Planning for Stewardship Interventions and Appropriate Use of Antibiotics: Guidelines

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Objectives

- Objectives:
  - Understand evidence based measures for appropriate use of antibiotics
  - Understand planning for stewardship interventions/guidelines
  - Understand facilitators, barriers for antiimicrobial stewardship in LMIC

Areas where antibiotic use can be improved

- Overprescribing
- Too broad spectrum
- Too many antibiotics or fixed dose combinations
- Wrong dose, wrong interval, wrong route
- Wrong duration
- Too slow (not started soon enough)

Intervention options

- Education
- Guidelines (include surgical, outpatient)
- Pre prescription review and restrictions
- Post prescription review (48 to 72 hrs)
- The “Time out” (48 to 72 hrs)
- Stop orders
- De escalation, redundant therapy
- IV to oral conversion
- Optimize dosing
- Ward rounds
- Audit and feedback
- Vendor restriction
- Use of EMR/ how IT can be of benefit
- Duration
- Allergy evaluation
- Regulatory

Core Elements of Hosptial Antimicrobial Stewardship Programmes

- Senior hospital management leadership supports
  - Identified as a priority and included in key performance indicators
  - Has dedicated support, follow national or international standards
- Accountability and responsibilities
  - Hospital has a formal/written antimicrobial stewardship programme/strategy
  - Hospital has a formal organizational multidisciplinary structure
  - Healthcare professional identified as a leader, roles responsibilities clearly defined
- Available support and expertise on infection management
  - Access to timely laboratory/imaging/IT services
  - Access to, trained and experienced professionals in infection management
- Education and practical training
  - Hospital offers a range of educational resources
  - Antimicrobial stewardship team members receive regular training in antimicrobial prescribing and stewardship

Pulcini C, et al., Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach, Clinical Microbiology and Infection (2018), https://doi.org/10.1016/j.cmi.2018.03.033

Core Elements of Hospital Antimicrobial Stewardship Programmes

- Formulary and Guidelines and Audit
  - Hospital has an antimicrobial formulary and if drugs are unrestricted, restricted
  - Hospital has recommendations for infection management
  - Hospital has a written policy that requires prescribers to document antimicrobial use
  - Antimicrobial stewardship team reviews/audits courses of therapy for specified antimicrobial agents or clinical conditions
  - Advice from antimicrobial stewardship team members is easily available to prescribers
  - Regular infection and antimicrobial prescribing focused ward rounds
- Hospital Monitoring and surveillance
  - Monitors quality/quantity of antimicrobial use at the unit and/or hospital wide level
  - Monitors compliance with specific interventions put in place by the stewardship team
  - Monitors antibiotic susceptibility rates for key bacteria

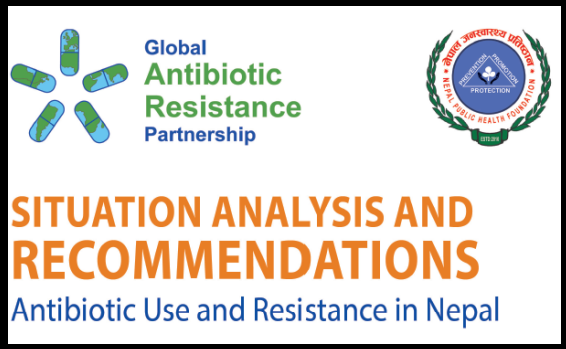
Pulcini C, et al., Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach, Clinical Microbiology and Infection (2018), https://doi.org/10.1016/j.cmi.2018.03.033

Antimicrobial Stewardship in Low and Middle-Income Countries: The Contextualization

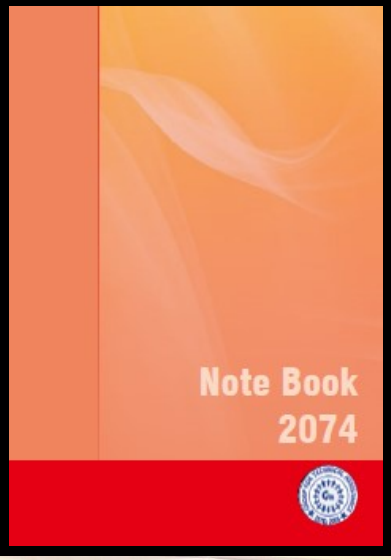
- Diagnostic challenges
  - High burden of infectious diseases and often limited laboratory capacity
- Knowledge and awareness
  - Health care workers prescribing antibiotics with different backgrounds, lack of information on antibiotic use. Guidelines limited by lack of locally applicable high level evidence.
- Access to quality assured antibiotics
  - Many LMIC have poorly regulated or limited access to essential antibiotics, non prescribed use, variable financial incentives
- Health care facilities often have limited infrastructure
  - Lack of infrastructure and equipment, availability of interdisciplinary personnel
- The road ahead
  - Local examples, initiatives at the facility and community level
  - National and international initiatives
  - WHO GAP sets out a roadmap needed to combat AMR
  - The WHO antimicrobial stewardship toolkit, plan for evaluation of feasibility in LMIC

