Dr Richard Everts

Infectious Disease Specialist

Microbiologist and General Physician, Nelson

Sunday, August 14, 2016

(Plenary)

8:55 - 9:20 Optimal Use of Antibiotics in General Practice

Optimum use of antibiotics in General Practice

Richard Everts FRACP ABMM

Infectious Diseases Physician and Microbiologist

NZ South GP Meeting 14 August 2016

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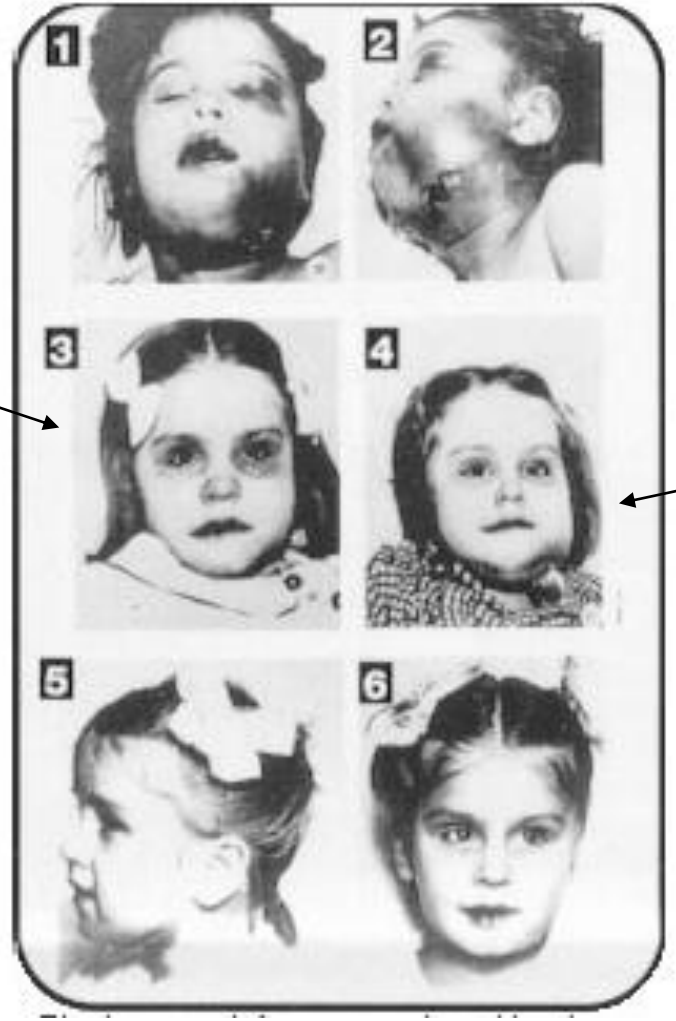
The miracle of penicillin - 1942

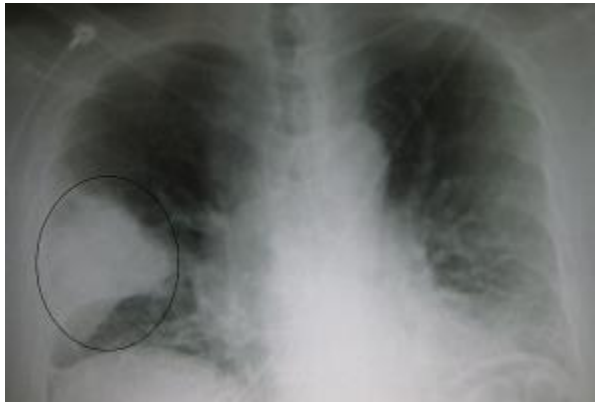


Day 4

Day 9

Recovered

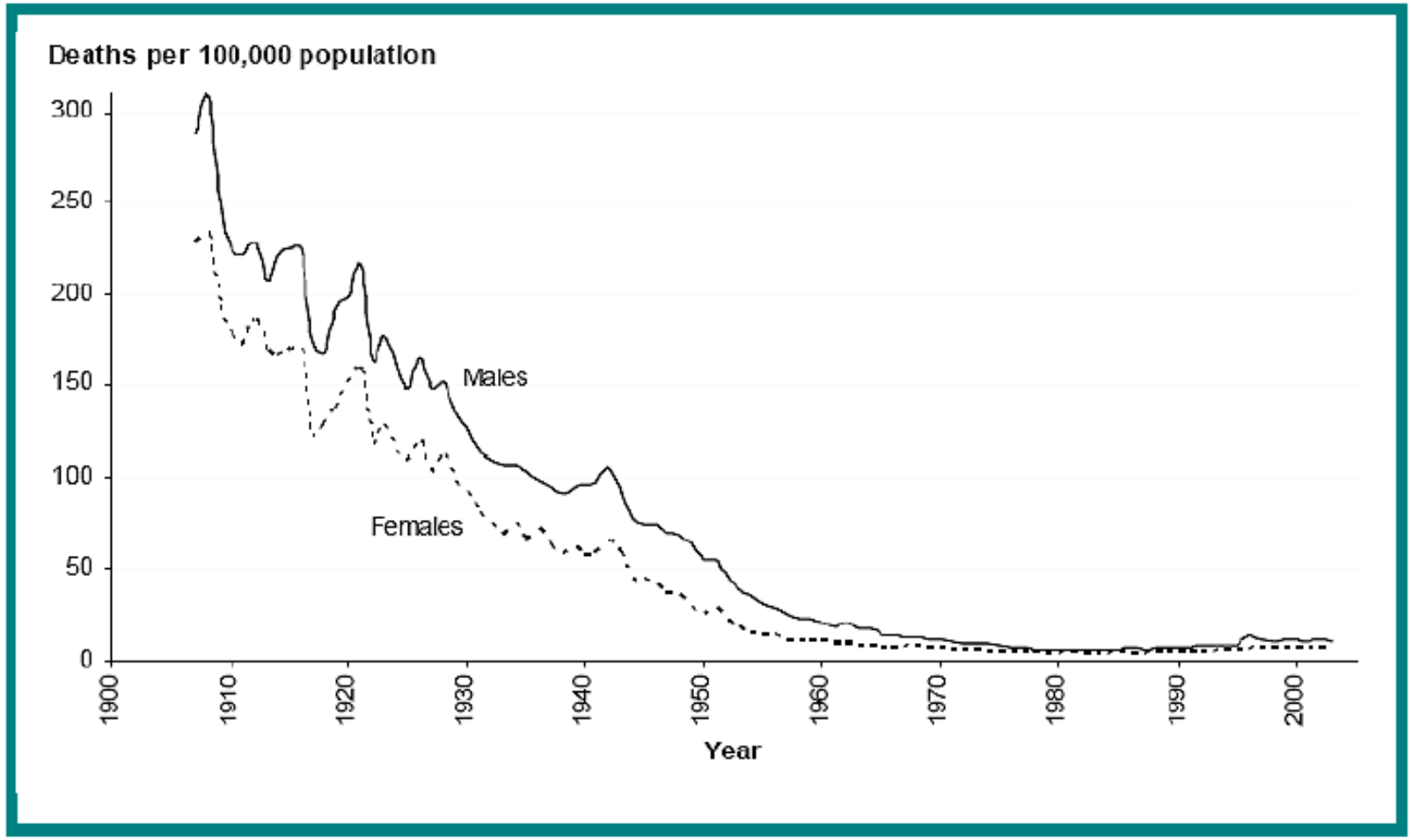
Sulfa antibiotics and pneumonia



- 1938 - controlled trial in pneumonia
  - Sulpha antibiotic: 8% died
  - No antibiotic: 27% died

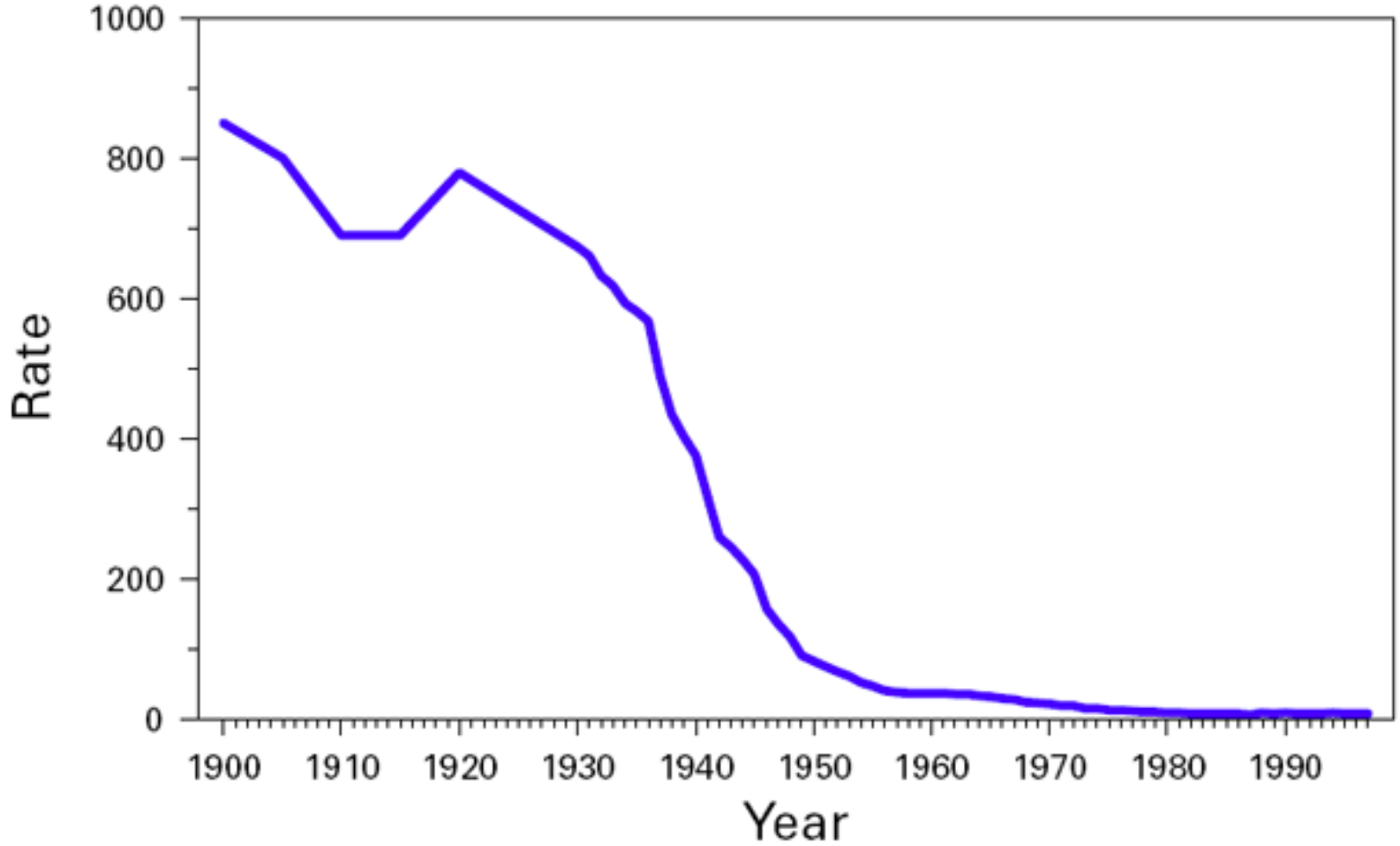
Evans GM, Gaisford WF. Treatment of pneumonia with 2-(p-aminobenzenesuphonamido)-pyridine. Lancet 1938;2:14-9

Figure 1.1: Dramatic decline in death rates for infectious diseases, 1907–2003



Source: AIHW, *Mortality over the twentieth century in Australia*, 2006, p. 36.

