How to improve/decrease global antibiotic consumption
Dilip Nathwani; Ninewells Hospital and Medical School, Dundee, UK
OUTLINE OF PRESENTATION

• The scale of the problem
• The impact of the problem
• Potential solutions
The failing machinery
More than 70 years of antibiotic use
 Millions of tons

Little investment in new antibiotics
# A Sense of Perspective

<table>
<thead>
<tr>
<th>Where used</th>
<th>Types of Use</th>
<th>Questionable use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human (50%)</td>
<td>20% Hospital</td>
<td>20-50% unnecessary</td>
</tr>
<tr>
<td></td>
<td>80% Community</td>
<td></td>
</tr>
<tr>
<td>Animal (50%)</td>
<td>20% Therapeutic</td>
<td>40-80% highly questionable</td>
</tr>
<tr>
<td></td>
<td>80% Prophylaxis/growth promotion</td>
<td></td>
</tr>
</tbody>
</table>

Wise et al. BMJ 1999; 317: 609-610
Australia vs. The World

Total outpatient antibacterial use in the United States and 27 European countries in 2004


Slide from Stephan Harbarth
"The more we use them the more we lose them"
THE MULTI-DIMENSIONAL APPROACH

ANTIBIOTIC ECOSYSTEMS

- Human medicine
  - Community
  - Hospital

- Veterinary medicine
  - Animal feed additives

- Agriculture
  - Plant protection

Environment
Disease treatments and medical procedures under serious threat

- Blood infections
- Care of preterm children
- Gonorrhea
- Major surgical procedures
- Safe child deliveries
- Antibiotic Resistance
- Surgical infections
- Trans-plantations
- Pneumonia
- Cancer treatment
- Typhoid fever
Sepsis in newborns in five countries in South Asia (India, Pakistan, Afghanistan, Nepal, Bangladesh)

One child dies every five minutes because the antibiotics given are not effective due to bacterial resistance

Zulfiqar Bhutta presentation at ReAct conference Sep. 2010
Antibiotic Resistance

Caused by human activity and by over-consumption of a global resource

A failure of public policy & global governance, research, prioritization and the current market system

It is a collective responsibility by governments, super national organizations and individuals to take action

Nasa 1969: Earthrise over the moon from Apollo
The EU-US Summit Declaration called for the establishment of “…a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us”.

WAAMDRO: jeancarlet@gmail.com
WHO 2011 policy

- 3. Ensure uninterrupted access to essential medicines of assured quality
  - a. Reinforce the system for supply of essential medicines
  - b. Assure the quality of drugs according to international standards

- 4. Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care
  - a. Promote and enforce standard treatment guidelines
  - b. Enforce prescription-only use of antimicrobials
  - c. Promote education on antimicrobial medicines and their use
  - d. Reduce antimicrobial use in food-producing animals

- e. Work to reduce financial incentives that encourage irrational use of medicines
Chennai Declaration holds key for antibiotic resistance

1 Tip to Shed 9lbs Weekly - Cut 9 pounds of stomach fat every week by using this 1 weird old tip
www.thehealthandwellness.com/diet

AARTI DHAR

Its recommendations could become the backbone of a national policy, says international expert Professor Goossens

Indian medical experts and politicians reacted emotionally to the international uproar caused over two years ago by a study of the extent of antimicrobial resistance.

This response even stalled the discussion on antibiotic resistance in India; the scientific repercussions were equally damaging as Indian researchers could neither collaborate nor share samples, bacterial isolates or data with international groups, the latest edition of The Lancet Infectious Diseases says.

FELT ‘EXPOSED’

According to an article in the British medical journal, politicians and physicians felt “very exposed” after the publication of the study by Karthikeyan Kumarsamy and his colleagues in the Lancet in 2010 on the possible implications of multidrug-resistant organisms such as Escherichia coli harbouring NDM-1.