HFHS International AMR work

- South America, Nepal, Micronesia, India
- Post prescription optimization to reduce unneeded antibiotics



Guidelines


Note Book
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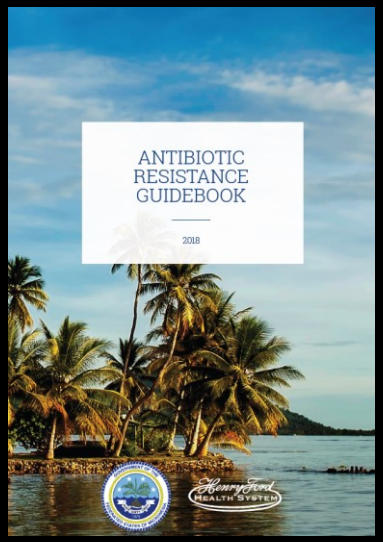

ANTIBIOTIC
RESISTANCE
GUIDEBOOK
2018
Henry Ford
HEALTH SYSTEM


Assessing and promoting antimicrobial
stewardship in Kathmandu Model Hospital and
its catchment areas in Nepal
KICK OFF MEETING
November 2016
ANTIBIOTICS


EXIT

Guidelines

- Evidence based standard recommendations
- Based on
  - Local antibiotic resistance patterns (antibiogram)
  - What agents are available
  - What agents are cost effective
- Develop with broad base consensus
  - Develop as a process to involve others
- Available at point of care
- Keep it simple!!

Guideline Content

- Empiric antibiotic selection
  - Organism and disease state specific
- Definitive antibiotic selection
  - Organism and disease state
- IV to oral conversion
- Renal dosing
- Duration of therapy

Purpose of Guidelines

- Improve patient outcome & quality of care
- Reduce inappropriate variation on practice
- Encourage proven treatments
- Educate providers
- Improve efficiency of healthcare