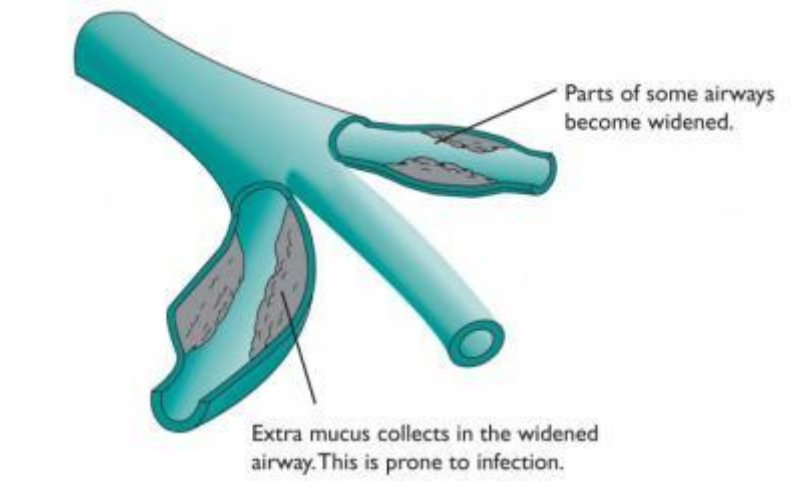
FIGURE 2. Maternal mortality rate,* by year — United States, 1900–1997

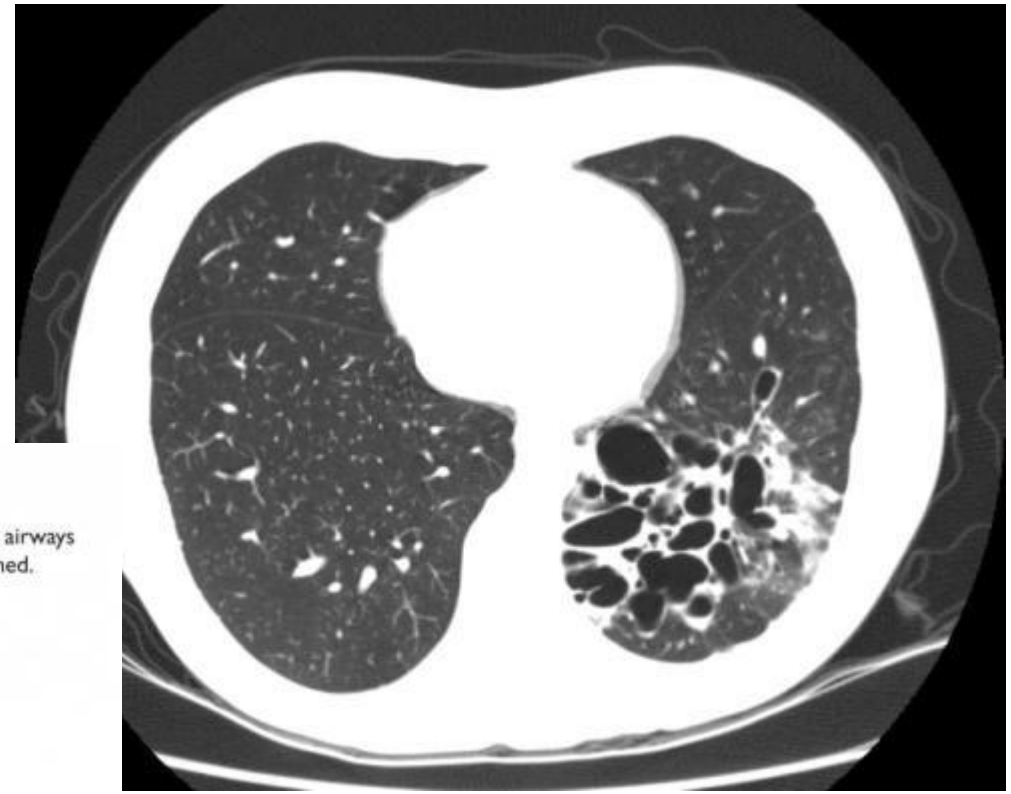


*Per 100,000 live births.

