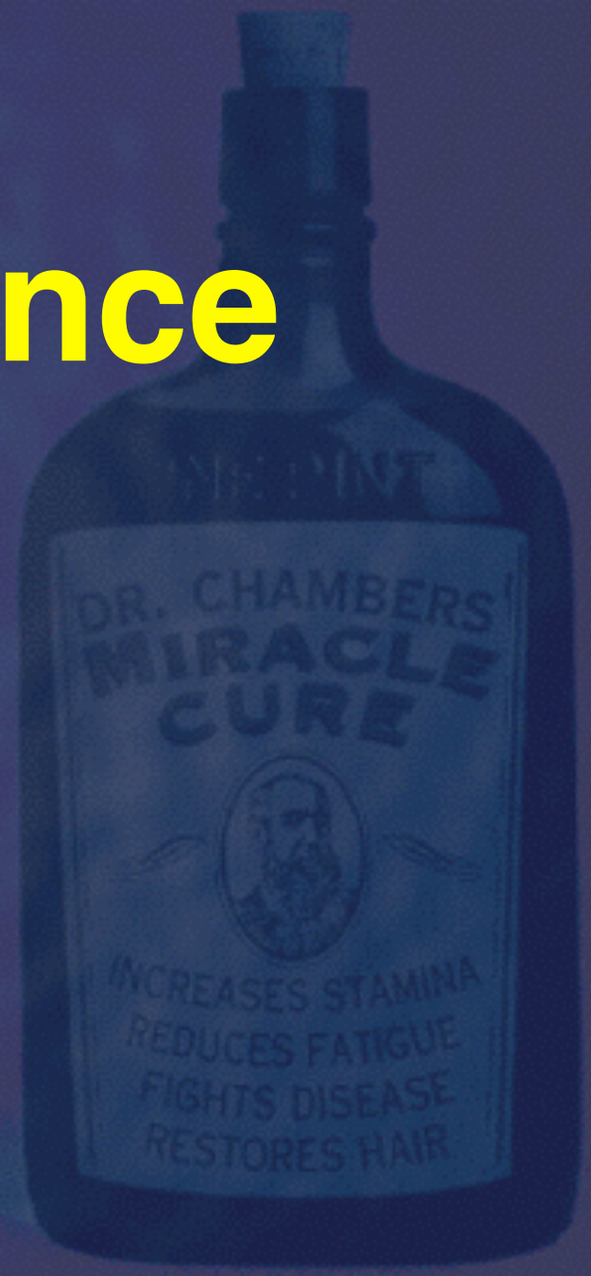
Antibiotic Resistance



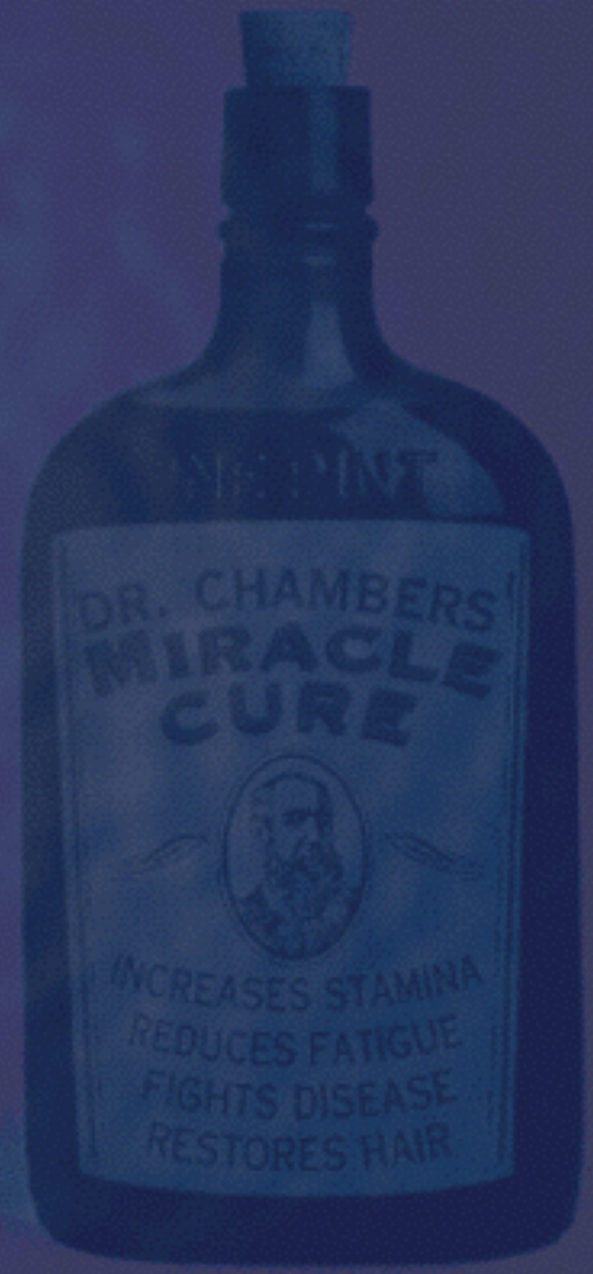
By the end of this lecture you should be able to

- formulate treatment strategies to reduce the development of antibiotic resistance in the animals you treat and their contacts.

Every time you use an antibiotic you exert selection pressure for resistance on pathogens and commensals

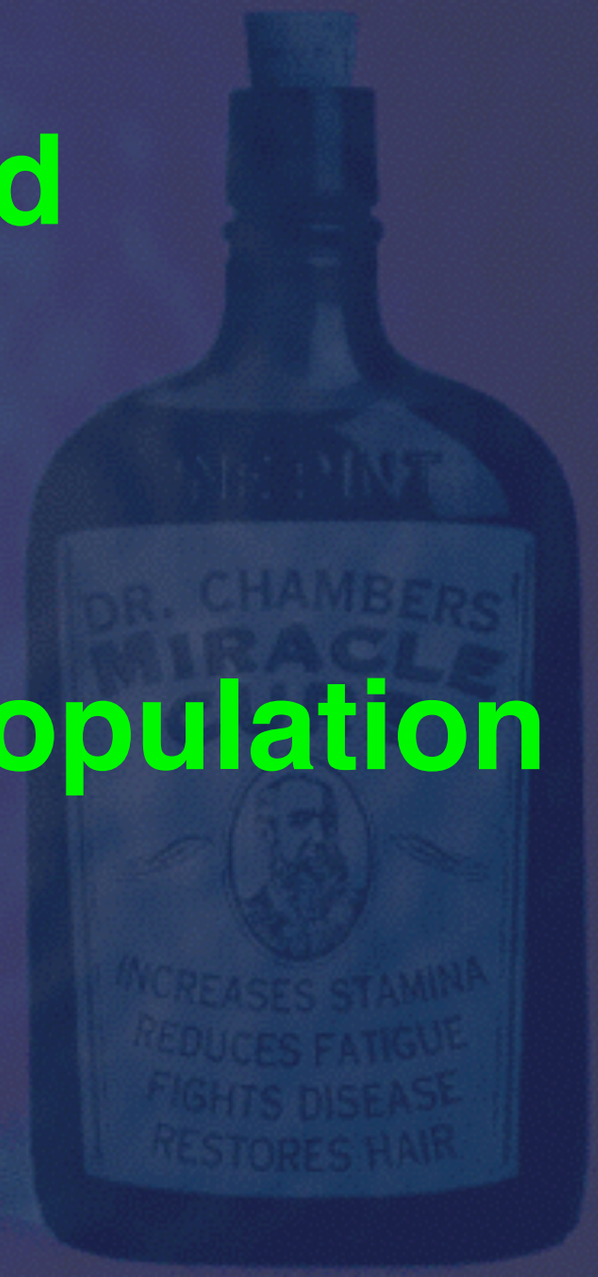
4 yr old bull terrier

- **scratching ears**
- **previously treated**
  - –broad spectrum antibiotics
  - –steroids
  - –acaricides



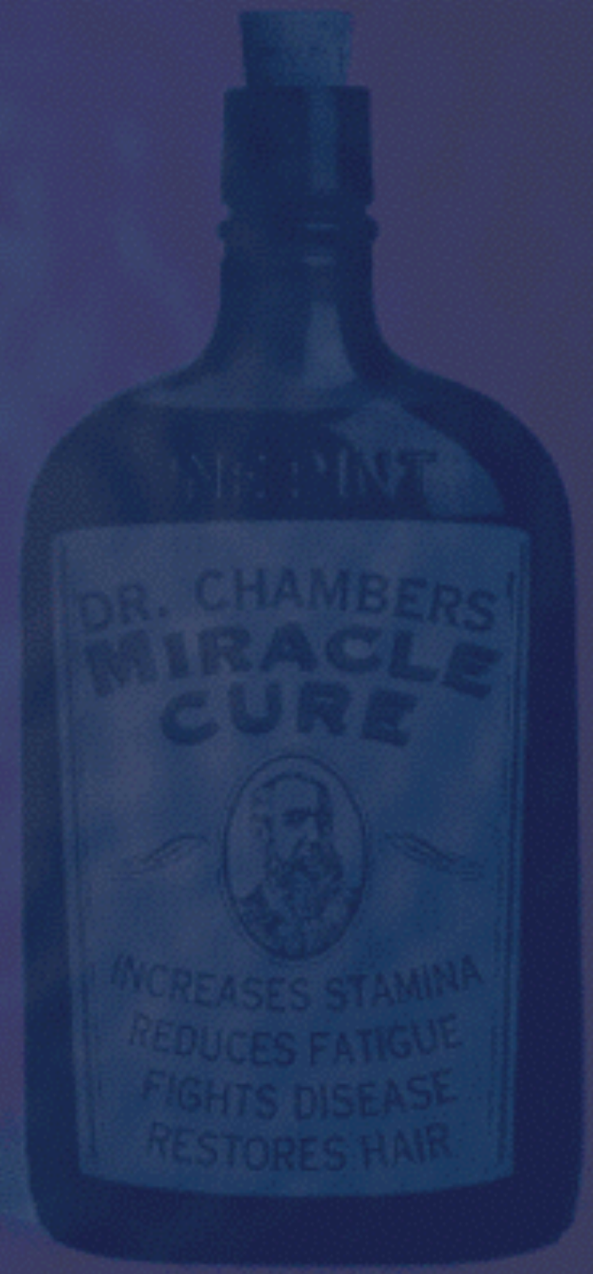
resistance

- in the animal being treated
- in contact animals
- in the owner
- in the environment / NZ population