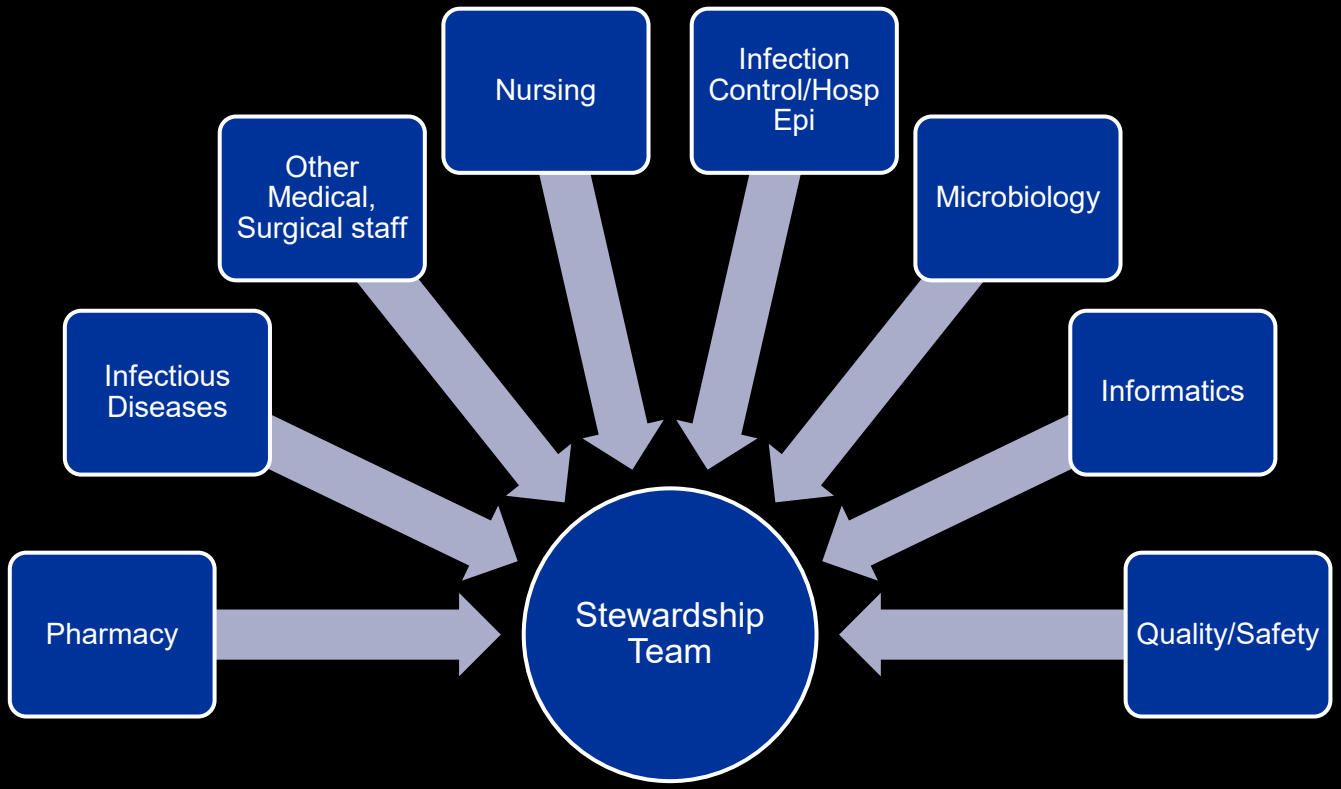
Outcomes of Guidelines

Good Outcomes	Bad Outcomes
• Improve quality and consistency of care	• Cost increase with no improved effectiveness
• Reduce morbidity and mortality	• Time & resources directed away from other important priorities
• Improve health outcomes	• Compromised operating efficiency
• Minimize non-evidence-based, wasteful practice	

Difference between guideline/pathway

Characteristic	Guideline	Pathway
Scope	Generic recommendations	Details local structures, systems, and timeframe
Format	Flexible, may include a pathway	Diagram or flow-chart with defined decision-points
Resources	Literature review or external guideline Local data	Guideline or systematic review data Internal forms, processes, alert systems, committees, personnel

Multidisciplinary Collaboration



The Development Team- The Heart of your Guideline

Building Your Guideline

- Prioritize
- Gather best data
- Assemble the team
- Make it pretty / formatting, parts
- Roll out
- Evaluate/measure

Choosing your topic

- Conserve resources (high-cost agents, drug shortages)
- Local priorities (Microbiology/Infection Control targets, Medication Use Evaluation results)
- Inappropriate Variances (Core measures, Costs)
- Known interventions that improve outcome (documented evidence)
- Feasible (no new resources required)

What Evidence Do You Need/Have?

Type Of Evidence	OPAT	Presumptive Candidiasis	Abx Restriction
National Guideline (or Cochrane review)	✓	✓	✓
High quality RCT or meta-analysis		✓	✓
Local Drug Utilization Pattern			
Local Microbiology			
Local Disease Incidence			

Accessorize Important Elements of a Guideline

- Key Decisions & Their Consequences
- Review of relevant evidence (Benefits, risks and costs)
- Concise, Accessible Format

How Do You Change Behavior?

- Electronic alerts, forcing functions
- Peer – to – peer education
- Audit and feedback
- Communicate, communicate, communicate

Important Steps for Guideline Communication

- Alerts in order entry system/Other IT programming
- Memos, Newsletters
- Posters
- Grand rounds
- Huddles, informal departmental meetings
- When do you bring in the Public Relations experts?

Monitor and Report

- Specify metrics at initiation
- Feasible to show improvement
  - Measurable within existing infrastructure
  - Associated with strong evidence
- Reporting Structure
  - To whom?
  - How often?

Proposed Guidelines

- Empiric Antibiotic Therapy
- Definitive Antibiotic Therapy
- Duration of Antibiotic Therapy by Indication
- IV to PO conversions
- Renal Dosing Guidelines

Empiric Antibiotic Therapy-Community Acquired Pneumonia

Diagnosis	Suspected Pathogens	Empiric Therapy
Pneumonia, community-acquired Inpatient therapy	*S. pneumoniae, H. influenzae, Mycoplasma* sp., *Chlamydophila* sp., *Legionella* sp.	• Ceftriaxone + azithromycin OR doxycycline • Amoxicillin ± azithromycin

Diagnosis	Suspected Pathogens	Empiric Therapy
Pneumonia, community-acquired Outpatient therapy	*S. pneumoniae, H. influenzae, Mycoplasma* sp., *Chlamydophila* sp., *Legionella* sp. (e.g. atypicals)	• Azithromycin PO For patients with comorbidities: • Amoxicillin + azithromycin PO

Definitive Antibiotic Therapy

- How often are cultures obtained?
- Is this feasible?

