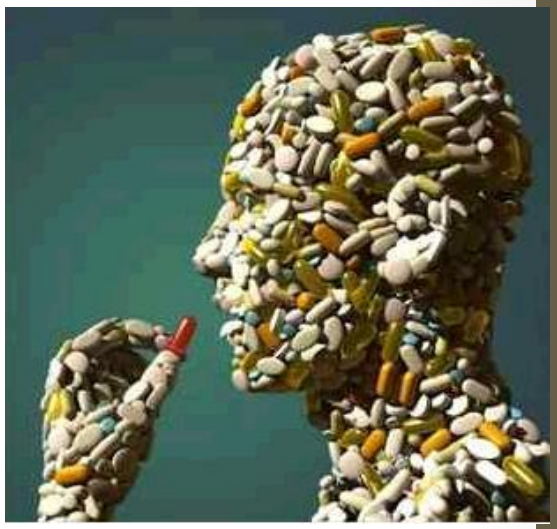
NSW GOVERNMENT Health
Hunter New England Local Health District

Antimicrobial Resistance and Prescribing



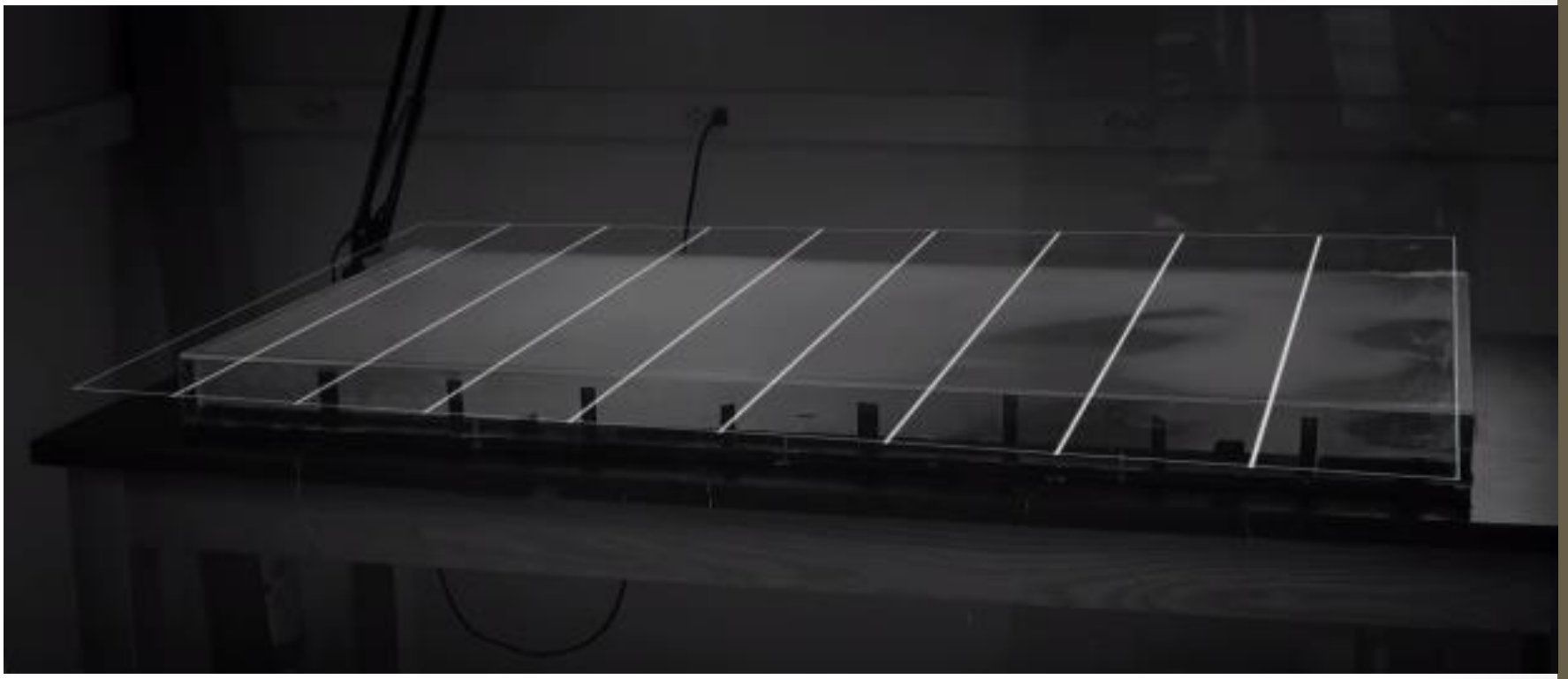
John Ferguson, Microbiology & Infectious Diseases, John Hunter Hospital, University of Newcastle, NSW, Australia

Year 5, Medicine

UPNG 2017

Tw @mdjkf http://idmic.net

Watching antibiotic resistance evolve…



https://www.youtube.com/watch?v=yybsSqcB7mE

What is Antimicrobial Resistance (AMR)?

Medicines for treating infections lose effect because the microbes change;

1. mutate
2. acquire genetic information from other microbes to develop resistance

Types of AMR

1. **Antibacterial resistance** (e.g. to antibiotics and other antibacterial drugs)
2. **Antiviral resistance** (e.g. to anti-HIV medicines)
3. **Antiparasitic resistance** (e.g. to anti-malaria medicines)
4. **Antifungal resistance** (e.g. to medicines used to treat *Candidiasis*)

AMR is a natural phenomenon accelerated by use of antimicrobial medicines. Resistant strains survive and aggregate.

The Future of Antibiotics and Resistance

Brad Spellberg, M.D., John G. Bartlett, M.D., and David N. Gilbert, M.D.

In its recent annual report on global risks, the World Economic Forum (WEF) concluded that "arguably the greatest risk . . . to human health comes in the form of antibiotic-resistant bacteria. We live

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Traditional pra
tion control, anti
ship, and new ant

ment are cornerstones of society's approach to combating resistance and must be continued. But the WEF report underscores the facts that antibiotic resistance and the collapse of the antibiotic research-

karyotes (bacteria) "invented" antibiotics billions of years ago, and resistance is primarily the result of bacterial adaptation to eons of antibiotic exposure. What are the fundamental implications of

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In its recent annual report on global risks, the World Economic Forum (WEF) concluded that "arguably the greatest risk . . . to human health comes in the form of antibiotic-resistant bacteria. We live in a bacterial

2016-17 DRAFT PNG NATIONAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

Antimicrobial resistance now a priority agenda for the Ministry of Health. Country situation analysis Sept 2016

January 2017: National AMR multi-sector symposium took place

Recommendations drafted against the WHO policy package on AMR under these headings:

1. National coordination mechanisms (governance)
2. Access to, and quality of, essential medicines
3. Surveillance and laboratory capacity
4. Rational use of medicines in humans and animals
5. Infection prevention and control
6. Research and development

Country Situation Analysis

- “In general, the analysis revealed that the current level of activities addressing AMR in PNG across these six elements is low.
- The most significant challenge relates to rational use of medicines in humans and animals. This challenge is driven by patients and providers alike. Patients typically self-prescribed before seeking care services, and providers over-prescribe at the point of care.
- Similarly, there is no regulation to restrict the use of critically important medicines for human use in animals, and there is no regulation to restrict the use of antimicrobials as growth promoters.”

1. Antimicrobial resistance kills

Antimicrobial resistant infections often fail to respond to standard treatment, resulting in *prolonged illness, higher health care expenditures, and a greater risk of death.*

14 yr old girl, PMGH Feb 2013

- Presented with sepsis, acute onset

- Febrile, hypotensive, thin
- Suspected endocarditis but no direct evidence
  - Given gentamicin and flucloxacillin
  - Poor response to treatment

Day 4 - Blood cultures: Gram positive cocci (staph)- identified as MRSA (methicillin-resistant *Staphylococcus aureus*)

PMGH stats- *Staphylococcus aureus* from blood

- 2011-12 60% of 41 events due to MRSA

- Empiric cover required

[MRSA is resistant to all available betalactam (penicillin-type) antibiotics]

Increase in sepsis due to multi-resistant enteric gram-negative bacilli in Papua New Guinea

THE LANCET • Vol 353 • June 26, 1999

Trevor Duke, Audrey Michael

Between April 1998 and March 2000, multi-resistant enteric gram negative sepsis occurred in 106 of 5331 paediatric admissions (2%), but caused 87 (25%) of 353 deaths

Bacteria	Nosocomial	Community acquired	Chloramphenicol sensitivity	Gentamicin sensitivity
Klebsiella sp*	12	2	0	3
*Pseudomonas aeruginosa**	7	4	0	2
*Escherichia coli**	1	7	1	5
Citrobacter freundii	1	2	1	0
Enterobacter sp	3	4	0	3
Morganella morganii	0	2	2	2
Burkholderia capacia	2	1	1	0
Proteus mirabilis	2	1	0	2
Acinetobacter sp	1	0	0	1
Serratia sp	0	2	0	1
Providentia sp	0	1	1	1
Aeromonas sp	0	1	0	1
Alcaligenes sp	0	1	0	1

*We could not be certain of the origin of one additional isolate of each of these three bacteria.

