What is AMS and its different types

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Outline

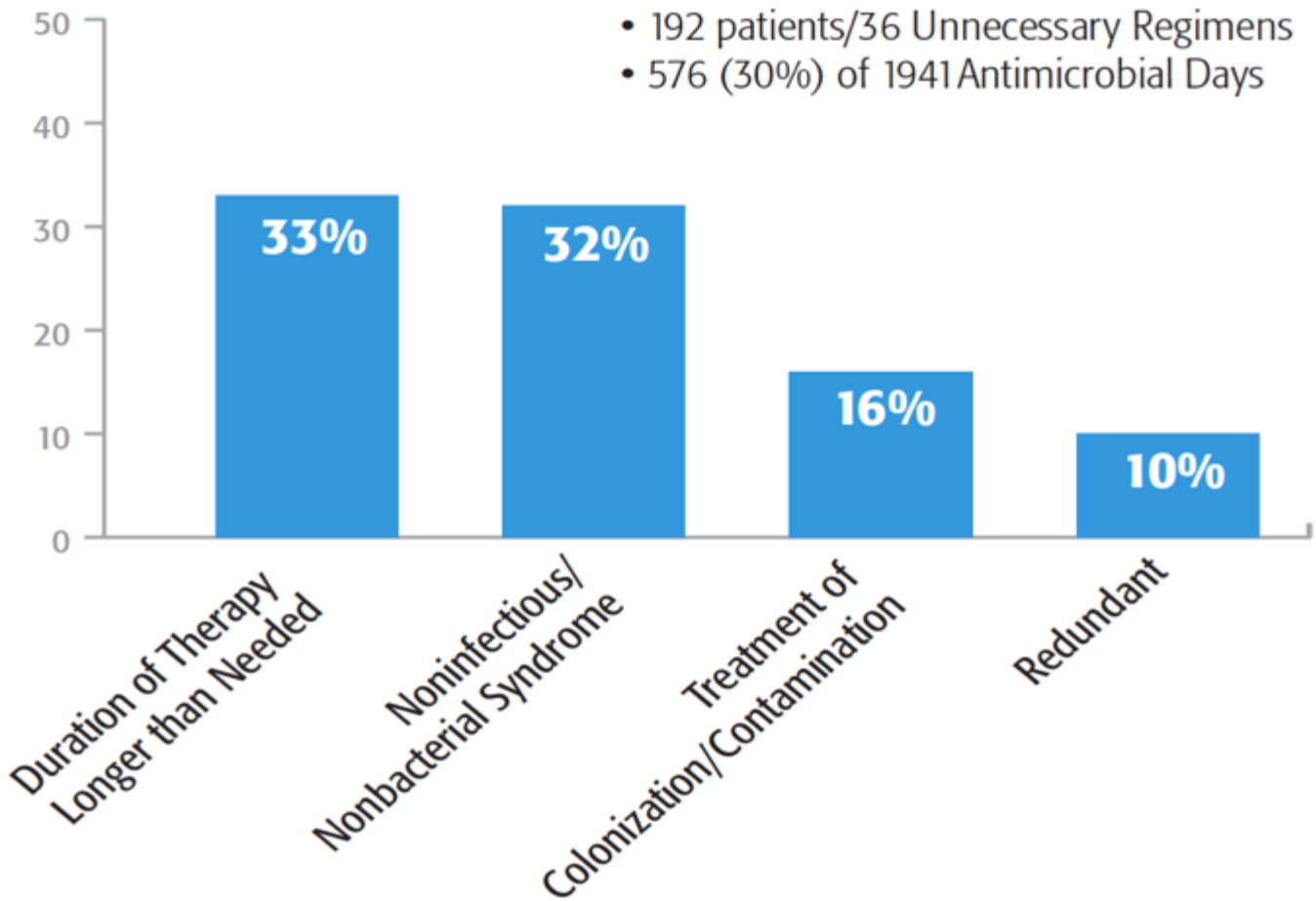
- The problem of inappropriate antibiotic use
- What is Antimicrobial Stewardship
- Types of ASP
- The impact of ASP
- Conclusions

