Good antimicrobial stewardship is a practice to ensure …

- optimal selection, dose, and duration of an antimicrobial therapy …
- best clinical outcome …
- producing the fewest toxic effects …
- the lowest risk for subsequent resistance…

“Antibiotic stewardship refers to a multifaceted approach … to optimise prescribing, including policies, guidelines, surveillance, education and audit.”
What does it mean…

Afrikaans: “Antibiotika rentmeesterskap”
• Rentmeester = oikonómos (Greek)
  – manager of household or of household affairs

Zulu: “nobuphathi antibiotic”
• Other nouns
  – Umphathi = manager, holder, conductor / “the boss”
  – Inceku = household servant
Where did it start?

“An epic struggle for survival between single-celled bacteria and developing mammalian species has existed from time immemorial.”

“Pan-drug–resistant”
“Extremely drug-resistant” pathogens

Robert C. Owens Jr, Diagnostic Microbiology and Infectious Disease 2008
Where did it start?

- "He (the prescriber) is under great pressure to prescribe the 'newest', 'best', 'broadest' antibiotic preparation, prescribe it for any complaint whatever, quickly, and preferably without worrying too much about specific etiologic diagnosis or proper indication of the drug"

(Jawetz, 1956)

- 1970s and 1980s: a formal program at Hartford Hospital formed the ASP
- RCT in the late 1990s: antimicrobial use could be significantly reduced without adversely impacting clinical outcome
- In 2007: Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) jointly published guidelines for the development of ASP
South Africa…

*Wake up, South Africa! The antibiotic ‘horse’ has bolted…*

Emergence:

- New Delhi metallo-β-lactamase-1 (NDM-1)
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Klebsiella pneumoniae carbapenemases (KPCs)

“…we must force a return to rational antibiotic prescribing, with equal emphasis on addressing IPC…”

“*not the domain of the few, but the responsibility of all*”
South Africa…

Unlike the case of drug-resistant tuberculosis or HIV…

MDR Gram-negative bacteria (ie. CRE) cannot be blamed on poor patient compliance, or resistant strains from foreign climes.

This is a home-grown problem, generated and perpetuated by doctors, nurses and allied healthcare workers in South Africa.
Publications

- Wake Up South Africa the 'Antibiotic Hope' Has Failed [SAMJ 2012]
- Prevalence of Infection in South African Intensive Care Units (PSIA) Study [SAMJ 2012]
- Groote Schuur Hospital AIMS Programme [PloS One 2013]
- Carbapenem Resistant OXA-181 Producing Klebsiella Pneumoniae in South Africa [JMI Clin Microbiol 2013]
- Hand hygiene Patient Empowerment [SAJE 2014]
Antibiotic stewardship programmes (ASP)

- Two main types:
  - Restrictive (formulary restriction and pre-authorisation)
  - Educational (audit and feedback)

<table>
<thead>
<tr>
<th>Tactic</th>
<th>Level of evidence</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines and clinical pathways</td>
<td>A-I</td>
<td>Core activity, but implementation plans are critical.</td>
</tr>
<tr>
<td>Education</td>
<td>A-III</td>
<td>Critical, but must be ongoing and interactive</td>
</tr>
<tr>
<td>Antimicrobial cycling/mixing/diversity</td>
<td>C-II</td>
<td>Might work if done very frequently</td>
</tr>
<tr>
<td>Antimicrobial order forms</td>
<td>B-II</td>
<td>Diversity probably best</td>
</tr>
<tr>
<td>PK/PD dose optimisation</td>
<td>A-II</td>
<td>Focused decision making</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>C-II</td>
<td>Shortens duration of treatment</td>
</tr>
<tr>
<td>Streamlining or de-escalation</td>
<td>A-II</td>
<td>Prevents resistance</td>
</tr>
<tr>
<td>Intravenous to oral switch</td>
<td>A-III</td>
<td>Reduces costs and length of intravenous access</td>
</tr>
</tbody>
</table>

* Strength of recommendation: A, good evidence to support a recommendation for use; B, moderate evidence to support a recommendation for use; C, poor evidence to support a recommendation for use.