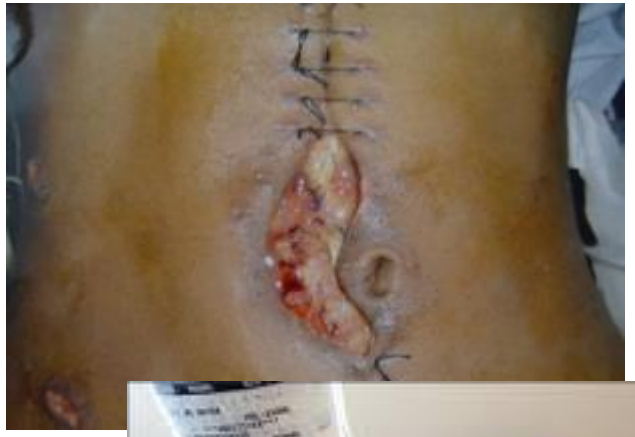
Antibiotics save body damage

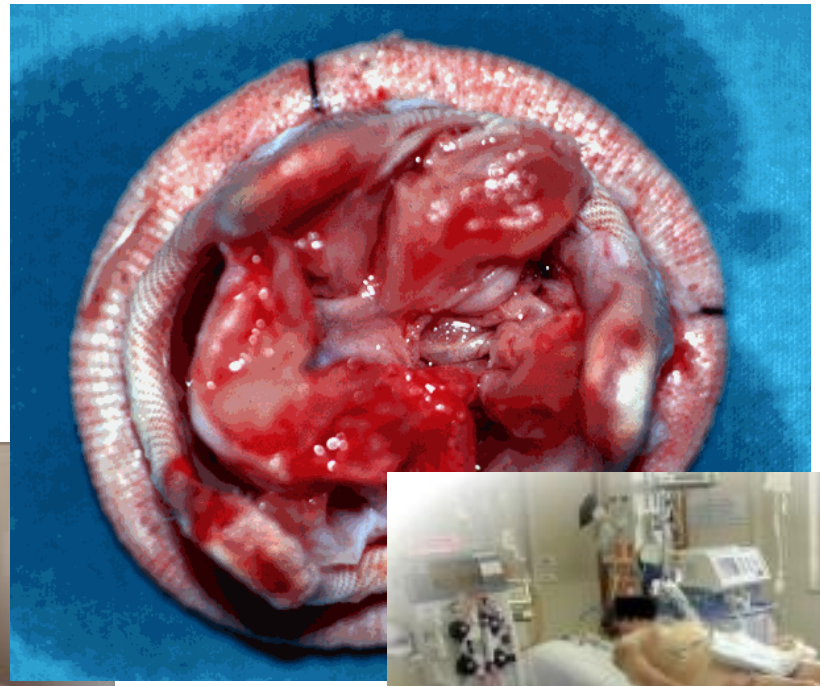
Bronchiectasis



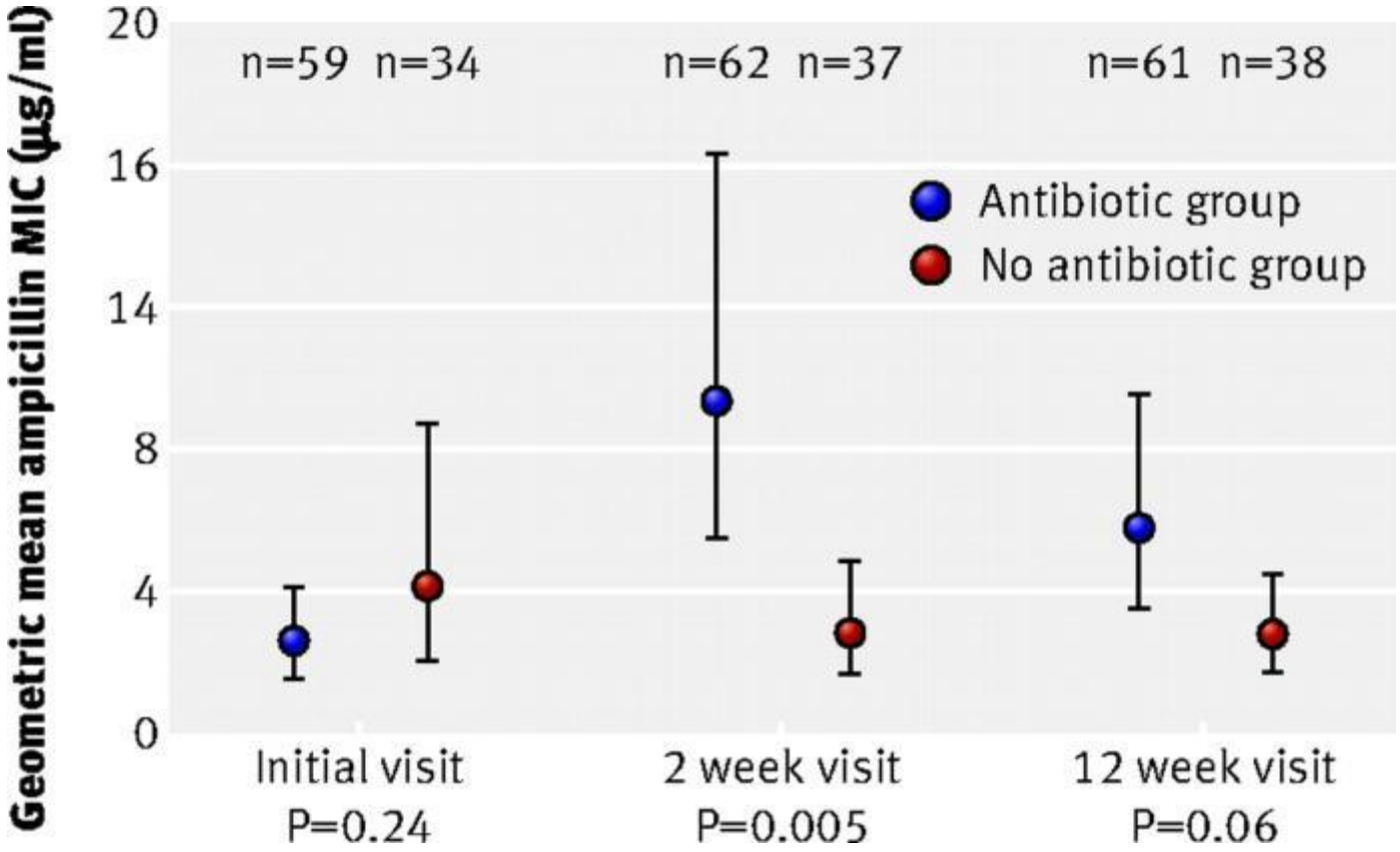


Antibiotics enable surgery, ICU care, anti-cancer treatment

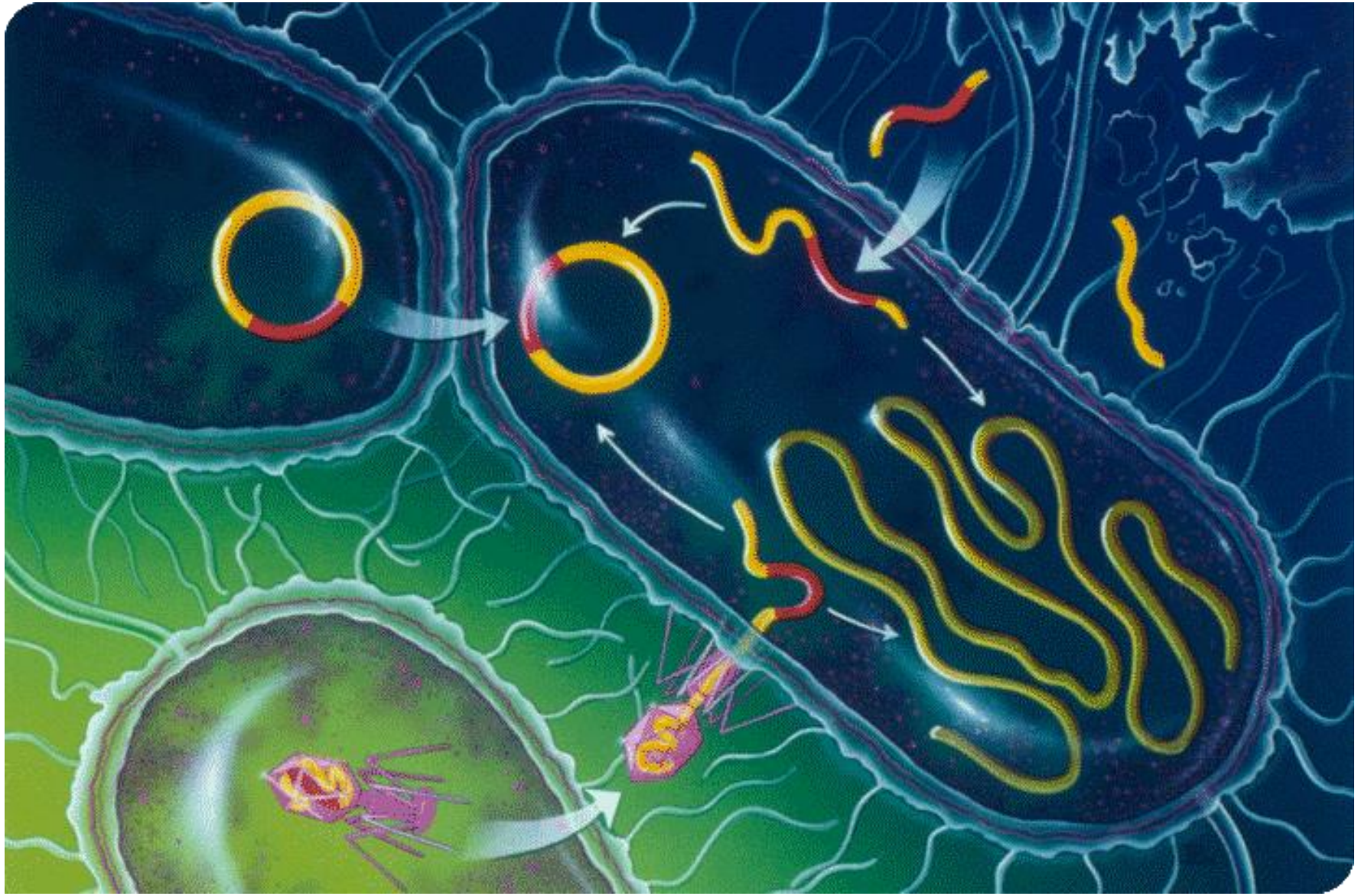




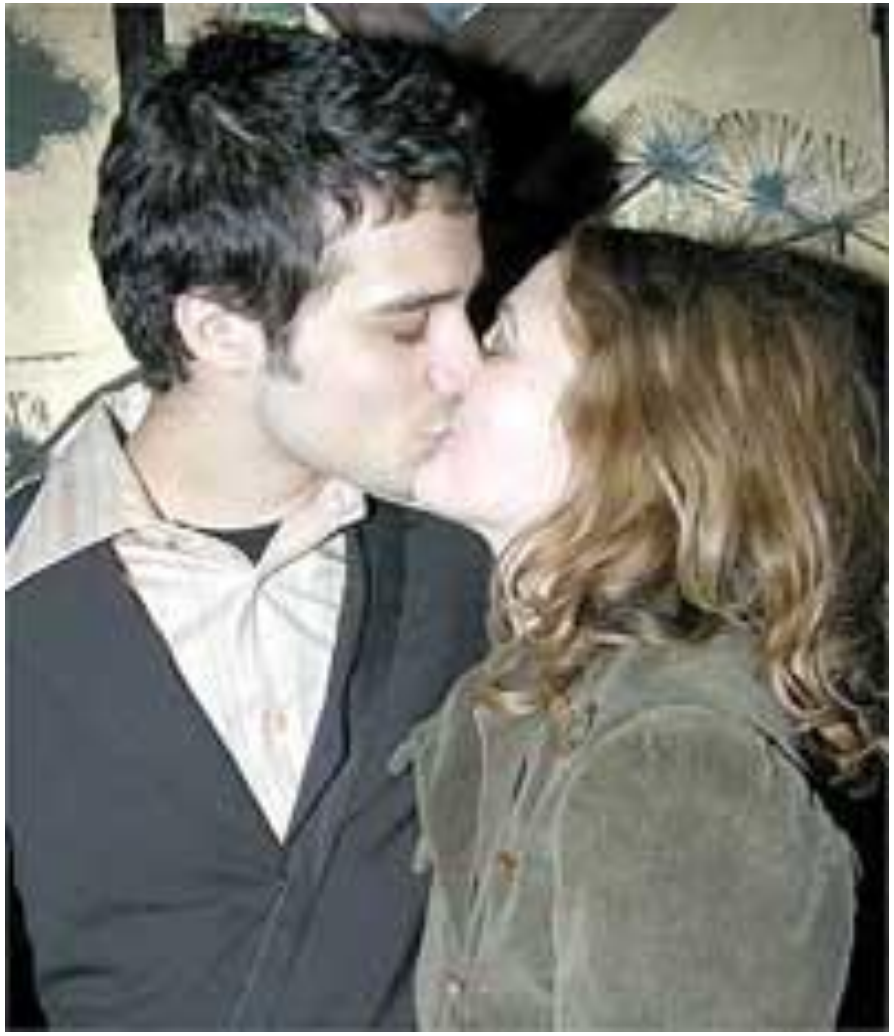
Geometric mean minimum inhibitory concentration (MIC) for ampicillin of isolates from children according to whether or not they received antibiotics (error bars show 95% confidence intervals; P values based on t test)



