Reducing bacterial resistance: possible approaches to therapeutics and stewardship in PNG

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Overview

1. The Why and How of antimicrobial resistance (AMR)
2. Practical and therapeutic options that are effective and reduce AMR

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**

How does resistance arise?

1. mutational change in bacterial chromosome

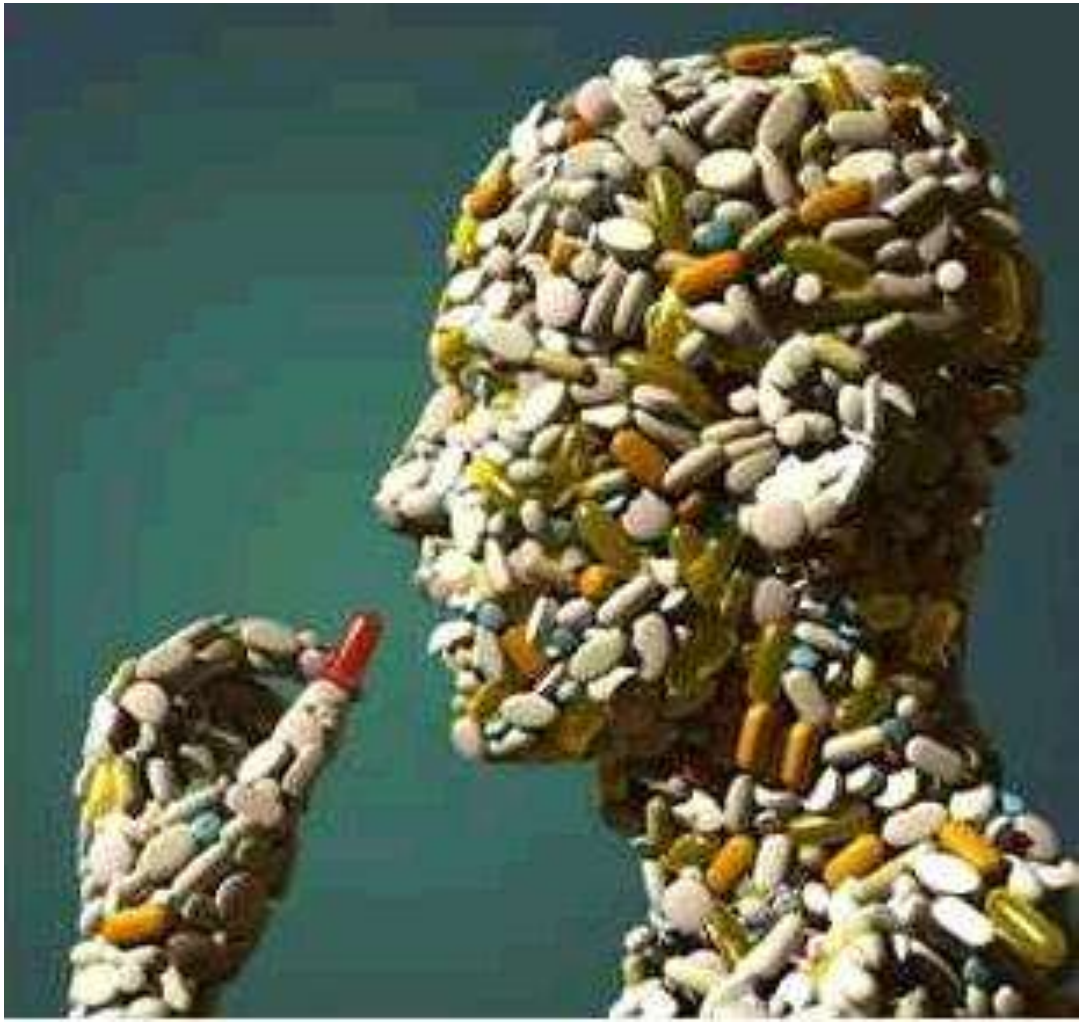
AND/OR

2. horizontal transfer of new resistance gene(s) from another bacterial species

Antibiotic exposure increases the rate of both processes

Antibiotics select and promote growth of resistant subpopulations

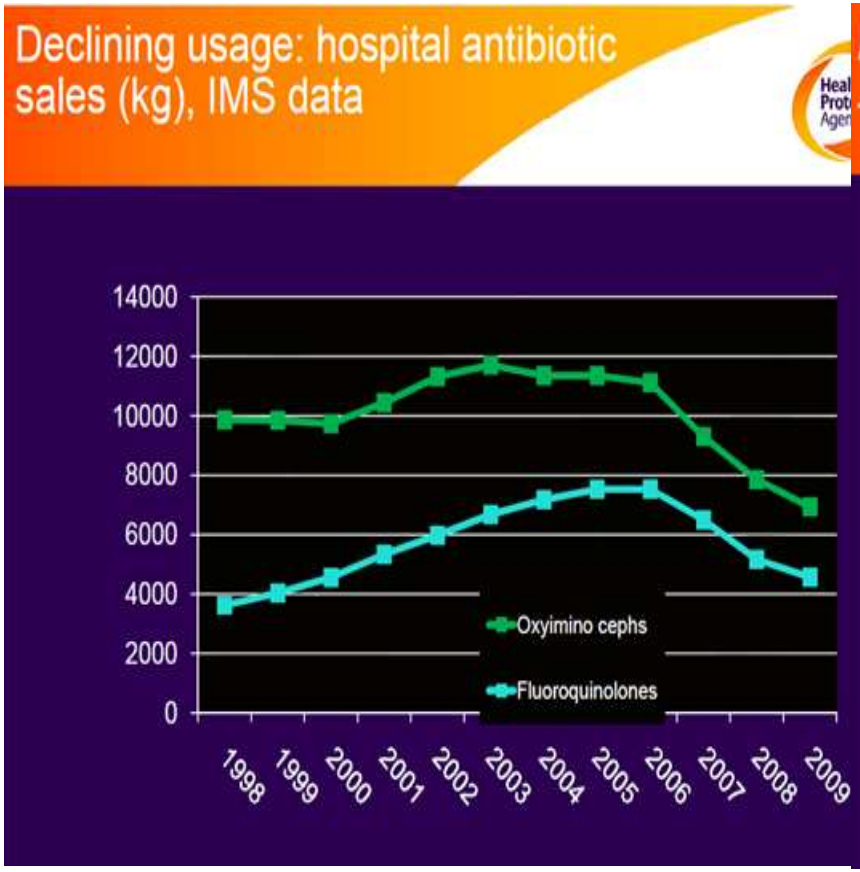
Antibiotic usage drives resistance!

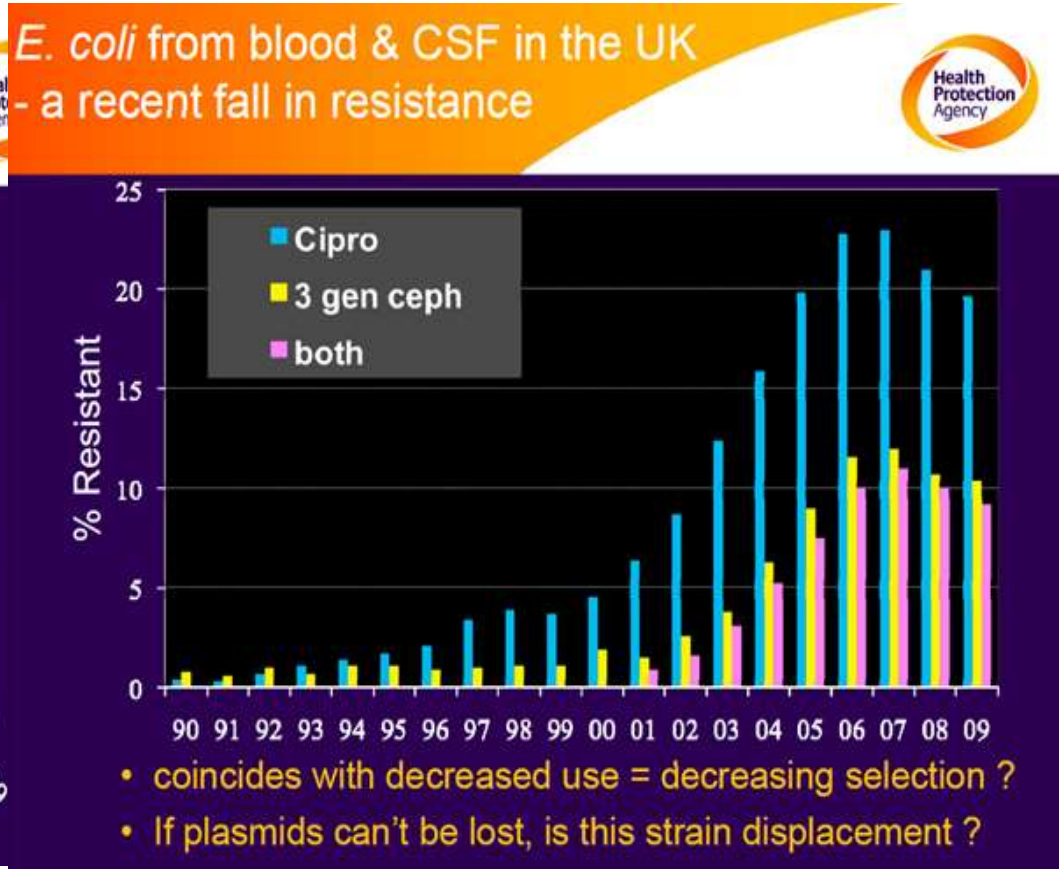


How are antibiotics used in PNG?