Quality of evidence: I, evidence from >1 properly randomized, controlled trials; II, evidence from >1 well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 controls); from multiple time-series; or from dramatic results from uncontrolled experiments; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Antibiotic stewardship programmes (ASP) in paeds

• Strategies:
  – Core (restriction and/or audit and feedback)
  – Supplemental

**TABLE 1. Antimicrobial Stewardship Strategies**

<table>
<thead>
<tr>
<th>Antimicrobial Stewardship Strategy</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core Strategies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective-audit with feedback</td>
<td>Review and provide feedback on antibiotics after they have been ordered</td>
<td>3</td>
</tr>
<tr>
<td>Prior approval</td>
<td>Review and approve antibiotic prior to initiation</td>
<td>4</td>
</tr>
<tr>
<td>Supplemental Strategies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>Lectures, educational conferences, handbooks</td>
<td>12</td>
</tr>
<tr>
<td>Clinical guidelines</td>
<td>Guidelines can incorporate appropriate antibiotic selections and dosing</td>
<td>13</td>
</tr>
<tr>
<td>Streamlining/de-escalation therapy</td>
<td>Focus on identifying bug-drug mismatches* and stopping antibiotics when cultures are negative</td>
<td>4, 8</td>
</tr>
<tr>
<td>IV to PO conversion</td>
<td>Changing antibiotics with good bioavailability to oral (eg, linezolid, clindamycin, fluoroquinolones)</td>
<td>14</td>
</tr>
<tr>
<td>Dose optimization</td>
<td>Assuring the appropriate doses are being administered for the given clinical condition</td>
<td>4, 8</td>
</tr>
<tr>
<td>Antimicrobial order forms</td>
<td>Require clinicians to justify antibiotic use and can provide automatic stop orders within the form</td>
<td>15</td>
</tr>
</tbody>
</table>

*Bug-drug mismatch—When the spectrum of the antibiotic being used to treat the organism is either too broad (eg, vancomycin to treat methicillin susceptible *Staphylococcus aureus*) or too narrow (eg, the organism is resistant).
Antimicrobial Stewardship in Pediatrics
How Every Pediatrician Can Be a Steward

• Goals of AS:
  – to optimize outcomes while minimizing consequences (toxicity, the selection of pathogenic organisms, and the emergence of resistance)

• 2010:
  – Pediatric Infectious Diseases Society (PIDS) formed the Pediatric Committee on Antimicrobial Stewardship:
    • advance pediatric AS
    • promote research in pediatric AS
    • develop AS educational programs
    • sponsor and organize an annual conference on pediatric AS
### Table 1. Principles and Strategies for AS Programs

<table>
<thead>
<tr>
<th>Principles</th>
<th>Examples of Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timely antibiotic therapy management</td>
<td>Ensuring prompt initiation of antibiotic therapy when indicated</td>
</tr>
<tr>
<td></td>
<td>Critical illness such as sepsis</td>
</tr>
<tr>
<td></td>
<td>High-risk patients with serious bacterial infections</td>
</tr>
<tr>
<td></td>
<td>Avoiding use of antibiotics when not indicated</td>
</tr>
<tr>
<td></td>
<td>Viral upper or lower respiratory tract infections</td>
</tr>
<tr>
<td></td>
<td>Asthma exacerbations</td>
</tr>
<tr>
<td></td>
<td>Viral pharyngitis</td>
</tr>
<tr>
<td></td>
<td>Use of clinical guidelines and algorithms that facilitate provider recognition of clinical syndromes that do and do not require antibiotics</td>
</tr>
<tr>
<td>Appropriate selection of antibiotics</td>
<td>Ensuring that proper antibiotic regimens are selected for specific clinical syndromes and infections</td>
</tr>
<tr>
<td></td>
<td>Minimizing redundant antibiotic regimens for gram-negative or anaerobic bacterial infections</td>
</tr>
<tr>
<td></td>
<td>Use of antibiograms and clinical guidelines to optimize antibiotic selections</td>
</tr>
<tr>
<td>Appropriate administration and de-escalation of antibiotic therapy</td>
<td>Ensuring proper dosing of antibiotics</td>
</tr>
<tr>
<td></td>
<td>Peer review of antibiotic use at 48-72 h after initiation to determine if therapy should be continued, changed, or discontinued</td>
</tr>
<tr>
<td></td>
<td>Monitoring for serum therapeutic levels of antibiotics</td>
</tr>
<tr>
<td></td>
<td>Proper administration of antibiotics for surgical prophylaxis</td>
</tr>
<tr>
<td>Use of expertise and resources at point of care</td>
<td>Formation of multidisciplinary AS committees</td>
</tr>
<tr>
<td></td>
<td>Obtaining administrative and leadership support</td>
</tr>
<tr>
<td>Continuous and transparent monitoring of antibiotic use</td>
<td>Auditing antibiotic use to identify opportunities for stewardship and education</td>
</tr>
<tr>
<td></td>
<td>Prospective monitoring to assess efficacy of AS program</td>
</tr>
</tbody>
</table>