Sensitivity of bacterial isolates and place of acquisition

Risk of Death is Higher in Patients Infected with Resistant Strains

		Deaths (%)		
	Outcome (number of studies included)	**Resistant**	**Not resistant**	**RR (95% CI)**
***Escherichia coli* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	23.6	12.6	2.02 (1.41 to 2.90)
Fluoroquinolones	Bacterium attributable mortality (n=1)	0	0	
***Klebsiella pneumoniae* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	20	10.1	1.93 (1.13 to 3.31)
Carbapenems	Bacterium attributable mortality (n=1)	27	13.6	1.98 (0.61 to 6.43)
***Staphylococcus aureus* resistant to:**				
Methicillin (MRSA)	Bacterium attributable mortality (n=46)	26.3	16.9	1.64 (1.43 to 1.87)

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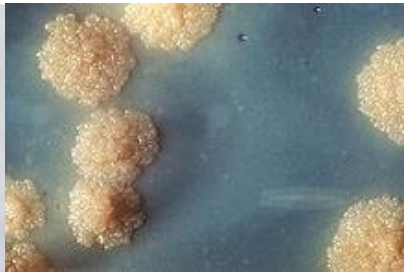
Resistant organisms - Up to twice the risk of dying

2. AMR hampers the control of infectious diseases

AMR reduces the effectiveness of treatment; thus *patients remain infectious for a longer time, increasing the risk of spreading* resistant microorganisms to others.

Catherina Abraham



Aged 20 years, flew to Cairns from Torres Strait, 2012 diagnosed with XDR-TB.

After almost a year in an isolation ward at Cairns Base Hospital, she died on 8 March 2013.

Secondary case, aged 32 also died.

Tony Kirby Med J Aust 2013; 198 (7): 355.

3. AMR increases the costs of health care

Resistant infections require more expensive therapies and longer duration of treatment

Catherina's treatment cost Queensland Health about $500 000 and would have cost $1 million had she lived to complete it.

4. The achievements of modern medicine are put at risk by AMR

- organ transplantation
- cancer chemotherapy
- major surgery

5. AMR threatens health security, damages trade and economies

WHO 2014

Why is antimicrobial resistance important?

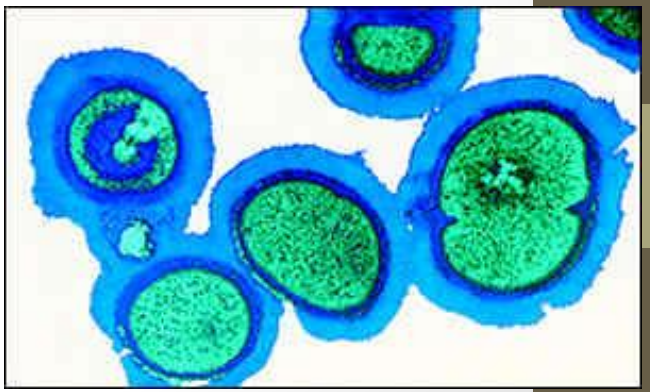
1. **Antimicrobial resistance kills-** mortality higher for resistant pathogens
2. **AMR hampers the control of infectious diseases** – prolonged infectivity – eg. Mdr-TB
3. **AMR increases the costs of health care**
4. **Achievements of modern medicine are put at risk by AMR-** eg. Leukaemia treatment
5. **AMR threatens health security, damages trade and economies**

AMR in PNG

1. WHY is it an important problem?
2. **HOW has the problem arisen?**
3. WHAT do we have to do?

Bacterial perspective

- 3.5 billion years of evolutionary diversification
- Estimated 10^{21} bacteria; one billion progeny/ day
- Adapted to innumerable niches
- Sense their environment, exhibit cooperative behaviours and adaptive stress responses
- Antibiotic resistance genes are ancient
- Humans carry 2-3 kg of bacterial biomass acquired from diverse sources

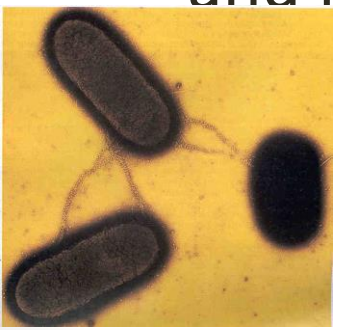


How does resistance arise?

1. mutational change in bacterial chromosome with clonal expansion of a resistant subpopulation

AND/OR

2. horizontal transfer of new resistance gene(s) from another bacterial species by direct transfer and recombination



Antibiotic exposure increases the rate of both processes

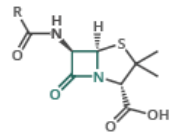
Antibiotics select and promote growth of resistant subpopulations

DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

Key: COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION — COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH

β-LACTAMS

MOST WIDELY USED ANTIBIOTICS IN THE NHS



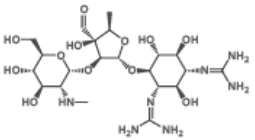
All contain a beta-lactam ring

EXAMPLES
Penicillins (shown) such as amoxicillin and flucloxacillin; *Cephalosporins* such as cefalexin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

AMINOGLYCOSIDES

FAMILY OF OVER 20 ANTIBIOTICS



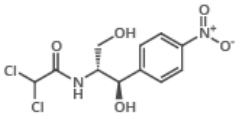
All contain aminosugar substructures

EXAMPLES
Streptomycin (shown), neomycin, kanamycin, paromomycin.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

CHLORAMPHENICOL

COMMONLY USED IN LOW INCOME COUNTRIES



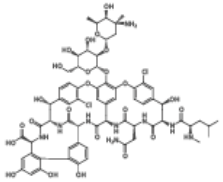
Distinct individual compound

MODE OF ACTION
Inhibits synthesis of proteins, preventing growth.

No longer a first line drug in any developed nation (except for conjunctivitis) due to increased resistance and worries about safety.

GLYCOPEPTIDES

COMMON 'DRUGS OF LAST RESORT'



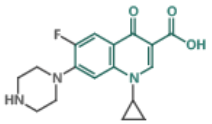
Consist of carbohydrate linked to a peptide formed of amino acids

EXAMPLES
Vancomycin (shown), teicoplanin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

QUINOLONES

RESISTANCE EVOLVES RAPIDLY



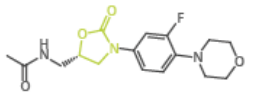
All contain fused aromatic rings with a carboxylic acid group attached

EXAMPLES
Ciprofloxacin (shown), levofloxacin, trovafloxacin.

MODE OF ACTION
Interfere with bacteria DNA replication and transcription.

OXAZOLIDINONES

POTENT ANTIBIOTICS COMMONLY USED AS 'DRUGS OF LAST RESORT'



All contain 2-oxazolidone somewhere in their structure

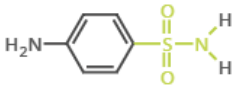
EXAMPLES
Linezolid (shown), posizolid, tedizolid, cycloserine.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

DISCOVERY 1930 1940 1950 1960 1970 1980

SULFONAMIDES

FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES



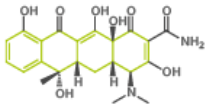
All contain the sulfonamide group

EXAMPLES
Prontosil, sulfanilamide (shown), sulfadiazine, sulfisoxazole.