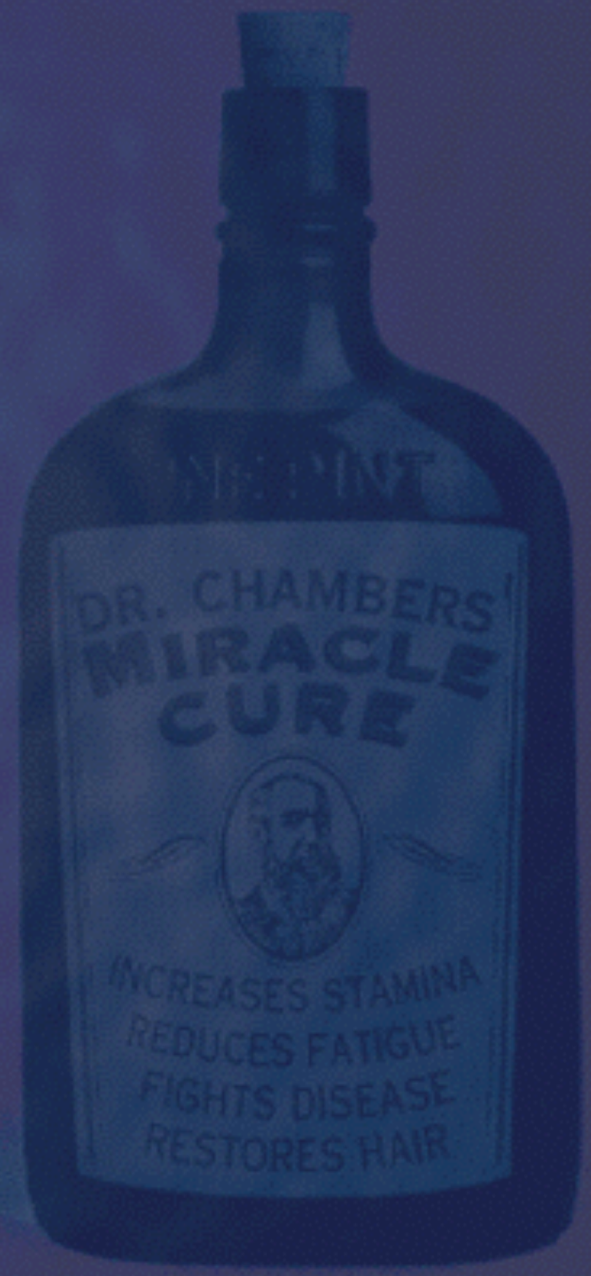
resistance mechanisms

- **drug does not reach its target**
  - –Pseudomonas
- **drug is inactivated**
  - –Staph aureus
  - –E.coli
- **target is changed**
  - –MRSA
  - –streps



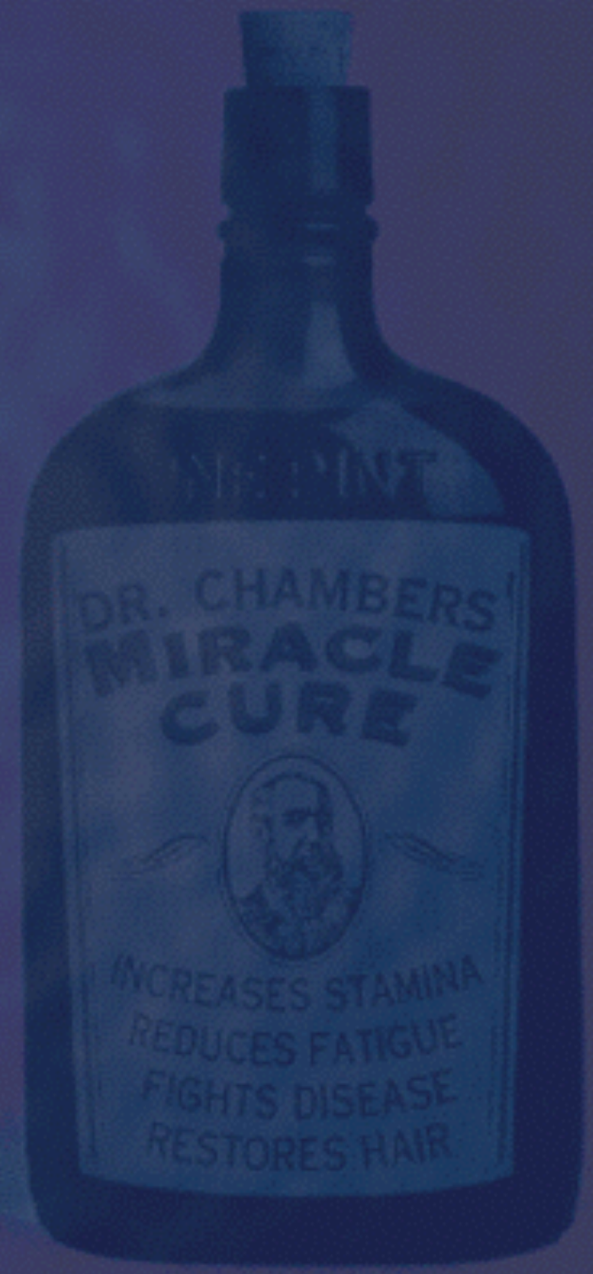
resistance

- intrinsic
- acquired



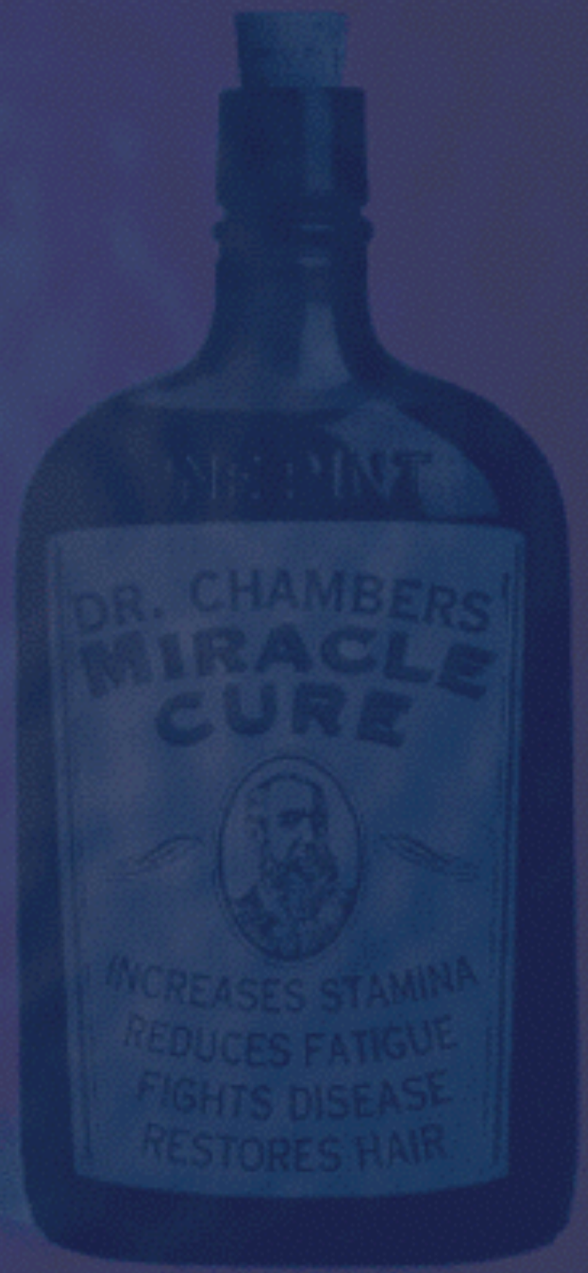
resistance genes

- chromosomes
- plasmids
- transposons
- integrons
- gene cassettes



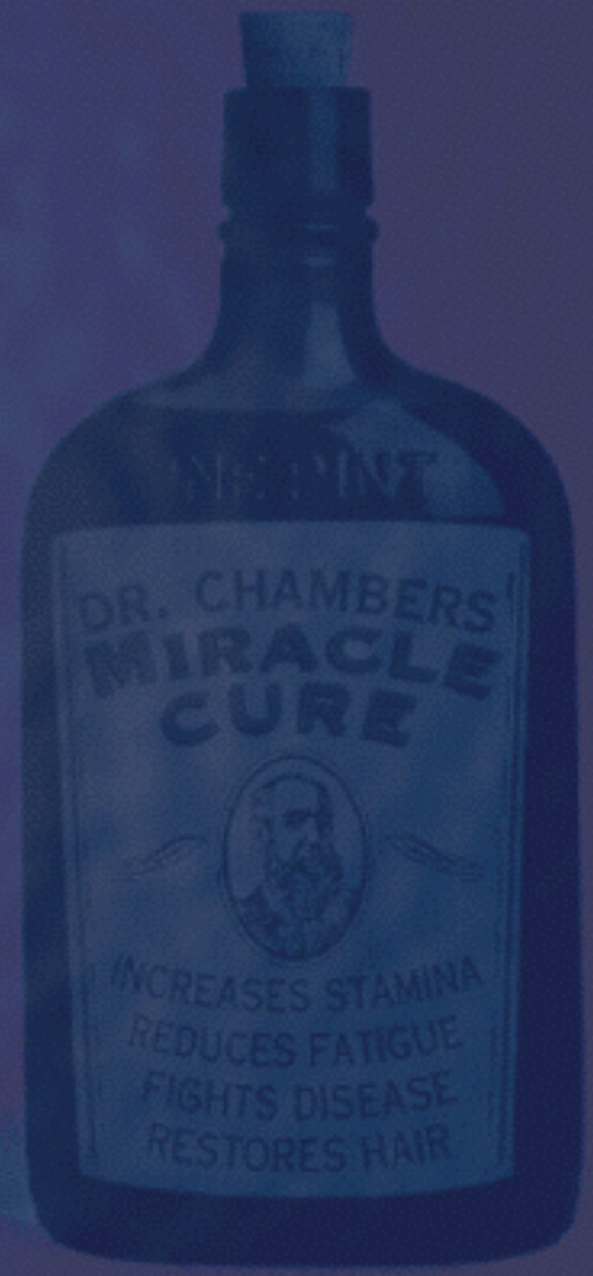
acquired resistance

- **conjugation**
  - –coliforms
  - –cocci
- **transduction**
  - –Staphs
- **transformation**
  - –cocci?