Abbreviation: AS, antimicrobial stewardship.
1. Appropriate and Prompt Antimicrobial Therapy Initiation

- “All or nothing…”
  - Risk factors for serious bacterial infections (CVP/HIV) = prompt and appropriate antimicrobial therapy when an infection is suspected
  - Protocols and interventions to reduce time to antibiotic administration (prompt physician order and AB access in emergency carts)
  - Prevent overuse of antibiotics in clinical situations where antibiotics are not indicated (asthma, pharyngitis, and RSV bronchiolitis)

- Education and feedback to prescribers
2. Appropriate Selection of Antibiotics

• “All or something…”

• Appropriate empirical antimicrobial regimen

• Prerequisite:
  – Local antibiograms
  – Clinically relevant antibiograms

  *Escherichia coli first episode of urinary tract infection vs strain from 3rd episode and VU reflux*

  – Appropriate testing / sampling*
3. Appropriate Administration and De-escalation

- “Double-check the script…”
- Correct dosing: prospective surveillance and therapeutic level monitoring
  (vancomycin, aminoglycosides, voriconazole)
- “Time for a change…”
- Appropriate and timely de-escalation or discontinuation
  (best recognized and most widely adopted principle of AS)
  - Reducing the number of antibiotics
  - Selecting narrow- over broad-spectrum antibiotics
  - Converting parenteral to oral therapy
Let’s Go PO - Transitional Antimicrobial Therapy

Benefits of Oral Therapy
- Equally effective as IV
- Shortened Length Of Stay
- Fewer bacteremias
- Reduction in administration and preparation time
- Decreased drug cost

Which Antimicrobial Agents?
- Agents with >90% bioavailability:
  - Ciprofloxacin
  - Gentamicin
  - Nitrofurantoin
  - Cefadroxil
  - Metronidazole
  - Trimethoprim/Sulfamethoxazole

- Agents not absorbed well or at all:
  - Vancomycin
  - Neomycin
  - Polymyxin
  - Nitrofurantoin (good for UTIs only)

When to Transition?
- Functional GI tract
- Stable renal function
- Non-steroidal anti-inflammatory
- None of the above

Which Infections?
Infections amenable to transitional therapy:
- Urinary tract infections
- Urinary tract infections including prostatitis
- Mild and soft tissue infections
- Intrabdominal infections

Avoid:
- Meningitis
- Acute exacerbations
- Endocarditis
- Necrotizing bacteremia or sepsis of unknown origin
- Unchecked abscesses
- Septic shock
- Nonsurgical fever and neutropenia
- Meningitis

How to Transition:
Transitioning from the same drug to the same drug is straightforward:
- E.g.: Ciprofloxacin IV to Ciprofloxacin PO (400 mg every 12 hours)

Other options:
- Trimethoprim/Sulfamethoxazole
- Ciprofloxacin + doxycycline
- Ciprofloxacin + amoxicillin/clavulanate
  - Gentamicin
  - Metronidazole

Corticosteroids:
- Ciprofloxacin + corticosteroids
  - Gentamicin (low dose corticosteroids if documented P. aeruginosa)

Immunosuppression:
- Ciprofloxacin + immunosuppression
  - Dicloxacillin + clavulanate or flucloxacillin/clavulanate

Oral: clindamycin
  - Ciprofloxacin
  - Gentamicin
  - Macrolide

Check cultures and susceptibilities results.