Definitive Antibiotic Therapy

Organism	Preferred Therapy (Confirm with susceptibilities)	Alternative Therapy (Depending on allergies and susceptibility)
Escherichia coli	ampicillin, cefazolin, trimethoprim/sulfamethoxazole or ciprofloxacin preferred for oral therapy	Preferred: ceftriaxone or gentamicin ceftazidime, cefepime, ciprofloxacin, piperacillin/tazobactam Oral therapy options: amoxicillin/clavulanic acid, ciprofloxacin, nitrofurantoin (cystitis ONLY)
Extended spectrum beta-lactamase producer	Imipenem or meropenem, piperacillin/tazobactam (if urine source ONLY)	Trimethoprim/sulfamethoxazole
Haemophilus influenzae Beta-lactamase negative Beta-lactamase positive	ampicillin, amoxicillin amoxicillin/clavulanic acid, ceftriaxone	azithromycin, doxycycline, trimethoprim/sulfamethoxazole

Duration of Treatment

- Treating infections longer is not always better

Diagnosis	Duration of Therapy
Intra-abdominal Infection, community-acquired (Cholecystitis, cholangitis, diverticulitis)	4 days with adequate source control

Intravenous to Oral Dose Conversion

For an intravenous to oral conversion, the following criteria must be met:

- **Inclusion Criteria**
- Patient is admitted to a non-intensive care unit (ICU)/general practice unit (GPU)
- Patient has received and is tolerating at least 1 dose of a medication administered enterally or is tolerating an enteral diet
- Patient has received the medication to be converted intravenously for at least 24 hours

- **Exclusion Criteria**
- Patient is admitted to an intensive care unit (ICU) (including ICU step-down or mixed ICU unit)
- Nonfunctioning gastrointestinal tract
  - Gastric obstruction or ileus
- Persistent nausea and vomiting
- Strict NPO (for a procedure or other medical reason)
- Patients receiving treatment for an active GI bleed

Intravenous to Oral Dose Conversion

- **<u>Inclusion Criteria – Anti-Infectives</u>**
- Afebrile (T <38°C, 100.4°F) for at least 24 hours
- Resolving/normalizing WBC (unless on oral or injectable steroids)

- **<u>Exclusion Criteria – Anti-infectives</u>**
- Neutropenia (ANC <1000)
- Endocarditis
- Meningitis or brain abscess
- Clostridium difficile infection
- S aureus bacteremia
- Feeding tubes with intestinal access only (applies to fluoroquinolones only)

Antibiotic Renal dosing

- How are antibiotics usually dosed?

- **Cockroft-Gault Creatinine Clearance Equation**
- **CrCL = $\frac{(140 - \text{Age}) \times \text{weight}}{(72 \times \text{SCr})} \times 0.85$ (if female)**

Antibiotic Renal Dosing - Amoxicillin

Creatinine Clearance (mL/minute)	Standard Regimen	Community-acquired pneumonia (in combination with a macrolide)
> 30	500 mg PO every 8 hours OR 875 mg PO every 12 hours	1000 mg PO every 8 hours
10 to 30	500 mg PO every 12 hours	1000 mg PO every 12 hours
< 10	500 mg PO every 24 hours	500 mg PO every 24 hours
Hemodialysis	500 mg PO every 24 hours, schedule after HD on HD days	500 mg PO every 24 hours, schedule after HD on HD days