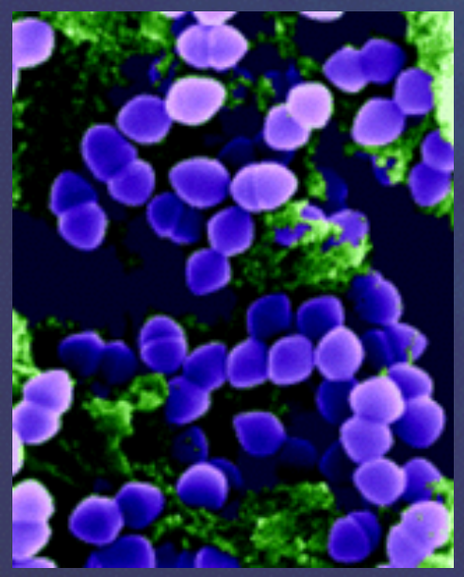


resistance

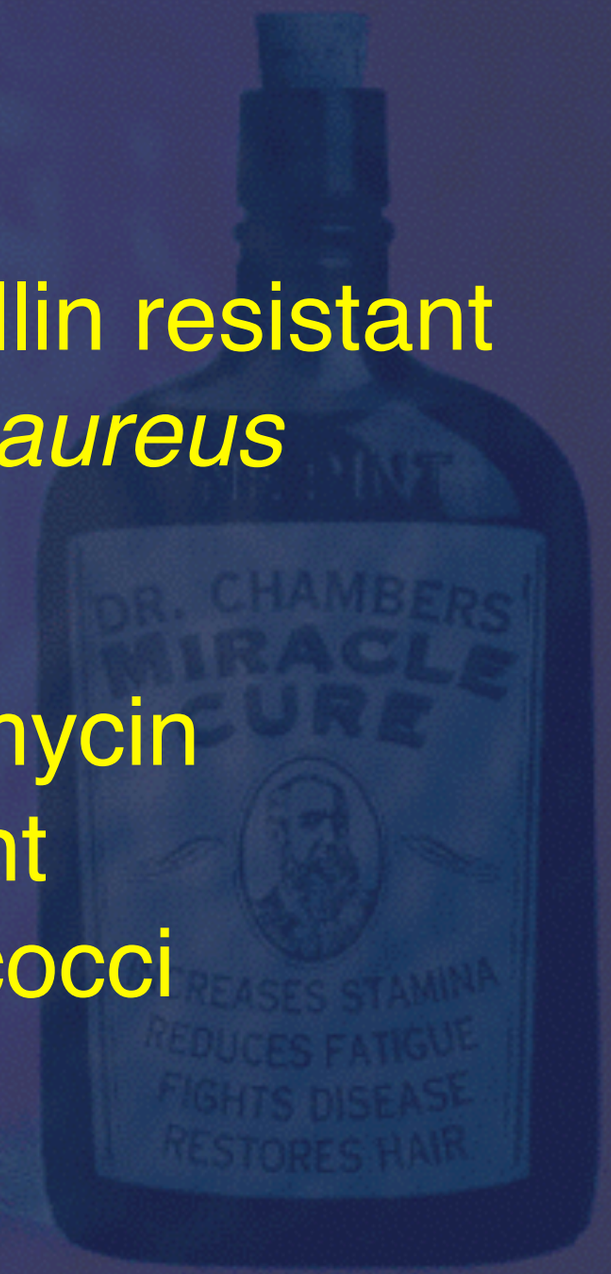
- pathogens
- commensals



human pathogens

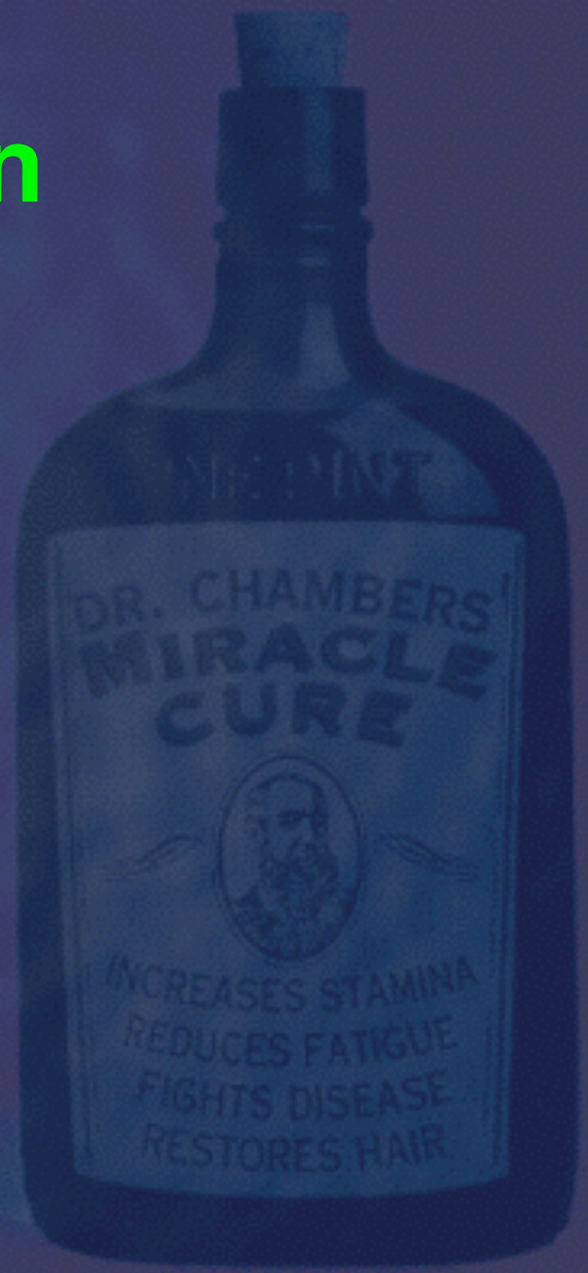


- **MRSA**
  - Methicillin resistant *Staph. aureus*
- **VRE**
  - Vancomycin resistant enterococci



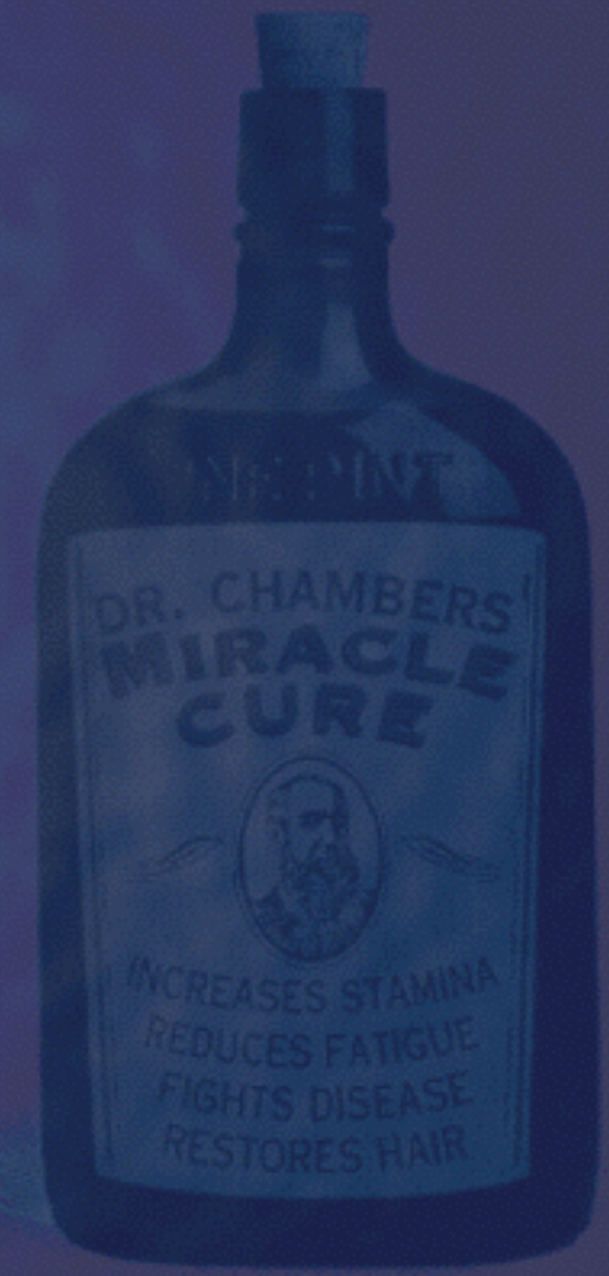
MRSA

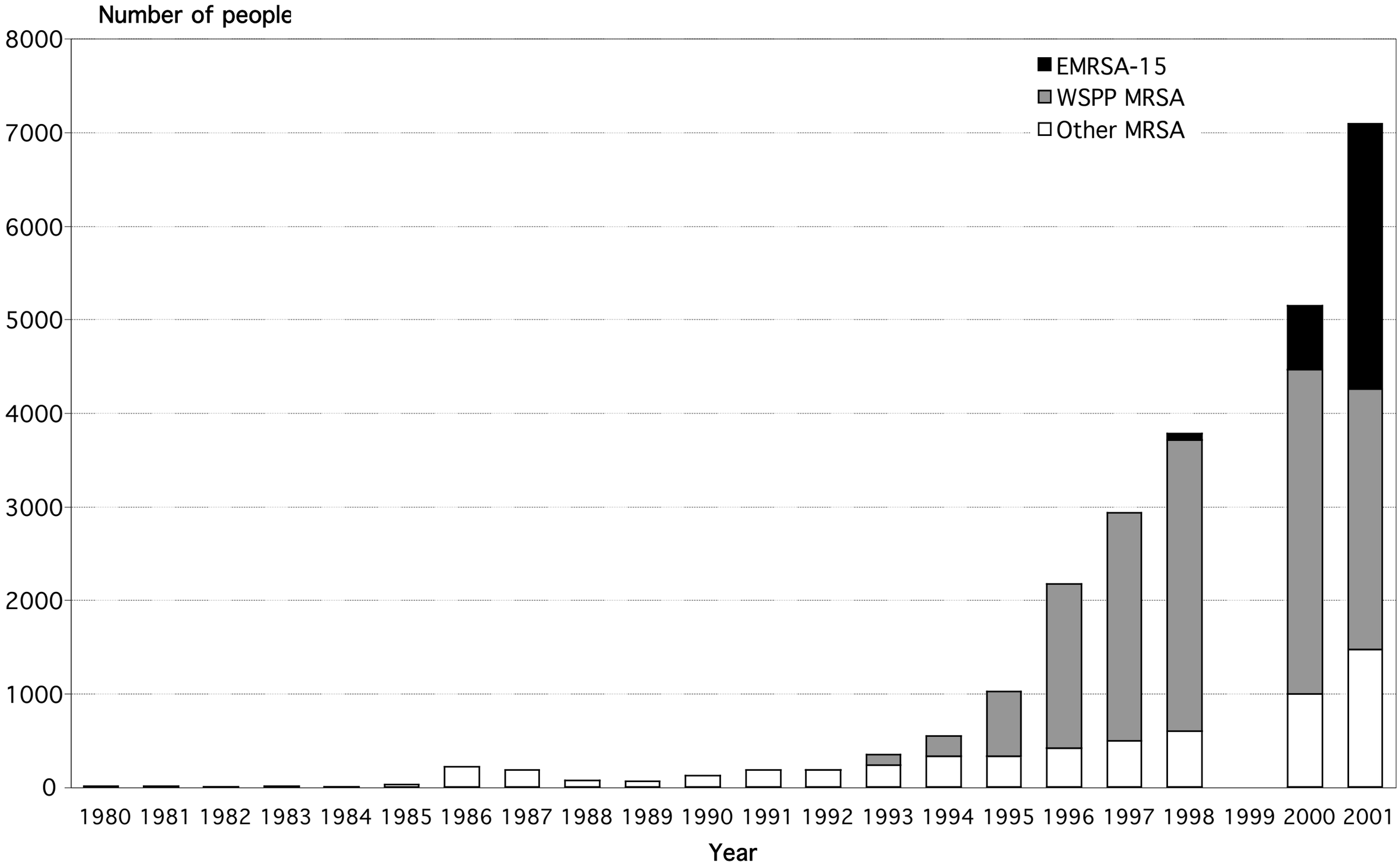
- **14% SA isolates 2001**
- **Western Samoan phage pattern**
  - –39% MRSA isolates 2001
  - –community acquired
  - –Pacific islanders
  - –Auckland
- **epidemic MRSA 15**
  - –40% MRSA isolates 2001
  - –from UK
  - –acquired in hospital

