Rational use of anti-infective medicines

By

Prof Dimie Ogoina
MBBS, FWACP, FMCP-Infectious Disease, FACP, Cert Clinical Leadership (UK)

Department of Internal Medicine, Infectious Disease Unit, Niger Delta University/Niger Delta University Teaching Hospital, Bayelsa State, Nigeria

WASP 2019
Outline

• Introduction /Background
• Concept of rational use of anti-infective medicines
• Trends and patterns of antimicrobial consumption
• Determinants of rational and irrational use
• Consequences of irrational use
• Strategies promoting rational use
• Conclusion
• Conflict of interest- None
• Declaration- None
Background

- Anti-infective medicines are medicines used to stop the growth/replication or kill micro-organisms causing infectious diseases
- Also called antimicrobial medicines
- Include: antibacterial, antivirals, antiparasitic and antifungals
Scope of use anti-infective medicines

- Anti-infective medicines
  - Humans
    - Hospitals
    - Community
  - Animals
  - Plants and food
Residues of anti-infective medicines

- Hospitals
- Animal
- Plant
- Community
- Environment
Historical Impact of Anti-infective medicines

- Discovery of penicillin revolutionised treatment of infectious disease
- Increased life expectancy due to ability to prevent and treat infection

Crude mortality rates for all causes, non infectious causes and infectious diseases over the period 1900-1996.

Misuse of antibiotics fueling resistance (1)

- In 1928, Alexander Fleming first discovered the antibiotic Penicillin
- In his Nobel Prize acceptance speech, Fleming warned the world of the dangers of misusing antibiotics.
- He had already noted bacteria in his lab becoming resistant to penicillin, just a few years after its discovery!
Misuse of antibiotics fueling resistance (2)

4. Sir Alexander Fleming, Nobel Lecture, December 1945
What is rational use of anti-infective medicines?

• Rationale defined as
  • a set of reasons or a logical basis for a course of action or belief

• According to WHO (1985)- medicines are
  • used ‘rationally’ (i.e., appropriately, properly, correctly, responsibly) when patients receive the appropriate medicines, for appropriate indications, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and society, and with appropriate information.

• ‘Irrational’ (i.e., inappropriate, improper, incorrect) or unnecessary use of medicines occurs when one or more of these conditions is not met

• WHO estimates that 50% of medicines used in human medicine are prescribed, dispensed or sold inappropriately

https://www.who.int/medicines/areas/rational_use/en/
Spectrum of irrational use of anti-infective medicines

Prescribers ➔ Dispensers ➔ Users

Misuse or overuse

No clinical indication

No prescription

Failure to investigate for cause of infection when possible e.g. cultures

Drug mismatch - microbiology, combination, spectrum (narrow vs broad), adverse effects, interactions, cost

Dose mismatch; too high, too low

Route mismatch

Inadequate documentation - indication, start/review/stop

Delay in starting

Failure to review - deescalate or discontinue

Duration/frequency - too long or too short, too frequent/inadequate frequency

Non-compliance with local guidelines

Surgical prophylaxis >24hrs
Trends and patterns of antimicrobial consumption

Sources of data
- Self-reported
- Drug imports/sales/procurement
- Hospital-based sales/prescriptions/point prevalence

Categorize Consumption
- Hospital, community, national, regional, global
- Human or animal/food

Quantitative or qualitative
Global antibiotic consumption by country: 2000–2015. (A) Change in the national antibiotic consumption rate between 2000 and 2015 in DDDs per 1,000 inhabitants per day. (B) Antibiotic consumption rate by country for 2015 in DDDs per 1,000 inhabitants per day.

National studies using drug imports/sales

Consumption by DDD increased by 65% and consumption rate by 39%
National studies using drug imports/sales

Change in global antibiotic consumption by country: 2000–2015.

Eili Y. Klein et al. PNAS 2018;115:15:E3463-E3470
National studies using drug sales at country level

Global antibiotic consumption by country: 2015.