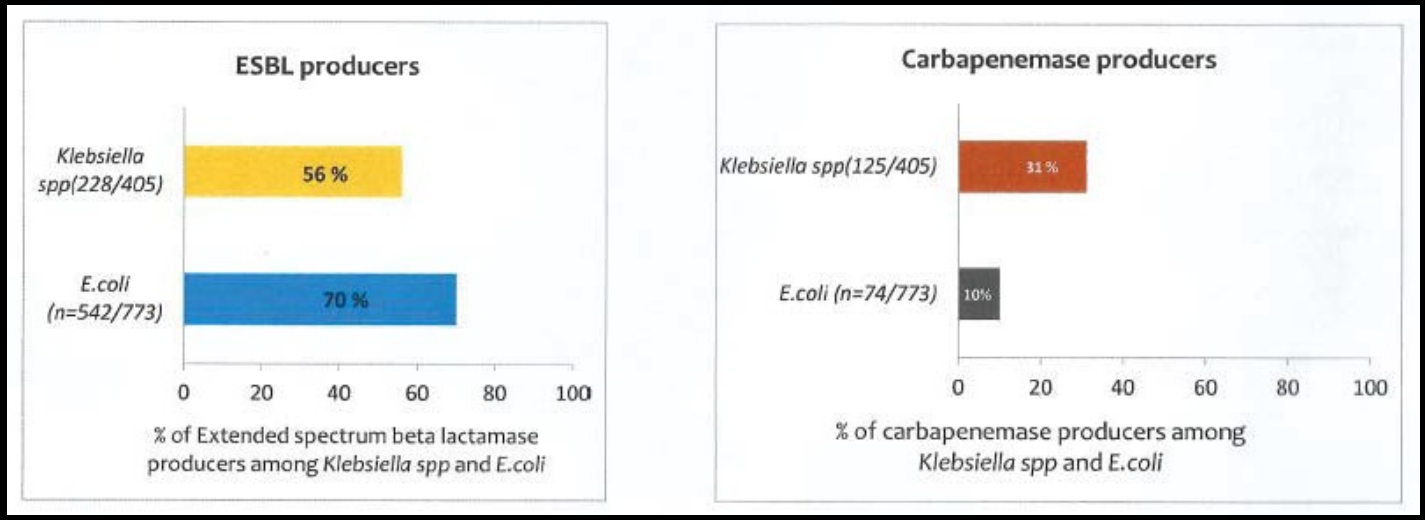
Christian Medical College

- Established in 1900
- 2300 bedded hospital
- OPD - 8313 per day*
- IP - 2071 per day*
- BMT - 233*
- Renal transplant - 111*
- ID dept –
  - Annual outpatient visits - 13046*
  - Admissions - 288*

All data are for 2016. Data for ID dept is only for adults Source: CMC yearbook 2016

CMC, Vellore Stewardship Initiative

Gram positive & gram negative organism resistance percentage			
	Overall %	Child %	Adult %
MRSA (n = 104/267)	40	44.1	38.2
VRE (n = 41/262)	15.6	17.9	18.6
PNSP (n = 16/88)	18.18	22.2	17.14
	ESBL		
E.coli (n=542/773)	70	74	70
Klebsiella spp (n = 228/405)	56	52	61
	CRO		
E.coli (n=74/773)	10	30	8
Klebsiella spp (n=125/405)	31	26	32



Results: 8.9% reduction in carbapenems,
9.0% reduction in colistin
9.5% reduction in days of antibiotics overall

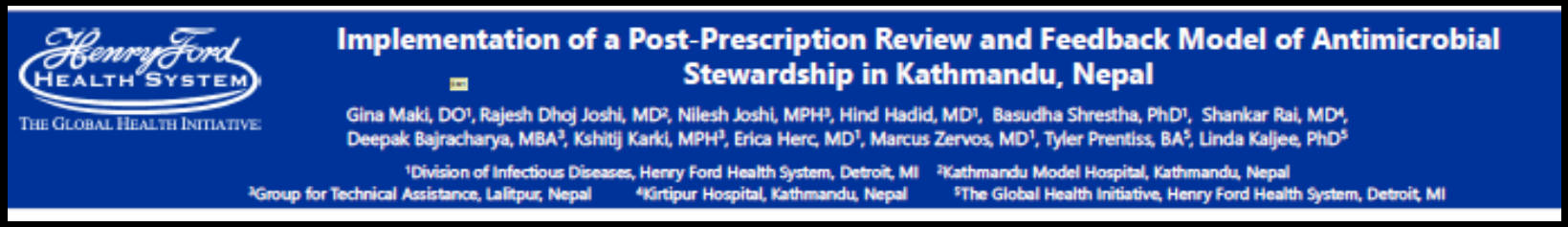
Rupali P et al ICHE 2019; in press

Hospital Characteristics

- Kathmandu Model Hospital
  - 125 inpatient-bed academic center
  - wide variety of clinical and diagnostic services

- Pokhara Academy of Health Sciences is a 500 bed government facility and 2nd largest hospital in Nepal. It is a referral hospital for the Western Region of Nepal and covers sixteen districts, including urban and rural areas

- Kirtipur Hospital
  - 100 inpatient-bed academic center
  - Burn and Plastic Surgery center



- Kathmandu Model, 451 patient charts were reviewed; 221 at baseline and 230 at post-intervention
  - Patients were hospitalized an average of 6.71 days during baseline vs 6.38 during intervention.
  - The mean days for cephalosporin were reduced from 2.8 days per course at baseline to 2.2 days at post-intervention (p=0.026).
  - Accurate treatment rationale by physicians increased from baseline (60%) to post-intervention (71%) (p=0.016).
  - Definitive therapy recommendations increased from 49% to 60% (p=0.026).

- Kirtipur Hospital, 241 patients were reviewed: 128 at baseline and 113 at post-intervention.
  - Justified antibiotic courses increased from 31% at baseline to 61% at post-intervention (p=<0.001).
  - Justified antibiotic use during the first 72 hours of therapy increased from 33% to 63% (p=<0.001).