Chung, A. et al. BMJ 2007;0:bmj.39274.647465.BEv1-bmj.39274.647465.BE

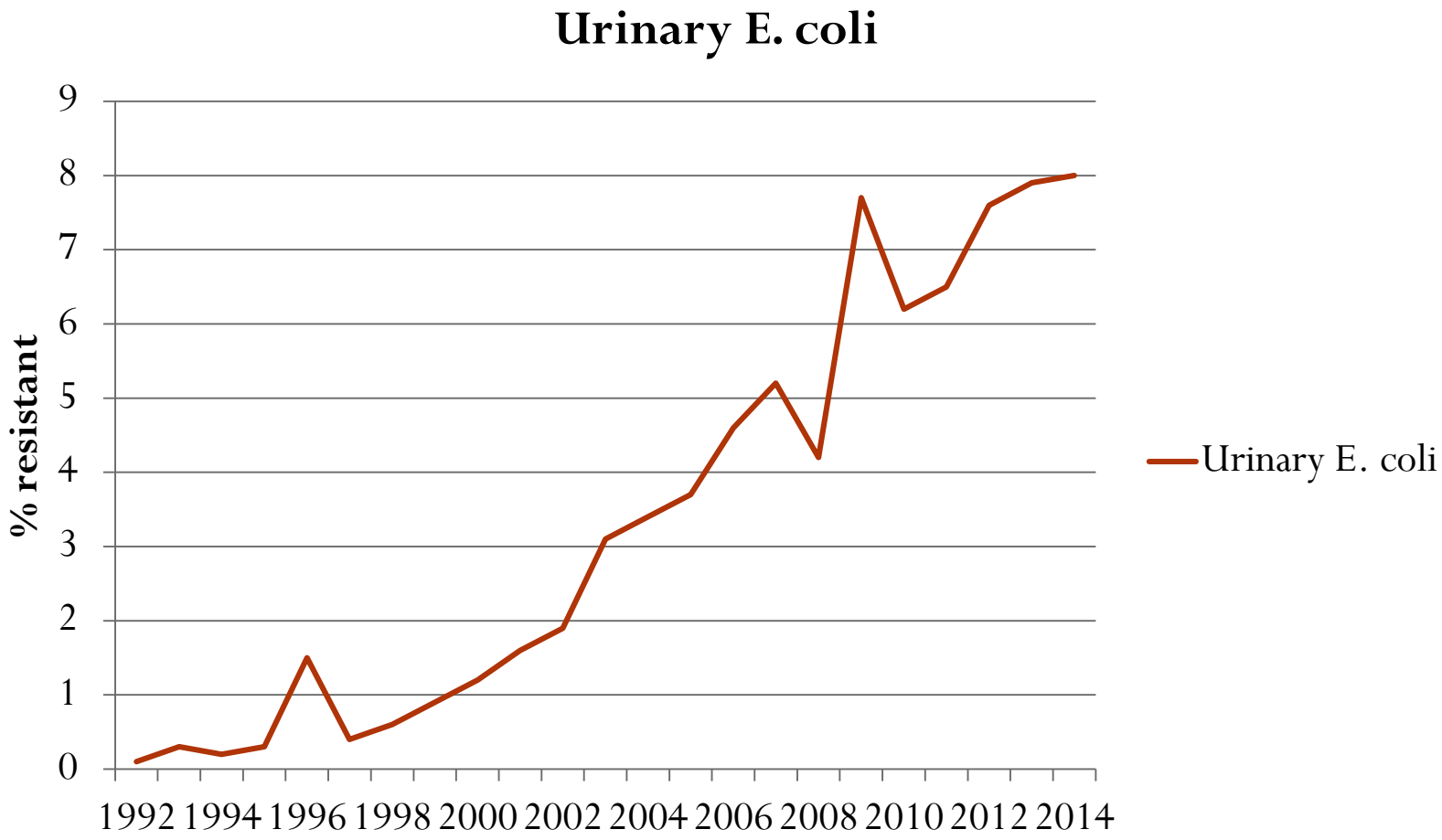


Genes pass between bacteria

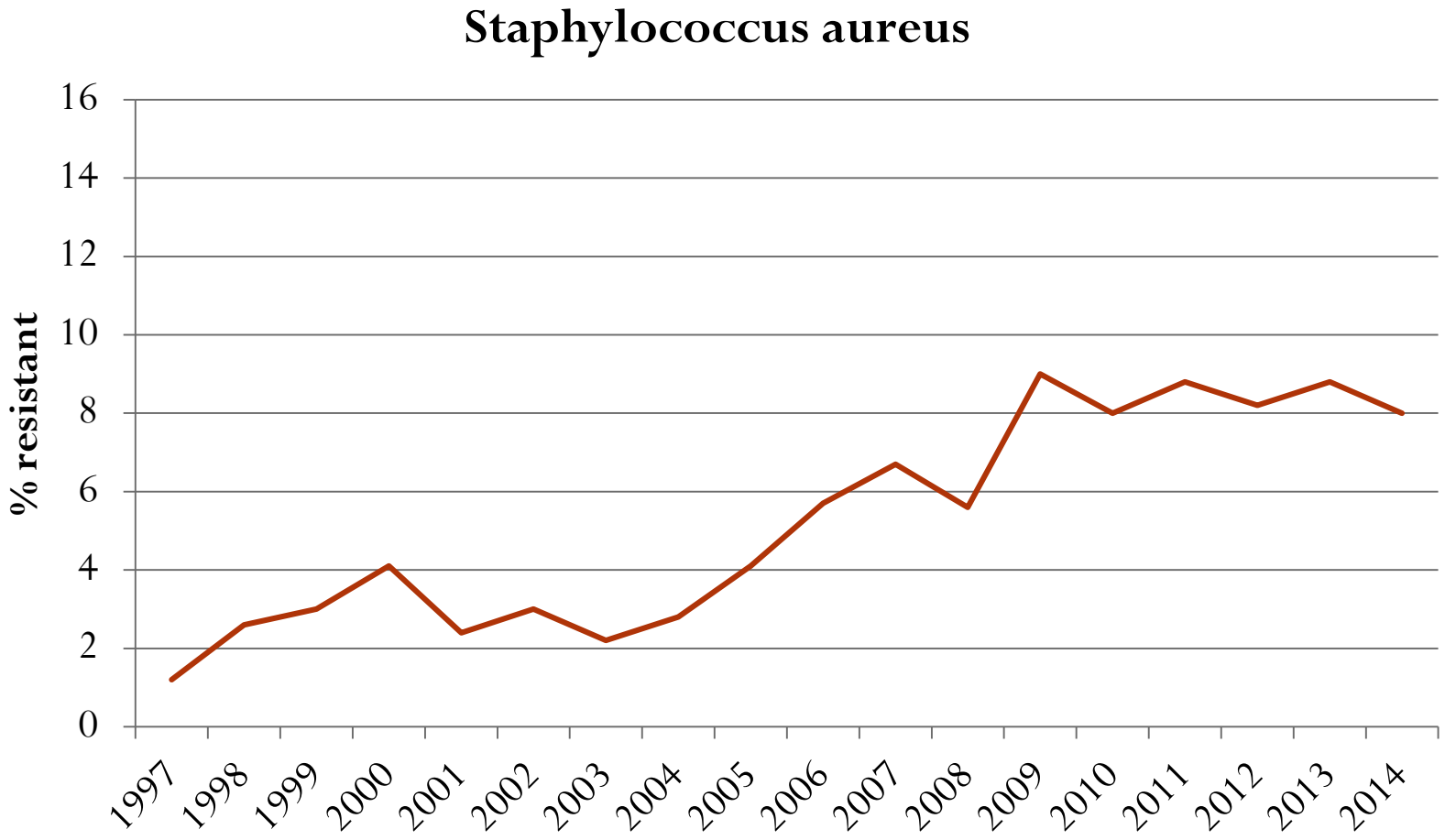


Resistant bacteria spread
from one human to another

Ciprofloxacin resistance in NZ

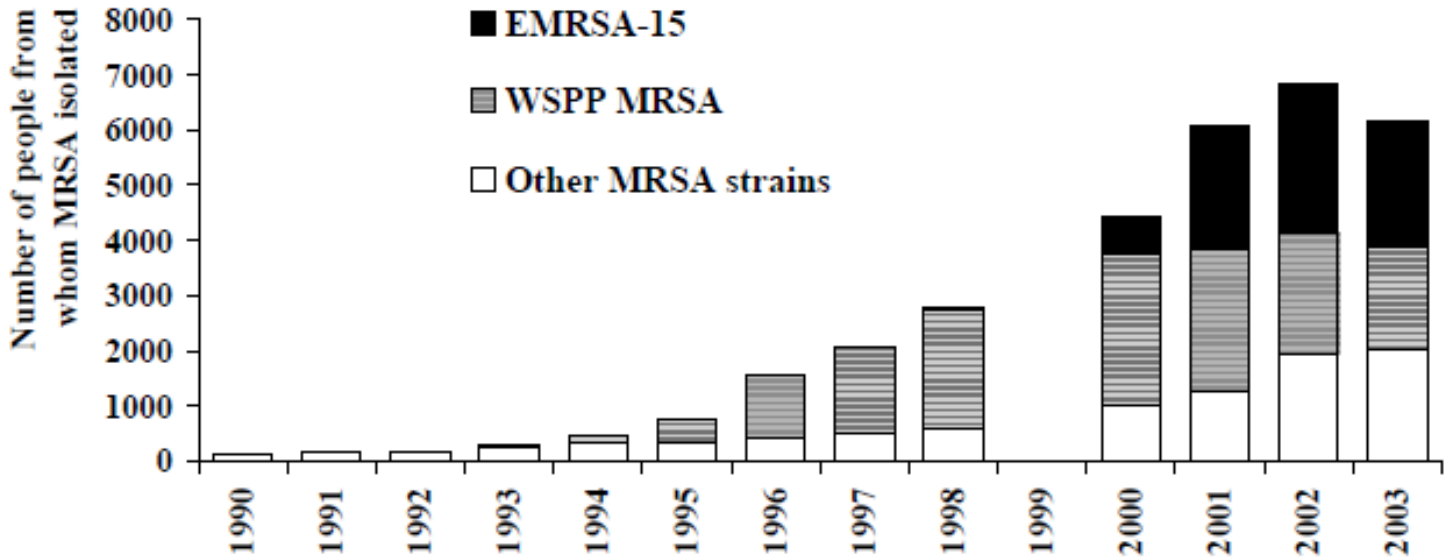


Clindamycin resistance in NZ



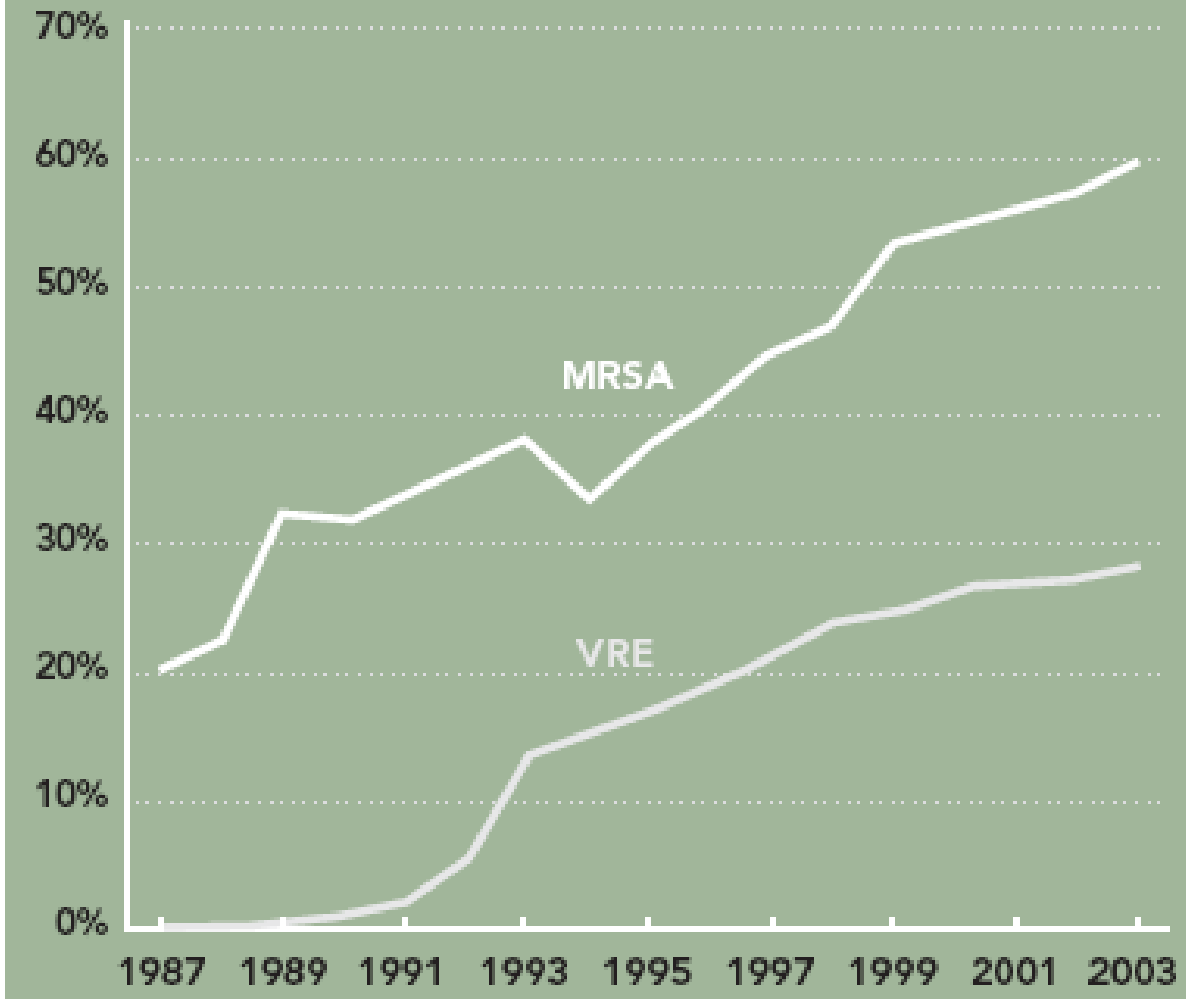
MRSA in NZ

Figure 1. MRSA isolations, 1990-2003



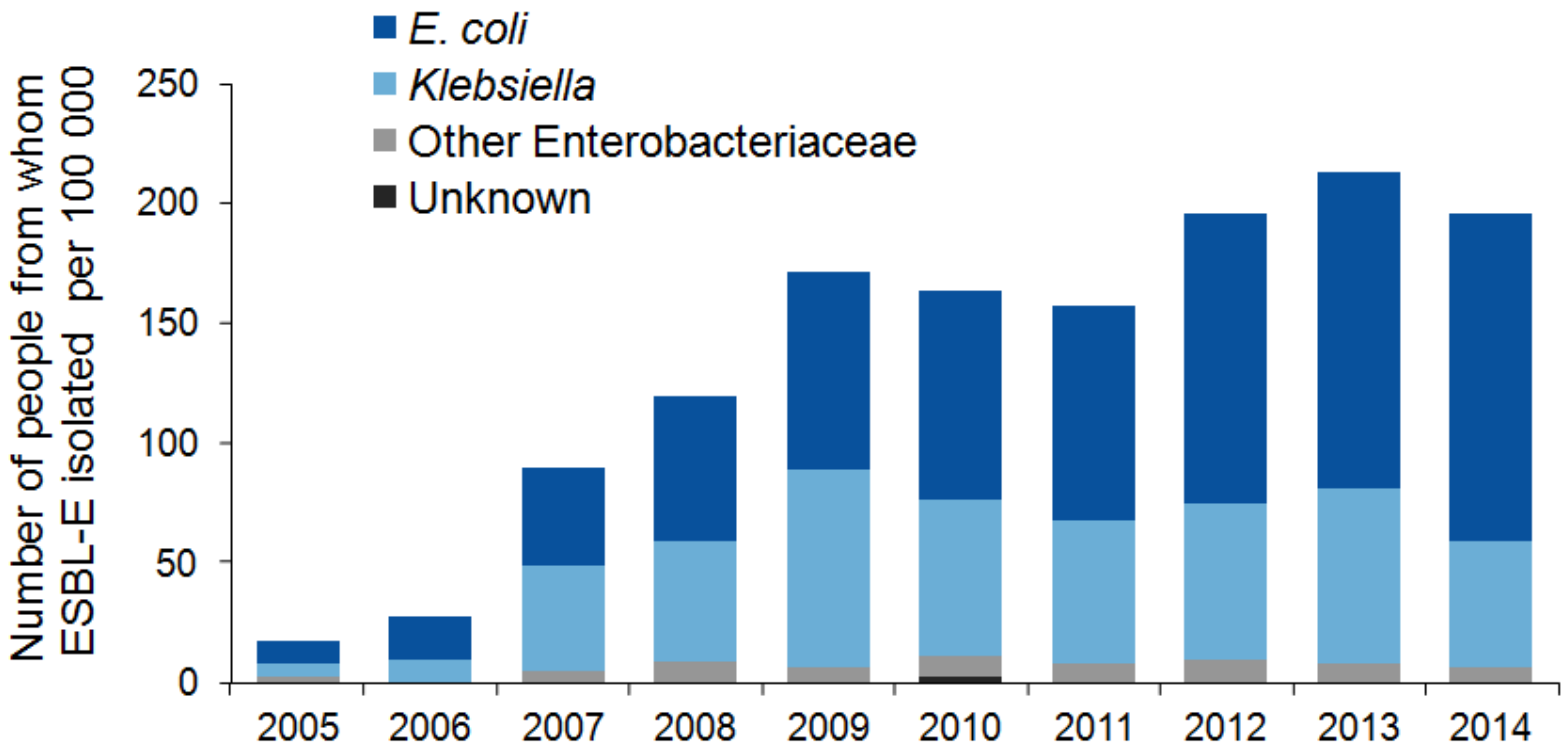
Data for 1990 to 1998 are based on continuous surveillance of all MRSA isolations. Data for 2000 to 2003 are annualised and based on one-month surveys conducted in these years. No survey was undertaken in 1999.

The proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcal (VRE) infections is increasing (1987–2003)



Note: Data refer to infections in intensive care unit (ICU) patients only.

ESBL-producing Enterobacteriaceae incidence rates, 2005-2014



Thanks to Helen Heffernan, ESR

From SE Asia to Nelson, with love

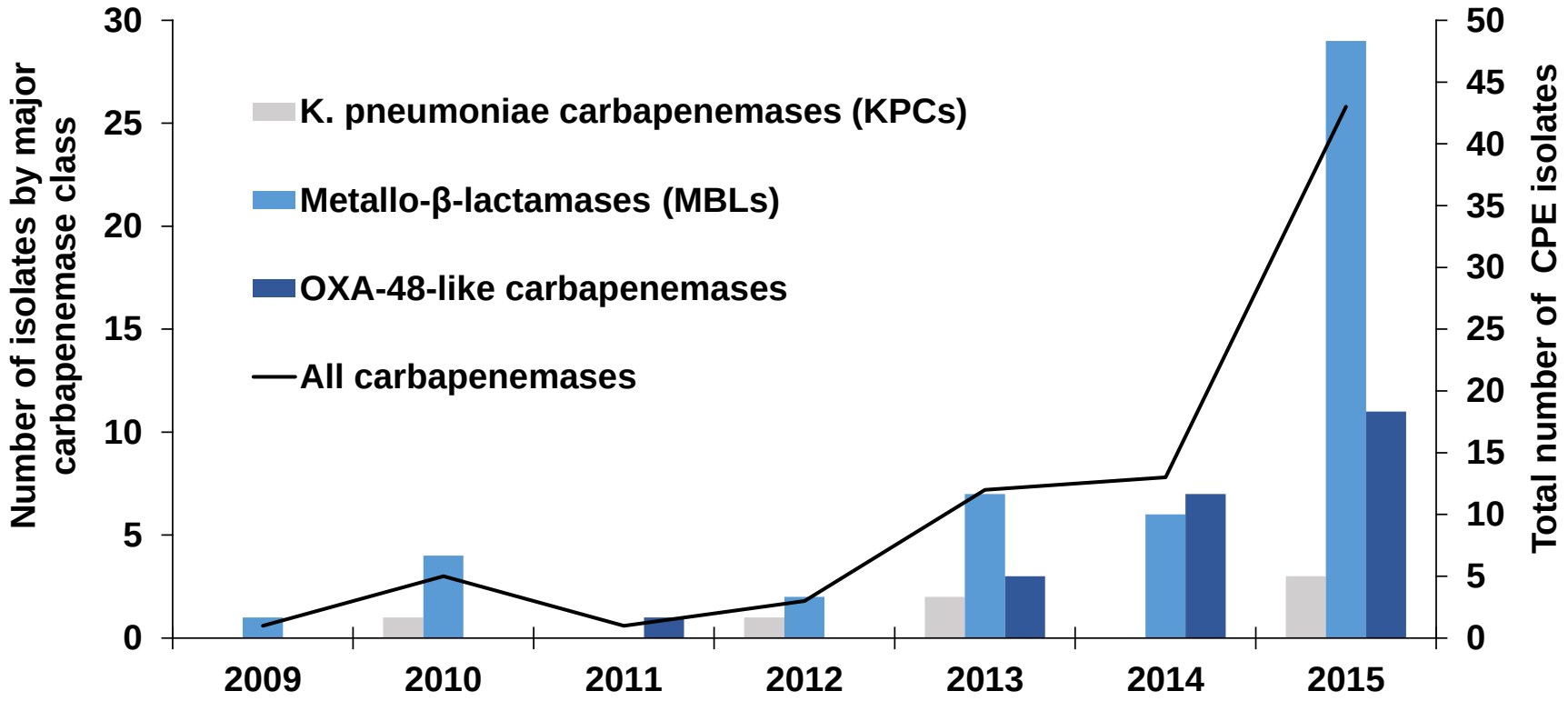
Urine culture:

(1) >100 x 10(6)/L PSEUDOMONAS AERUGINOSA

	(1)
Trimethoprim	R
Ampi/Amoxycillin	R
Amoxycillin/clavulanic	R
Cefaclor	R
Nitrofurantoin	R
Ciprofloxacin	R
Ceftriaxone	R
Cefoxitin	R
Cefepime	R
Ceftazidime	R
Tazobactam/piperacillin	R
Gentamicin	R
Tobramycin	R
Amikacin	R
Imipenem	R
Meropenem	R
Ertapenem	R
Colistin/Polymyxin	S

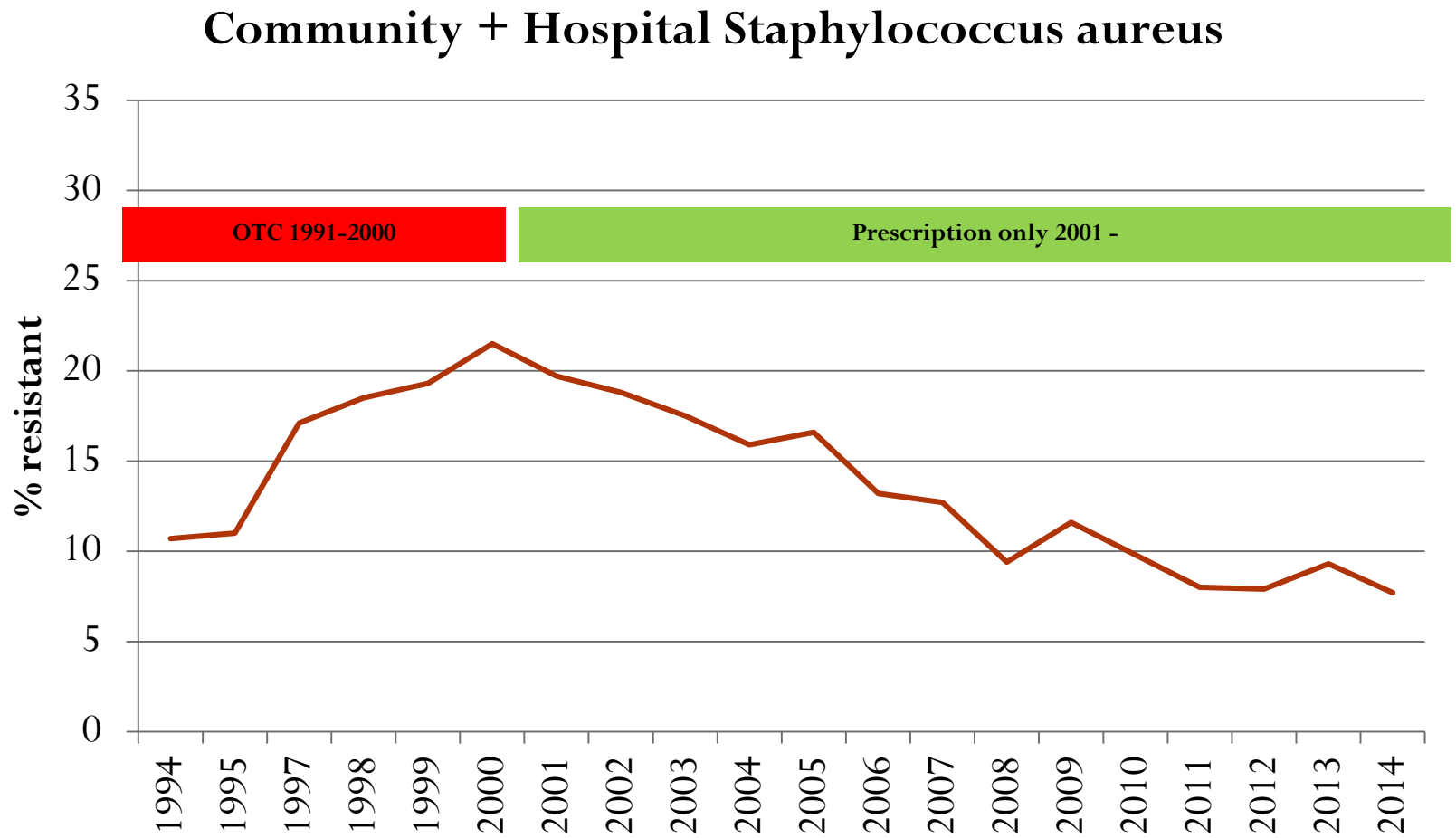
ESR report on MIC levels sent seperately.