Though the data from this study should have stimulated widespread discussion on resistance in India and the rest of the world, the debate that followed was skewed towards the effects on health tourism.
Antimicrobial stewardship: A collaborative partnership between infection preventionists and health care epidemiologists

Julia Moody MS, SM(ASCP)\textsuperscript{a,b}, Sara E. Cosgrove MD, MS\textsuperscript{b}, Russell Olmsted MPH, CIC\textsuperscript{c}, Edward Septimus MD, FACP, FIDSA, FSHEA\textsuperscript{d}, Kathy Aureden MS, MT (ASCP)\textsuperscript{e}, CIC\textsuperscript{f}, Shannon Oriola BSN, RN, CIC, COHN\textsuperscript{g}, Gita Wasan Patel RPh, PharmD, BCPS\textsuperscript{h}, Kavita K. Trivedi MD\textsuperscript{h}

\textsuperscript{a}Workgroup Chair, HCA, Inc., Nashville, TN
\textsuperscript{b}George Washington University Medical Institutions, Baltimore, MD, SHEA Advisor
\textsuperscript{c}Trinity Health, Ann Arbor, MI, 2011 APIC President
\textsuperscript{d}HCA, Inc., Nashville, TN, SHEA Advisor
\textsuperscript{e}Sherman Hospital, Elgin, IL
\textsuperscript{f}Sharp Metropolitan Medical Center, San Diego, CA
\textsuperscript{g}HCA Supply Chain Services, Dallas, TX
\textsuperscript{h}Center for Health Care Quality, California Department of Public Health

APIC-SHEA Position Paper

and WHO are leading voices working towards an international solution with a three-pronged focus: 1) optimizing use of existing...
Global survey by continent

662 returns validated returns worldwide

Howard & Nathwani on behalf Of ESGAP/ISC ECCMID 2013
What are the three key objectives for your current or planned antimicrobial stewardship programme?

- Reduce Clostridium difficile infection and other healthcare acquired infection: 92.6%
- Improve clinical outcomes: 59.3%
- Reduce amount of antibiotic prescribing: 47.2%
- Reduce or stabilise resistance: 45.4%
- Prevent unintended harm: 24.1%
- Reduce cost: 18.5%
- Reduce mortality: 4.6%
- Reduce length of stay: 2.8%

AMS Programme:
- 78% yes
- 17% planned
- 5% don’t
GLOBAL STEWARDSHIP SURVEY
2012: Barrier’s

Howard P, Nathwani D et al ECCMID 2013, POSTER 2448

Barriers to providing a planned AMS Programme

- Lack of funding/people (Planned ASP)
- Higher priorities (Planned ASP)
- Admin not aware (Planned ASP)
- Prescriber opposition (Planned ASP)
- Lack of IT (Planned ASP)
- No barriers (Planned ASP)

Regions:
- Oceania
- South America
- North America
- Europe
- Asia
- Africa

Percentage of barriers:
- Lack of funding/people: 29%
- Higher priorities: 23%
- Admin not aware: 34%
- Prescriber opposition: 32%
- Lack of IT: 29%
- No barriers: 20%
- Other regions and barriers not specified in the image.
What is Antimicrobial Stewardship? Messages for the medical profession

- An activity that optimises antimicrobial management and includes selection, dosing, route and duration of antimicrobial therapy and prophylaxis
- Also include clinical infection management and improving clinical outcomes: “beneficience”
- Selection of antimicrobials from each class of drugs that does the least collateral damage e.g. MRSA, ESBLs, C. difficile and does not cause unintended harm [more complications, toxicity, mortality] : “maleficience”
- Appropriate de-escalation when culture results are available
- Marriage of infection control and infection management - “team working” with shared goals
- Need for clinical and organisational leadership & measurement

Impact of Stewardship on SAFETY?

The reductions in antimicrobial utilization associated with stewardship interventions have not been associated with any worsening in nosocomial infection rates, length of stay or mortality among intensive care patients.”

• “Stewardship interventions were associated with … fewer antibiotic adverse events.”

Vancomycin use rates reduced by 40% in two neonatal ICUs after introduction of a vancomycin use guideline.

“Causes of infection, duration of bacteremia, and incidence of complications or deaths attributable to late-onset infection did not change significantly.”

WHO 2011 policy

• 3. Ensure uninterrupted access to essential medicines of assured quality
  - a. Reinforce the system for supply of essential medicines
  - b. Assure the quality of drugs according to international standards

• 4. Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care
  - a. Promote and enforce standard treatment guidelines
  - b. Enforce prescription-only use of antimicrobials
  - c. Promote education on antimicrobial medicines and their use
  - d. Reduce antimicrobial use in food-producing animals
    - (i) Provide national leadership and promote intersectoral collaboration
    - (ii) Create and enforce an enabling regulatory framework
    - (iii) Strengthen surveillance and monitoring
    - (iv) Promote education and training on antimicrobial use in food-producing animals
    - (v) Reduce the need for antimicrobials through better animal husbandry
  - e. Work to reduce financial incentives that encourage irrational use of medicines
Non-prescription use occurred worldwide and accounted for 19–100% of antimicrobial use outside of northern Europe and North America.