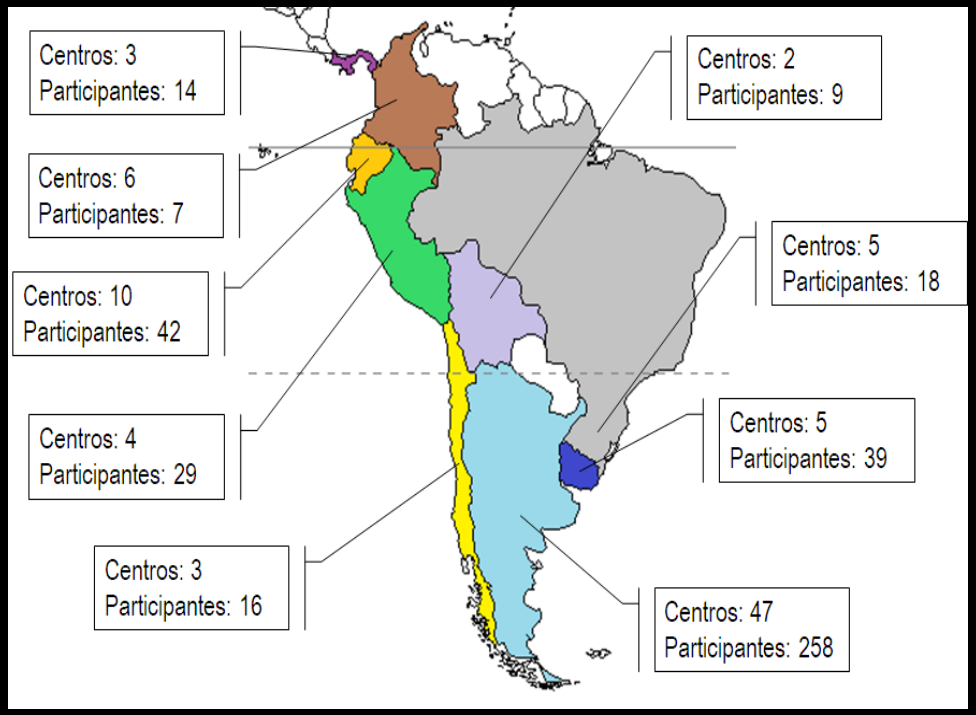
- Overall, 108 (78.3%) of recommendations were followed by the prescribing physician.

Maki G et al ID week 2018

Latin American Experience

Project for the Implementation and Evaluation of PROA In Latin American Adult Intensive Care Units

Quiros, RE; Maki G; Bardossy, AC; Aleman, RW; Angeleri, P; Carneiro, M; Castañeda, X; Cuellar, Luis; Guerra, A; Guerra, S Medina, J; Munita, J; Vega, S; Zurita, J; Prentiss, T; Escobar, E; Zervos, M. **Grupo Projeto PROA**



Practical Implementation of Programs for Optimizing the Use of Antibiotics (PROA) in hospitals

Objectives:

- To plan, develop, implement, monitor, and adjust a PROA

Participants:

- Targeted to Regional Coordinators, Principal Investigators, and Co-Investigators.

Evaluation: A 20 multiple-choice question exam per unit (>75% correct to pass)

Content:

UNIT I: Infections associated with health care: preventing emergence and transmission of MMDR — Exams: 209 Average score: 90

- ✓ Infections associated with health care (IACS)
- ✓ MMDR: A growing problem
- ✓ Strategies for the prevention and control of the emergence and transmission of MMDR

UNIT II: Basic principles for the effective implementation of a PROA — Exams: 202 Average score: 92

- ✓ Present state of the use of antibiotics
- ✓ Strategies to implement a PROA
- ✓ International experiences
- ✓ Impact of a PROA

UNIT III: Role of the Clinical Pharmacist as a member of a PROA — Exams: 198 Average score: 92

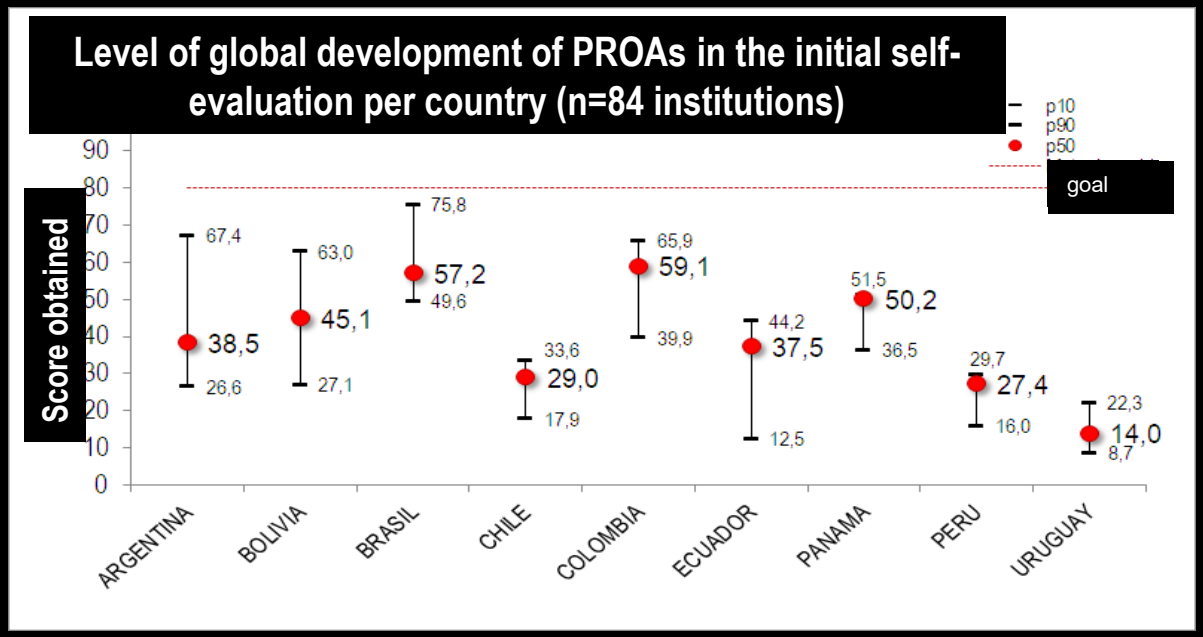
- ✓ Optimization of doses: principles (PK/PD)
- ✓ Detection of medical interactions
- ✓ Implementation of a system of hospital pharmacovigilance

