0.02

Effect of LGG yoghurt on *Clostridium difficile*-associated diarrhoea

Month	Specimens	No.positive	% positive
November	77	10	12.9
December	127	15	11.8*
January	133	7	5.2*
February	59	4	6.7

*P < 0.05

Saccharomyces boulardii

- A nonpathogenic yeast that:
  - Survives gastric acid
  - Multiplies to high numbers
  - But need to keep taking
  - Not inhibited by antibiotics
  - Does not affect normal flora
  - Prevents CDAD in animals
- Is it effective in preventing human CDAD?

Human studies with *S.boulardii*

- 11 of 13 patients with recurrent CDAD cured (Surawicz *et al*. 1989)
- *S.boulardii* plus antibiotics resulted in a significantly reduced risk of recurrence of CDAD versus antibiotics and placebo (McFarland *et al*. 1994)
- Significant reduction in AAD (McFarland *et al*. 1995) versus none (Lewis *et al*. 1998)

- No help with preventing primary infections
- But may help prevent recurrences
- Most of the expense related to CDAD is probably associated with recurrences.

How does *S.boulardii* work?

- *S.boulardii* secretes a protease which:
  - digests toxin A and B molecules
  - digests toxin A and B receptors on brush border membrane

  (Castagliuolo *et al*. 1996, 1999)

Experiences with *S.boulardii*

- So far we've treated 25 patients with recurrent CDAD
- All elderly
- Given vancomycin for 7 days plus lyophilised *S.boulardii* (500 mg bd) concurrently and then continuing for another 3 weeks
- 24 or the 25 patients cured
- 1 patient non-compliant!

Conclusions on *S.boulardii*

- Clear evidence that "*S.boulardii*" is a useful adjunctive agent
- In vitro evidence to explain such an effect
- The effect appears to be strain (?species) specific
- Further in vitro and clinical work warranted

Naturally-occurring antimicrobials

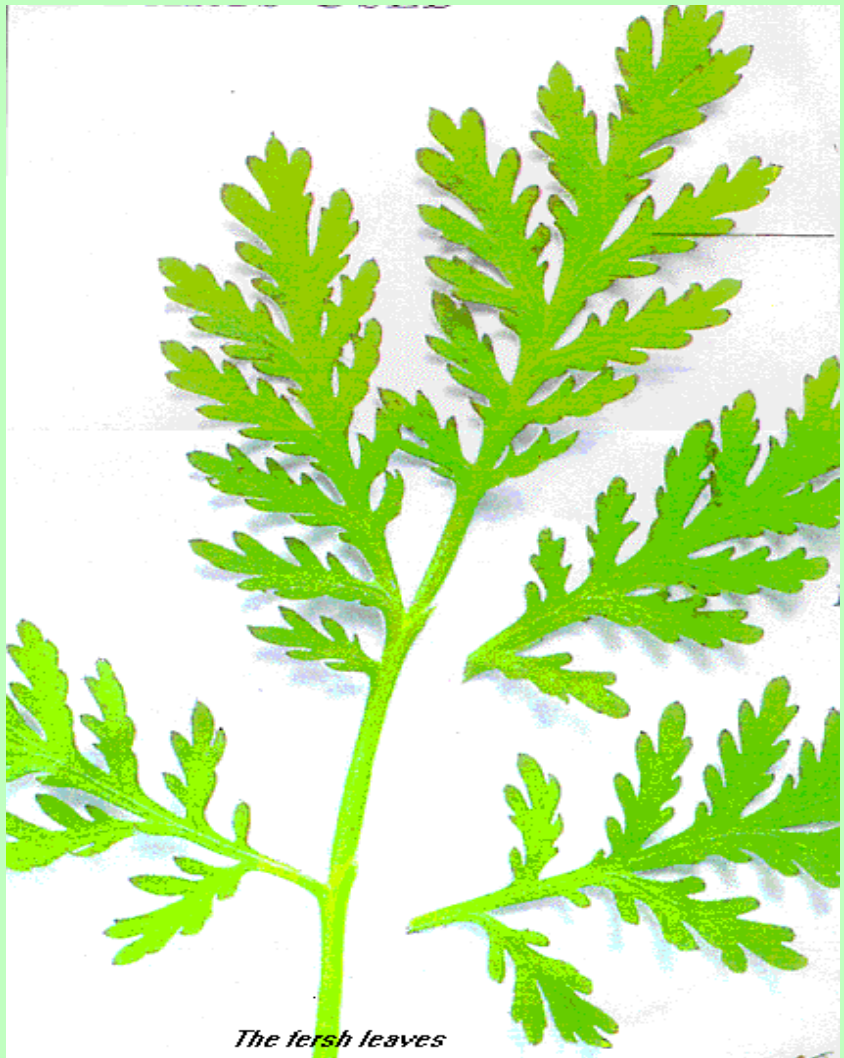
- garlic
- qinghaosu
- cranberries
- honey
- tea tree oil
- “Dysentery bush” (*Grewia retusifolia*)
- “Jelly leaf” (*Sida rhombifolia*)
- “Quinine tree” (*Alstonia constricta*)
- “Caustic bush” (*Sarcostemma australe*)