MODE OF ACTION
Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

TETRACYCLINES

BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE



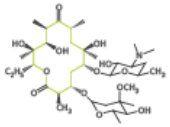
All contain 4 adjacent cyclic hydrocarbon rings

EXAMPLES
Tetracycline (shown), doxycycline, limecycline, oxytetracycline.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

MACROLIDES

SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS



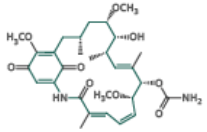
All contain a 14-, 15-, or 16-membered macrolide ring

EXAMPLES
Erythromycin (shown), clarithromycin, azithromycin.

MODE OF ACTION
Inhibit protein synthesis by bacteria, occasionally leading to cell death.

ANSAMYCINS

CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY



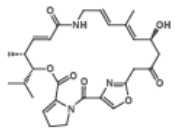
All contain an aromatic ring bridged by an aliphatic chain.

EXAMPLES
Geldanamycin (shown), rifamycin, naphthomycin.

MODE OF ACTION
Inhibit the synthesis of RNA by bacteria, leading to cell death.

STREPTOGRAMINS

TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGISTICALLY



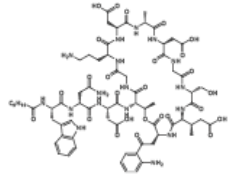
Combination of two structurally differing compounds, from groups denoted A & B

EXAMPLES
Pristinamycin IIA (shown), Pristinamycin IA.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

LIPOPEPTIDES

INSTANCES OF RESISTANCE RARE

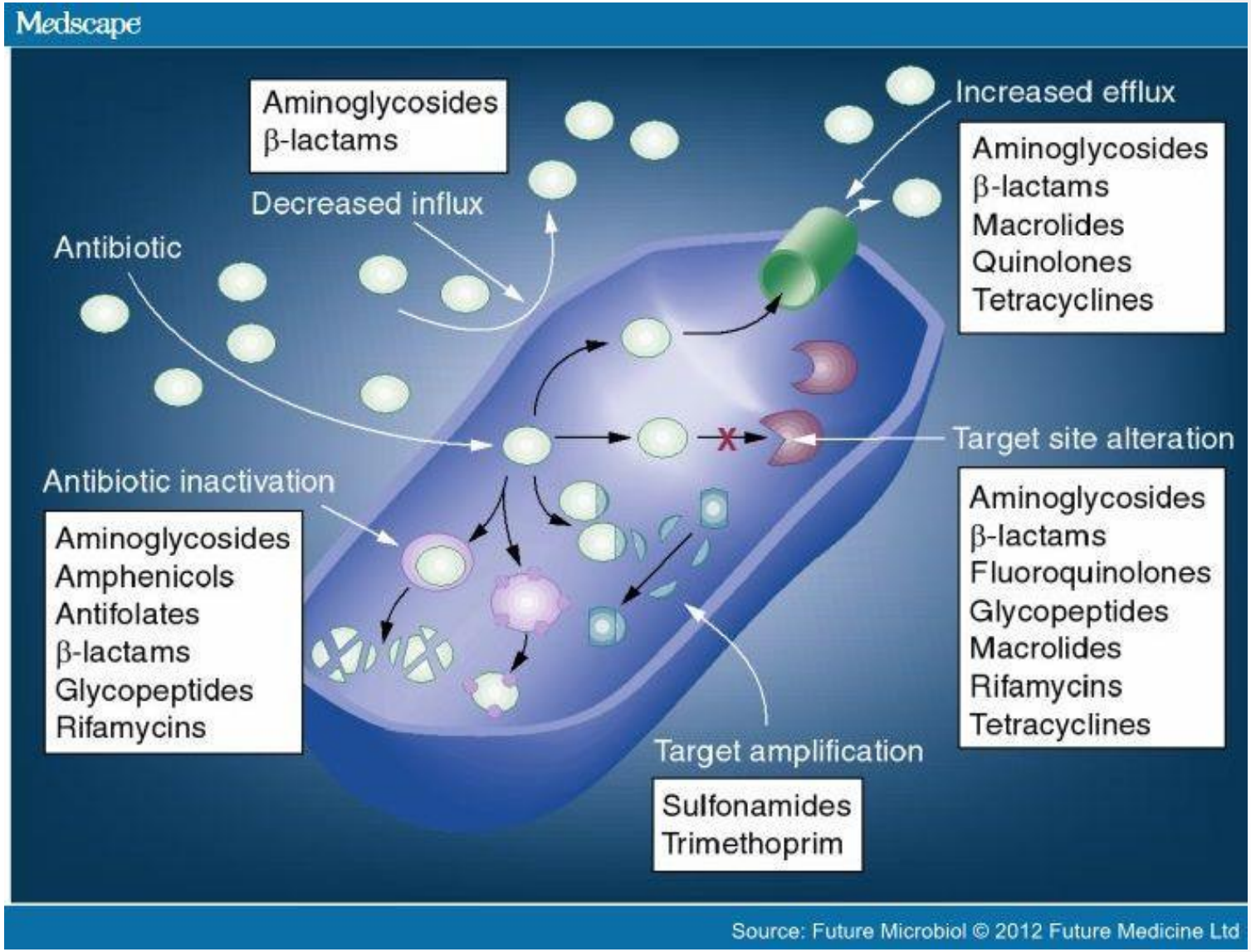


All contain a lipid bonded to a peptide

EXAMPLES
Daptomycin (shown), surfactin.

MODE OF ACTION
Disrupt multiple cell membrane functions, leading to cell death.

http://aimed.net.au



Medscape description

http://www.medscape.com/viewarticle/756378_2

RESEARCH ARTICLE

The Burden of Drug-Resistant Tuberculosis in Papua New Guinea: Results of a Large Population-Based Survey

Paul Aia[1], Margaret Kal[1], Evelyn Lavu[1], Lucy N. John[1], Karen Johnson[2], Chris Coulter[3], Julia Ershova[4], Olga Tosas[5], Matteo Zignol[6], Shalala Ahmadova[7], Tauhid Islam[8]*

Cluster-randomised sampling of newly registered smear-positive pulmonary TB patients identified by public healthcare services in Madang, Morobe, Western Provinces and National Capital District.

Number of clusters in the survey set to 40 which were distributed in 27 health centres selected using a probability-proportional to size cluster sampling strategy.