UNIT IV: Role of the ID Doctor as a member of a PROA — Exams: 198 Average score: 92

- ✓ Adaptation of the clinical guidelines in an age of multi-resistant bacteria
- ✓ Descalation
- ✓ Combined antimicrobial treatment: What is the evidence telling us?

Number of centers: 85 (9 countries); Total participants: 432

Latin American Experience



Trends in antibiotic* use in hospital ICUs. PROA-LATAM project

Trend	# of center	Initial score	DDDs c/100 días-paciente			Trend graph (Ro)	Corr. Coefficient	R^2
			Jul 2018	Ago 2018	Sep 2018			
Reduction	26	41,4	106,3	89,5	78,7		-0,99	0,98
Maintenance	12	40,7	102,1	105,4	100,4		-0,34	0,12
Increase	24	41,8	77,6	93,1	117,6		0,99	0,98

* Betalactams+inhib; 3rd and 4th gen. Cephalosporins; Monobactams; Carbapenems; Glycopeptides; Fluoroquinolones; Aminoglycosides

Latin American Experience

Appropriateness: Daily prevalence

Trends in indicators of appropriateness* in hospital ICUs. PROA-LATAM project

Indicator	Jul 2018	Ago 2018	Sep 2018	Trend graph (Ro)	Corr. Coefficient	R^2
Validation of the indications per pharmacist	60,9%	67,5%	62,6%		0,25	0,06
Record in medical history	97,2%	97,7%	95,4%		-0,76	0,58
Adherence to guidelines	68,7%	75,6%	73,3%		0,65	0,42
Periodic revision with devolution	78,2%	81,6%	84,9%		1,00	1,00
Acceptance of the ID recommendation	88,3%	88,6%	85,9%		-0,82	0,68
One dose of aminoglycosides	85,7%	88,0%	91,3%		0,99	0,99

* Rate of appropriateness: number of indications accomplishing the indicator x 100 / Total indications

Indicators de impact

Trends in indicators of impact* in hospital ICUs. PROA-LATAM project

Indicator centers	# of	Jul 2018	Ago 2018	Sep 2018	Trend graph	Ro	R^2
Infection with MDRO* (events every 1000 pt-days)	62	13,21	13,19	12,04		-0,88	0,77
Infection with *C. difficile* (event every 1000 pt-days)	48	0,49	0,06	0,38		-0,24	0,06
Net mortality (deaths every 100 discharges)	62	19,73	20,58	18,55		-0,58	0,33

* MDRO: MRSA; VRE; ESBL; Enterobacteriacae resistant to carbapenems; *P. aeruginosa* resistant to carbapenems; *Acinetobacter spp* resistant to carbapenems

Latin American Experience

- The institutions **value positively** their participation in this type of project
- The success **of this of projects** depended on:
  - ✓ The **consolidation of the team over time** (ID doctor, clinical pharmacist, and microbiologist)
  - ✓ The **leadership of the members**
  - ✓ The **support of senior management**
- The **loss of institutional support** was the main barrier
- There is **limited availability** of **qualified resources** for the **time required**
- **Limited Information Technology support**

WHO Antimicrobial Stewardship Programmes in Hospitals in Low and Middle-Income Countries