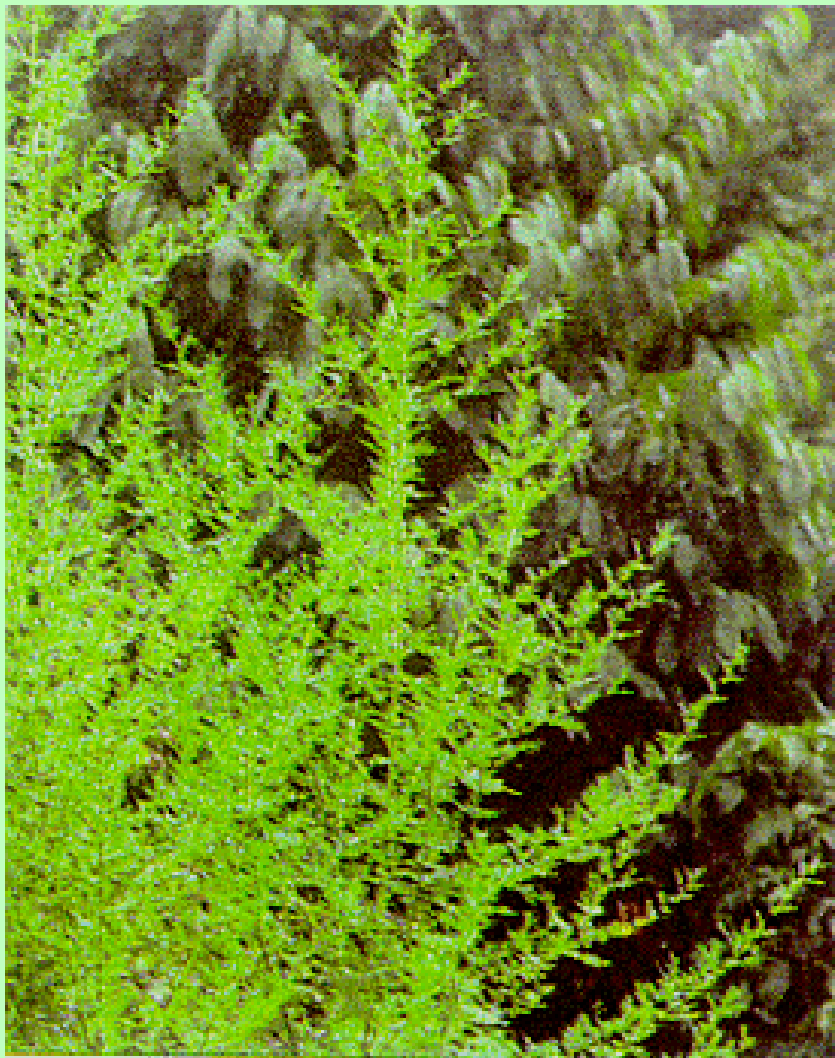
Garlic

Garlic (*Allium sativum*)

- First used in 3000BC by the Sumerians
- Juice used by French and English in W W I to treat infected wounds
- Antimicrobial properties attributed to allin which converts to allicin
- Di-allyl tri- & tetrasulphides very potent
- Active against many bacteria and fungi including dermatophytes

Qinghaosu





Qinghaosu

- Extract of *Artemisia annua* first described in China for malaria in 1596
- Derivatives made chemically of parent compound artemisinin
- An oral form (artesunate) gives cure rates of around 90%
- When combined with mefloquine cure rates increase to 100%

(Looareesuwan *et al*. *Lancet* 1992; 339: 821-824)