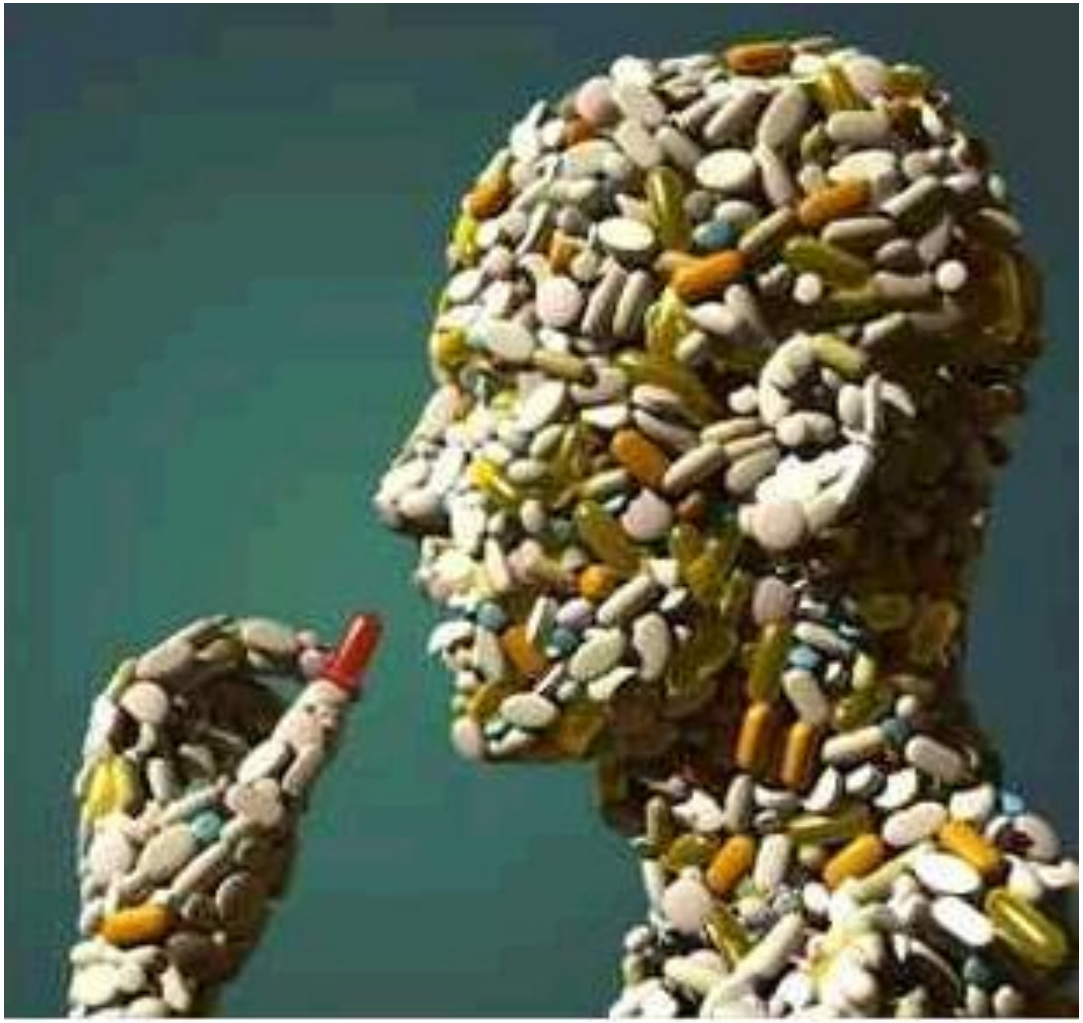
Results

- 1,182 patients with sputum-smear positive pulmonary
- TB enrolled.
- Of them, 1,027 were newly diagnosed cases, 154 patients had previous history of TB treatment
- 1,146 patients were detected with TB (999 new cases, 146 previously treated cases and 1 case with undocumented history).
- HIV status available for 57% of cases - 32 (5%) were HIV positive.
- Of the 57 cases with culture and DST result, 44 (77%) cases had additional resistance to isoniazid.
- Of the 44 MDR-TB cases 20 were in new and 24 were in previously treated TB cases.

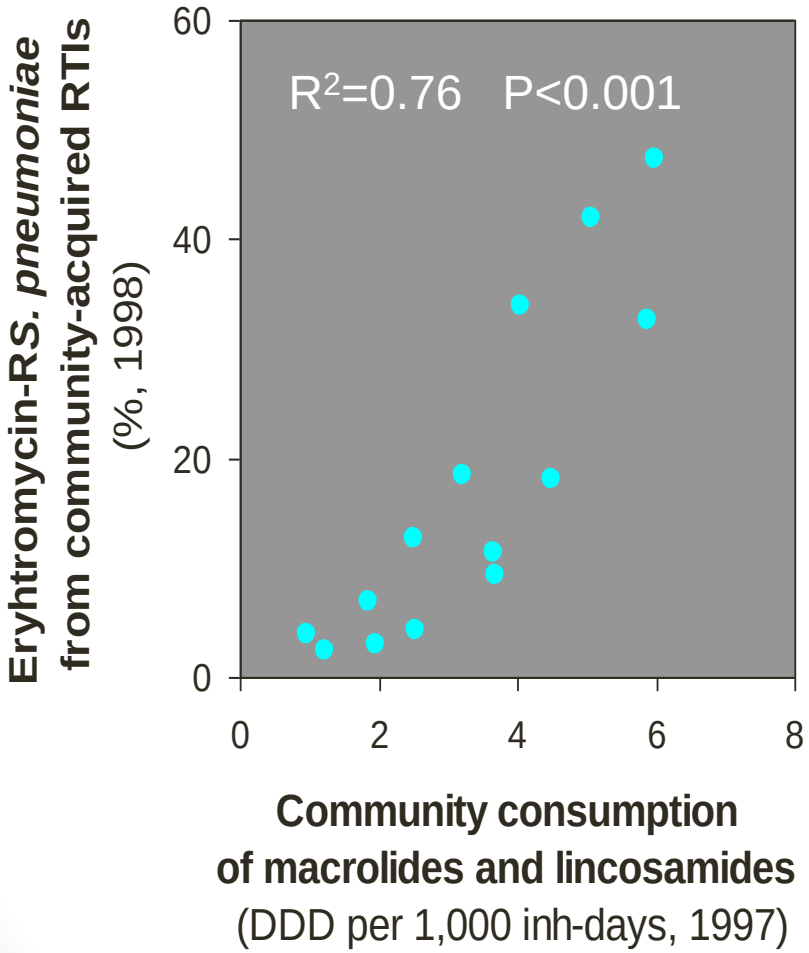
Significance

- The levels of MDR-TB found in PNG are higher than those reported by neighbouring countries:
  - PNG current study (2.7% in new and 19% in previously rx TB)
  - Indonesia (1.9% in new and 12% in previously treated TB cases)
  - Australia (1.7% in new and 10% in previously treated TB cases)
  - Philippines (2.0% in new and 21% in previously treated TB cases)
  - Viet Nam (4.0% in new and 23% in previously treated TB cases).

Antibiotic usage drives resistance!



Correlation of resistance with Antimicrobial Use in Community-Acquired Infections in Europe, 1997-2000

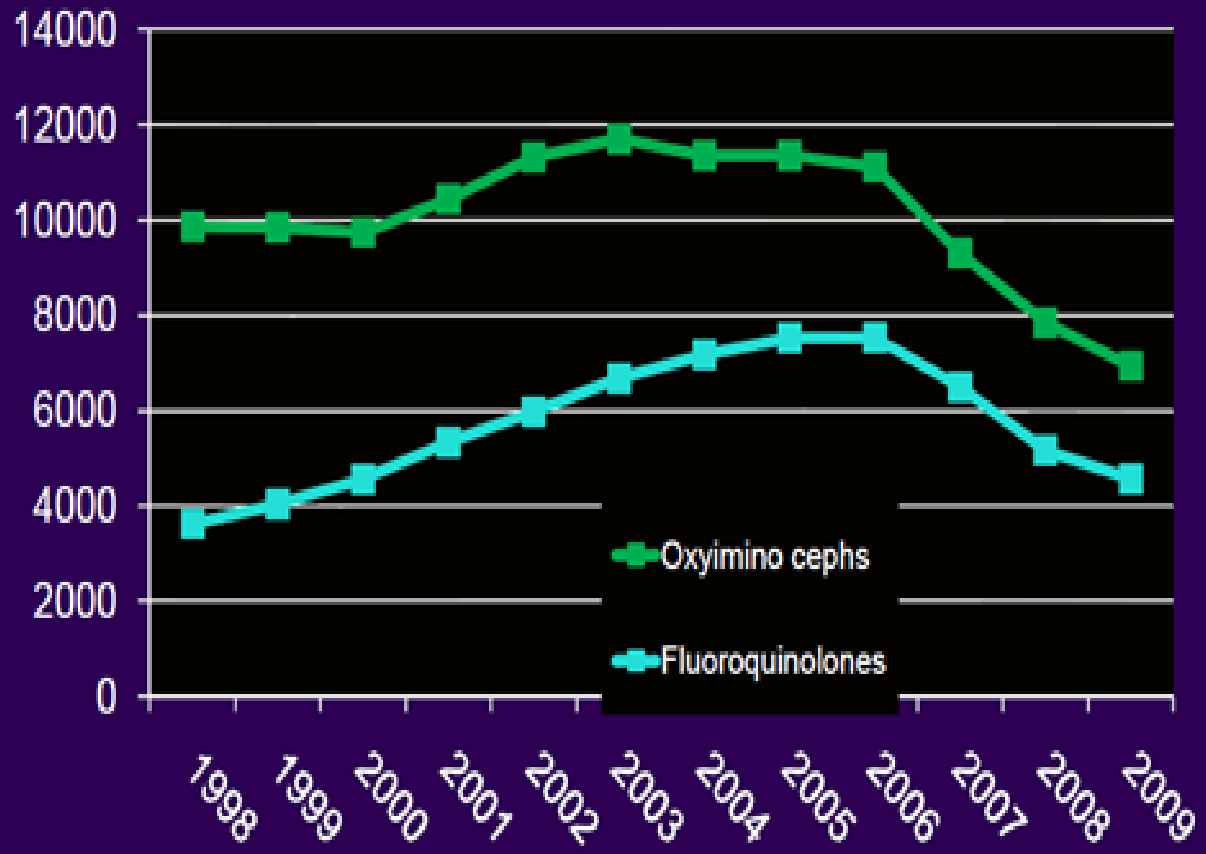


Each dot represents a different European nation

A very tight relationship between overall community consumption and resistance (erythromycin is a macrolide)

Source: Alexander Proj., FINRES, STRAMA, DANMAP and Cars O, et al. Lancet 2001.