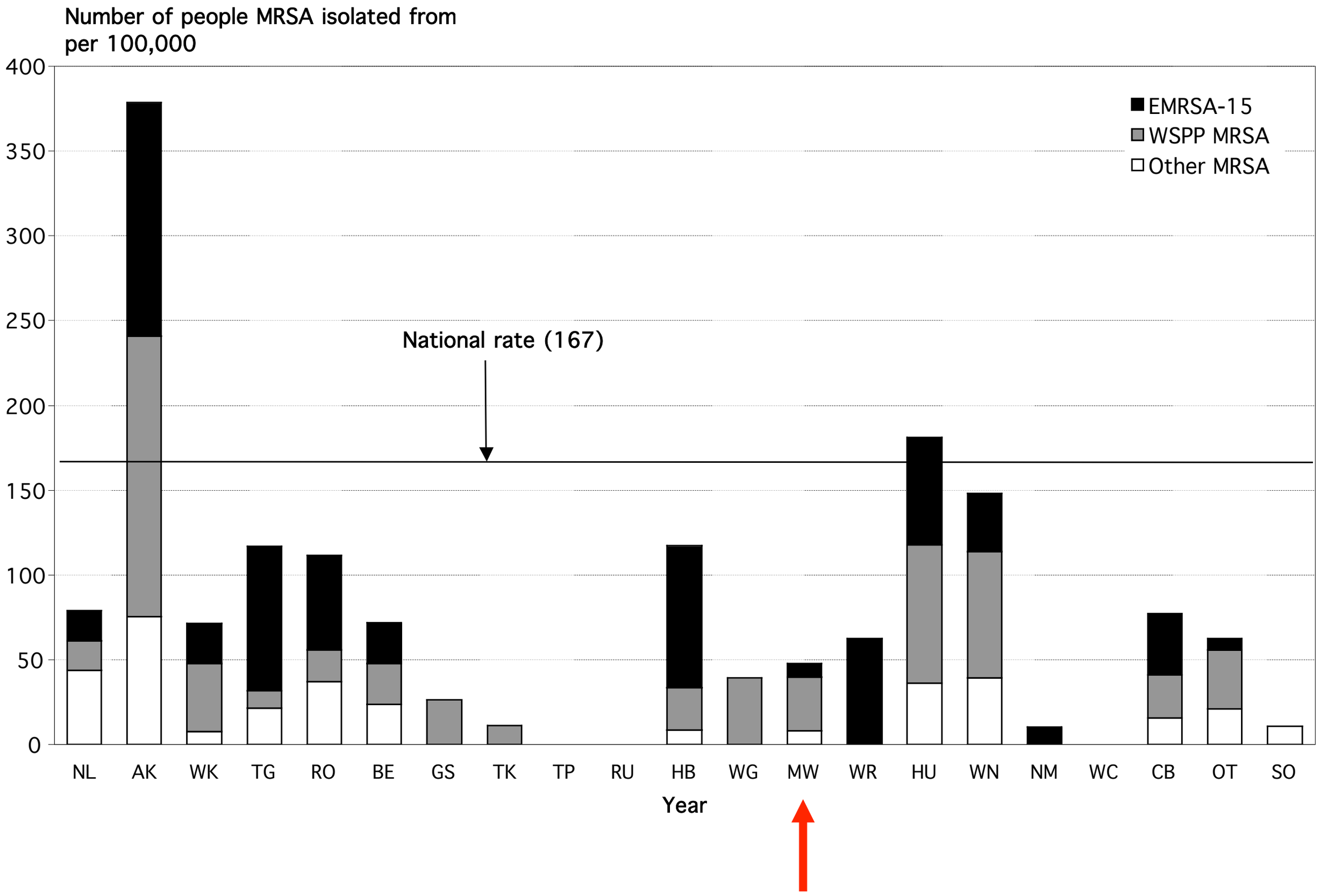


MRSA 2002

- **EMRSA 15 (UK)**
  - –67.5% isolates
- **AKh4 (Aus)**
  - –12.3%
- **WR/AK1**
  - –7.1%
- **WSPP (Samoa)**
  - –2.1%
- **EMRSA 16 (UK)**
  - –1.9%




Number of people
8000
7000
6000
5000
4000
3000
2000
1000
0
EMRSA-15
WSPP MRSA
Other MRSA
1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001
Year

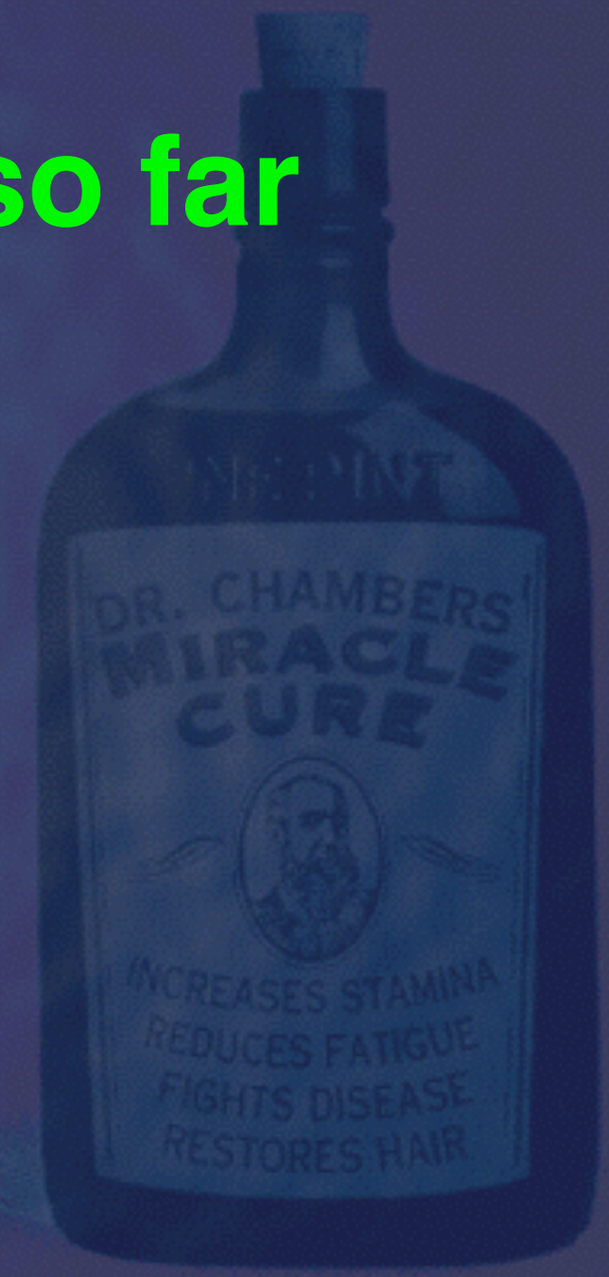

Number of people MRSA isolated from per 100,000
400
350
300
250
200
150
100
50
0
EMRSA-15
WSPP MRSA
Other MRSA
National rate (167)
NL
AK
WK
TG
RO
BE
GS
TK
TP
RU
HB
WG
MW
WR
HU
WN
NM
WC
CB
OT
SO
Year

VISA

- **vancomycin intermediate *Staphylococcus aureus***
  - –*1-2* isolates per year
  - –MRSA patients treated with vancomycin

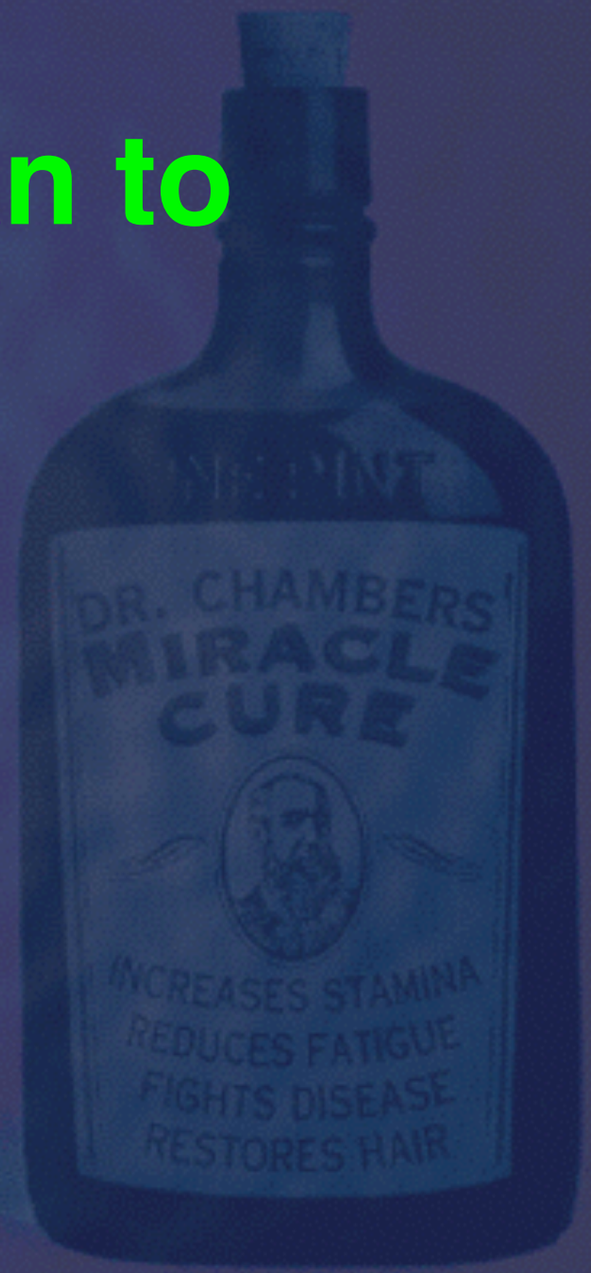
VRE

- 15 human isolates in NZ so far
- chickens in Otago



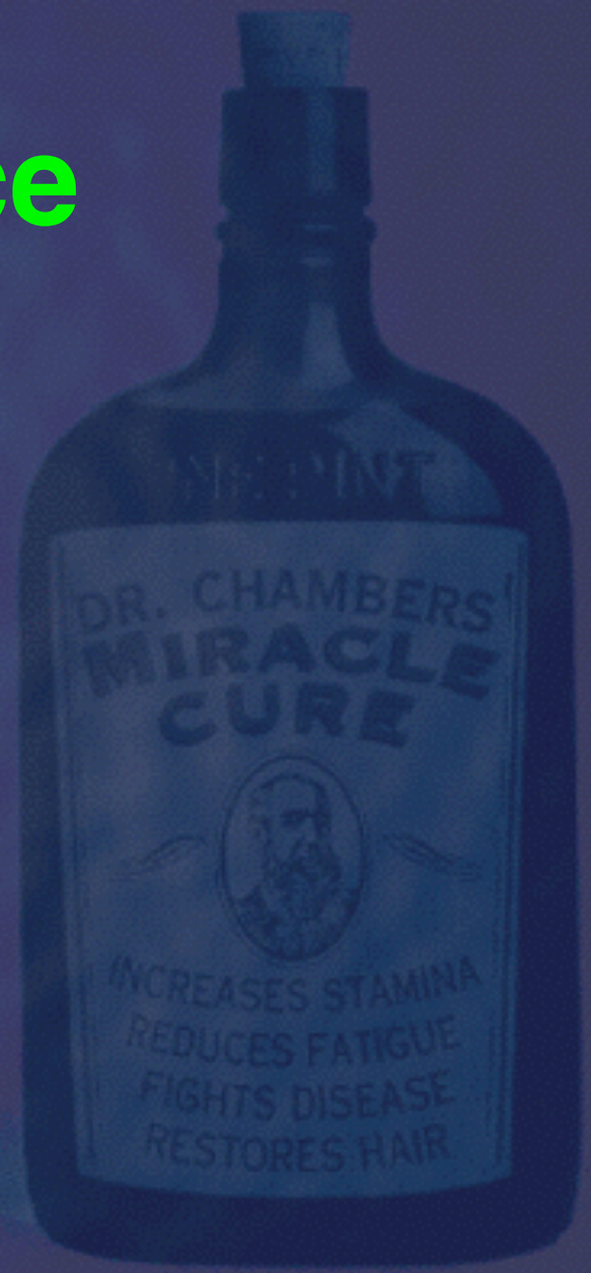
animal *Staph aureus*

- **more resistant than human to**
  - –clindamycin / lincomycin
  - –co-trimoxazole
  - –fluoroquinolones
  - –gentamicin
  - –tetracyclines