The problem

- 25-50% of hospitalized patients receive antimicrobials
- 30-50% of antimicrobial use is inappropriate
- Strong link between antimicrobial use and resistance
- Patients infected by drug resistant bacteria have a two-fold increase in mortality as compared to those infected by sensitive bacteria

EXAMPLES OF INAPPROPRIATE USE OF ANTIMICROBIAL AGENTS

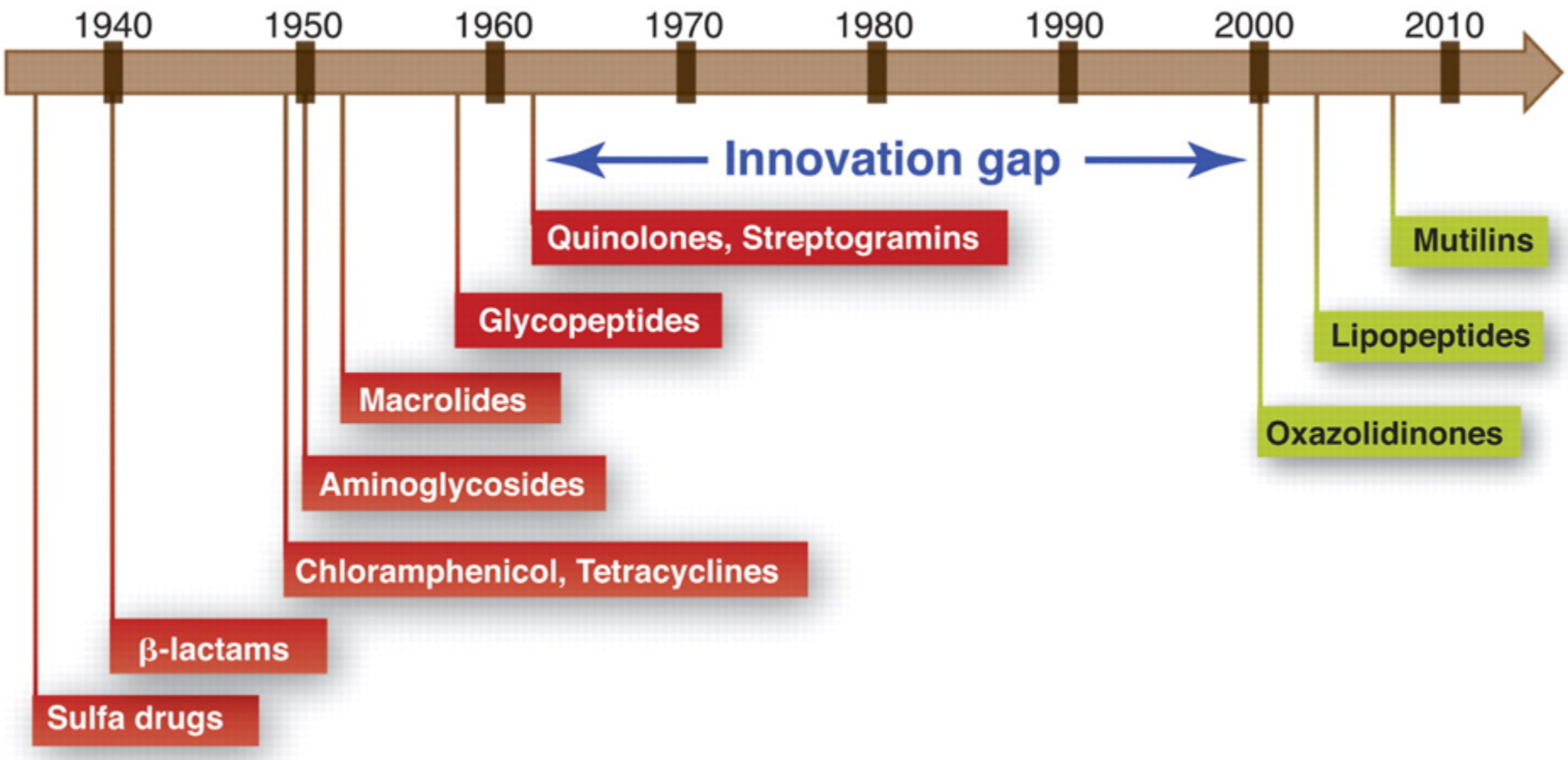
Figure 2. "Unnecessary" Antimicrobial Therapy.