Number of carbapenemase-producing Enterobacteriaceae isolates identified in New Zealand, by major β-lactamase class, each year from 2009 to 2015



Thanks to Helen Heffernan, ESR

Mupirocin resistance in NZ



Resistance and total antibiotic use

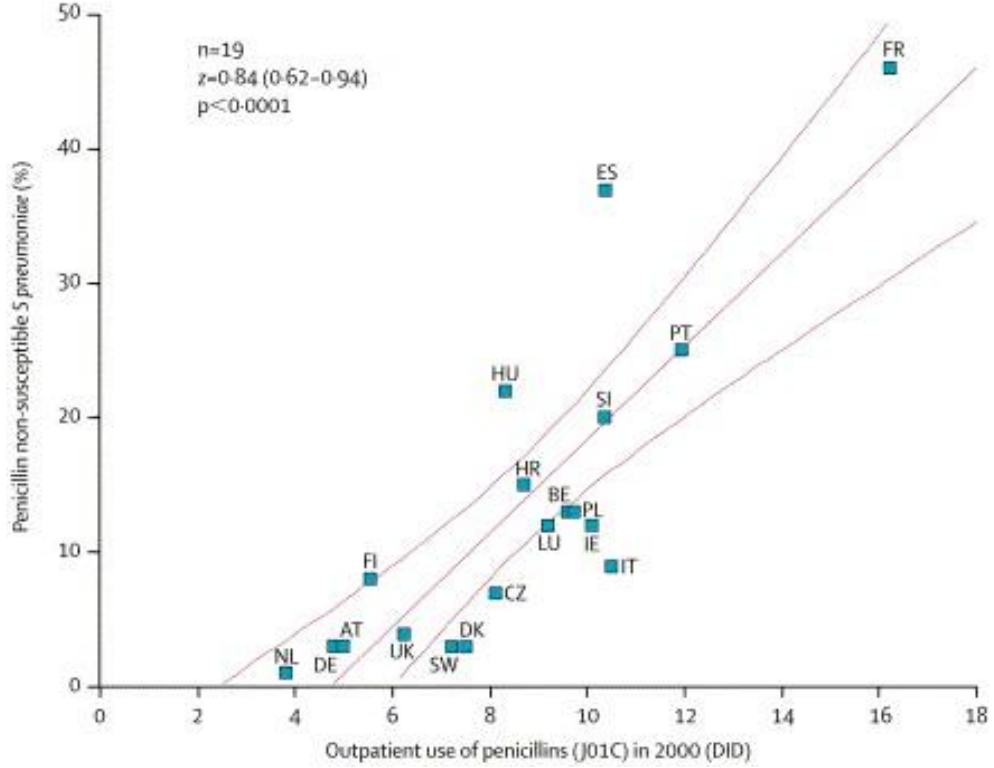
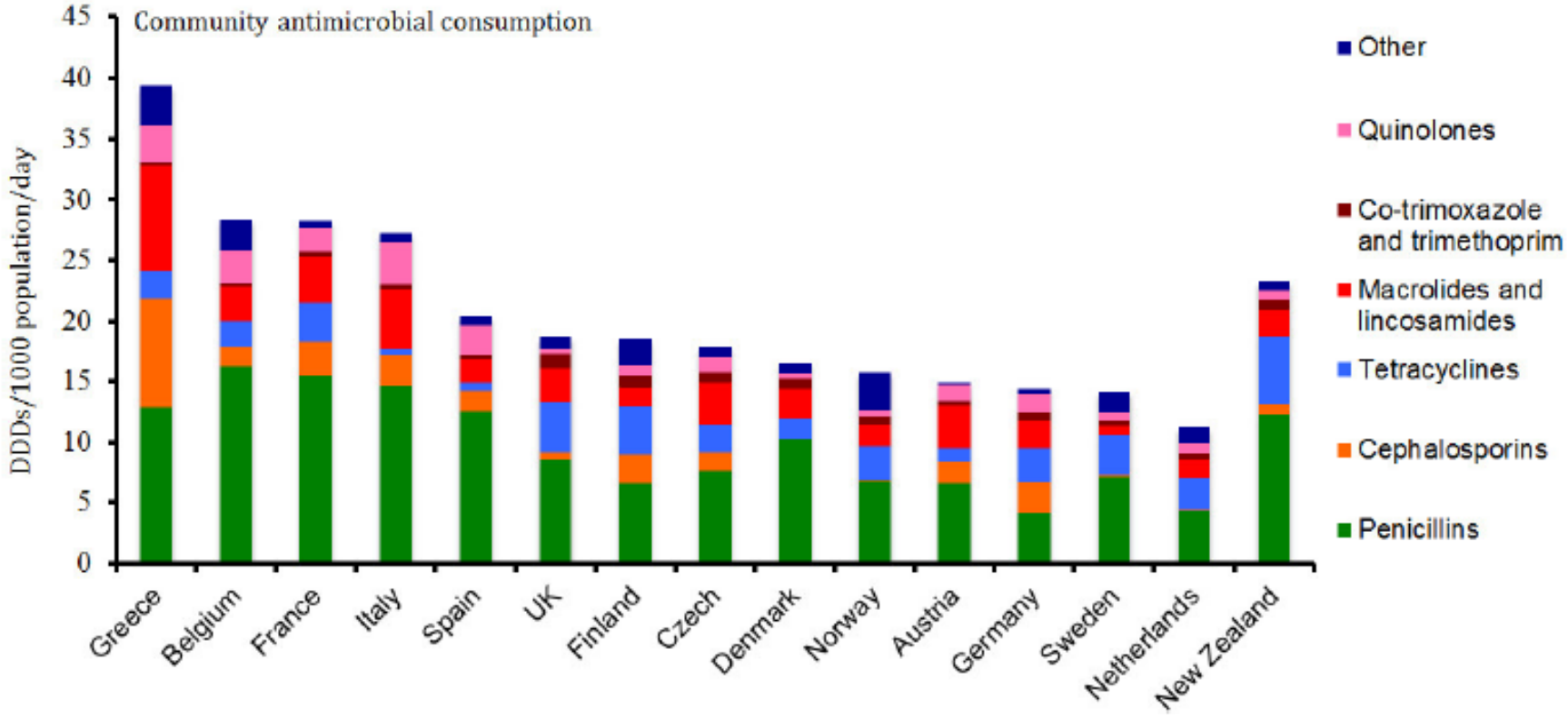


Figure 6. Correlation between penicillin use and prevalence of penicillin non-susceptible *S pneumoniae*

AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only.

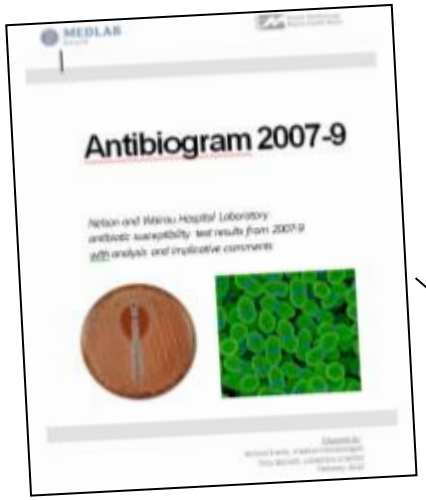
Lancet 2005; 365(9459): 548-

Figure 4. Annual per capita consumption of antimicrobials by community-based patients, in various European countries [10] and in New Zealand, during 2010, measured in DDDs/1000 population/day



Mark Thomas. NZMJ 2014; 127: 1394

Use antibiotics wisely



Guidelines

- BPAC
- Health Pathways

Restrictions - PHARMAC

Antibiotic stewardship

in primary care

Education

Telephone advice

Community Pharmacists

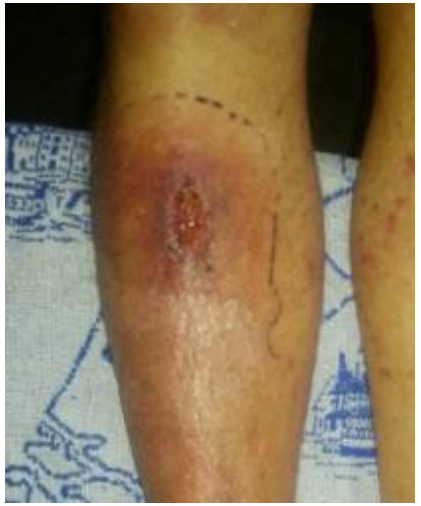
Audit and feedback.

10 antibiotic pearls for GPs

1. Topical antiseptics for preventing wound infections after trauma or minor procedures
2. Infected eczema
3. Who needs an antibiotic?
4. Choosing an antibiotic – MDRO risk factors
5. Choosing an antibiotic – macrolides and FQ
6. Dosing for obesity
7. Getting the right dose – flucloxacillin
8. Probenecid boosting
9. Compliance – flucloxacillin with food
10. Duration – should you always finish the course?

Acute traumatic wounds

- 2% to 17.5% get infected.
- Risk factors - diabetes, legs or hands, crush injury, contamination, delay >24 hr
- Cleansing and debridement ↓ infection
  - Tap water = saline
- Topical antiseptics ↓ infection by 10-70%
  - 11+ animal studies; 13+ human trials
  - Microdacyn, Savlon (chlorhex + cetrimide), H2O2, povidone-iodine, manuka honey, dilute bleach (cheapest)
- Dressings (moisture) benefit wounds.



Minor dermatologic procedures

- Overall 1.3 to 1.5% infection risk
- Skin prep and dressing probably important
- Topical antibiotics or antiseptics
  - Meta-analysis of > 4000 patients, 4 RCTs (Bacitracin, chloramphenicol, mupirocin, or gentamicin ointment)
  - Pooled odds of infection 0.71
  - Authors' conclusion: not indicated due to low risk

J Derm Treatment 2015; 26(2): 151-8

- My recommendation: if high-risk – Microdacyn, H2O2, Savlon – not chloramphenicol, mupirocin

Infected eczema

- Dilute bleach (NaClO) baths – effective for submerged skin

Pediatrics 2009; 123: e808-14

Ped Dermatol 2003; 30(3): 308-15

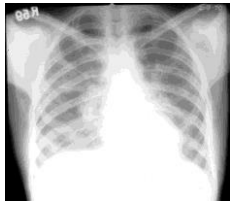
- Microdacyn-like products – effective

Cutis 2012; 90: 97-102

Allergy 1997; 52: 1012-6

Add 1/4 to 1/2 cup bleach to bath or 3 teaspoons bleach to a 10 L bucket of water. Then soak or wipe over skin for 5 to 10 min, rinse in fresh water, apply emollients etc…

Predictors of pneumonia



- 10-20 studies in adults, including > 4500 adults:
  - Absence of runny nose (2 studies)
  - RR > 25/min (4+ studies)
  - Fever (6+ studies)
  - Tachycardia (5+ studies)
  - Crackles (4+ studies)
  - Reduced breath sounds (3+ studies)
- GRACE study
  - 2820 patients with acute cough (< 4 weeks)
  - Predictors of pneumonia (5%):
    - Dyspnoea, no coryza , reduced breath sounds, crackles, pulse > 100 and fever > 37.8
    - CRP

BMJ 2013; 346:f2450

Nelson-Marlborough Calculated Risk of Pneumonia Score

CRP-2 (Calculated Risk of Pneumonia) score*

Scope: adults presenting with acute cough – includes those with respiratory comorbidity (e.g., COPD, asthma).