Eili Y. Klein et al. PNAS 2018;115:15:E3463-E3470
WHO Report on Surveillance of Antibiotic Consumption 2015

Knowledge of antibiotics

- 25% believed “It’s okay to use antibiotics that were given to a friend or family member, as long as they were used to treat the same illness”
- 43% believed self-medication with antibiotics is okay
- Believed that sore throats (70%) and colds and flu (64%) should be treated with antibiotics
- 32% believed that antibiotics should be stopped when they feel better irrespective of duration recommended

Percentage of respondents who took antibiotics

Hospital-based studies

Antimicrobial consumption using Point Prevalence Survey (PPS) in hospitalized adult patients in 53 countries

Participation of African countries to the Global-PPS in 2015, 2017 and/or 2018

Degree of participation in 2017

<table>
<thead>
<tr>
<th>Country</th>
<th>N hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGYPT</td>
<td>17</td>
</tr>
<tr>
<td>GUINEA</td>
<td>14</td>
</tr>
<tr>
<td>NIGERIA</td>
<td>10</td>
</tr>
<tr>
<td>SOUTH AFRICA</td>
<td>3</td>
</tr>
<tr>
<td>TUNISIA</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>45</strong></td>
</tr>
</tbody>
</table>

Lancet Glob Health 2018; 6: e619–29
Regional differences in antibiotic consumption: quality indicators

<table>
<thead>
<tr>
<th>Region</th>
<th>Country(n)</th>
<th>Hospitals(n)</th>
<th>% Antimicrobial use</th>
<th>% reason stated</th>
<th>% stop/review date doc</th>
<th>% prescription by guidelines</th>
<th>% without local guidelines &gt;24hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>5</td>
<td>12</td>
<td>50</td>
<td>70.4</td>
<td>36.6</td>
<td>67.9</td>
<td>26.7</td>
</tr>
<tr>
<td>West/central Asia</td>
<td>9</td>
<td>27</td>
<td>43.8</td>
<td>72.8</td>
<td>19.8</td>
<td>66.3</td>
<td>40.5</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>13</td>
<td>53</td>
<td>39</td>
<td>69.5</td>
<td>29.1</td>
<td>70.8</td>
<td>29.6</td>
</tr>
<tr>
<td>North America</td>
<td>2</td>
<td>24</td>
<td>38.6</td>
<td>84.9</td>
<td>39.6</td>
<td>85.8</td>
<td>18.5</td>
</tr>
<tr>
<td>East &amp; south Asia</td>
<td>6</td>
<td>29</td>
<td>37.2</td>
<td>74.6</td>
<td>43.5</td>
<td>81.5</td>
<td>21.4</td>
</tr>
<tr>
<td>Oceania</td>
<td>2</td>
<td>9</td>
<td>37</td>
<td>85.1</td>
<td>27</td>
<td>73.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Latin America</td>
<td>4</td>
<td>19</td>
<td>36.8</td>
<td>81.4</td>
<td>40.3</td>
<td>64.1</td>
<td>19.9</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>5</td>
<td>36</td>
<td>34.4</td>
<td>81.4</td>
<td>51.6</td>
<td>83.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Western Europe</td>
<td>5</td>
<td>118</td>
<td>28.1</td>
<td>80.5</td>
<td>40.3</td>
<td>78.7</td>
<td>10.1</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>2</td>
<td>8</td>
<td>27.4</td>
<td>64.3</td>
<td>50.5</td>
<td>85.7</td>
<td>19.2</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>335</td>
<td>34.4</td>
<td>76.9</td>
<td>38.3</td>
<td>77.4</td>
<td>19.2</td>
</tr>
</tbody>
</table>

Lancet Glob Health 2018; 6: e619–29
Global Antimicrobial Point Prevalence Survey: Patterns of use

Proportion of prescribed antibiotics for systemic use (ATC4 level, N=36,792) among adult inpatients in 2015, by region
PPS: Prescription quality among adult inpatients in Nigeria and Ghana

**Nigeria** (prescription rate 69.7%)
4 tertiary hospitals - Lagos, Oyo, Abuja, Kaduna

**Ghana** (prescription rate 64%)
1 tertiary hospital (Kumasi)

A point prevalence survey of antimicrobial prescribing in four Nigerian Tertiary Hospitals. Ann Trop Pathol 2017;8:42-6

Non-prescription use of antimicrobials in the general population

Global trend of antimicrobial use in food animals

- More than 73% of all antimicrobials sold in the world are used in animals.