The Cranberries

Cranberries

Juice
10 oz. of 27% juice cocktail

=

Fresh
1-1⅛ cups fresh or frozen

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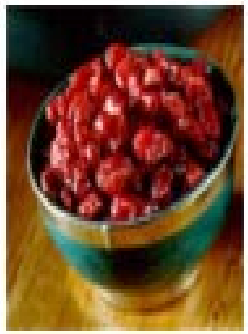


Dried
1 oz. sweetened

=

Sauce
½ cup

Cranberries

- American folk remedy for UTI
- In vitro studies show that CJ diminishes expression of fimbriae and binding of *E.coli* to cells (Zafriri *et al*. *AAC* 1989; 33: 92-98)
- A recent prospective, randomised, placebo-controlled trial showed a 50% reduction in incidence of bacteriuria

  (Avorn *et al*. *JAMA* 1994 271: 751-754)

Honey

- Long recorded history of use
- Antibacterial activity against a range of organisms: *E.coli*, *Pseudomonas*, enterococci and *H.pylori*
- Activity attributed to high osmolarity, low pH, presence of H_2O_2 but there is something else
- Renewed interest in wound care

Tea tree oil

www.meddent.uwa.edu.au/teatree


9
6
1
2

Tea tree oil

- leaves of Australian plant *Melaleuca alternifolia*
- extracted by steam distillation
- leaves yield approx 1-2% dry weight
- clear/pale yellow oil
- viscous volatile lipophilic liquid
- distinct odour

Components of tea tree oil

- approximately 100 components
- compositional levels may vary
- partly regulated by the international standard for ‘tea tree’ oil (ISO 4730)
- 7 components comprise 80-90% of the whole oil

Components of tea tree oil

- terpinen-4-ol
- 1,8-cineole
- δ-terpineol
- α-terpinene
- δ-terpinene
- terpinolene
- ρ-cymene
- linalool

MICs (%) of TTO against skin flora

Organism (no.)	MIC_{90}	MBC_{90}	
***Corynebacterium* spp.(10)**	**2**	**2**	commensal
***Micrococcus* spp. (11)**	**0.5**	**6**	
CNS (60)	**1**	**6**	
***E. coli* (113)**	**0.25**	**0.25**	transient
***K. pneumoniae* (14)**	**0.25**	**0.25**	
***S. marcescens* (11)**	**0.25**	**0.25**	
***Staph. aureus* (163)**	**0.5**	**2**	