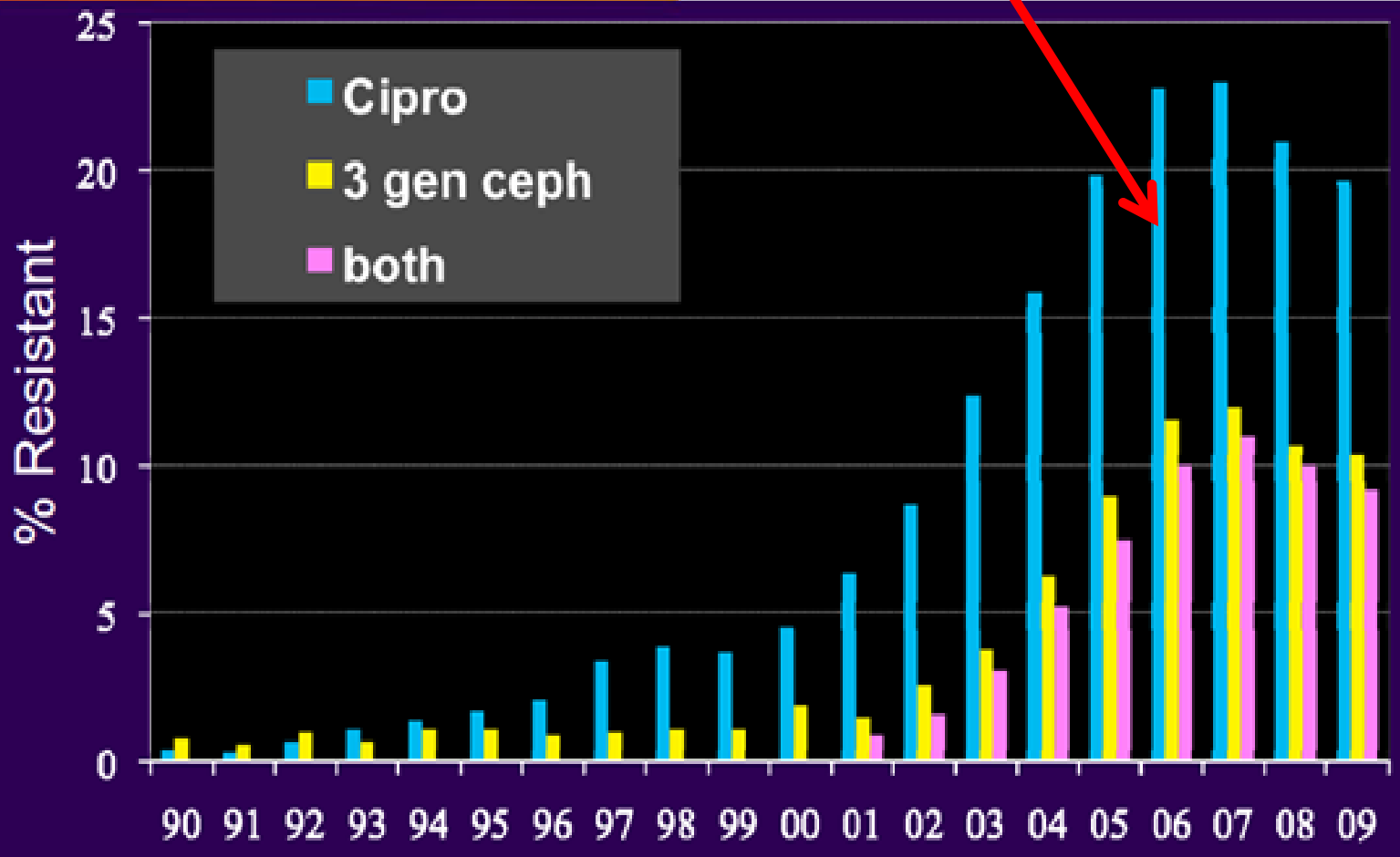
Declining usage: hospital antibiotic sales (kg), IMS data



Slides courtesy of Neil Woodford, HPA 2012

E. coli from blood & CSF in the UK - a recent fall in resistance

Health Protection Agency



- coincides with decreased use = decreasing selection ?
- If plasmids can't be lost, is this strain displacement ?

How are antibiotics used in PNG?

- PMGH (Steven Yennie, 2012)
  - Medical ward 72% of patients receiving an anti-infective (excluding TB and ARV treatment)
- Alotau Hospital (Nick Ferguson, Nov 2012)
  - Medical ward: 60% of patients on anti-infective
  - Obstetric ward: 34%

Common survey findings

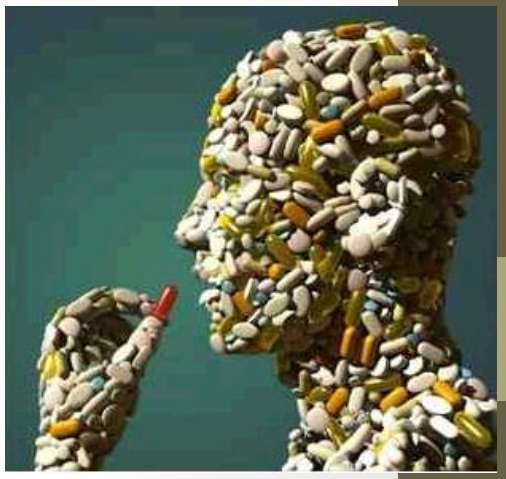
- Very prolonged courses, prolonged IV courses
- Undocumented reasons for therapy
- Treatments not in accord with Standard Treatment Guidelines

Antibiotic exposure: unintended consequences

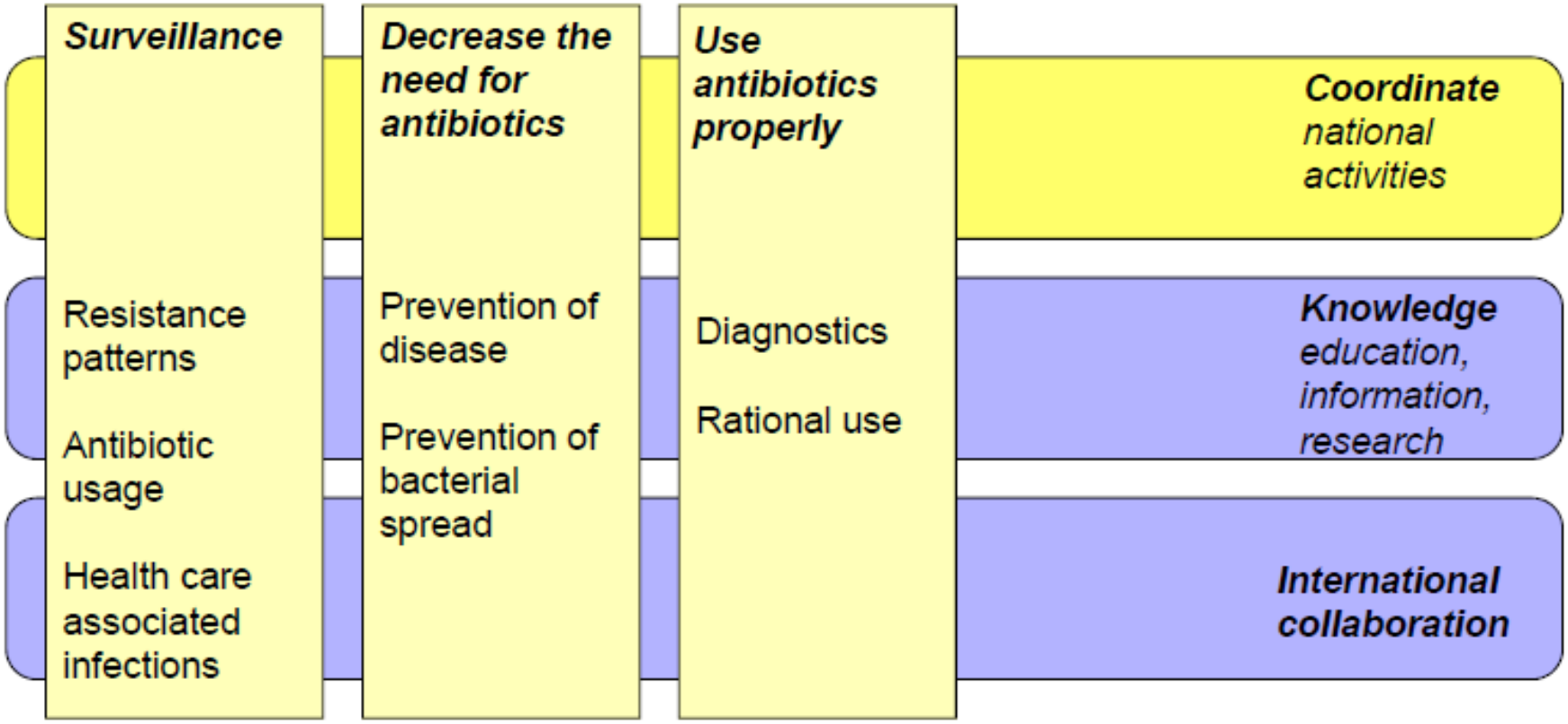
- Increased susceptibility to colonisation and infection by antimicrobial resistant organisms
- Prolonged changes to the bowel flora (microbiota) associated with onset of type 2 diabetes, inflammatory bowel disease, obesity, lowered lung immunity …
- Drug interactions/side effects: e.g.
  - sudden death increase in elderly patients on ACE inhibitors + trimethoprim or bactrim (hyperkalaemia)
  - Prolonged QT and sudden death increase- macrolines, fluoroquinolones