- Five countries with the greatest projected % increases in consumption by 2030:
  - Myanmar (205%)
  - Indonesia (202%)
  - Nigeria (163%)
  - Peru (160%)
  - Vietnam (157%)
<table>
<thead>
<tr>
<th>Sn</th>
<th>Determinants</th>
<th>Prescriber</th>
<th>Dispenser</th>
<th>Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lack of knowledge on antibiotics and therapeutics</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>Lack of trust in or delayed laboratory results</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Desire to meet patient demand</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fear of clinical failure, desire to stay on safe side</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Economic incentives/considerations</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6</td>
<td>Unstable or inadequate drug supply/quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Inappropriate peer norm / poor modeling by seniors or local physicians</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Marketing influences</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>9</td>
<td>Folk beliefs and traditions on antibiotic use</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>10</td>
<td>Lack of regulation and enforcement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Unclear role as health care providers</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>12</td>
<td>Use of trained and untrained sources of advice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Unrestricted access to antimicrobials</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Lack of access to appropriate health care</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>15</td>
<td>Diagnostic uncertainty</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Inadequate supervision/audits</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Low antibiotic resistance risk perception</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Availability and left-over antimicrobials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Inadequate awareness, acceptance and application of guidelines</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Inadequate ID/drug specialists</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

[http://apps.who.int/medicinedocs/en/m/abstract/Js16782e/](http://apps.who.int/medicinedocs/en/m/abstract/Js16782e/)
Consequences of irrational use of anti-infective medicines

- Emergence of drug resistant infections
- Clostridium difficile infection
- Increase cost of healthcare
- Poor health outcomes

Prolonged use of broad-spectrum antibiotics strongly associated with CDI

Unnecessary antibiotic use responsible for $163 million in potentially avoidable hospital costs in USA

*Journal of Antimicrobial Chemotherapy (2009) 63, 1272–1275*
Antibiotic use is associated with resistance

A systematic review of 243 studies showed a strong association between antibiotic use and resistance

Bell et al. BMC Infectious Diseases 2014, 14:13
The goal of rational use is not always to reduce antimicrobial use, but to ensure that the use is appropriate.

Many low- and middle-income countries struggle with limited access to antimicrobial, which can also drive inappropriate use.
WHO access, watch, reserve (AWaRe) strategy

- To improve access to life saving antimicrobial medicines and prevent resistance;
  - WHO in 2017 revised the Model List of Essential Medicines, where antibiotics were grouped into three AWaRe categories: Access, Watch and Reserve

WHO recommends country-level target of at least 60% of antibiotic consumption being from medicines in the Access Group. This indicator was included to monitor access to essential medicines and progress towards UHC.
The Access, Watch and Reserve Lists

**ACCESS**
- amoxicillin
- amoxicillin + clavulanic acid
- ampicillin
- benzathine benzylpenicillin
- benzylpenicillin
- cefalexin / cefazolin
- chloramphenicol
- clindamycin
- cloxacinilin
- doxycycline
- gentamicin / amikacin
- metronidazole
- nitrofurantoin
- phenoxymethylpenicillin
- procaine benzylpenicillin
- spectinomycin
- sulfamethoxazole + trimethoprim

**WATCH**
- azithromycin*
- cefixime*
- cefotaxime*
- ceftriaxone*
- ciprofloxacin*
- clarithromycin*
- piperacillin + tazobactam*
- meropenem*
- vancomycin*

* denotes antibiotics which are also in the Watch group

**RESERVE**
- Aztreonam
- Cephalosporins, 4th Generation (e.g. cefepime)
- Cephalosporins, 5th Generation (e.g. ceftaroline)
- Daptomycin
- Fosfomycin (IV)
- Oxazolidinones (e.g. linezolid)
- Polymyxins (e.g. colistin, polymyxin B)
- Tigecycline
Global antibiotic consumption belonging to WHO Access group

Total consumption belonging to Access antibiotics

-50%  50-60%  +60%

All other countries are not tracking antibiotic consumption, a key step in containing AMR

WHO 12 core components to promote the rational use of medicines

1. A mandated multi-disciplinary national body to coordinate medicine use policies
2. Clinical guidelines
3. Essential medicines list based on treatments of choice
4. Drugs and therapeutics committees in districts and hospitals
5. Problem-based pharmacotherapy training in undergraduate curricula
6. Continuing in-service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff
Overall, effective strategies address the barriers to rational use of anti-infective medicines.