Germ tube formation

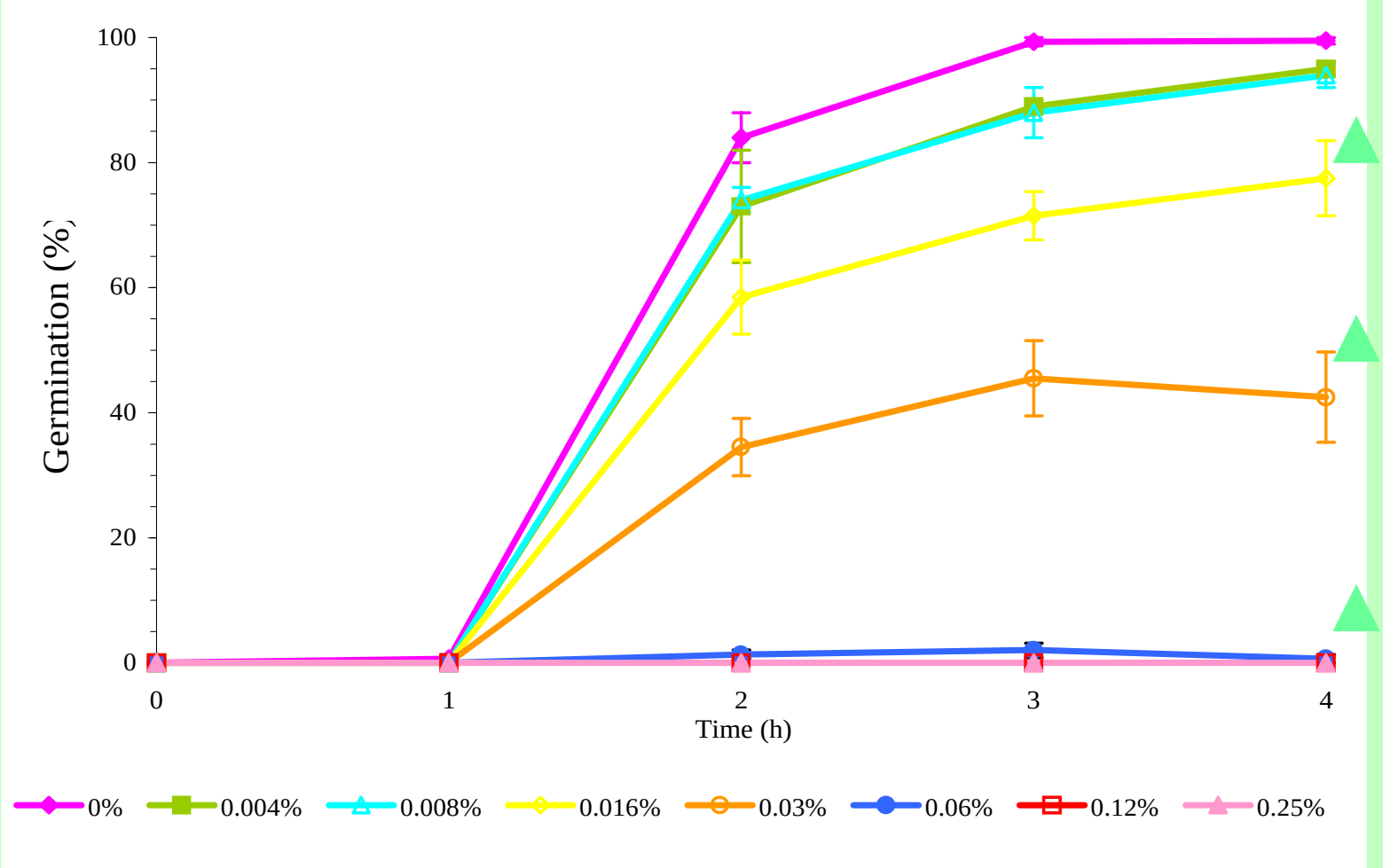
- Germ tubes may be important in the pathogenesis of candidal disease

  ↑ adherence and penetration of epithelial cells

- Tea tree oil is potentially useful in the treatment of superficial candida infections

Aim: To determine whether tea tree oil inhibits germ tube formation in *C. albicans*

Germ tube formation by *C. albicans* 10231 in the presence of tea tree oil



In vivo tea tree oil studies

- acne trial (Bassett *et al*., 1990)
  - tto gel as efficacious as benzoyl peroxide in the treatment of acne, fewer side effects
- tinea trial (Tong *et al*., 1992)
  - symptomatic relief only
- onychomycosis trial (Buck *et al*., 1994)
  - tea tree oil as efficacious as clotrimazole
- oral candidiasis (Jandourek *et al*., 1998)
  - mycological and symptomatic response

Cold sores

- caused by Herpes simplex viruses
  - produces lesions on/around lip
  - usually HSV1, sometimes HSV2
  - causes recurrent infections
  - multiple episodes per year
  - episodes last 1-2 weeks
- few current treatments (Zovirax)
  - limited evidence

Cold sore pilot study

- pilot study Sept 1999 - March 2000
  - randomised
  - single-blind
  - placebo-controlled
  - 20 patients

Cold sore pilot study

- patient presents when cold sore first develops
- apply ointment 5 times daily
  - 6% tea tree oil gel
  - placebo gel
- keep diary
- seen daily until completely healed (approx 1-2 weeks)
- specimen taken daily (except Sun)

Cold sore pilot study results

	Treatment	
Time (days) to:	TTO (n=9)	placebo (n=9)
crust	3.7	4.6
re-epithelialisation	9.9	12.0
PCR negative	6.5	7.9