animal *Staph aureus*

- **fluoroquinolone resistance**
  - –1999 - 0%
  - –2000 - 6.6%
  - –2001 - 12.5%
  - –2002 - stopped monitoring!
  - –mostly dogs

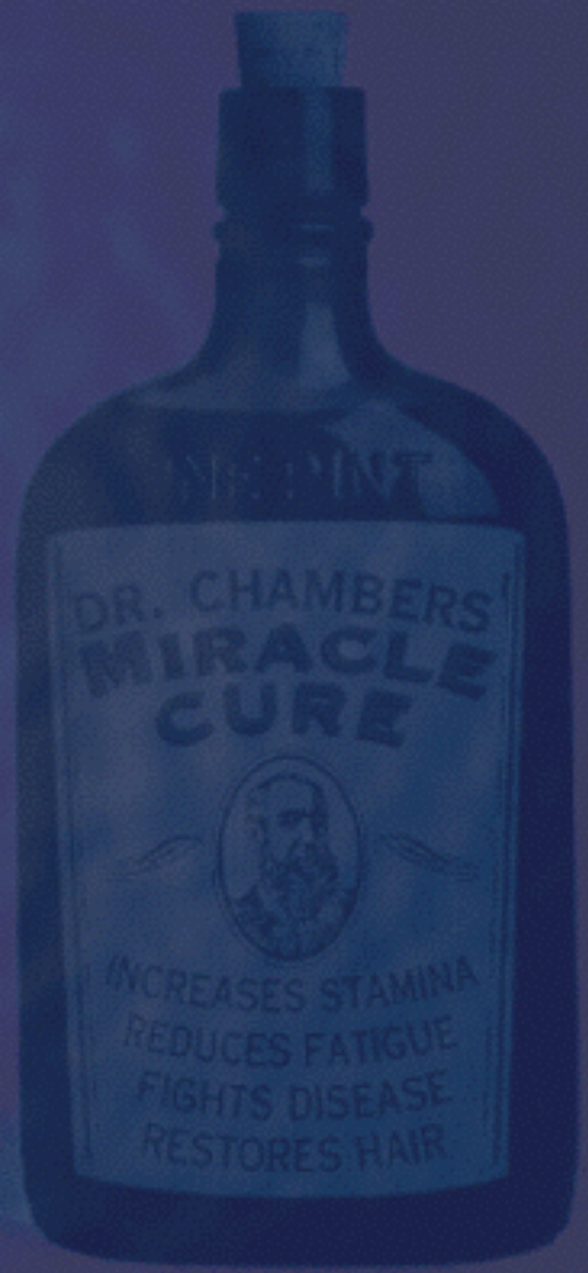


food poisoning

- **Salmonella spp (DT104)**
  - –rare in NZ
    - 39 human & 3 animal isolates 1992 - 2001
- **Campylobacter**
- **E.coli O157**
  - –92 cases NZ 2005
- **(Shigella)**

fluoroquinolone resistance

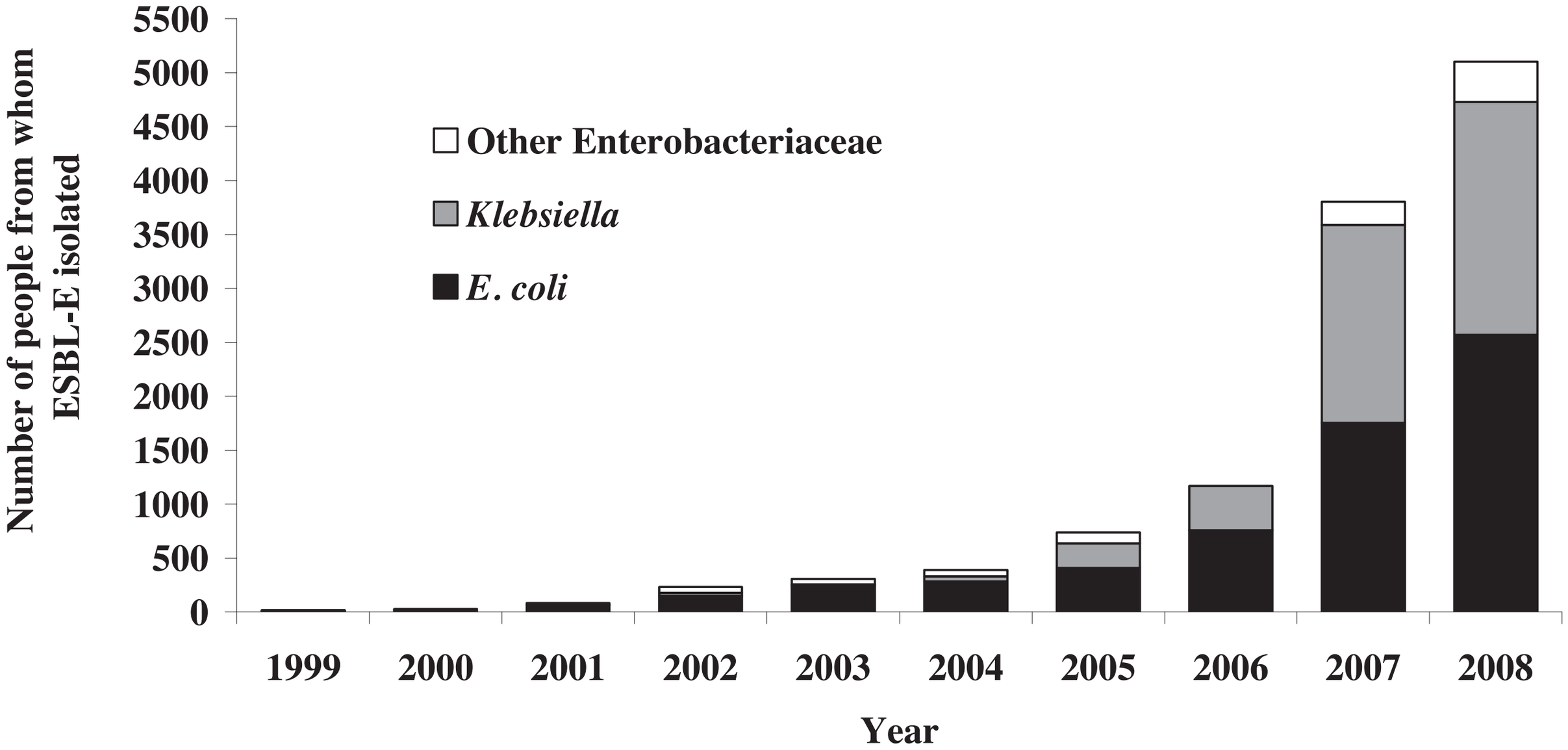
- **Salmonella spp (DT104)**
  - –NZ 1998 0%
- **Campylobacter**
  - –no figures
- **E.coli (all)**
  - –animals 2000/1 2.4%, 1999 0.9%
    - 2001 4.3% dog isolates
  - –people 2000 1.3%
- **(Shigella)**



ESBLs

- extended spectrum beta lactamase producing coliforms
- emerged in Hawke's bay
- now in Auckland
- resistant to cephalosporins
  - –veterinary use of cephalosporins???