Adapted from Hecker MT. et al. Arch Intern Med. 2003;162:972-978.

The problem

Since 1998 only 10 new antibiotics have been approved. Only 2 (linezolid and daptomycin) have new targets of action.



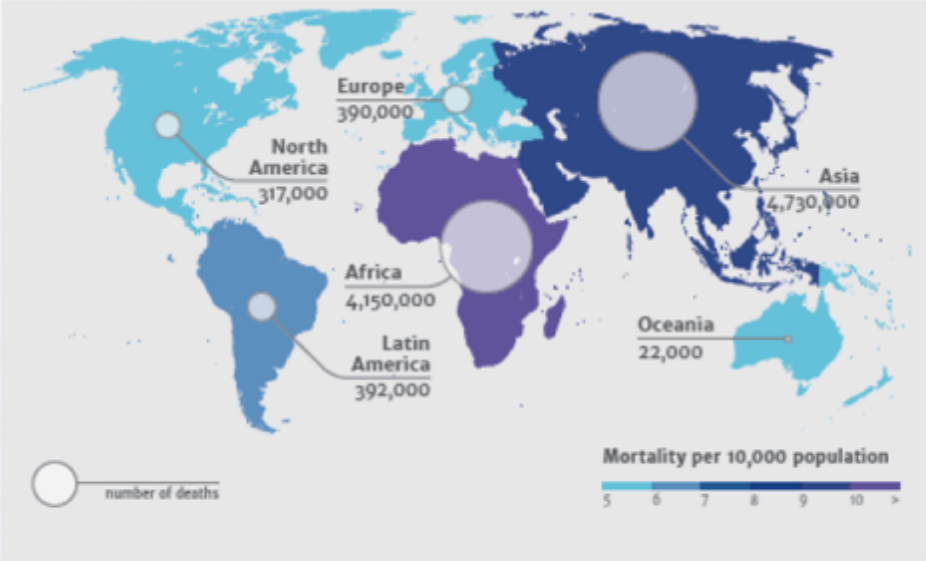
Clin Infect Dis 2011;52(S5):S397–S428

Increasing Awareness and Political Commitment

Mortality and Economic Impact

- In 2050, up to 10 million deaths/year
- 2-3.5 percent reduction of GDP
- Total global cost of up to $USD 100 billion

Deaths Associated to AMR each year until 2050



J. O'Neil, 2014. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations.

Global Action Plan for Antimicrobial Resistance

Organización Mundial de la Salud

Pan American Health Organization

World Health Organization
Regional Office for the Americas

The solution
Actions to prevent and control antimicrobial resistance and nosocomial infections

- New antimicrobial agents
- Infection prevention and control
- Prudent use of antimicrobial agents
  - only when needed, correct dose, correct dose intervals, correct duration

Antimicrobial Stewardship: What is it?