no significant differences between treatments due to small sample size

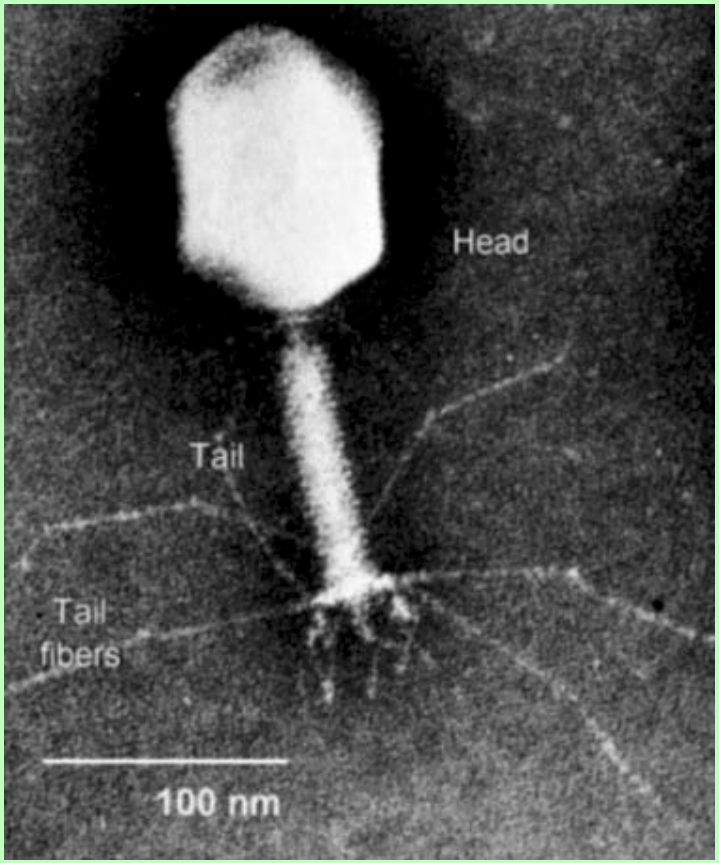

TEATREE RD
GINGIN

Other clinical studies completed, underway or planned

- Mouthwash for *Candida*
- Impetigo
- Bacterial vaginosis
- *Candida* vaginitis
- Ulcers
- Several MRSA decolonisation studies

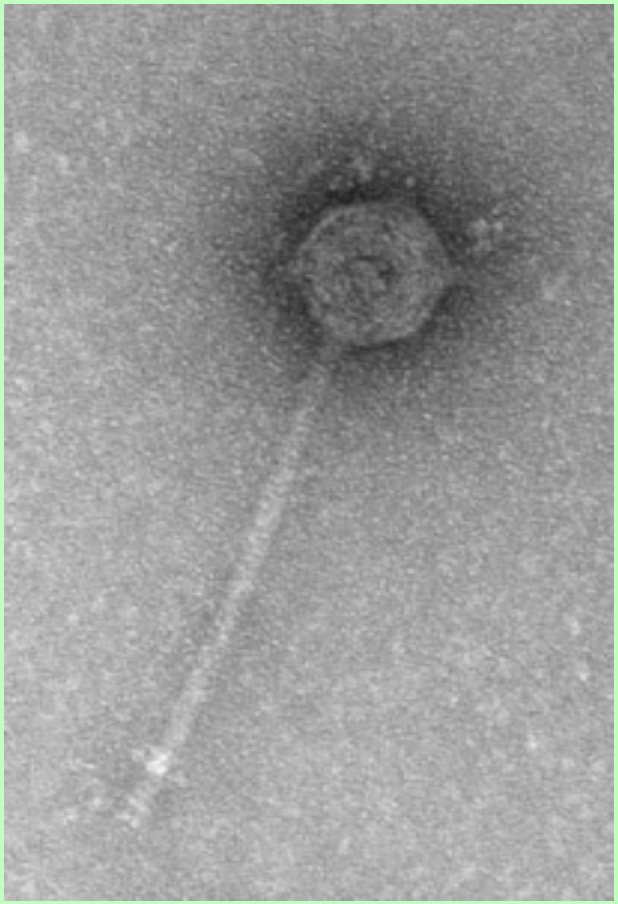
Bacteriophage therapy D'Herelle/Twort

Bacteriophage therapy



- Ignored apart from Soviet bloc countries
- Reports in 1970s/80s of treating SA infections
- In UK, phage used to treat diarhoeal disease in animals due to *E.coli*
- Phages for *Acinetobacter* and *Pseudomonas* infections successful

Bacteriophage therapy



- Bioavailability
- Some MRSA less susceptible to phage
- Safety concerns
  - Phage antibody
  - Toxins in preparations
  - Lysogenic conversion
- Development of resistance

Bacteriophage therapy

- Phages applied either topically, s/c, or via irrigation or drains

Conclusions

- “Natural” therapies are viewed favourably by patients
- Less side effects than antibiotics
- Some problems relating to quality
- Lack of good data
- Worthwhile exploring further as adjunctive or replacement therapy