Two major areas to target:
- Reduction of frequency of usage of anti-infective medicines through:
  - Preventing of infection
  - Alternatives to antibiotics/New antibiotics
- Appropriate sales, dispensing, prescription and use of anti-infective medicines
Prevention of infection

• Improve water, sanitation and hygiene activities
• Implement infection and prevention control in hospitals
• Waste management
• Vaccination and immunization
• Food hygiene and safety
• Improve nutrition
• Health education, risk communication, behavior change communication
• Sustainable development
WHO priority pathogens list for R&D of new antibiotics

**Priority 1: CRITICAL**
- Acinetobacter baumannii, carbapenem-resistant
- Pseudomonas aeruginosa, carbapenem-resistant
- Enterobacteriaceae, carbapenem-resistant, ESBL-producing

**Priority 2: HIGH**
- Enterococcus faecium, vancomycin-resistant
- Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
- Helicobacter pylori, clarithromycin-resistant
- Campylobacter spp., fluoroquinolone-resistant
- Salmonellae, fluoroquinolone-resistant
- Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

**Priority 3: MEDIUM**
- Streptococcus pneumoniae, penicillin-non-susceptible
- Haemophilus influenzae, ampicillin-resistant
- Shigella spp., fluoroquinolone-resistant

ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT

• Others
  • Quorum Sensing inhibitors
  -quorum sensing inhibitors simply attenuate bacterial virulence
Optimize use of anti-infective medicines through antimicrobial stewardship

• What is antimicrobial stewardship?

• The optimal selection, dosage and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance

• Organizational or healthcare system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness

• THE RIGHT
  • The right antibiotic for the right patient
  • At the right time
  • With the right dose
  • And the right route
  • Causing the least harm to the patient and future patients
• Overarching goals fall under the following categories
  • Improve patient care and outcomes
  • Reduce collateral damage and
  • Impact costs

## Core Elements of Hospital Antibiotic Stewardship Programs

### Table

**CDC’s seven core elements of antimicrobial stewardship**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Leadership commitment</td>
</tr>
<tr>
<td>2</td>
<td>Accountability</td>
</tr>
<tr>
<td>3</td>
<td>Drug expertise</td>
</tr>
<tr>
<td>4</td>
<td>Action</td>
</tr>
<tr>
<td>5</td>
<td>Tracking</td>
</tr>
<tr>
<td>6</td>
<td>Reporting</td>
</tr>
<tr>
<td>7</td>
<td>Education</td>
</tr>
</tbody>
</table>
Types of interventions
- Persuasive
- Restrictive
- Pharmacy-driven
- Infection-driven
- Broad
Gold standard for detection of organisms (culture) is time consuming – may take 48-72 hours or even longer.

Without laboratory diagnosis antibiotic prescription is empirical and may be inappropriate.

A good rapid diagnostic tests should:

- Rapidly detect pathogen
- Detect multiple pathogens simultaneously
- Speciate pathogen
- Determine antimicrobial susceptible and resistant strains
- Be highly sensitive and specific
- Distinguish active from non-active infection
- Simple

Promoting rapid laboratory diagnosis

- Acute phase proteins
- C-Reactive Protein
- Procalcitonin
- Nucleic acid based
- NAAT
- Microarrays
- PNA FISH
- Next generation sequencing
- Non-nucleic acid based
- T2MR
- MALDI-TOF
Technology and anti-microbial stewardship

- Technology driven education
  - OpenWHO https://openwho.org/courses/AMR-competency
  - WHO antibiotic game
  - Other serious games