- Antimicrobial stewardship is a systematic approach to optimizing the use of antimicrobials
- It is used by healthcare institutions to:
  - Reduce inappropriate antimicrobial use
  - Improve patient outcomes
  - Reduce adverse consequences, including antimicrobial resistance, toxicity and unnecessary costs

Dellit TH *et a*l. Clin Infect Dis 2007;44:159-177
MacDougall C. Clin Micro Rev 2005; 18:638-656

AMS

- ✓ 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

www/cdc.gov/getsmart/healthcare/inpatient-stewardship

The ASP core team

- Successful ASPs require an inter-disciplinary team approach (frontline staff and senior administrators) including:
  - Infectious Diseases Physician(s)
  - Clinical pharmacist with infectious disease training
  - Clinical microbiologist
  - Information system specialist
  - Infection control professional
  - Hospital epidemiologist
  - Require the support and collaboration of hospital administration, medical staff leadership, and local providers.

Dellit T *et al*. Clin Infect Dis 2007;44:159-177
SHEA, IDSA and PIDS. ICHE 2012;33:322-327

Interventions to improve antibiotic use

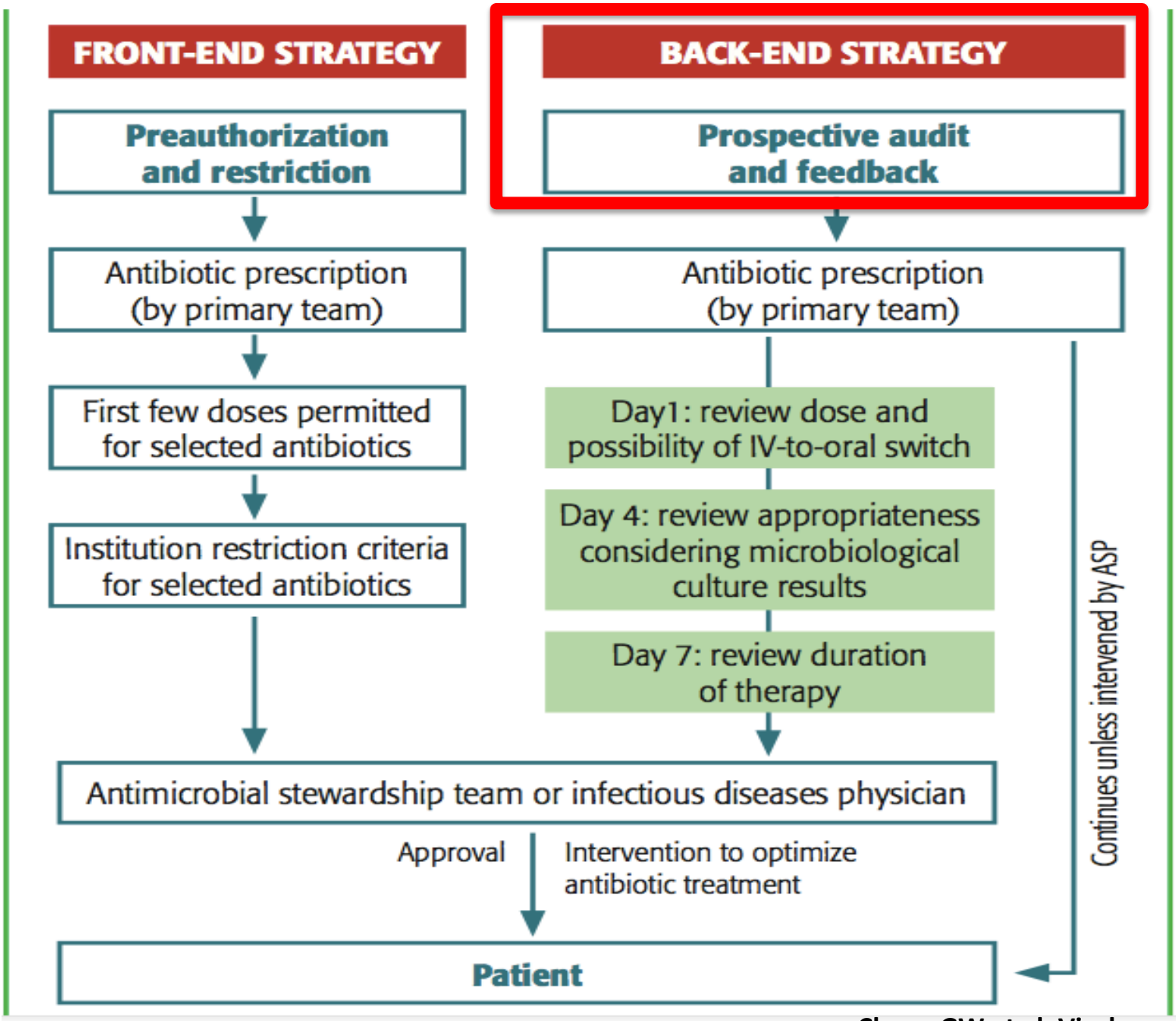
- Broad
    - Prior authorization
    - Prospective audit and feed back
    - Antibiotic ‘time outs’
- Pharmacy driven
- Syndrome specific