AMR in PNG

1. WHY is it an important problem?
2. HOW has the problem arisen?
3. **WHAT do we do now?**



The containment of antibiotic resistance needs coordination



ReAct
Actionen Antibiotic Resistance

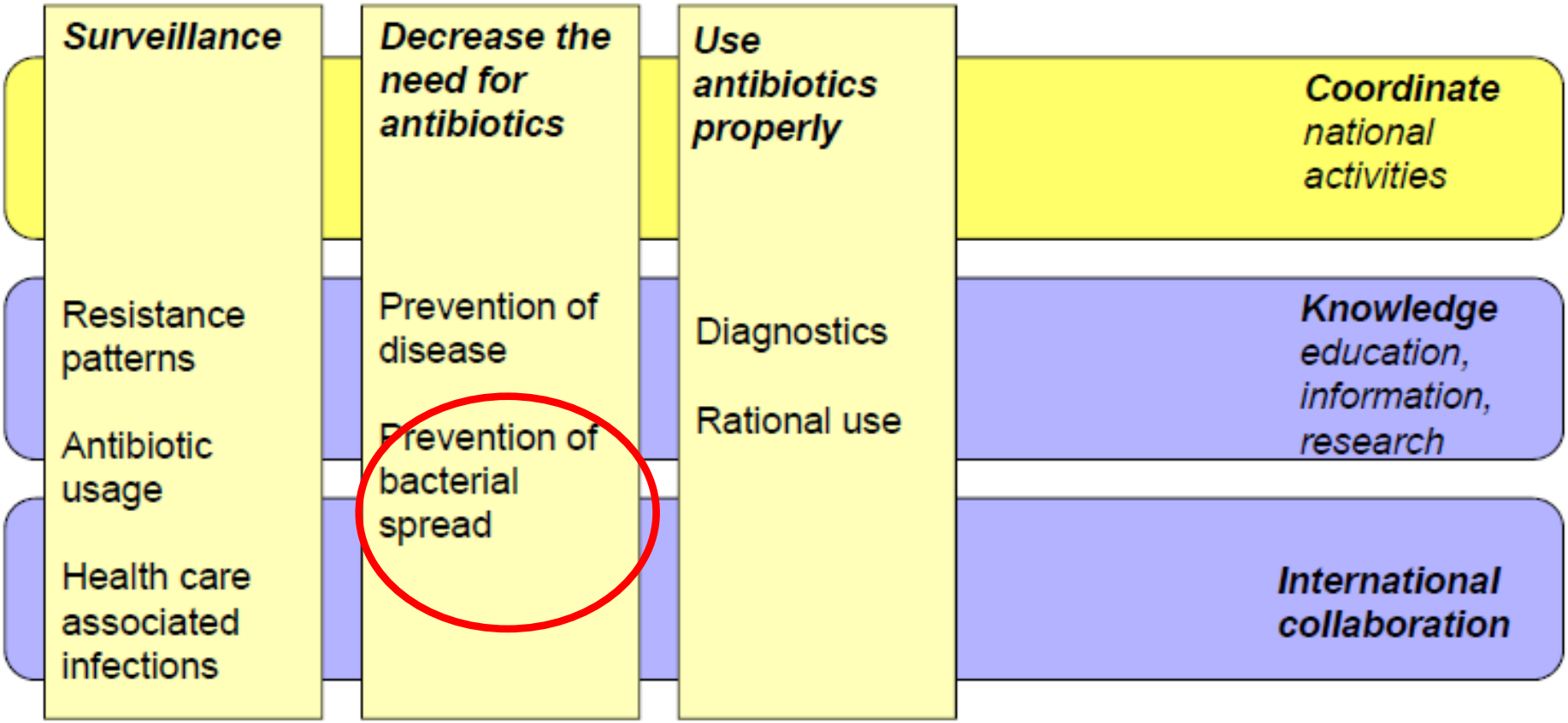
Vital question - how do we preserve a scarce resource?

Personal responsibility & accountability– responsible antibiotic use and infection control