Daniel J Morgan, Iruka N Okeke, Ramanan Laxminarayan, Eli N Perencevich, Scott Weisenberg

Non-prescription antimicrobial use worldwide: a systematic review

The Lancet Infectious Diseases Volume 11, Issue 9 2011 692 - 701

http://dx.doi.org/10.1016/S1473-3099(11)70054-8
Strategies to Curb Resistance in Belgium

- **Seven multimedia campaigns to promote the prudent use of antibiotics in outpatients**
- Two national campaigns to promote hand hygiene in hospitals
- Antibiotic management teams in ALL Belgian hospitals
- Several practice guidelines
- Antibiotic guide for ambulatory care
- Improve infection control practices (better financing and clear organisation)
- Finance surveillance programmes on antibiotic use and resistance in humans and animals
Suggested logo/slogan

COLD? FLU?
TAKE CARE
NOT ANTIBIOTICS

An initiative of the European Union
Antibiotic Stewardship
Essential: All Healthcare facilities
A PATIENT SAFETY PRIORITY

• Clear vision with aims, objectives and measurables [identify quick wins, focus] – identify benefits to all key stakeholders – consider the patient voice
• AM organisational and clinical leadership, accountability, structure and organisation [networks of support- local, regional and national]
• Operational multi-disciplinary stewardship team with clinician champion
• Key effective intervention tools adopted for local needs, geography, organisation and resource [key is to reduce diagnostic uncertainty]
• Measurement [improvement v judgement’s scrutiny, external inspection, feedback
• Education: face to face, e-learning, reflective learning in the workplace
• Communication
COMMUNICATION: KEY IN EFFECTIVE STEWARDSHIP
Organisation and structures for antimicrobial stewardship

INTEGRATED NETWORKS
Evidence based interventions including Antibiotic Stewardship program in Vietnamese hospitals.

1. Indicators
   • antibiotic use,
   • resistance,
   • health care associated infections
   • infection control

2. Improved Susceptibility Testing

3. Antibiotic Stewardship groups 16 hospitals
Driver Diagram for Antimicrobial stewardship

What Type of Intervention?

Davey et al Cochrane review  EID 2006

- Structural
- Healthcare system (restrictive)
- Reminders
- Audit and feedback
- Patient-mediated interventions
- Local opinion leaders
- Educational outreach visits
- Educational meetings
- Distribution of educational materials

Ambulatory (n=40)
Hospital (n=106)
Antimicrobial Stewardship Toolkit:

Quality of Evidence to support interventions

- Prospective audit with intervention and feedback A1
- Education BIII [Education with an active intervention AIII]
- Formulary restriction and pre-authorisation
  - AII for rapid decrease in antibiotic in use
  - BII for control of outbreak
  - BII/III may lead to unintended increase in resistance
- Guidelines and clinical pathways AII
  - With education and feedback on outcomes AIII
- Antimicrobial cycling CII
- Antimicrobial order forms BII
- Combination therapies CII
  - In critically unwell patient with high risk of MDRO AII
- De-escalation-review AII
- Dose optimisation AII
- Parenteral to oral conversion AIII
- Computerised decision support, surveillance BII
- Laboratory surveillance and feedback BII

Adapted from Dellit et al. Clinical Infectious Diseases 2007; 44:159-77
ASP’s are cost-effective

• Non computerised ASP programme for improving appropriateness of treatment of BSI’s $2367 /QALY

• Beta-blockers for treatment of myocardial infarction $4500/ QALY

• Screening middle aged men for hypertension $1600 / QALY

• Use of drive side airbags $24000/QALY
General workflow schematic for a two-step prospective audit and feedback strategy as well as formulary restriction and preauthorization strategy for antimicrobial stewardship.

Chung GW et al. Antimicrobial stewardship: A review of prospective audit and feedback systems and an objective evaluation of outcomes
Longevity of Value of Interventions Mean and 95% CI; Restrictive – Persuasive [Cochrane review update 2013]
THE HIGH COST OF POOR DIAGNOSIS

Lack of diagnosis

No treatment

Individual health
- Continued illness
- Mis- or over-treatment
- Drug side effects

Public health
- Continued transmission
- Waste of resources
- Drug resistance

Overall impact
- Increasing burden of disease
- Breakdown in disease control
- Health system failure

Syndromic treatment
In my patient, urine culture not indicated and antibiotic not needed
Flow diagram for incorporating PCT into clinical practice. Diagnostic criteria and treatment recommendations as per appropriate guidelines.76–78.