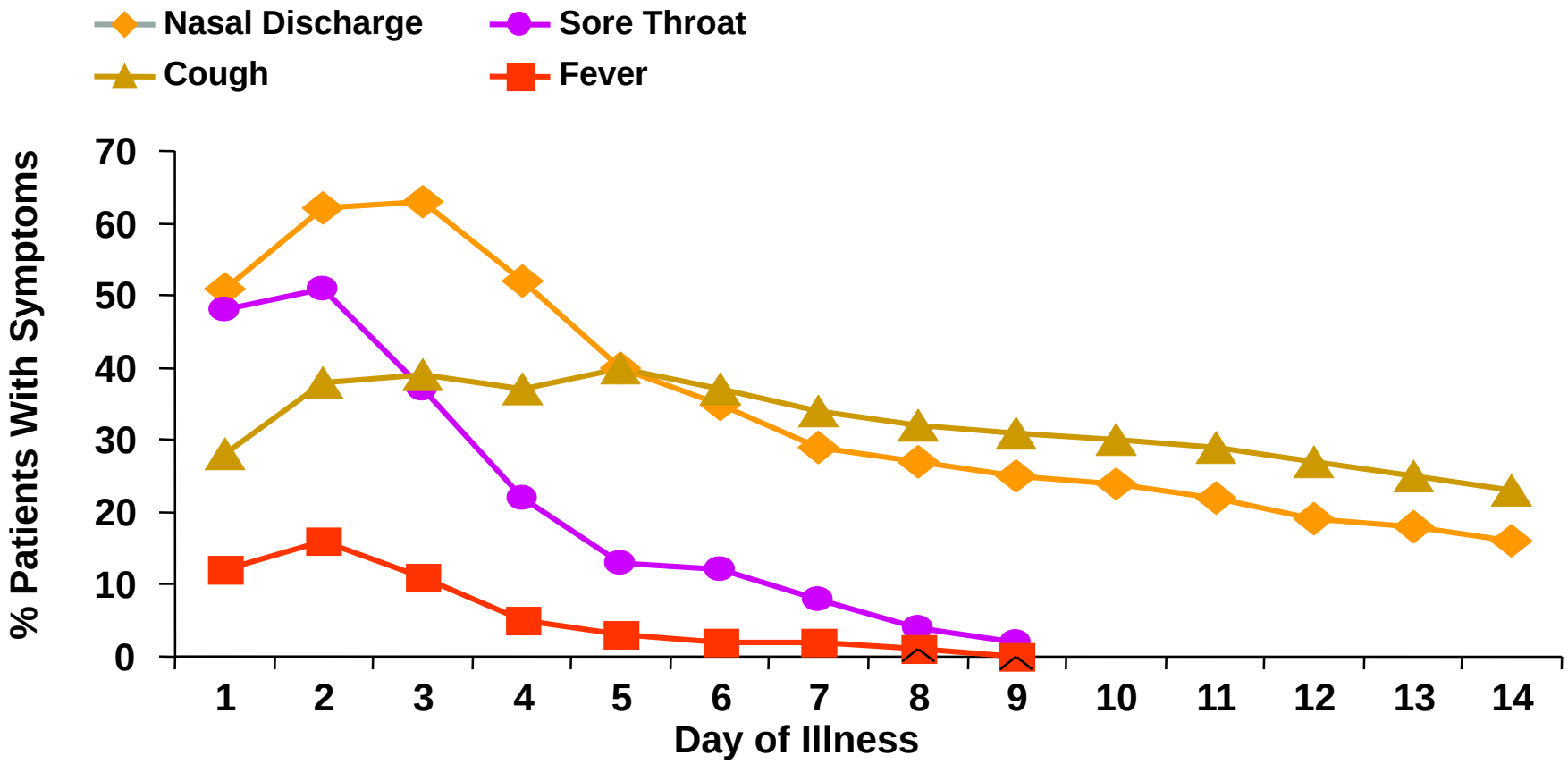
History		Vital signs		Chest signs	
absence of runny nose	+1	fever (> 37.8°C)	+2	crackles	+3
diarrhoea	+1	fast pulse (>100/minute)	+2	reduced breath sounds	+3
		rapid breathing rate	+2		

Add up the points to give a total score.

Score	Action
0-1	No antibiotic treatment or investigation
2	Provide patient information. Advise clinical review if new or worsening symptoms
3-4	Request CRP to help determine likelihood of pneumonia. If CRP >30 treat with antibiotics
5+	Treat with antibiotics

* Dixon/Everts 2014 *Adapted from* Br Med J *2013. 346:f24503*

Duration of symptoms in Rhinovirus upper respiratory infections (‘the common cold’)



APBRS diagnosis may be made in a patient with a viral URTI that is not better after 10 days or worsens after 5–7 days and is accompanied by associated symptoms.

Adapted from Sinus and Allergy Health Partnership (SAHP). *Otolaryngol Head Neck Surg.* 2004;130(1 Suppl):1-45; Adapted from Gwaltney JM. *JAMA*. 1967;202:158-164.

COUGH, PNEUMONIA & ANTIBIOTICS

WHAT CAUSES COUGHING?

Most coughs are caused by a virus infection. Some people have other causes of cough (like heart problems, medicine side-effects, or asthma) so it's important that your doctor checks you out for these. About 1 in 20 people who are coughing have pneumonia (a lung infection).

DO YOU HAVE PNEUMONIA?

A cough can be a sign of pneumonia but usually there are other symptoms to suggest this, such as a high temperature, shortness of breath, or fast pulse. Coughing for a long time or bringing up coloured sputum (spit) does not necessarily mean you have pneumonia. If you are feeling very unwell or you are worried about pneumonia, get checked out by your doctor.

Signs of pneumonia to watch out for:

- *Shortness of breath*
- *Chills, sweats or fever*
- *Rapid breathing or racing pulse.*

DO YOU NEED ANY TESTS?

Pneumonia can often be diagnosed by your symptoms and examination of your chest. If the doctor needs more information, he/she may request a blood test or occasionally a chest x-ray. A useful test is the CRP test (C-reactive protein) – the more CRP in your blood the more likely it is that you have pneumonia or another bacterial infection.

WHAT TREATMENT DO YOU NEED?

Most coughs are caused by a virus, which does not need any treatment other than simple medicines like paracetamol to make you feel more comfortable. Antibiotics do not help a virus infection and may cause side effects or resistant bacteria in your body. If your doctor suspects pneumonia, you will be prescribed antibiotics.

Antibiotics help pneumonia, not other causes of cough

WHAT IF YOU ARE NOT GETTING BETTER?

It can take weeks for coughing to stop after a virus infection, so don't be concerned. If you are getting worse or getting new symptoms, however, tell your doctor. In particular, watch out for symptoms of pneumonia like shortness of breath, shivering chills, sweats or fever (you can measure your temperature with a thermometer), rapid breathing or racing pulse (get someone to count your breaths and measure your heartbeat). Other signs of a bad infection include coughing blood, new diarrhoea or vomiting, feeling confused or drowsy, feeling faint or getting a skin rash.

If you get any of these problems then go back to your doctor or follow the instructions you might have been given (your doctor may provide a blood test form or a prescription for antibiotics to pick up later).

PREVENTING THE SPREAD OF INFECTION

If you have a chest infection, stay away from other people until you are well. Cough or sneeze into your hands, your elbow or a tissue, then wash your hands or use an alcohol hand sanitizer.

If you are caring for someone with a chest infection, wash your hands or use hand sanitizer after you touch them to reduce the chance of catching the infection yourself.

Think about getting vaccinated against influenza each autumn, especially if you have other health conditions like asthma, heart disease or diabetes.

Kimi Hauora Wairau

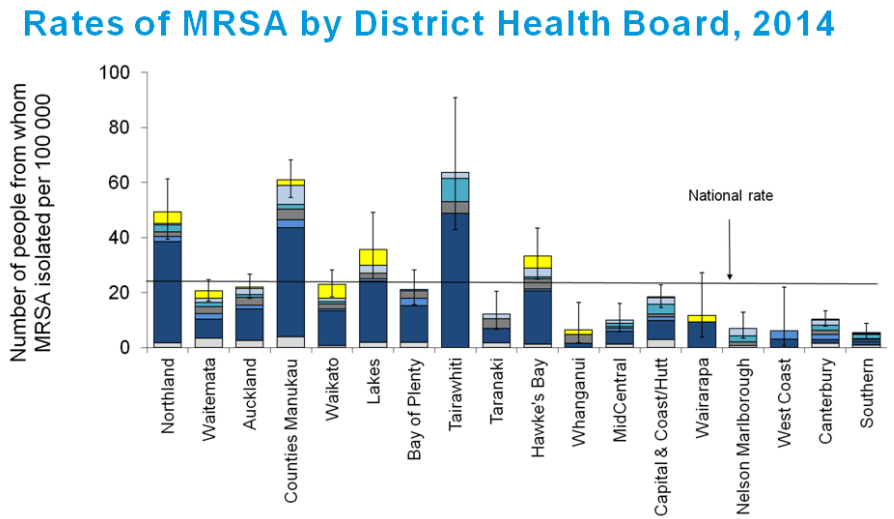
Prepared by Richard Everts - April 2014

How did it work in Nelson, 2014?

- Positive feedback from GPs: 'empowering'
- 21% increase in CRP test use
- A reduction in all May to October respiratory antibiotic prescribing for adults > 16y:
  - Amoxicillin – 309 (4.6%) fewer
  - Macrolides – 470 (12.4%) fewer
  - Doxycycline – 98 (4.7%) fewer
- No significant change in hospital admissions for chest infection.

Choosing an antibiotic – MRSA?

- Skin infection – flucloxacillin first choice – but not if high-risk MRSA:
  - Region of NZ
  - Country of origin – Northern Hemisphere, Pacific Islands
  - Past MRSA-positive (within 6 to 12 months)
  - Failing flucloxacillin.



Choosing an antibiotic – TMP-R?

- Cystitis – trimethoprim first choice – but not if high-risk TMP-R:
  - 'Complicated UTI'
  - Travel to Asia, Middle East, Africa within 6 months
  - Past ESBL-positive
  - Past trimethoprim-use (3 to 6 months)
  - Recurrent UTI (unless always TMP-S)

Which macrolide?

	Azithromycin	Roxithromycin	Erythromycin
Absorption	OK	OK	OK
Tissue/serum concentration	10-100x (sputum, lung, alveolar macrophages)	1-5x	1x
Half life	15-40 hours (tissue 2 to 4 days)	10-12 hours	2 hours
Dosing	Daily for 3 days	Daily for 7 days	2-4 times daily
Indigestion	8%	5%	16-20%
QT prolong /arrhythmia	Mild	Mild+	Worst
Pregnancy	Probably safe	Probably safe	Safe
Interactions	Few	Few	Many
Cost per course	$2.00	$2.09	$4.75

Ciprofloxacin, not norfloxacin

- More potent (4- to 8-fold)
- Better penetration of tissue – ?pyelonephritis
- 3 days cipro = 7 days norflox in complicated UTI study
- Toxicity lower
  - Overall 5.8% versus 9.1%
  - Less dizziness
  - Tendonopathy equal
- Less selection of resistant mutants
- Cost 2/3.

Antibiotic dosing for obesity

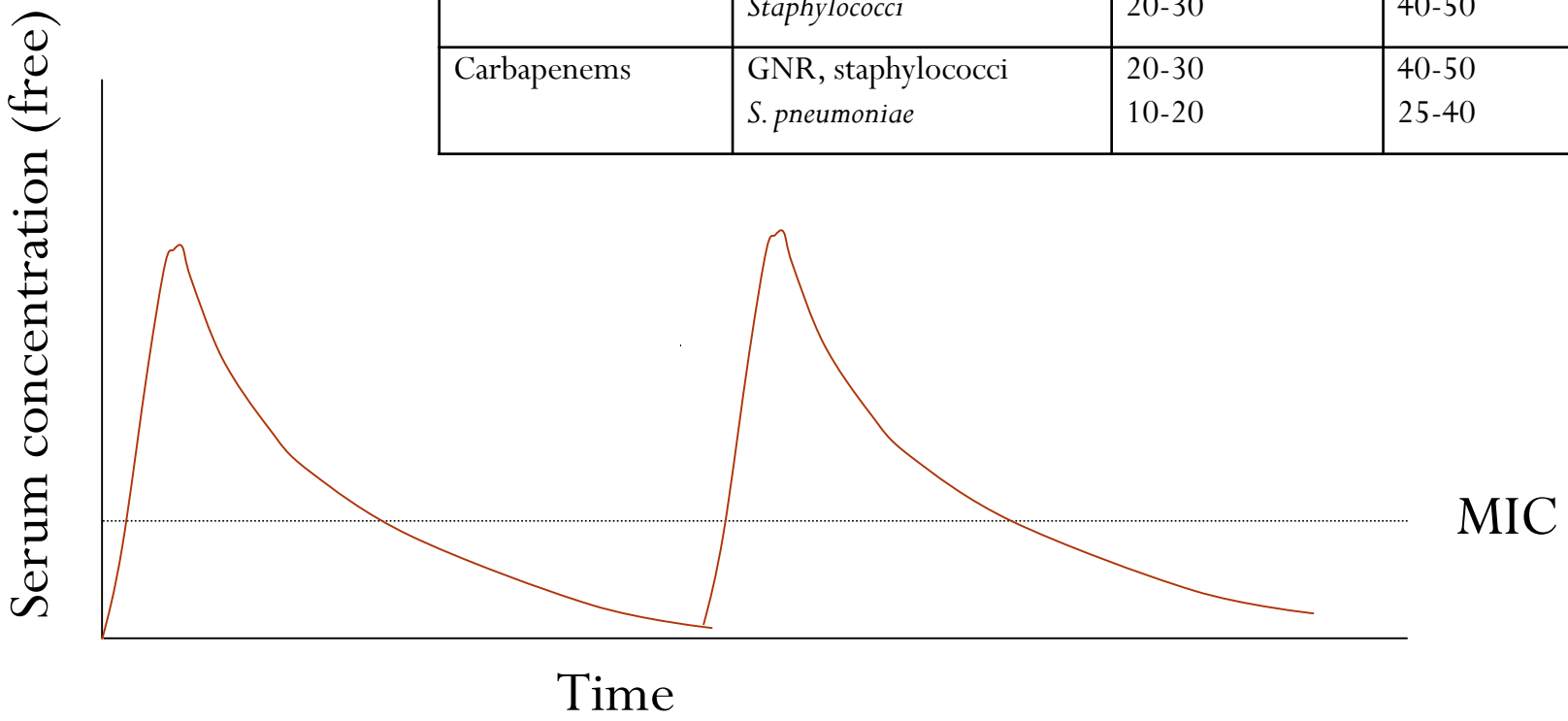
Adults: 50% more for first 2 days

Children: NZF for children – by weight

Time > MIC targets

For free (unbound) antibiotic

Antibiotic class	Organism	Time > MIC goal for stasis (%)	Time > MIC goal for optimum kill (%)
Penicillins	GNR, *S. pneumoniae* *Staphylococci*	30-40 ~~20-30~~	60-70 ~~40-50~~
Cephalosporins	GNR, *S. pneumoniae* *Staphylococci*	40-50 20-30	70-80 40-50
Carbapenems	GNR, staphylococci *S. pneumoniae*	20-30 10-20	40-50 25-40