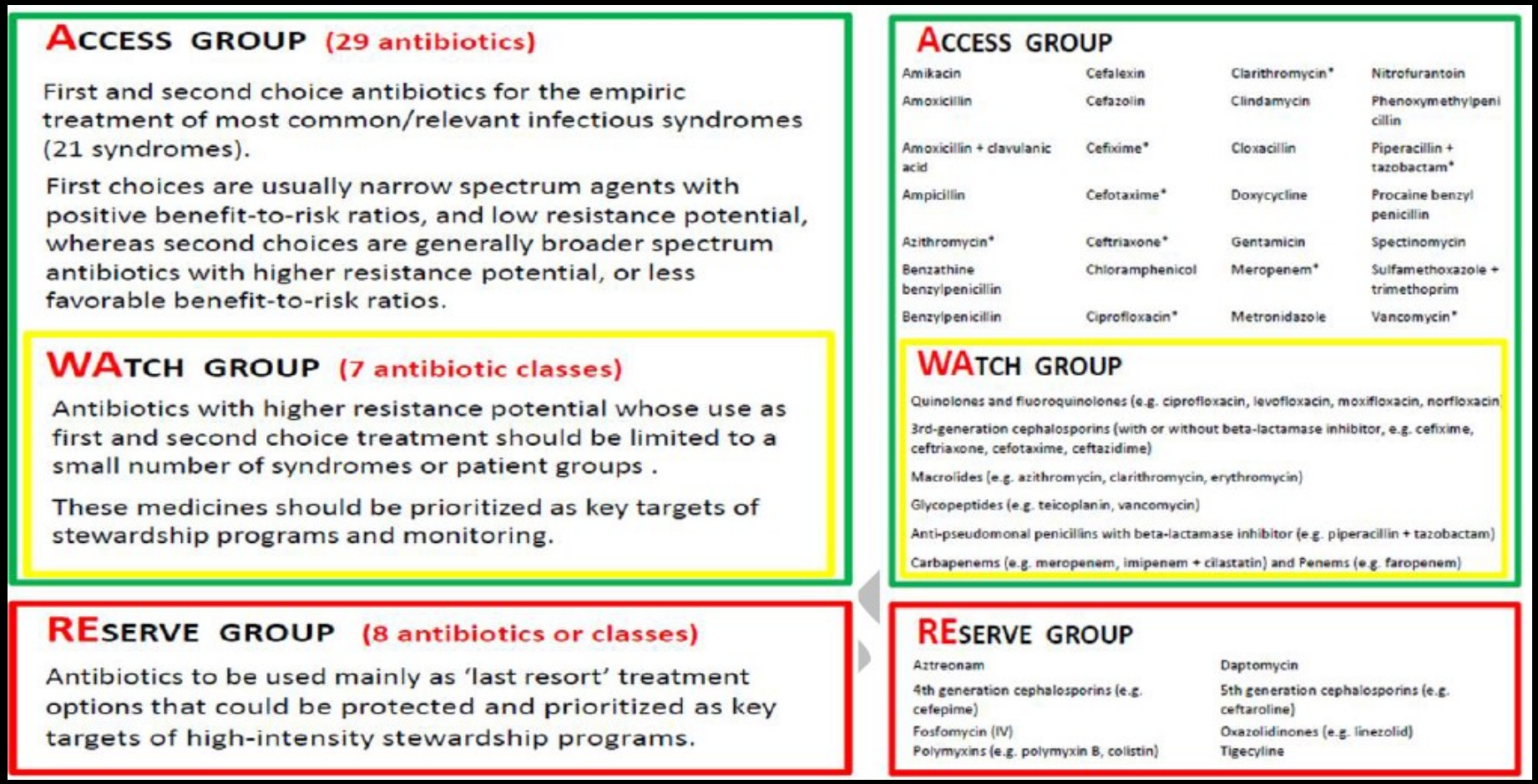
a practical toolkit draft

- **Developed as a draft toolkit by multiple stakeholders and experts**
- **The aim of an AMS programme is:**
  - to promote optimal antibiotic treatment/prophylaxis to patients to improve the quality of health-care and outcomes;
  - to optimize the use of existing antibiotics, and thereby extend their lifespan;
  - to reduce the further development, selection and spread of AMR; and
  - to limit the adverse economic impact of AMR.

Measures of Antimicrobial Use

- DDD per 1000 patient days
- DDD per admission
- Days of Therapy per 1000 patient days
- Proportion of DDD in ACCESS, WATCH, RESERVE and other categories
- Documented indication for use
- Stop/review date
- Compliance with guidelines (including surgical)
- Length of therapy
- 48-72 hour review
- Deescalation
- IV to oral switch

WHO Aware Categorization of Antibiotics



Assessment of Outcomes

- In hospital mortality
- Lengh of stay
- Readmission at 30 days after discharge
- C difficile rate per 10,000 or 100,000 patient days
- MDRO rate

Conclusion

- The implications of this project are local and global, findings will be disseminated in collaboration with WHO and regional and local.
- The global crisis on antimicrobial resistance is getting major international attention
- Our goal is that the WHO toolkit will serve as an important resource for LMIC in antimicrobial stewardship efforts
- We must pool our greatest resources—our imagination and intellect—to fight this collective fight. For as Joshua Lederberg noted, “Pitted against microbial genes, we have mainly our wits.”