“If you cannot measure it, you cannot improve it”

Lord Kelvin, 1824-1907
<table>
<thead>
<tr>
<th>ANTIBIOGRAMMES</th>
<th>(1)x1</th>
<th>(2)x1</th>
<th>(3)x1</th>
<th>(4)x1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acinetobacter baumanii</td>
<td>E.coli</td>
<td>MRSA</td>
<td></td>
</tr>
<tr>
<td>Penicilline G</td>
<td></td>
<td></td>
<td>RESIST</td>
<td>RESIST</td>
</tr>
<tr>
<td>Flucloxacilline</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
<td></td>
</tr>
<tr>
<td>Amoxicilline</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
<td></td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>INTERM</td>
<td>RESIST</td>
<td>RESIST</td>
<td></td>
</tr>
<tr>
<td>Piperacilline</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
<td></td>
</tr>
<tr>
<td>Piperac.+tazob</td>
<td>RESIST</td>
<td>RESIST</td>
<td>INTERM</td>
<td></td>
</tr>
<tr>
<td>Cefalotine</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
</tr>
<tr>
<td>Cefoxitine</td>
<td>RESIST</td>
<td>RESIST</td>
<td>S</td>
<td>RESIST</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>INTERM</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
</tr>
<tr>
<td>Cefepime</td>
<td>INTERM</td>
<td>RESIST</td>
<td>RESIST</td>
<td>RESIST</td>
</tr>
<tr>
<td>Imipenem</td>
<td>S</td>
<td>INTERM</td>
<td>S</td>
<td>RESIST</td>
</tr>
<tr>
<td>Aztreonam</td>
<td></td>
<td></td>
<td></td>
<td>RESIST</td>
</tr>
<tr>
<td>Amikacine</td>
<td>RESIST</td>
<td>S</td>
<td>RESIST</td>
<td>INTERM</td>
</tr>
<tr>
<td>Gentamicine</td>
<td>RESIST</td>
<td>RESIST</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Tobramycine</td>
<td></td>
<td>RESIST</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Norfloxacine</td>
<td>RESIST</td>
<td>RESIST</td>
<td>S</td>
<td>RESIST</td>
</tr>
<tr>
<td>Ciprofloxacine</td>
<td></td>
<td>RESIST</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Clindamycine</td>
<td></td>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Erythromycine</td>
<td></td>
<td></td>
<td>RESIST</td>
<td></td>
</tr>
<tr>
<td>Acide fusidique</td>
<td></td>
<td></td>
<td></td>
<td>RESIST</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>RESIST</td>
<td>RESIST</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Fosfomycine</td>
<td></td>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Rifampicine</td>
<td></td>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Vancomycine</td>
<td></td>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Teicoplanine</td>
<td></td>
<td></td>
<td></td>
<td>S</td>
</tr>
</tbody>
</table>

Is this patient in your ICU?
Can you treat his infection?
Can you prevent cross-infection?
DEVELOPMENT OF QUALITY METRICS FOR ASP’S THROUGH A MODIFIED DELPHI TECHNIQUE
ICHE 2012; 33[3]: 500-506

- **ANTIMICROBIAL CONSUMPTION MEASURES**
  - Days of therapy per 1000 patient day

- **ANTIMICROBIAL RESISTANCE MEASURES**
  - No of patients with specific drug resistant organism/total number of patients admitted to ward/unit

- **PATIENT OUTCOME MEASURES**
  - Mortality related to AR pathogens
  - Conservable days of therapy among CAP, SSTI, BSI & sepsis
  - Unplanned hospital readmission within 30 days after hospital discharge

ACCOUNTABILITY MEASURES/PUBLIC REPORTING

QI MEASURES/INTERNAL USE
Summary
Antibiotic Stewardship in developed, developing and emerging nations

**Surveillance**
- Antibiotic use and precision
- Resistance
- Health care associated infections

**Decrease the need for antibiotics**
- Reduce disease incidence
- Prevent spread of bacteria

**Use antibiotics properly**
- Improve diagnostics
- Improve dosing, length of treatment
- Improve review of prescribing & microbiology

**Infection control**
- Improved hand disinfection
- Prevent health care associated infections

**Coordinate national activities**

**Knowledge education, information research**

**International collaboration**
Antimicrobial Stewardship in Hospitals, ESCMID Postgraduate Education Course
25 - 26 April 2013, Zeuthen near Berlin, Germany