Predicted Fluclox 'exposure' by dose

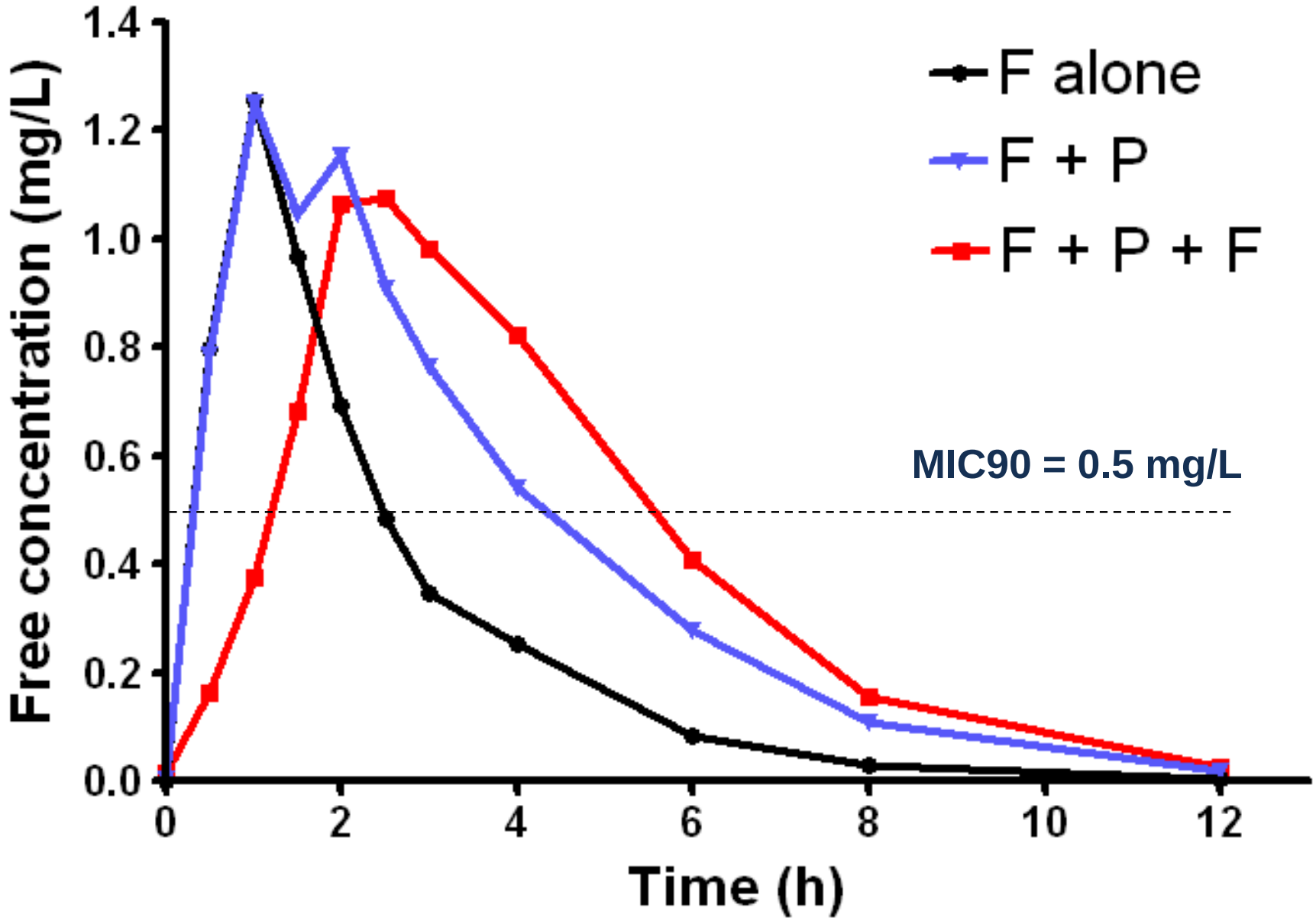
*based on 16 PK studies

Infection severity	$fT_{>0.5}$	Regimens that will achieve this*
Mild , intact immunity = 'stasis'	4.8-7.2 h/day	(Not: 250 po QID, 500 po TDS) (Borderline: 500 po QID, 750 po TDS) 750 po QID 1000 po TDS or QID
Moderate infection = 'optimum kill'	9.6-12 h/day	1000 IV 4-hourly 2000 IV 6-hourly
Severe infection	>18 h/day	2000 IV 4-hourly 2000 IV 8-hourly as 4-hour infusion 6 to 12g IV continuous infusion

F vs F+P vs F+P+food in volunteers

- Oral flucloxacillin 1 g
  - 11 volunteers
  - Low dose of probenecid (500 mg)
  - With and without 'an ordinary meal' (22 g fat)
  - Modern liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay
  - Measure free (unbound) fluclox.

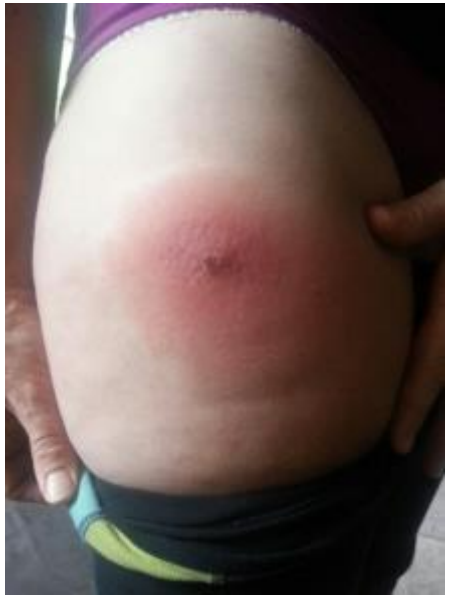
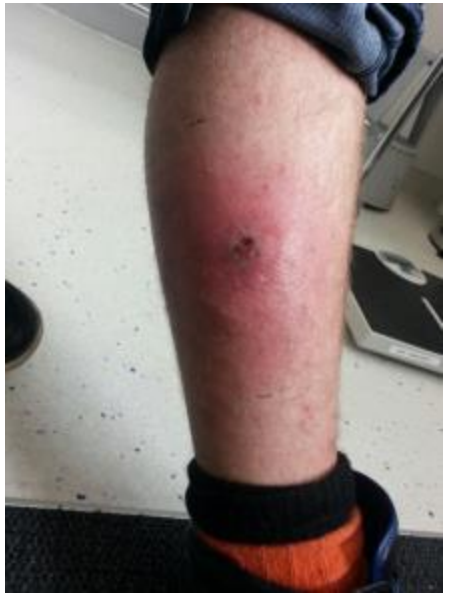
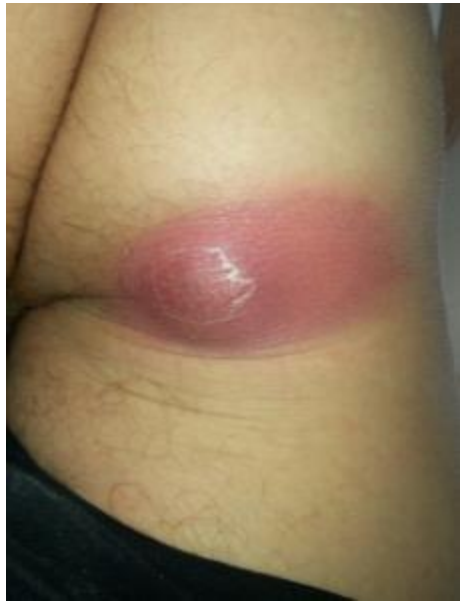
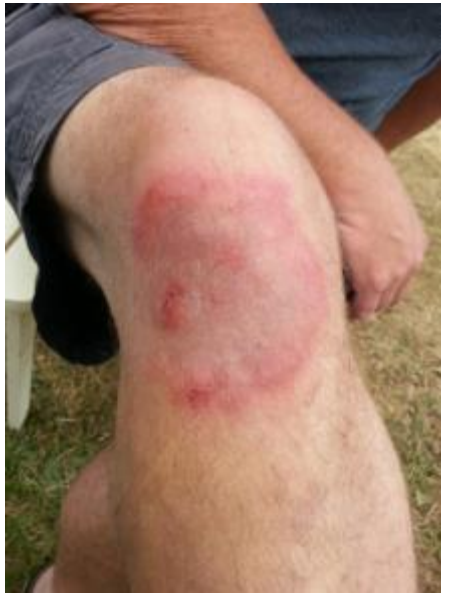
Flucloxacillin (free)

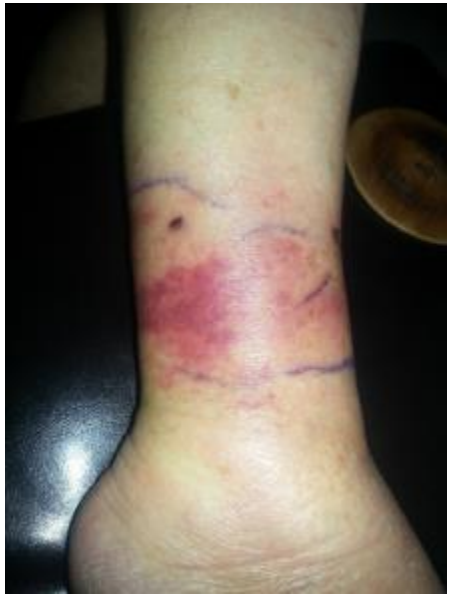
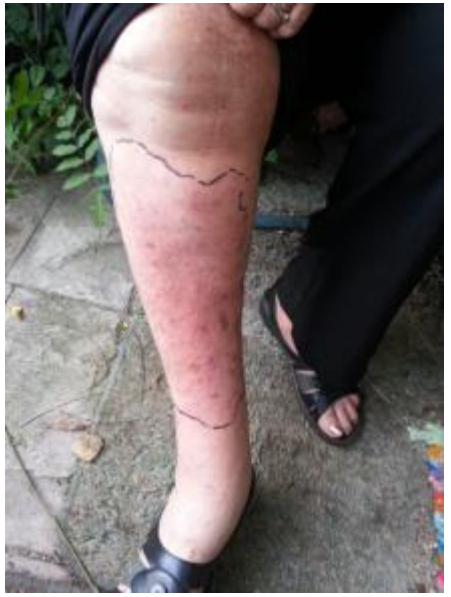
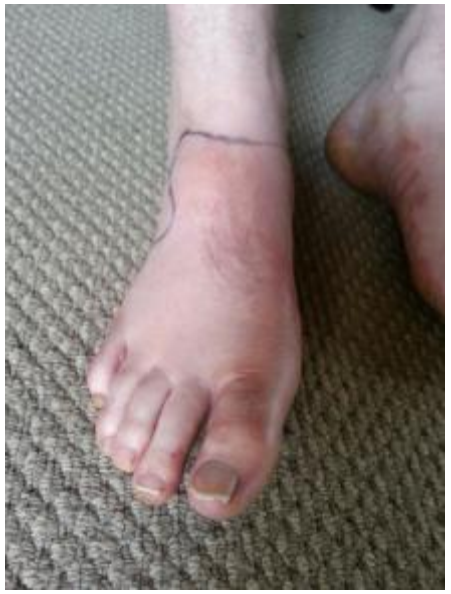


Predicted ‘exposure’ by dose

*based on 16 PK studies, including the present study

Infection severity	$fT_{>0.5}$	Regimens that will achieve this*
Mild , intact immunity = ’stasis’	4.8-7.2 h/day	(Not: 250 poQID, 500 poTDS) (Borderline: 500 po QID, 750 po TDS) 750 po QID 1000 po TDS or QID 1000 po + proben 500-1000 BD
Moderate infection = ‘optimum kill’	9.6-12 h/day	1000 po + proben 500-1000 TDS or QID 1000 IV 4-hourly 2000 IV 6-hourly
Severe infection	>18 h/day	2000 IV 4-hourly 2000 IV 8-hourly as 4-hour infusion 6 to 12g IV continuous infusion