- PMGH (Steven Yennie, 2012) - Medical ward 72% of patients receiving an anti-infective (excluding TB and ARV treatment) .
- Common issues:
  - Very prolonged courses, prolonged IV
  - Undocumented reasons for therapy
  - Treatments not in accord with Standard Treatment Guidelines

Reducing use reduces resistance: evidence from the United Kingdom





Slides courtesy of Neil Woodford, HPA 2012

Unintended consequences of antibiotic exposure

- Increased susceptibility to infection by antimicrobial resistant organisms
- Prolonged changes to the bowel flora associated with onset of type 2 diabetes, inflammatory bowel disease, obesity, lowered lung immunity …
- Diverse 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- macrolides, fluoroquinolones

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Point prevalence surveys

- Study how antibiotics are being used in your unit
- Assess appropriateness and compliance against guidelines
- Drive change – reduce or eliminate pointless use, develop and implement standard treatments

National Antimicrobial Prescribing Survey (NAPS)- Australia

- Online point prevalence survey tool survey with advanced reporting capability
- Scope for access from PNG

Eliminate unnecessary use

- Extended post operative prophylaxis or ‘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".**

Empirical antibiotic use

- Evaluate likelihood of sepsis or severe sepsis (organ dysfunction present)
- Withhold antibiotics if there is not a strong case and severe sepsis is absent
- Select empirical antibiotic(s) based on local guidelines (and local AMR incidence)
- Document the antibiotic indication in the patient record

Spectrum required

Gram positives predominate (penicillin, flucloxacillin, vancomycin)

- Skin/soft tissue infection
- Pneumonia

Gram negatives predominate (gentamicin, ceftriaxone, ciprofloxacin)

- UTI
- Intra-abdominal
- Biliary tract

Vancomycin: good choice for broad spectrum Gram positive cover in sepsis (MRSA)

- Slow onset of action
- Standard of care (Australia) - give loading dose of 25-30mg/kg (based on actual body weight)
- Then give 1.5g 12-hrly for GFR>90, lower dosing for patients with renal failure

Other alternatives for MRSA skin/soft tissue infection

- No antibiotics – limited evidence that antimicrobials benefit patient with boils
- oral cotrimoxazole, doxycycline, clindamycin or erythromycin at correct dose (avoid if systemic sepsis present)
- Don't chase *Pseudomonas* and other Gram negatives in chronic ulcers or diabetic feet

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

Clinical Infectious Diseases 2011;1–38

Aminoglycosides- still good choice for potential Gram negative sepsis

- Rapidly bactericidal if given at sufficient dose, (concentration-dependent killing)
- Avoid usage > 3 days in order to reduce toxicity
- Use in combination therapy if local aminoglycoside susceptibility < 80%.

Australian dosing recommendations: 4-5mg/kg (based on ideal body weight), 7mg/kg (septic shock), 3 daily doses (normal renal fx), 1 or 2 doses (impaired initial renal function).

Situations where narrow spectrum empirical agents are feasible

- Acute on chronic airflow limitation – doxycycline or amoxycillin (benzylpenicillin) – maximum 3 days
- Community acquired pneumonia (mild-moderate) – benzylpenicillin monotherapy
  - Gram stain of well-collected sputum provides reliable rapid guidance (extensive evidence)
- Skin/soft tissue infection without sepsis (culture, MRSA prevalence?)

Cochrane Database Syst Rev. 2012 Dec **Antibiotics for exacerbations of chronic obstructive pulmonary disease.**
Postma et al. **Antibiotic treatment strategies for community-acquired pneumonia in adults** N Engl J Med. 2015 Apr 2;372(14):1312-23.

Post-empiric management: evaluate at 48-72 hours

- 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
  - Is patient worsening – AMR ?

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),

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

Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, Willem N Hustinx, Paul Bresser, Guido E L van den Berk, Jan-Werner Poley, Bob van den Berg, Frans H Krouwels, Marc J M Bonten, Carla Weenink, Patrick M M Bossuyt, Peter Speelman, Brent C Opmeer, Jan M Prins

Interventions: Patients who had substantially improved after three days' treatment with intravenous amoxicillin were randomly assigned to oral amoxicillin (n = 63) or placebo (n = 56) three times daily for five days.

Outcome: No significant difference in outcome on any measure.

bmj.com 2006;332:1355

Is therapy 'AIMED'? – a standard for prescribers

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

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