*When these medications are transitioned from IV to PO, remember to space interacting medications such as cyclosporine, Met, Flu, AIs, Ca, and AIs by two hours before or after. 
4. Use of Expertise and Resources at POC

- Local AS teams or committees composed of experts from multiple fields…
- In addition, support from hospital administration…
- Newland (2010): “It is not possible to have an ASP without the support of the hospital administration.”
Use of Expertise and Resources at POC

Physicians
- Local champions of clinical areas
- Supervisor of clinical decisions
- Director or codirector
- Timely and appropriate antibiotic management
- Prospective audit with intervention and feedback
- Streamlining/decasulation
- Guidelines and clinical pathways

Infection Preventionists
- Surveillance
- Prevention emergence and cross-transmission of MDRIs
- Hand hygiene

Clinical Pharmacist
- Monitoring of antibiotic use
- Appropriate administration

Hospital Administrators
- Program funding
- Institutional policy

Microbiologist
- Timely and accurate reporting
- Novel biotechnology

Patient

Education
5. Continuous and Transparent Monitoring

- Surveillance...
- *Remember the context*...
- "M&M AB-pathogen profile"

![Graph showing antibiotic resistance percentages](image-url)
## Monitoring Outcomes

<table>
<thead>
<tr>
<th>ASP process measurement outcomes</th>
<th>Patient oriented clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics doses / 1000 pt days</td>
<td>Lengths of hospital or ICU stays</td>
</tr>
<tr>
<td>Cost benefits</td>
<td>HAIs</td>
</tr>
<tr>
<td>Prescription errors</td>
<td>Readmissions</td>
</tr>
<tr>
<td>Safe and appropriate transitions</td>
<td>Mortality</td>
</tr>
<tr>
<td></td>
<td>Clostridium difficile infections</td>
</tr>
<tr>
<td></td>
<td>Adverse drug-associated events</td>
</tr>
</tbody>
</table>
Outcome examples...

- “Impact on reducing targeted- and non targeted-antimicrobial use”
- “Reduction vancomycin utilization and vancomycin prescribing errors”
- “Interventions: (1) Targeting the known or suspected pathogens (20%); (2) Consultation (43%); (3) Optimize antimicrobial treatment (33%); and (4) Stop treatment (4%)”
Outcome examples…

• “Three of the 84 (3.5%) patients recommended to receive alternative therapy developed an infection not covered by the ASP recommendations or the antimicrobial initially requested by the clinician.“

• “18% viewed the program as an obstacle, 70% wanted additional feedback. Compliance was 79%. Costs decreased by 6.4% the 1st year and 2.2% the 2nd year.”
Monitoring Outcomes…

- Research data linking decreased antibiotic resistance
directly to ASP difficult…
  - Confounding variables and interventions other than AS that affect
    resistance prevalence ("bundled" interventions)
  - Limitations of non-randomized study designs
  - Resistance prevalence outcomes = long term measurement
Daily practice…

A 10-year-old boy, previously well

- 2 days of fever, vomiting, and abdominal pain localized to the right lower quadrant
- CT abdo: perforated appendicitis
- Percutaneous fluoroscopy-guided drainage (cultures)
- Postoperatively, combination of piperacillin sodium and tazobactam sodium, gentamicin sulfate, and metronidazole was started
- 14-day course of parenteral antibiotic therapy (CVP)
Daily practice…

<table>
<thead>
<tr>
<th>Agent</th>
<th>Minimum Inhibitory Concentration</th>
<th>Susceptibility Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin sodium</td>
<td>8</td>
<td>S</td>
</tr>
<tr>
<td>Cefazolin sodium</td>
<td>8</td>
<td>S</td>
</tr>
<tr>
<td>Cefepime hydrochloride</td>
<td>&lt;2</td>
<td>S</td>
</tr>
<tr>
<td>Cefotetan disodium</td>
<td>&lt;16</td>
<td>S</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Ciprofloxacin hydrochloride</td>
<td>&lt;1</td>
<td>S</td>
</tr>
<tr>
<td>Cefotaxime sodium</td>
<td>&lt;4</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&lt;1</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>4</td>
<td>S</td>
</tr>
<tr>
<td>Piperacillin and tazobactam</td>
<td>&lt;16</td>
<td>S</td>
</tr>
<tr>
<td>Sulfamethoxazole and trimethoprim (Septra)</td>
<td>&lt;3/16</td>
<td>S</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&lt;1</td>
<td>S</td>
</tr>
</tbody>
</table>
Consider…

“It is interesting to note that only specialists in oncology can prescribe and administer the drugs used for the treatment of cancer but that almost any clinician can prescribe antimicrobial agents.

Perhaps antibiotic prescribing should only be possible by doctors and other health professionals who have been certified as competent, probably after undergoing educational programmes in the field. Gone should be the days when all doctors can prescribe what they like, when they like.”

Thank you