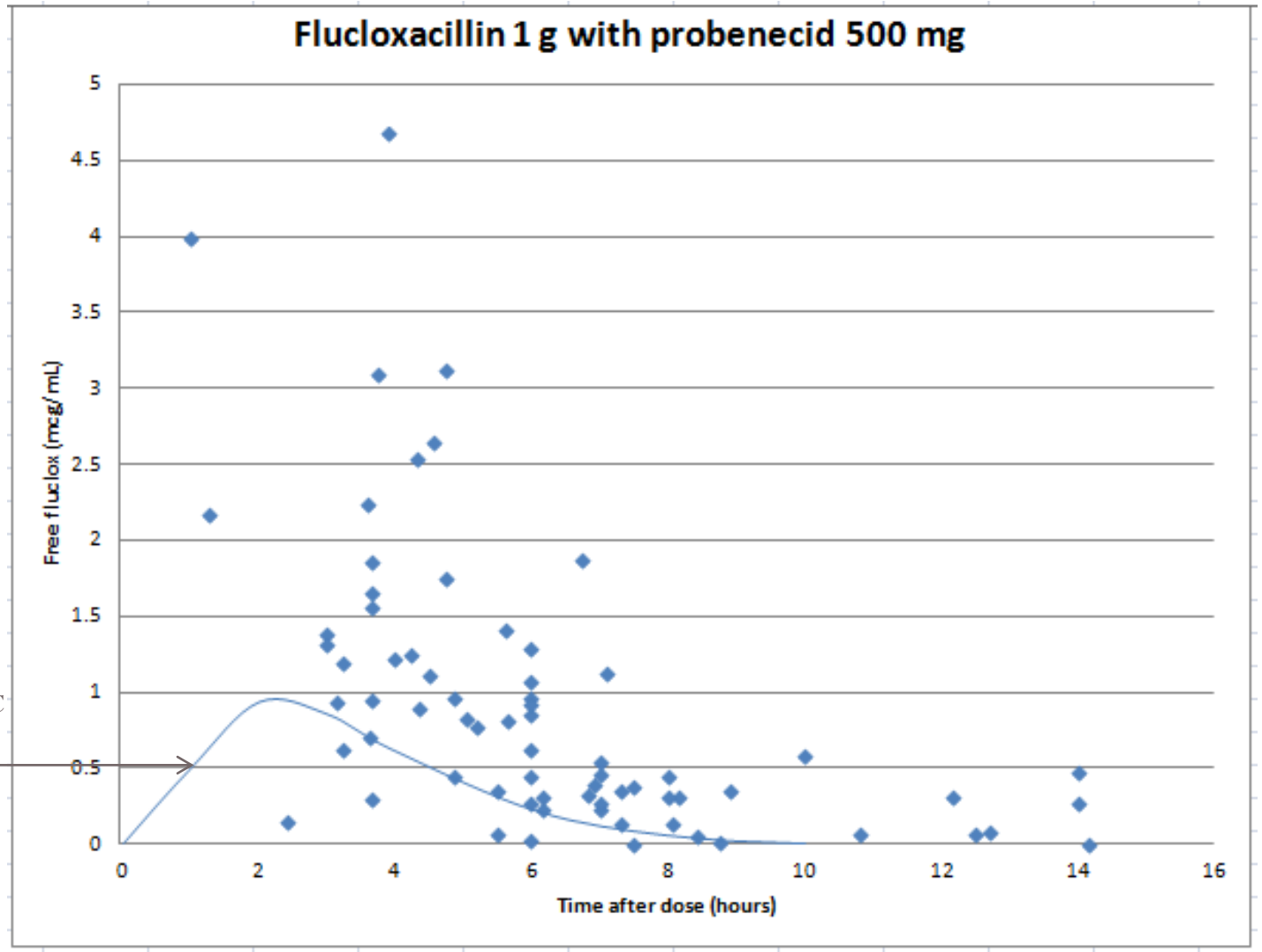





Results - efficacy

	F alone QID n=20	F+P BD n=19
> 20% reduction infection size at 48-72 hours	14 (70%)	13 (68%)
> 30% reduction pain score at 48-72 hours	13 (65%)	14 (74%)
Resolution 7 to 14 days after treatment, without extra antibiotics	17 (85%)	16 (84%)

71 levels in 48 patients with ‘deep infections’



Target for TDS dosing in moderate deep GPC infections ($fT_{>0.5}$ > 50%)

Moderate to severe infections

- IV fluclox if septic, then or otherwise…

Flucloxacillin 1 g PO

plus

Probenecid 500 mg PO

with meals

Three times daily

Four times daily

Probenecid - warnings

- Contra-indications/warnings
  - Recent gout
  - GFR < 35 mL/min
  - Uric acid kidney stones
- Side effects
  - Nausea (3% overall, less with food, lower dose) *Bogor 1965*
  - Headache
- Other interactions
  - Paracetamol (↓ by 50%); NSAIDS (↓ by 30%)
  - Methotrexate.

Cephalexin + probenecid

- *S. aureus* MIC_{90} 8 mg/L
- Protein binding 10%
- Probenecid doubles $fT_{>8}$

Appl Microbiol 1969; 17: 457-

Brit J Pharm 1969; 37: 738-47

Appl Microbiol 1968; 16: 1684-

Clin Med 1968, Nov: 14-22

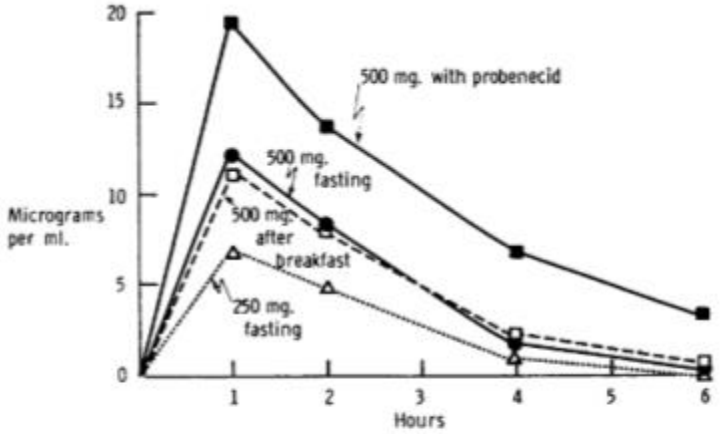


FIG. 3. *Mean serum concentrations of cephalexin (μg/ml) in seven volunteers who had received 250 and 500 mg in the fasting state, 500 mg after breakfast, and 500 mg preceded by 0.5-g doses of probenecid, 7 and 1 hr-before.*

NM probenecid prescribing

Pharmacy Financial Summary Dashboard

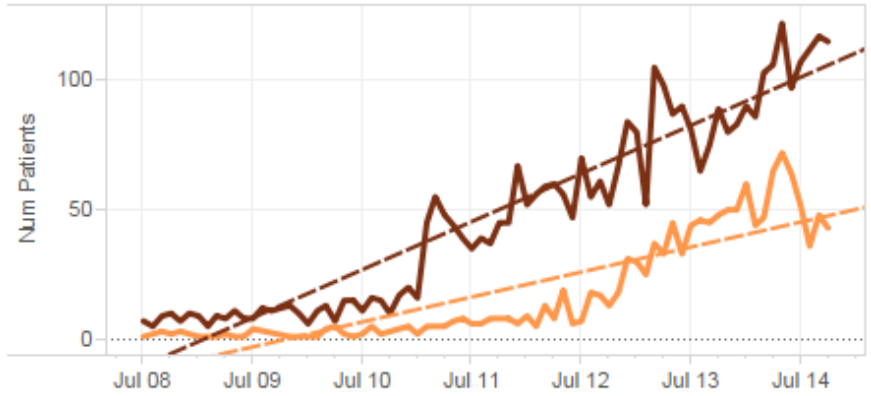
Top-Level Summary Stats for FY 2015

	Nelson Bays PHO	Marlborough PHO	Grand Total
Reimb. Cost	$0.009M	$0.003M	$0.013M
Num Claims	506	191	697
Num Patients	388	155	543
Cost/Patient	$24	$22	$24
Claims/Patient	1	1	1

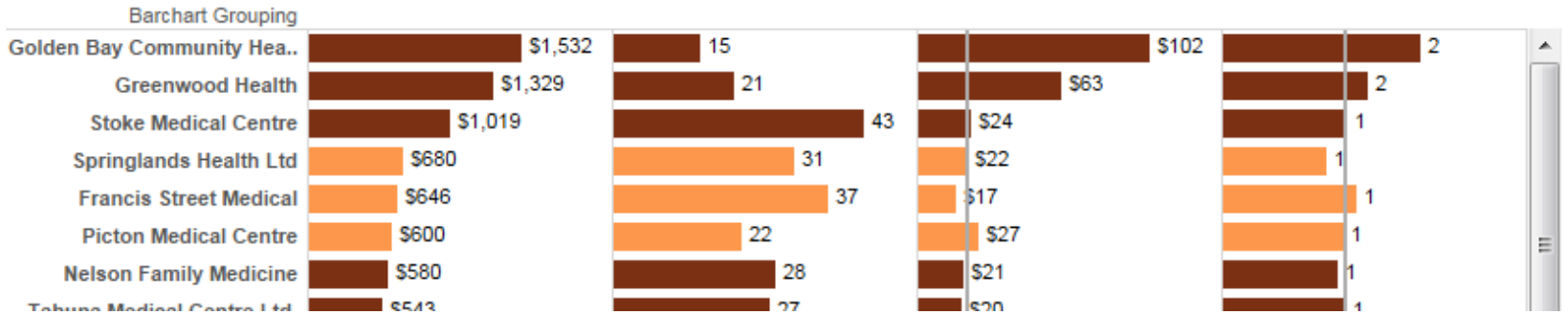
Include Claims w/o NHI ID

False

Multi-Year Trend for Num Patients

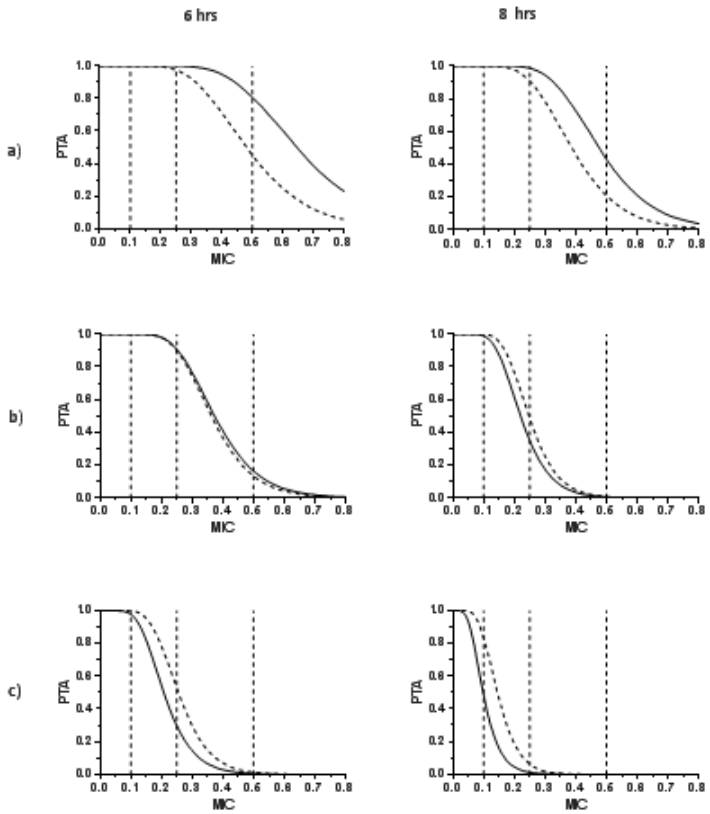


Detail-Level Summary Stats by Practice for FY 2015



Flucloxacillin with food

- Reduces absorption
- Spreads out concentration-time curve
- Overall mixed effect on T > MIC
- Minor disadvantage compensated for by convenience, adherence, less nausea.



Unpublished. Sharon Gardiner

SHOULD ONE FINISH A COURSE OF ANTIBIOTICS?

Pilot randomized trial of standard versus symptom-based antibiotic duration on efficacy for common bacterial infections in adult primary care patients

Richard Everts[1], Steve Chambers[2,3], Vivien Edge[4], Juliet Elvy[5], Gabrielle Everts[1], Francesca Dalzell[1], Sharon Gardiner[2,6,7], Heidi Mayer[8], Richard Thomas[9]

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ABSTRACT

The long-established advice to complete every course of antibiotics for infections in primary care should be challenged. We randomised 71 adult patients with moderate-severity,

RESULTS – INITIAL TREATMENT RESPONSE

One patient in each group failed oral antibiotic treatment and required admission to hospital for intravenous antibiotic treatment.

and

RESULTS – KEY OUTCOMES

Table 2. Outcome of 66 patients who completed antibiotic treatment

	Standard duration (n = 31)	Symptom-based duration (n = 35)
Days of antibiotic treatment (mean (SD))	5.1 (1.7)	4.3 (1.9) p=0.057
Defined daily dose (mean (SD))	7.4 (5.6)	5.4 (5.1) p=0.13
Treatment-emergent adverse events (TEAE)	7 (23%, none severe)	6 (17%, none severe) NS
Immediately needed more antibiotic at end of treatment	1 (3%)	- NS
Relapse within 3 weeks of completing treatment	2 (6%)	2 (6%) NS

Thank you

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