Figure 1. ESBL-producing Enterobacteriaceae, 1999-2008

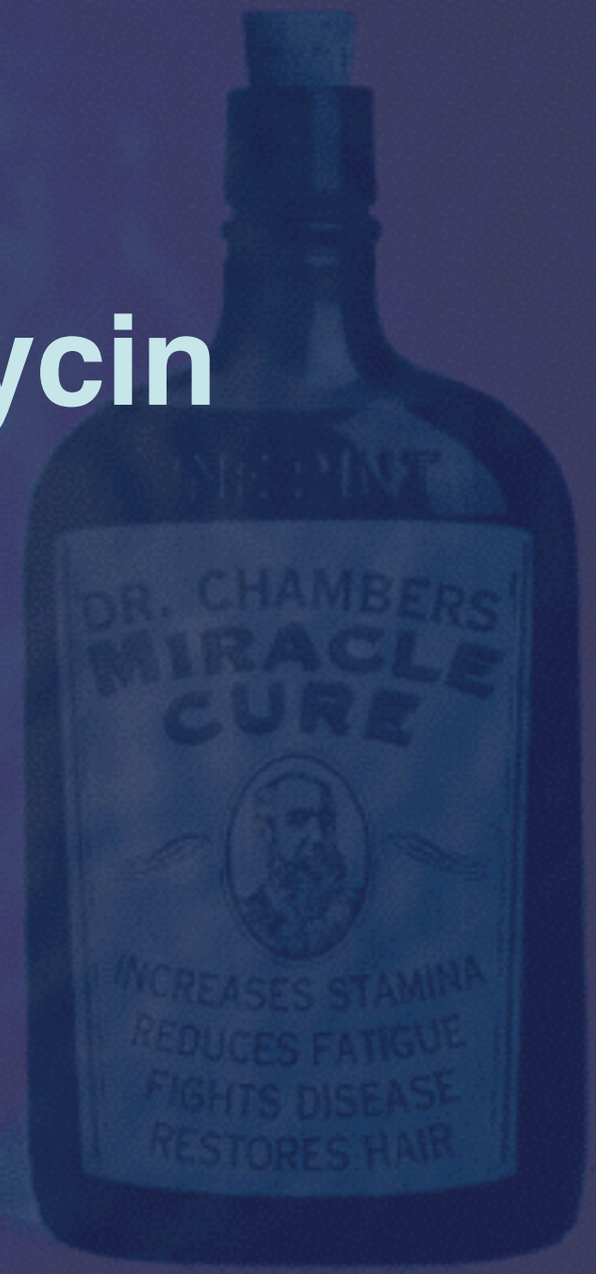


TB

- 2002 0.6% MDR, 13% single drug resistant
- most cases in people born overseas

TB drugs

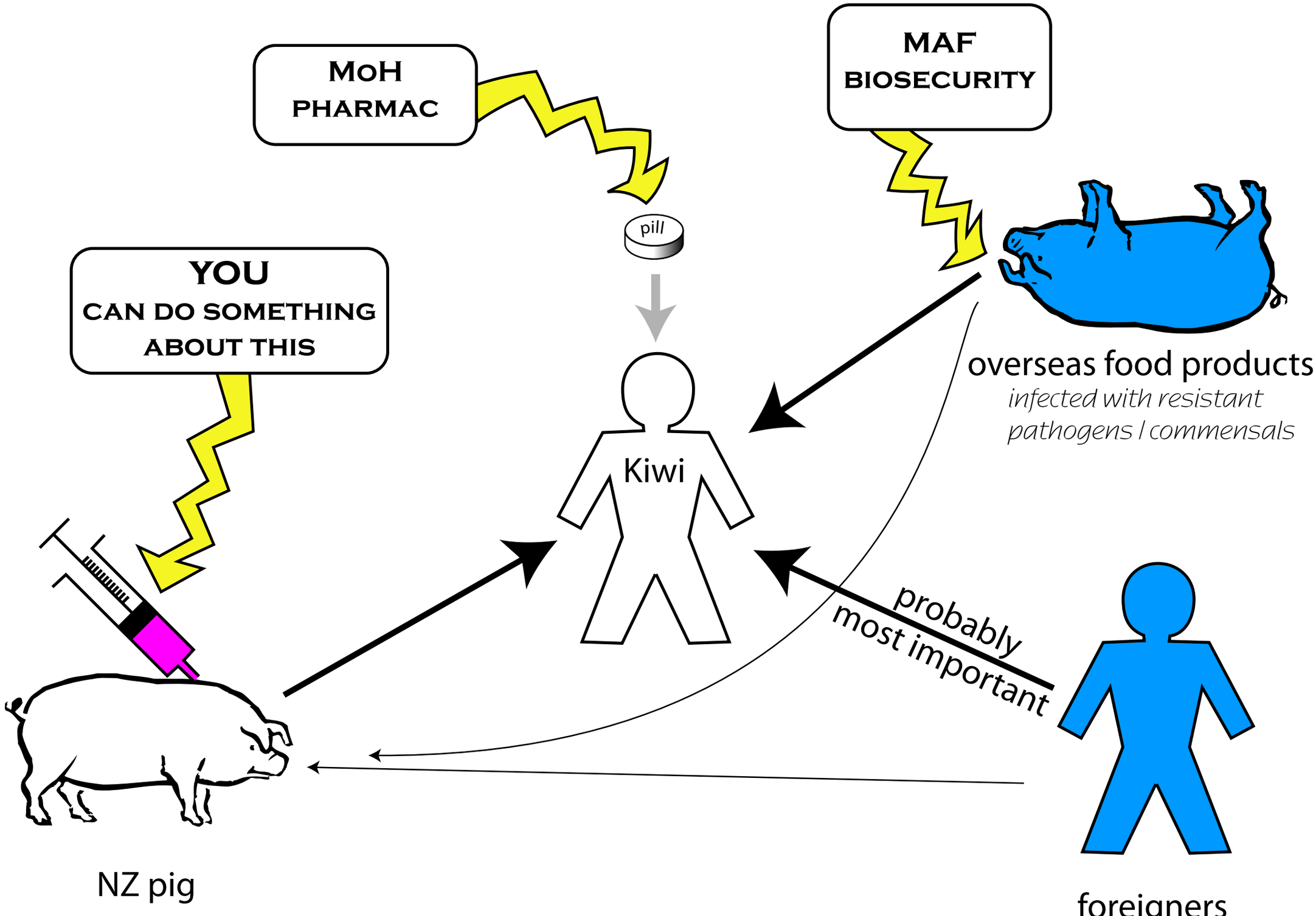
- rifampicin
- clarithromycin / azithromycin
- ethambutol
- isoniazid
- pyrazinamide
- streptomycin



veterinary pathogens

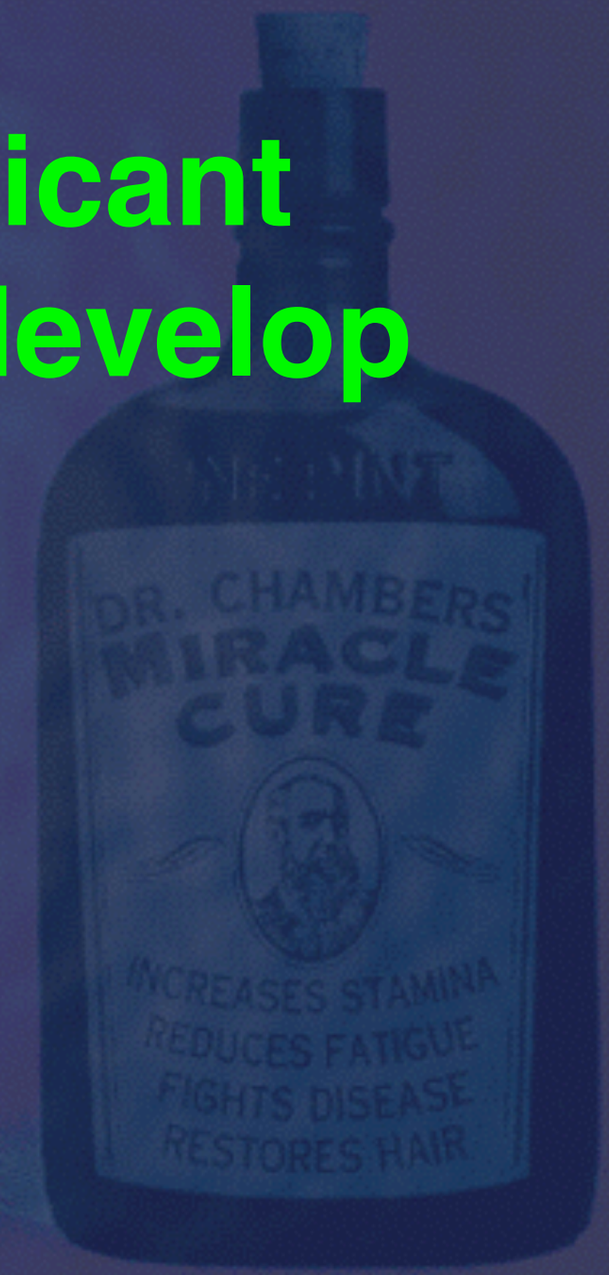
- **Pseudomonas aeruginosa**
  - –large genome
  - –lots of drug efflux pumps
  - –lots of redundant systems
  - –common after inappropriate antibiotics
  - –causes problems in people too

Where do resistant bacteria come from?



controlling resistance

- use drugs to which significant resistance is unlikely to develop
- infection control



Are you PROTECTing your antibacterials?

PROTECT

P ractice policy

- A practice policy for empirical prescribing (whilst awaiting cultures) can optimize therapy, and minimize inappropriate use of antibacterials

R educe prophylaxis

- Antibacterials are **not** a substitute for surgical asepsis
- Prophylactic antibacterials are only appropriate in a few medical cases (e.g. immunocompromised patients)

O ther options

- Reduce inappropriate antibacterial prescribing (e.g. due to client pressure, in uncomplicated viral infections or self-limiting disease) by providing symptomatic relief (e.g. analgesia, cough suppressants)
- Use cytology and culture to diagnose bacterial infection correctly
- Effective lavage and debridement of infected material reduces the need for antibacterials
- Using topical preparations reduces selection pressure on resistant intestinal flora

T ypes of bacteria and drugs

- Consider which bacteria are likely to be involved, e.g. anaerobic/aerobic, Gram +ve *versus* Gram -ve
- Consider the distribution and penetration of the drug
- Consider any potential side effects

E mploy narrow spectrum

- It is better to use narrow-spectrum antibacterials as they limit effects on commensal bacteria
- Avoid using certain antibacterials as first line agents; only use when other agents are ineffective (ideally determined by culture and sensitivity testing)

C ulture and sensitivity

- Culture promptly when prolonged courses are likely to be needed (e.g. pyoderma, otitis externa, deep/surgical wound infection) or when empirical dosing has failed

T reat effectively

- Treat long enough and at a sufficient dose – **and then stop**
- Avoid underdosing
- Repeat culture after long courses

BSAVA BRITISH SMALL ANIMAL VETERINARY ASSOCIATION

SMALL ANIMAL MEDICINE SOCIETY

Updated March 2012

170EPUBS12

Write your practice policy on empirical antibacterial use in the boxes below

Periodontal disease

amoxicillin OR amoxicillin/clavulanate OR ampicillin OR clindamycin OR metronidazole + spiramycin. With or without chlorhexidine mouthwash.

Practice Policy:

Respiratory infections

Bacterial pneumonia (including aspiration):
- cats: amoxicillin/clavulanate OR doxycycline.
- dogs: aminoglycoside* + metronidazole* OR amoxicillin + fluoroquinolone OR amoxicillin + metronidazole* OR doxycycline OR oxytetracycline.

Practice Policy:

Bacterial rhinitis, chronic rhinitis and sinusitis: amoxicillin/clavulanate

Practice Policy:

Kennel cough: no antimicrobials in mild cases; more severe: amoxicillin/clavulanate OR doxycycline OR oxytetracycline.

Practice Policy:

Suspected ***Mycoplasma*:**
- cats: azithromycin* OR doxycycline.
- dogs: azithromycin* OR doxycycline OR oxytetracycline.

Practice Policy:

Pyothorax:
- cats: amoxicillin/clavulanate
- dogs: ampicillin + fluoroquinolone OR clindamycin + fluoroquinolone OR metronidazole* + fluoroquinolone.

Practice Policy:

Gastrointestinal infections

Acute diarrhoea with complications: amoxicillin/clavulanate OR 1st generation cephalosporin.

Practice Policy:

Anal sacculitis: lavage plus topical installation (saline or chlorhexidine); amoxicillin/clavulanate.

Practice Policy:

Confirmed ***Campylobacter* (if clinically significant):** enrofloxacin OR erythromycin*.

Practice Policy:

Cholangitis/cholangiohepatitis: amoxicillin OR amoxicillin/clavulanate OR ampicillin OR cefalexin. Metronidazole* may be added in dogs.

Practice Policy:

Gastrointestinal bleeding or bacterial translocation: metronidazole* + amoxicillin/clavulanate OR metronidazole* + 1st generation cephalosporin. Add fluoroquinolones or aminoglycosides* to improve Gram -ve cover.

Practice Policy:

Suspected ***Helicobacter*:** amoxicillin + metronidazole* OR azithromycin* + tindizole OR clarithromycin* + metronidazole*. In combination with bismuth *(caution in cats)* OR famotidine OR omeprazole OR ranitidine.