Frame the program and develop a hypothesis about potential solutions

- No ‘one-size-fits-all’ approach to ASPs
- Depending on local antimicrobial use, size, staffing, personnel, infrastructures, and resources, different institutions may need different interventions to combat antimicrobial resistance.
- Avoid implementing too many policies and interventions simultaneously

Dellit T *et al*. Clin Infect Dis 2007;44:159-177
SHEA, IDSA and PIDS. ICHE 2012;33:322-327

Two core antimicrobial stewardship strategies



Chung GW et al. Virulence 2013; 4:1-7

Antibiotic "Time outs"

- Antibiotics are often started empirically
- An antibiotic "time out" prompts a reassessment of the continuing need of antibiotics when the clinical picture is clearer and more diagnostic information is available.
- All clinicians should perform a review of antibiotics 48 hours after antibiotics are initiated to answer these key questions:
  - Does this patient have an infection?
  - Is the patient on the right antibiotics, dose, and route of administration?
  - Can de-escalate?
  - How long should the patient receive the antibiotics?

https://www.cdc.gov/antibiotic-use/healthcare/pdfs/core-elements.pdf

Pharmacy-driven Interventions

- Automatic changes from intravenous to oral antibiotic therapy
- Dose adjustments
- Dose optimization
- Automatic alerts in situations where therapy might be unnecessarily duplicative
- Time-sensitive automatic stop orders
- Detection and prevention of antibiotic-related drug-drug interactions

https://www.cdc.gov/antibiotic-use/healthcare/pdfs/core-elements.pdf

Infection and syndrome specific interventions

- Community-acquired pneumonia
- Urinary tract infections (UTIs)
- Skin and soft tissue infections
- Empiric coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) infections
- *Clostridium difficile* infections
- Treatment of culture proven invasive infections

https://www.cdc.gov/antibiotic-use/healthcare/pdfs/core-elements.pdf

Table 5. Antimicrobial Stewardship Toolkit: Quality of Evidence to support interventions.

Core Strategies	Supplemental Strategies
Formulary restrictions and preauthorization*	Streamlining / timely de-escalation of therapy*
Prospective audit with intervention and feedback*	Dose optimization*
Multidisciplinary stewardship team*	Parenteral to oral conversion*
	Guidelines and clinical pathways*
	Antimicrobial order forms
	Education
	Computerized decision support, surveillance
	Laboratory surveillance and feedback
	Combination therapies
	Antimicrobial cycling

Adapted from Dellit et al. Clinical Infectious Diseases 2007; 44:159-77.

Formulary restriction and preauthorization

- The most effective approach to controlling the use of antimicrobial agents.
- Formulary restriction refers to limiting a facility's antimicrobial formulary based on factors such as efficacy, toxicity, cost, and redundancy.
- Preauthorization refers to a requirement to provide justification for using an antimicrobial agent before the drug is released from the pharmacy
- This authorization is typically provided by the stewardship team

Dellit et al. Clin Infect Dis 2007; 44:159–77

Formulary restriction and preauthorization

- Studies have associated antimicrobial restriction with
  - Interruption of *C. difficile* outbreaks
  - Increased rates of clinical cure
  - Increased antimicrobial susceptibility among gram-negative pathogens
  - Substantial cost savings
- Preauthorization has been most effective in reducing antimicrobial use when a dedicated stewardship team is responsible for providing the preauthorization.