Prevent over the counter access

Leadership and governance – national and local

Infection prevention & control

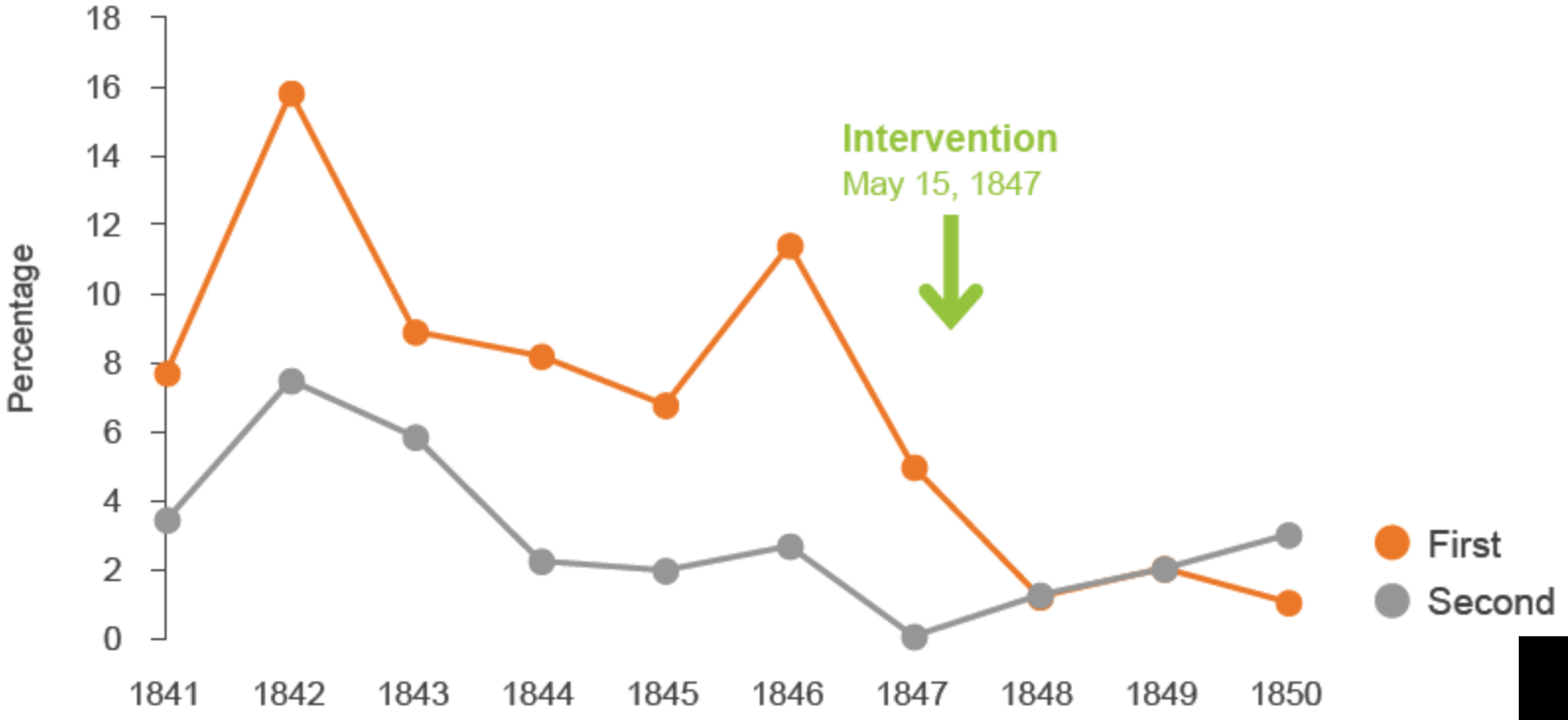


www.react.org

ReAct
Actieven Antibiotic Resistance

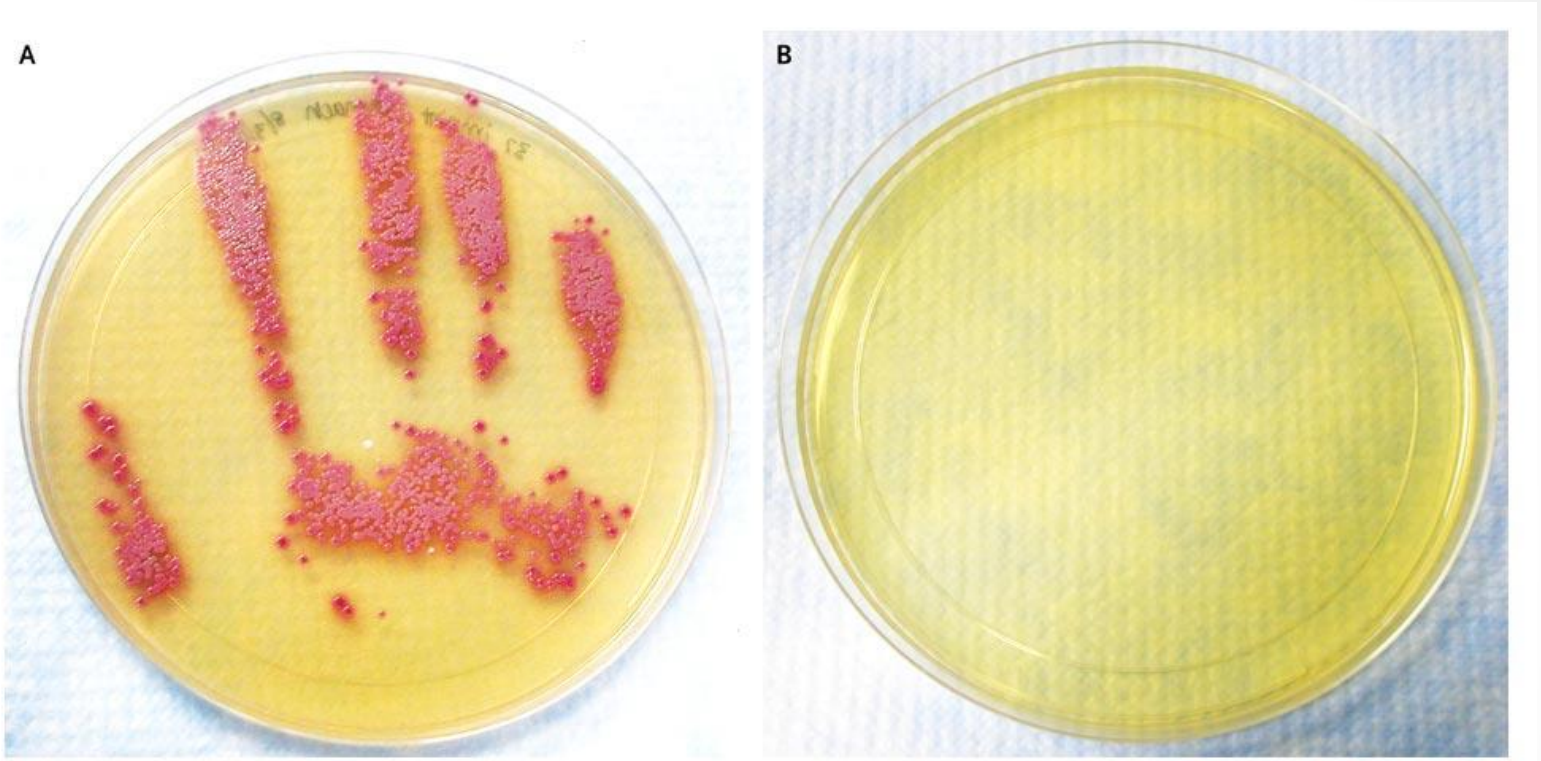
Lessons learned from Semmelweis (1861)

Hand disinfection saving women's lives in Vienna



No hand rub

Alcohol hand rub



Left- Hand imprint immediately after abdominal examination of a patient who was colonised with MRSA – pink colonies = MRSA

Right- hand imprint after disinfection with alcohol hand rub

Donskey C and Eckstein B. N Engl J Med 2009;360:e3

MRSA= methicillin-resistant *Staphylococcus aureus*

Point of care availability of Alcohol-based hand rub at PMGH, Goroka Hospital

- Rub hands BEFORE and AFTER EVERY patient contact
- Teach patients and relatives to use the rub

“Standard precautions” : the basis for protecting ALL patients & staff

Always follow these standard precautions

Perform hand hygiene before and after every patient contact

Clean and reprocess shared patient equipment

Use personal protective equipment when risk of body fluid exposure

Follow respiratory hygiene and cough etiquette

Use and dispose of sharps safely

Use aseptic technique

Perform routine environmental cleaning

Handle and dispose of waste and used linen safely

F-A-S-T strategy for TB & DR-TB control

Finding TB Patients:

The most infectious TB patients are the ones that we don't know about because they are not being treated. Undiagnosed TB patients can be in clinics, waiting areas, hospital emergency rooms, and wards that care for surgical or other medical problems. Asking all patients about TB symptoms, such as chronic cough, fever, and weight loss can lead to finding previously unsuspected TB cases, as can observing patients for cough in waiting rooms, registration areas, and admission holding areas.

Actively:

TB is usually diagnosed passively, occurring when patients' symptoms lead them to seek help. However, symptoms, such as cough, fever, and weight loss can be present for a long time, be attributed to other conditions, or be overshadowed by other pressing issues. The ***FAST*** strategy incorporates specifically trained staff called "cough monitors" or "cough surveillance officers" whose job is to identify patients with chronic cough and other TB symptoms, and promptly collect sputum, which would ideally be sent for rapid molecular testing.

Separating safely:

MDR-TB patients should be moved to a well-ventilated area to prevent the transmission of MDR-TB to other patients.