Practice Policy:

Genitourinary infections

Cystitis: amoxicillin/clavulanate OR trimethoprim/sulfadiazine. Many *cats* with cystitis do not have bacterial infections – routine antibacterials not required.

Practice Policy:

Endometritis/Pyometra: amoxicillin/clavulanate OR trimethoprim/sulfadiazine.

Practice Policy:

Suspected ***Leptospira*:** ampicillin OR pencillin G; doxycycline for carriers. Aminopenicillins treat bacteraemia but do not address carrier state.

Practice Policy:

Prostatitis (acute): fluoroquinolones OR trimethoprim/sulfadiazine. Culture required in chronic cases.

Practice Policy:

Pyelonephritis (acute): trimethoprim/sulfadiazine. Culture required in chronic cases.

Practice Policy:

Struvite urolithasis (dog): amoxicillin/clavulanate OR trimethoprim/sulfadiazine.

Practice Policy:

Orthopaedic infections

Discospondylitis/Osteomyelitis: amoxicillin/clavulanate OR 1st generation cephalosporin OR clindamycin. Long courses (6–8 wk) may be needed.

Practice Policy:

Septic arthritis: amoxicillin/clavulanate OR 1st generation cephalosporin.

Practice Policy:

Skin infections

Bite and other traumatic wounds: Lance, debride and lavage. In cat bites amoxicillin first choice; otherwise choice as for Pyoderma. Heavily infected/deeper injuries: metronidazole OR amoxicillin/clavulanate + fluoroquinolone are appropriate while awaiting culture results.

Practice Policy:

Infected traumatic wound: amoxicillin/clavulanate OR 1st generation cephalosporin.

Practice Policy:

Pyoderma:
Empirical choice of antibacterials suitable for surface and superficial pyoderma (if no resistance or treatment failure) but culture required for deep pyodermas.
- **Topical:** chlorhexidine AND/OR fusidic acid OR silver sulfadiazine*. (Antifungals for concurrent *Malassezia* often useful.)
- **Systemic:** amoxicillin/clavulanate OR cefadroxil OR cefalexin OR cefovecin (if problems expected with administration/compliance) OR clindamycin OR fluoroquinolones (if others inappropriate). Continue 1 week beyond resolution of clinical signs.

Practice Policy:

Pyoderma (idiopathic recurrent):
- **Topical therapy** important: antimicrobial shampoos/rinses, especially chlorhexidine.
- **Systemic:** Alternatives to antibacterials include immunostimulants (Staph Phage Lysate, autogenous vaccine). Last resort is pulse therapy 2–3 consecutive days/wk.

Practice Policy:

Pyoderma (confirmed MRSA/MRSP): choice based on sensitivity. If sensitivity not known, use topical chlorhexidine AND/OR fusidic acid OR systemic tetracyclines OR trimethoprim/sulfadiazine.

Practice Policy:

Pyogranuloma: as for Pyoderma but *culture essential and may need to be repeated.* Filamentous bacteria: clindamycin OR doxycycline OR trimethoprim/sulphonamide. Mycobacteria: fluoroquinolones ± doxycyline.

Practice Policy:

Ear infections

Otitis externa (erythroceruminous):
- **Topical:** fusidic acid OR framycetin OR gentamicin OR marbofloxacin OR orbifloxacin OR polymixin B/miconazole. (Antifungals to treat concurrent *Malassezia* will often be useful.) Combine with effective antibacterial ear cleaners with a low pH (chlorhexidine, chloroxylenol, isopropyl alcohol, PCMX.)
- **Systemic:** choice as for Pyoderma.

Practice Policy:

Otitis externa (suppurative) or otitis media:
- **Topical:** Choice (including ear cleaners) as for erythroceruminous OE. Enrofloxacin, marbofloxacin, aqueous gentamicin appear to be safe in the middle ear. Multidrug-resistant infections: 1.7% ceftazidime OR 2.8% clavulanate/ticarcillin OR 0.6% enrofloxacin OR 0.2% marbofloxacin OR 0.1–0.5% silver sulfadiazine (diluted in trisEDTA).
- **Systemic:** choice as for Pyoderma.

Practice Policy:

Eye infections

Bacterial conjunctivitis:
- **Topical:** cloxacillin OR fusidic acid OR gentamicin.

Practice Policy:

Suspected ***Chlamydophila*:**
- **Systemic:** doxycycline OR enrofloxacin. Topical fusidic acid may be added if desired.

Practice Policy:

Miscellaneous

Endocarditis: amoxicillin/clavulanate + enrofloxacin OR amoxicillin/clavulanate + metronidazole*.

Practice Policy:

Mastitis: amoxicillin/clavulanate OR trimethoprim/sulfadiazine.

Practice Policy:

Suspected ***Mycoplasma haemofelis*** *(*formerly *Haemobartonella)* (feline infectious anaemia): doxycycline OR fluoroquinolone.

Practice Policy:

Neutropenia: Mild: no antibacterial required. Severe but asymptomatic: trimethoprim/sulphonamide. Severe and with clinical signs: 1st generation cephalosporin + fluoroquinolone.

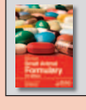
Practice Policy:

Septic peritonitis: amoxicillin/clavulanate OR ampicillin + cefotaxime OR ampicillin + gentamicin* OR clindamycin + enrofloxacin OR fluoroquinolone + ampicillin. Add metronidazole* if anaerobe suspected.

Practice Policy:

Septicaemia: ampicillin + cefotaxime OR ampicillin + gentamicin* OR clindamycin + enrofloxacin OR enrofloxacin + ampicillin OR fluoroquinolone + amoxicillin/clavulanate.

Practice Policy:



For further information on individual drugs and dosages, see *BSAVA Small Animal Formulary, 7th edition.*

Surgical prophylaxis

Prophylactic antimicrobial use is not a substitute for good aseptic technique.
- Perioperative antibiosis is appropriate:
  - for prolonged surgery (>1.5 hours) or surgery involving implants
  - for debilitated or immunosuppressed patients
  - where infections would be catastrophic (e.g. in CNS)
  - where there is an obvious break in asepsis
  - for all bowel surgery
  - for dental procedures where there is periodontal disease
  - for contaminated wounds or pre-existing infection.
- In most cases:
  - intravenous amoxicillin/clavulanate OR first-generation cephalosporin.
- Where anaerobic involvement is highly likely (e.g. periodontal disease):
  - *add or substitute* metronidazole.
- For significant bowel leakage in an otherwise metabolically stable animal:
  - combination may be most appropriate, e.g. ampicillin + aminoglycoside (e.g. gentamicin)
  - if patient volume-depleted, replace aminoglycoside with fluoroquinolone.

Practice Policy:

Antibacterials not indicated unless cytology and/or culture is positive

- Cardiorespiratory
  - Chronic bronchitis/allergic airway disease
  - Aspergillosis
  - Congestive heart failure
- Urinary
  - Feline lower urinary tract disease (including struvite urolithasis)
  - Urinary incontinence
- Gastrointestinal
  - Acute vomiting (uncomplicated)
  - Acute diarrhoea (uncomplicated)
  - Chronic gastroenteritis (unless 4-week treatment trial for antibiotic-responsive diarrhoea)
  - Pancreatitis (uncomplicated)
- Surgery
  - Routine castration and ovariohysterectomy
  - Removal of uninfected skin mass not involving major reconstruction
- Metabolic
  - Polyuria, polydipsia (unless pyogenic focus suspected)
  - Weight loss
- Skin and ears
  - *Malassezia* dermatitis
  - Acute non-specific pruritus, scaling, nodules, crusts, etc.

DO NOT USE

There are very strong arguments that antimicrobials with restricted use in human medicine (e.g. imipenem, linezolid, teicoplanin, vancomycin) should **not** be used in animals under any circumstances.

Second and Third Choice Antibacterials

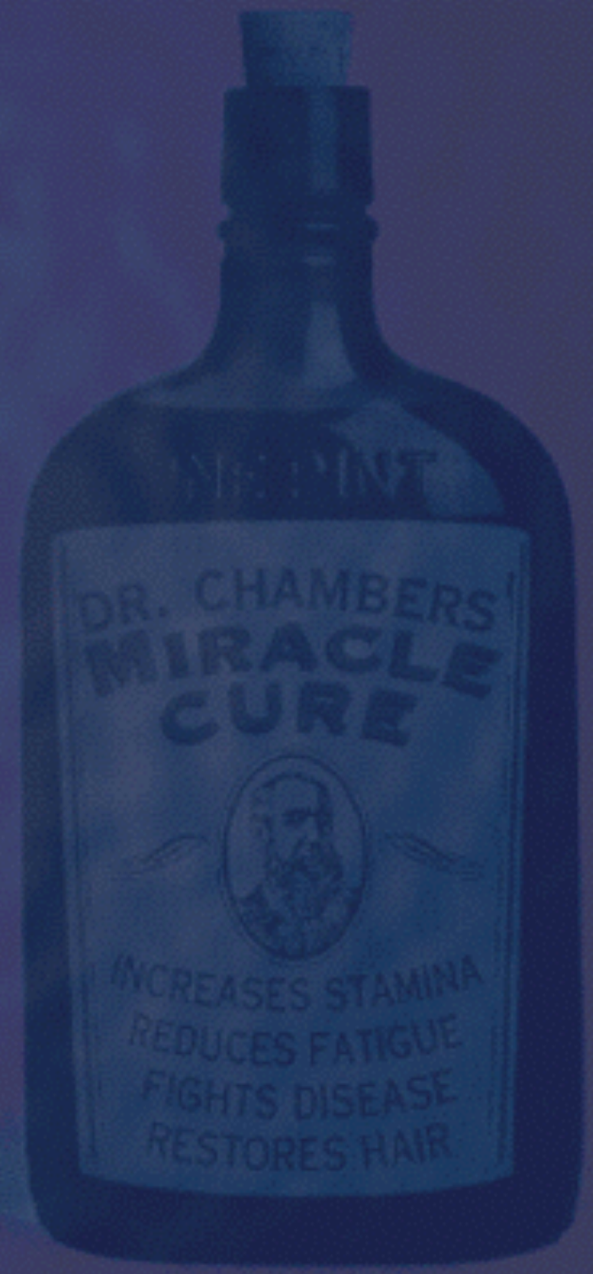
These include: amikacin, 3rd generation and 4th generation cephalosporins (except cefovecin) and fluoroquinolones. These antibacterials should be used only when other agents are inappropriate (e.g. in penicillin-sensitive individuals) and/or ineffective, *and* culture/sensitivity testing indicates that they will be effective.

Follow the Cascade

Suggested antibacterials for dogs and cats are listed in alphabetical order. Order of selection should follow the Prescribing Cascade. The following agents (*) are not authorized as sole agents for systemic use in small animals: aminoglycosides, azithromycin, erythromycin, gentamicin, metronidazole. Metronidazole is authorized for oral use in combination with spiramycin. Oxytetracycline is not authorized for use in the cat.