Clin Infect Dis 2016;62(10):e51–e77

A lot of studies have investigated CDI rates after an intervention to control anti-infectives

Year	Country	Stewardship method	*Pre-intervention	*Post-intervention	Reduction in CDI rates
1994	US	Restrictive use	15.8	1.9	88%
1997	UK	Restrictive use	5.3	2.3	57%
1998	US	Restrictive use	11.5	3.3	71%
2003	UK	Restrictive use	14.6	3.4	77%
2003	US	Prospective audit and feedback	2.2	0.3	86%
2004	UK	Restrictive use	46	22	52%
2004	US	Restrictive use	1.32	0.51	61%
2007	UK	Prospective audit and feedback	NR	NR	65%
2007	Canada	Restrictive use	2.03	0.82	60%
2011	UK	Restrictive use	2.22	0.45	80%
2012	Canada	Prospective audit and feedback	1.12	0.71	37%
2013	UK	Restrictive use	2.4	1.2	50%

Feazel LM et al. *J Antimicrob Chemother*. 2014; 69:1748-54.

Reduce resistance

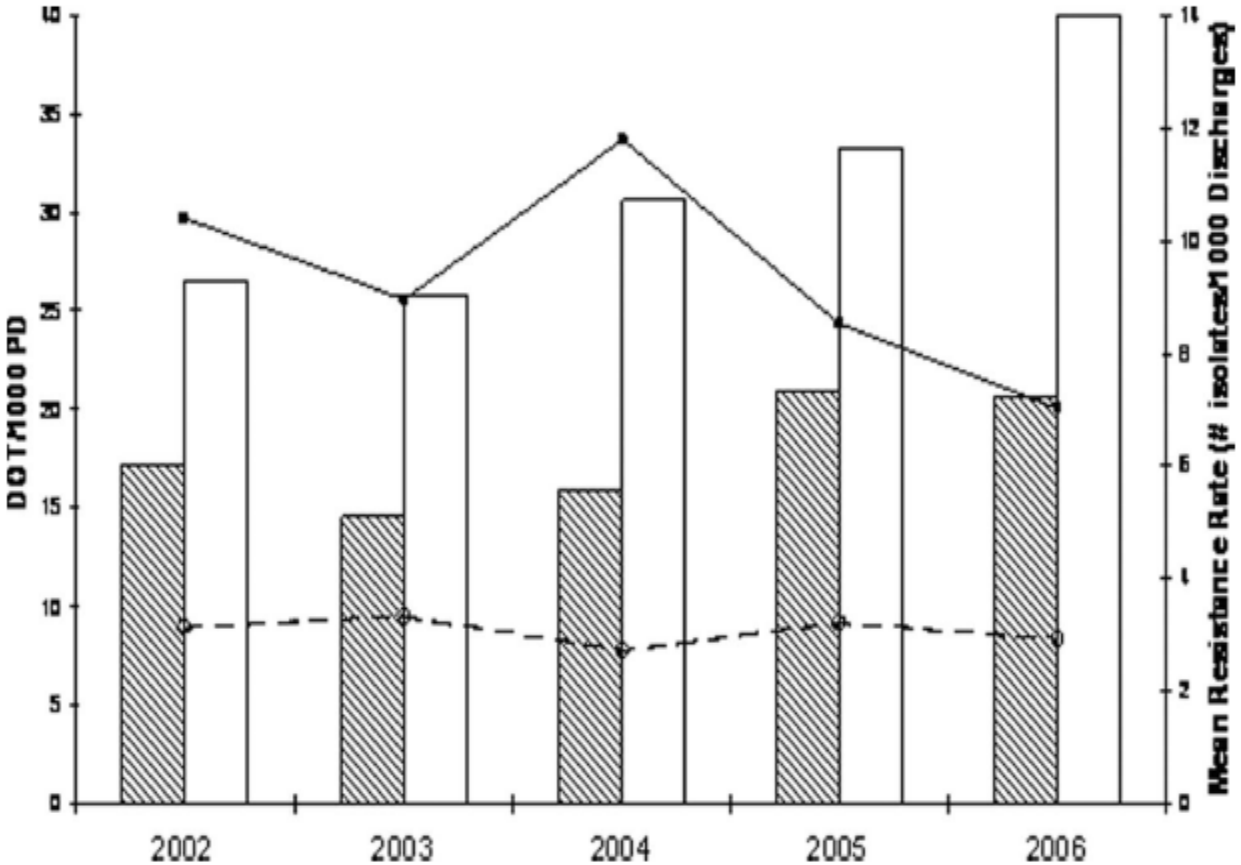


FIG. 1. Mean carbapenem use (DOT/1,000 PD) was significantly lower in hospitals that restricted (shaded bars) versus did not restrict (open bars) carbapenems ($P = 0.04$). Incidence rates of carbapenem-resistant *P. aeruginosa* (number of isolates/1,000 discharges) were lower for hospitals that restricted (dashed line) versus did not restrict (solid line) carbapenems ($P = 0.01$).

Antimicrob Agents Chemother. 2009;53:1983-6

THE EVIDENCE SUPPORTING ANTIMICROBIAL STEWARDSHIP STRATEGIES

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Note: CI, confidence interval; PPS, pre–post study; RCT, randomized controlled trial.

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Prospective audit with intervention and feedback

- With this strategy, antimicrobial prescriptions are audited on a prospective basis.
- Selection of prescriptions to be audited may be based on:
  - The specific drug prescribed
  - The location of the patient
  - The disease process being treated