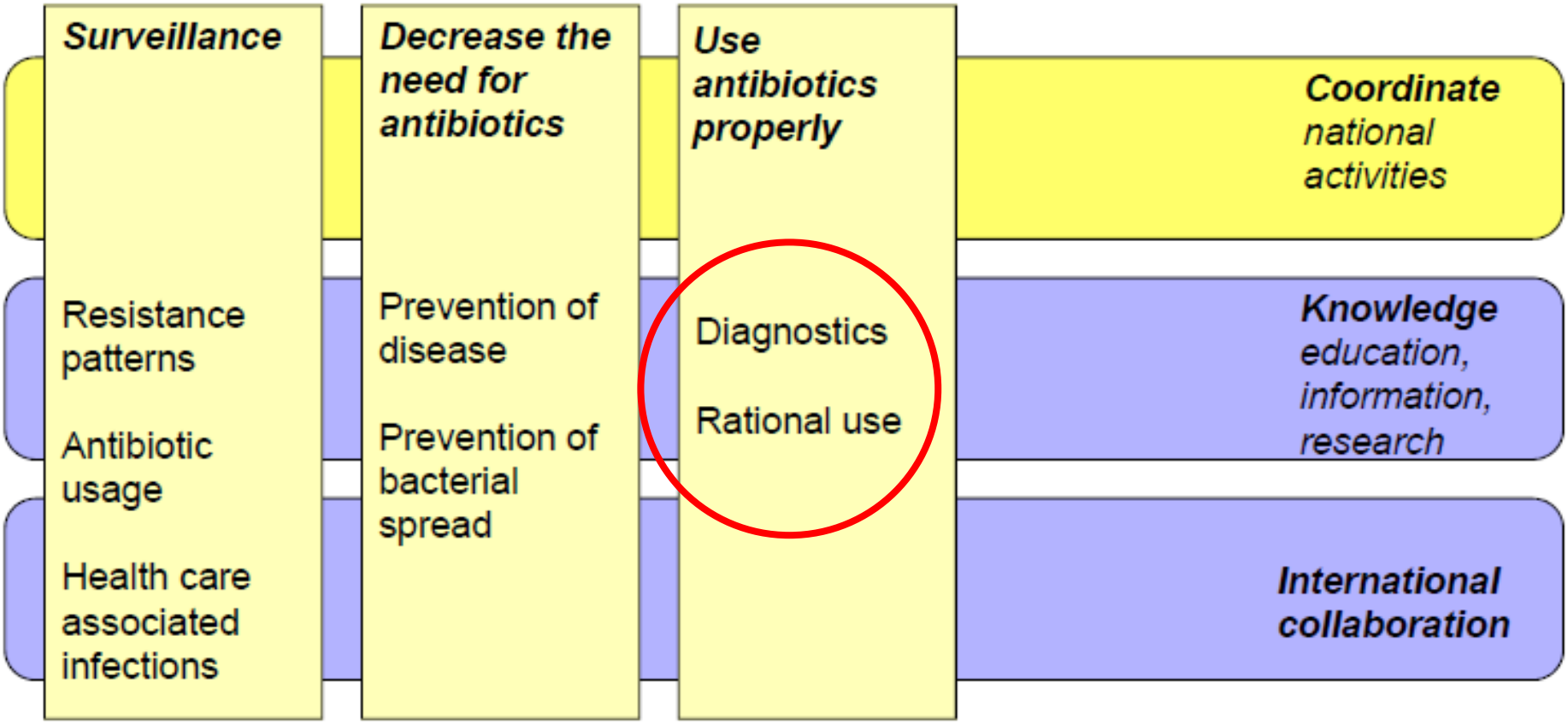
Treatment:

Treatment is the final and most important step in preventing transmission of TB to others. Patients become non-infectious soon after starting effective TB treatment.

F-A-S-T strategy for TB & DR-TB control

PMGH TB isolation facility

Practical and Therapeutic Options: using antibiotics properly



www.react.org

ReAct
Action Antibiotic Resistance

The AMR dilemma as a 'Tragedy of the Commons"

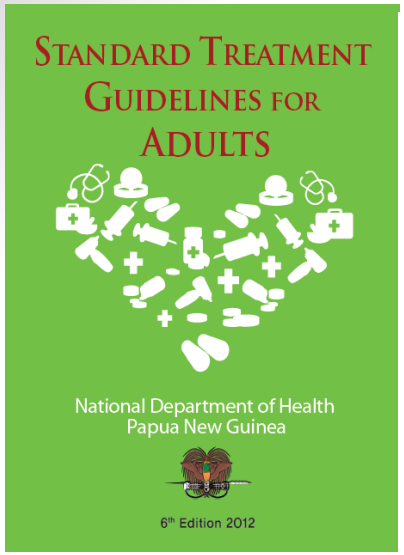
"A dilemma arising from the situation in which multiple individuals, acting independently and rationally consulting their own self-interest, will ultimately deplete a shared limited resource, even when it is clear that it is not in anyone's long-term interest for this to happen."

Wikipedia, G Hardin 1968

Antimicrobial stewardship

- Optimise treatment of patients with infection - target treatment- make sure the right patients are getting the right drug, right dose and duration
- Minimise individual and community adverse impacts of antimicrobials

AMR is dynamic – reducing antimicrobial usage generally leads to reductions in resistance



PNG therapeutic resources

Adult Medicine

- Adult medical standard treatment guide- 2012.
- HIV Adult standard treatment guideline 2009 March. This is the current version in use in 2012.

Paediatrics

- PNG Paediatric standard treatment guides Main resource site
- WHO Integrated Management of Childhood Illness resources
- Recommendations for management of common childhood conditions 2012. Excellent evidence-based extensive review.
- International Child Health Review Collaboration
- Royal Childrens Hospital Melbourne Paediatric Handbook 8th Edition
- WHO Treatment of Children living with HIV
- Manual on paediatric HIV care and treatment for district hospitals WHO 2011

Obstetrics and Gynaecology

- Current Standard PNG Treatment Book for O&G 6th Edition, 2010

Surgery

- Standard Treatment book - awaited
- WHO Guidelines for Safer Surgery 2009.

See also Safer surgery: resource poor countries

PNG Medical Journal

Full index to all issues with text links are available from here. The PNGMJ is indexed by Medline and so the easiest way to sear

See this quick start guide to PUBMED for more instructions. It is essential for practitioners in PNG to be aware of the local litera
PNG which have been well researched in the past.

http://hicsigwiki.asid.net.au/index.php?title=PNG_therapeutic_resources

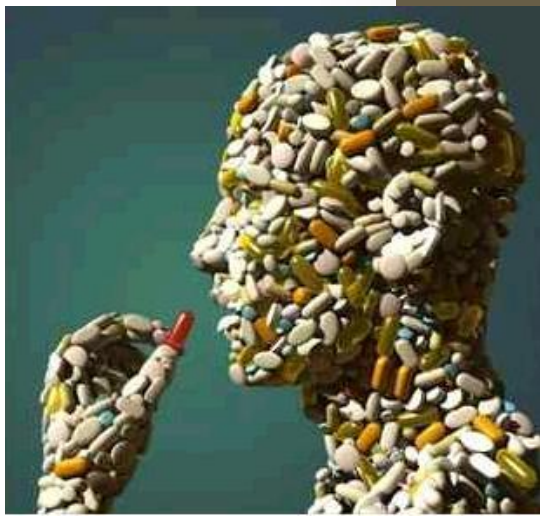
Is therapy 'AIMED'? – a standard for prescibers

- *Antimicrobial* selection and dosage should be compliant with guideline
- *Indication* for treatment should be documented
- *Microbiology before rx*
- *Evaluate* at 48-72hrs
- *Duration* or review date explici

www.aimed.net.au

Therapeutic factors promoting antibiotic resistance

1. Antibiotic selective pressure
   - Number of patients exposed (volume of use)
   - Breadth of spectrum
   - Duration of use
2. Inadequate dosing



Eliminate unnecessary use

- Patients may receive antibiotics for extended post operative prophylaxis or for ‘just in case’ situations where there is little actual evidence of infection
- These exposures put patients at great risk of acquiring resistant organisms and should be avoided

(Antibiotics do not protect patients from poor hygiene)

Barza M et al. Clin Infect Dis. 2002 Jun 1;34 Suppl 3:S126-30. **Excess infections due to antimicrobial resistance: the "Attributable Fraction".**

Rational empirical antibiotic use

- Evaluate likelihood of sepsis by presence of SIRS, other organ system dysfunction
- Withhold antibiotics if there is not a strong case and severe sepsis is absent
- Do pre-antibiotic microbiology tests
- Select empirical antibiotic(s) based on local guidelines and AMR incidence
- Document the reason for antibiotics in the patient record

Post-empiric management: evaluate at 48-72 hrs

- Response to treatment:
  - Clinical – temperature, control of sepsis, evaluation of source
  - Laboratory – WCC, CRP, culture results
- Assessment
  - Is there another non-infective cause?
  - Is antibiotic treatment still indicated?
  - If ongoing treatment indicated – consider early switch to oral

Limit durations of treatment

A very effective way to reduce selective pressure

Shorter duration treatments are feasible with:

- community pneumonia (3-5d)- extensive studies
- Intensive care unit pneumonia (7d)
- Localised UTI (3 days), UTI with sepsis (7-10d)
- Intra-abdominal sepsis with source controlled (1-7d),

Local guidelines need to specify recommended durations

Paterson-D et al . **Strategies for Reduction in Duration of Antibiotic Use in Hospitalized Patients** Clinical Infectious Diseases 2011: 52: 1232

Thank you!

Post graduate resources and access to online versions of current PNG STGs:
http://Idmic.net
http://aimed.net.au - Antimicrobial stewardship practical advice