4 yr old bull terrier

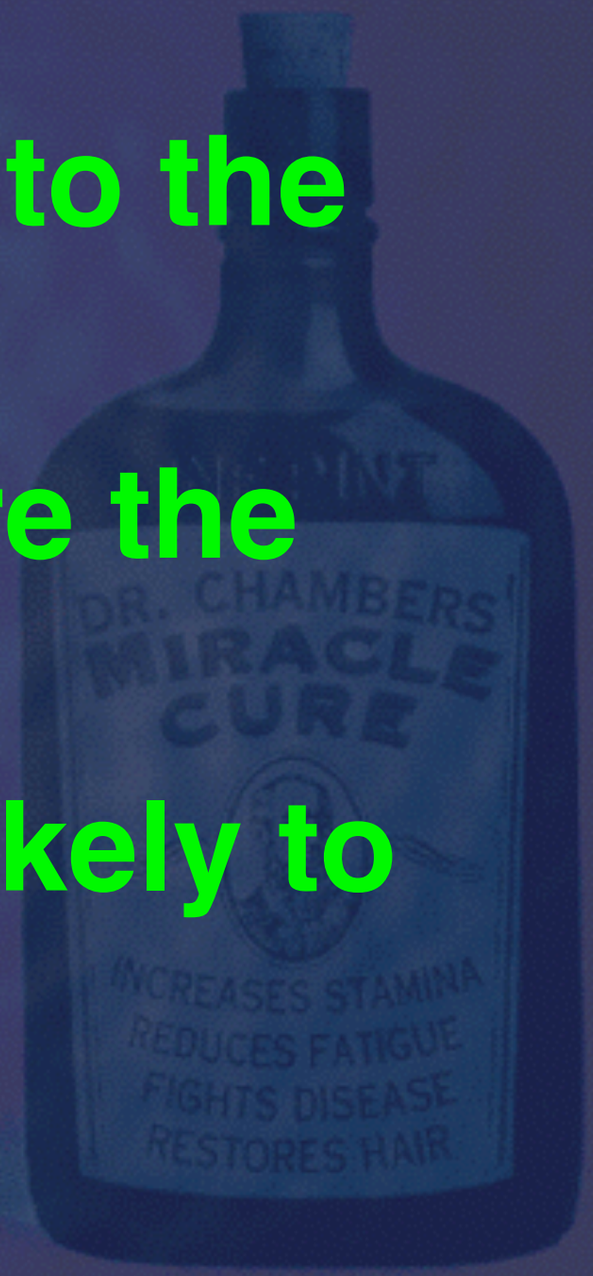
- **scratching ears**
- **previously treated**
  - –broad spectrum antibiotics
  - –steroids
  - –acaricides



What do you do?

antibiotic treatment

- are the bacteria sensitive to the drug?
- does the drug get to where the bacteria are?
- is significant resistance likely to develop?



clindamycin OR doxycycline OR trimethoprim/sulphonamide. Mycobacteria: fluoroquinolones ± doxycycline.

Practice Policy:

Ear infections

Otitis externa (erythroceruminous):

- **Topical:** fusidic acid OR framycetin OR gentamicin OR marbofloxacin OR orbifloxacin OR polymixin B/miconazole. (Antifungals to treat concurrent *Malassezia* will often be useful.) Combine with effective antibacterial ear cleaners with a low pH (chlorhexidine, chloroxylenol, isopropyl alcohol, PCMX.)
- **Systemic:** choice as for Pyoderma.

Practice Policy:

Otitis externa (suppurative) or otitis media:

- **Topical:** Choice (including ear cleaners) as for erythroceruminous OE. Enrofloxacin, marbofloxacin, aqueous gentamicin appear to be safe in the middle ear. Multidrug-resistant infections: 1.7% ceftazidime OR 2.8% clavulanate/ticarcillin OR 0.6% enrofloxacin OR 0.2% marbofloxacin OR 0.1–0.5% silver sulfadiazine (diluted in trisEDTA).
- **Systemic:** choice as for Pyoderma.

Practice Policy:

Eye infections

Bacterial conjunctivitis:

- **Topical:** cloxacillin OR fusidic acid OR gentamicin.

Practice Policy:

Suspected ***Chlamydophila*:**

- **Systemic:** doxycycline OR enrofloxacin. Topical fusidic acid may be added if desired.

Practice Policy:

Miscellaneous

Endocarditis: amoxicillin/clavulanate + enrofloxacin OR amoxicillin/clavulanate + metronidazole*

Ear infections

Otitis externa (erythroceruminous):

- **Topical:** fusidic acid OR framycetin OR gentamicin OR marbofloxacin OR orbifloxacin OR polymixin B/miconazole. (Antifungals to treat concurrent *Malassezia* will often be useful.) Combine with effective antibacterial ear cleaners with a low pH (chlorhexidine, chloroxylenol, isopropyl alcohol, PCMX.)
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- **Systemic:** choice as for Pyoderma.

Practice Policy:

Eye infections

Bacterial conjunctivitis:

- **Topical:** cloxacillin OR fusidic acid OR gentamicin.

Practice Policy:

Suspected ***Chlamydophila***:

- **Systemic:** doxycycline OR enrofloxacin. Topical fusidic acid may be added if desired.

Practice Policy:

Miscellaneous

Endocarditis: amoxicillin/clavulanate + enrofloxacin OR amoxicillin/clavulanate + metronidazole*.

Practice Policy:

Mastitis: amoxicillin/clavulanate OR trimethoprim/sulfadiazine.

Practice Policy:

Suspected ***Mycoplasma haemofelis*** *(*formerly *Haemobartonella)* (feline infectious anaemia): doxycycline OR fluoroquinolone.

Practice Policy:

Neutropenia: Mild: no antibacterial required. Severe but asymptomatic: trimethoprim/sulphonamide. Severe and with clinical signs: 1st generation cephalosporin + fluoroquinolone.

Practice Policy:

Septic peritonitis: amoxicillin/clavulanate OR ampicillin + cefotaxime OR ampicillin + gentamicin* OR clindamycin + enrofloxacin OR fluoroquinolone + ampicillin. Add metronidazole* if anaerobe suspected.

Practice Policy:

Septicaemia: ampicillin + cefotaxime OR ampicillin + gentamicin* OR clindamycin + enrofloxacin OR enrofloxacin + ampicillin OR fluoroquinolone + amoxicillin/clavulanate.

Practice Policy:

For further information on individual drugs and dosages

Antibacterials not indicated unless cytolo and/or culture is positive

- Cardiorespiratory
  - Chronic bronchitis/allergic airway disease
  - Aspergillosis
  - Congestive heart failure
- Urinary
  - Feline lower urinary tract disease (including struvite urolithasis)
  - Urinary incontinence
- Gastrointestinal
  - Acute vomiting (uncomplicated)
  - Acute diarrhoea (uncomplicated)
  - Chronic gastroenteritis (unless 4-week treatment trial for antibiotic-responsive diarrhoea)
  - Pancreatitis (uncomplicated)
- Surgery
  - Routine castration and ovariohysterectomy
  - Removal of uninfected skin mass not involving major reconstruct
- Metabolic
  - Polyuria, polydipsia (unless pyogenic focus suspected)
  - Weight loss
- Skin and ears
  - *Malassezia* dermatitis
  - Acute non-specific pruritus, scaling, nodules, crusts, etc.

DO NOT USE

There are very strong arguments that antimicrobials with restricted use in human medicine (e.g. imipenem, linezolid, teicoplanin, vancomycin) should **not** be used in animals under any circumstances.

Second and Third Choice Antibacterials

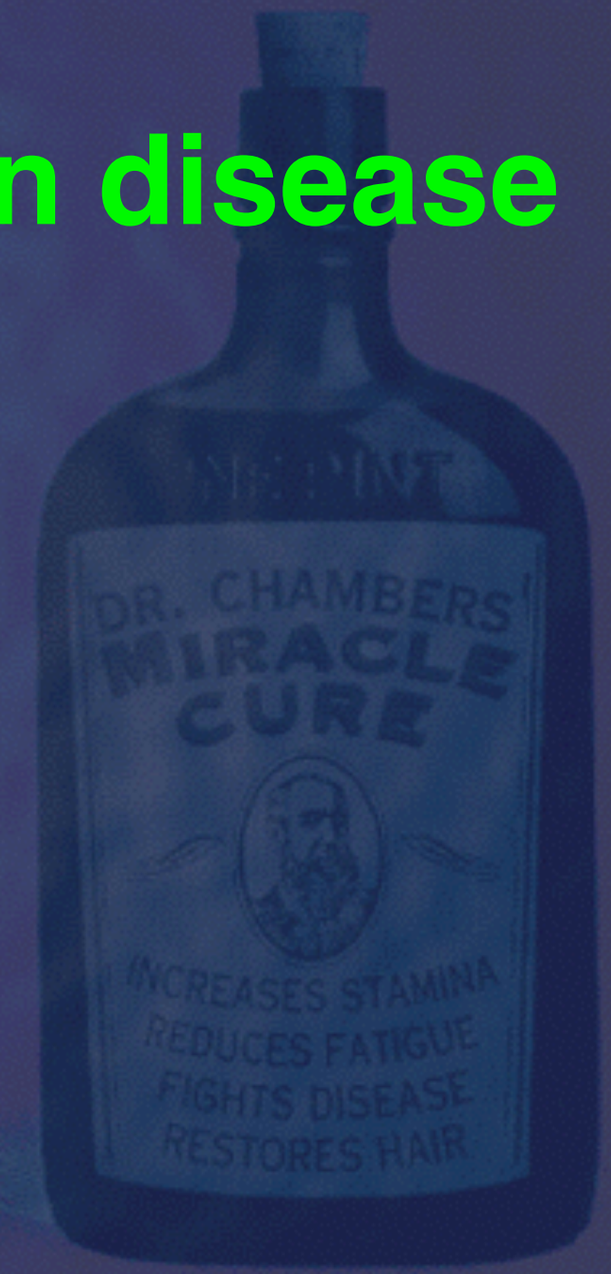
These include: amikacin, 3rd generation and 4th generation cephalosporins (except cefovecin) and fluoroquinolones. These antibacterials should be used only when other agents are inappropriate (e.g. in penicillin-sensitive individuals) and/or ineffective, *and* culture/sensitivity testing indicates that they will be effective.

Follow the Cascade

Suggested antibacterials for dogs and cats are listed in alphabetical order. Order of selection should follow the Prescribing Cascade. The following agents (*) are not authorized as sole agents for systemic use in small animals:

What do you do?

- check for generalised skin disease
- culture and sensitivity?
- flush and check ear
- parenteral antibiotics?
- parenteral steroids?
- non-antibiotic treatment?
- alter environment?



reducing resistance

- Choose a drug on resistance testing, where practicable.
- Use narrow spectrum antimicrobials whenever possible.
- Use the full effective dose for as short a period as possible.
- Isolate the patient (and wash your hands / gumboots!).
- Use antibacterials not prone to producing resistance.
- Restrict the prophylactic use of antimicrobials to high risk patients only.
- In chronic care patients, regularly (but not frequently) change antimicrobial drugs.
- With aminoglycosides, use the longest effective dosage interval.