- Measuring antibiotic consumption
  - Antimicrobial use calculator https://amu-tools.org/amctool/amctool.html

- Electronic health records
  - Antimicrobial data review, management and reporting

- Clinical decision support system
  - Gamified Antimicrobial Stewardship (AMS) decision support app for prescribing behaviour change (GADSA)
  - Others- TheraDoc (Premier), SafetySurveiller (Premier), MedMined (CareFusion) etc

- Artificial intelligence

- Telehealth
Advancing antimicrobial stewardship through electronic health records and clinical decision support system
Challenges of rational antimicrobial use in Nigeria

- Lack of coordination of, and comprehensive national reports on national antimicrobial consumption
- Lack of antimicrobial stewardship in both private and public sectors
- Guidelines on antimicrobial use in humans/animals are outdated, poorly disseminated and not adhered to
- Underfunded regulatory agencies with weak pharmacovigilance of anti-infectives
- High level of counterfeit medicines in circulation
- Unregistered practitioners and prescription of antimicrobial by unlicensed persons
- Poor coordination of research on antimicrobial use
- Funding and political will are lacking.
Nigeria’s national response to antibiotic use and AMR (NCDC)

- Strategic objectives:
  - Increase awareness and knowledge on AMR and related topics
  - Building a one health AMR surveillance system
  - Intensifying infection prevention and control in the tripartite sectors
  - Promoting rational access to antimicrobials and antimicrobial stewardship
  - Investing in AMR research and development
<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>STRATEGIC INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.1 Improve access to quality antimicrobial agents for infections in humans and animals</strong></td>
<td>4.1.1 Promote optimal procurement and distribution of quality antimicrobials and diagnostics for human and animal use</td>
</tr>
<tr>
<td></td>
<td>4.1.2 Enhance local production of quality antimicrobial agents and diagnostics for human and animal use</td>
</tr>
<tr>
<td></td>
<td>4.1.3 Expand NHIS coverage to include more enrollees</td>
</tr>
<tr>
<td><strong>4.2 Promote antimicrobial stewardship in human and animals</strong></td>
<td>4.2.1 Promote the use of up to date treatment guidelines and ensure prudent use in humans and animals</td>
</tr>
<tr>
<td></td>
<td>4.2.2 Promote optimal prescribing and dispensing of antimicrobials in humans and animals</td>
</tr>
<tr>
<td><strong>4.3 Strengthen regulatory agencies across all sectors (humans, animals and environment) to enable them perform their mandate with regards to antimicrobials</strong></td>
<td>4.3.1 Strengthen the capacity of regulatory agencies across ‘One Health’ sectors (i.e. human, animals, food products and environment)</td>
</tr>
<tr>
<td></td>
<td>4.3.2 Enhance inter-sectoral coordination and collaboration between/amongst regulatory agencies</td>
</tr>
</tbody>
</table>
Common errors and misconceptions about antibiotics use

- Using antibiotics for cold and flu infection
- Treating the microbiology report instead of the patient
- Treating asymptomatic self-limiting infection
- Treating colonization and contamination instead of an infection
- Undue preference for IV over oral antibiotics
- Failing to give narrow spectrum after culture result is available
- Failing to prescribe antibiotics for defined duration
- Undue preference for prolonged antibiotic duration (≥7 days)
- Failing to review the nurses chart
- Failing to stop antibiotics when it is not required
- Failing to realise that antibiotics resistance can occur without prior history of ingestion of antibiotics
Conclusion

• Promoting rational use of anti-infective medicines is a collective responsibility

• Interventions to promote rational use of medicines should target users, prescribers, dispensers and the health system in a one health approach

• The overall goal is to ensure continuity of successful treatment of infections with effective and safe medicines that are quality-assured, used in a responsible manner and available to all those who need them
Thank you for listening

MINDME
The Antimicrobial Creed

**M** microbiology guides therapy wherever possible
**I** indications should be evidence based
**N** narrowest spectrum required
**D** dosage appropriate to the site and type of infection
**N** minimise duration of therapy
**D** ensure monotherapy in most cases