Dellit et al. Clin Infect Dis 2007; 44:159–77

Prospective Audit and Feedback

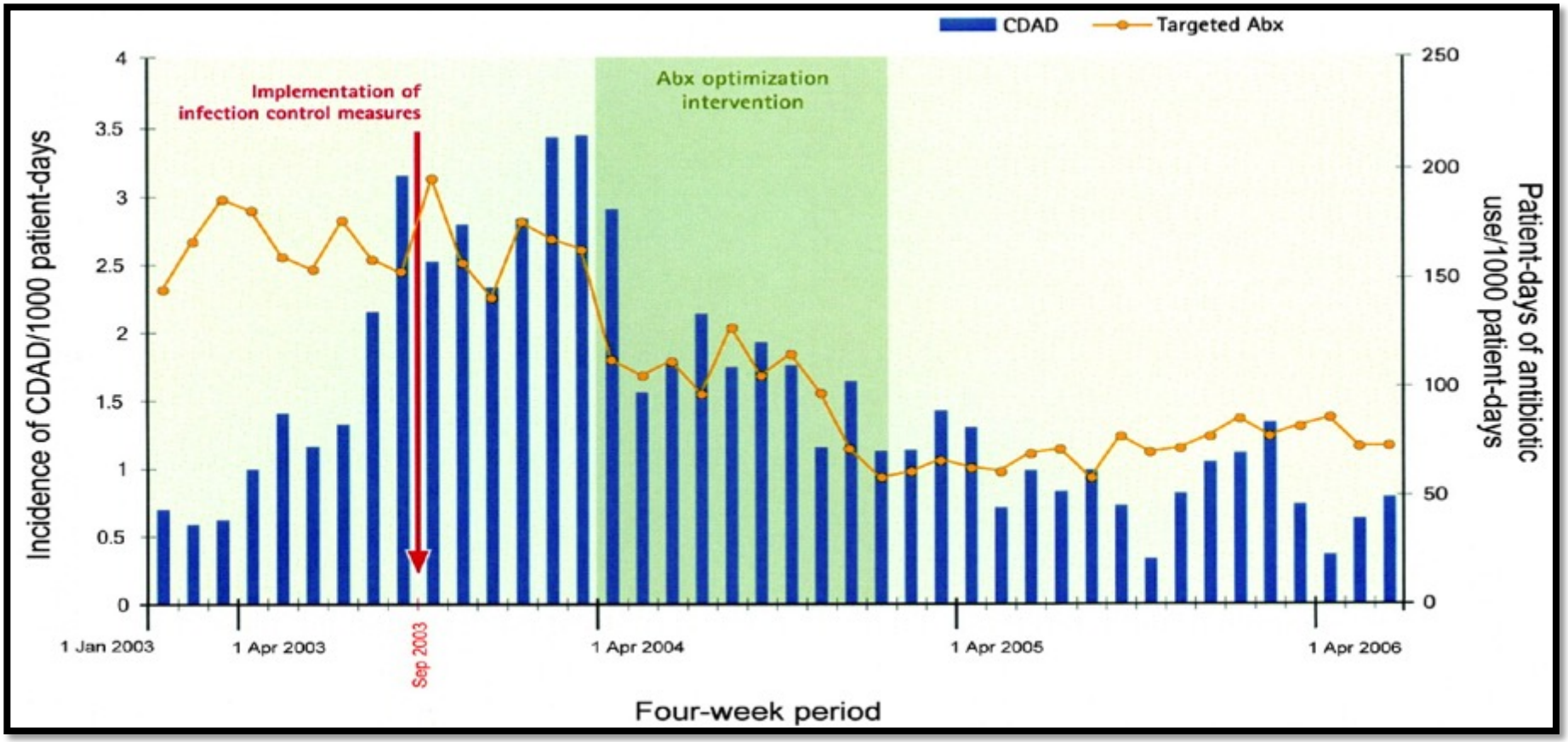
- The audit is performed by a physician and/or clinical pharmacist and addresses:
  - Appropriateness of selected agent based on microbiologic data
  - Local resistance patterns
  - Evidence-based practice with recommendation of alternative therapy, or no therapy.
  - Potential errors (e.g., allergies, dosing errors, medication interactions)
- Feedback may occur through direct interaction with the prescribing clinician or through notes left in the chart or electronic medical record.
- This strategy has been associated with reductions in inappropriate use of antibiotics, *C. difficile* infection rates, and costs.

Clin Infect Dis 2016;62(10):e51–e77

Improve patients safety

Targeted antibiotic consumption and nosocomial *C. difficile* disease

Tertiary care hospital; Quebec, 2003-2006



From 2003-2004 to 2005-2006, total and targeted antibiotic consumption, respectively, decreased by 23% and 54%, and the incidence of n-CDAD decreased by 60%.

Valiquette, et al. Clin Infect Dis 2007;45:S112.

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IMPACT OF ANTIMICROBIAL STEWARDSHIP PROGRAMS

Intervention for a More Successful Outcome

- Interventions to improve antibiotic prescribing in hospitals:
  - 89 Studies until 2009
    - 55 from North America
    - 37 from Europe
    - 3 from Far East
    - 3 from South America
    - 2 from Australia
- Persuasive and restrictive interventions

- Evidence to support beneficial impact on:
  - Decrease in antibiotic use does not increase mortality and can improve clinical outcomes
  - Better use of antibiotics will reduce SSI's
  - Decrease and better use of antibiotics reduces/stabilizes resistance and *C. difficile*
  - Emerging data on cost-reduction

Davey et al. Cochrane Database of Systematic Reviews. 2013

SUPPLEMENTAL STRATEGIES
Education

- Education is the key component of any AMS program but is most likely to be effective when combined with an active intervention (e.g., restriction or prospective audits).
- It should include health care professionals as well as patients and public and convince them that is important.
- A major cause of misuse of antimicrobials is insufficient knowledge.

- Guidelines suggest against relying solely on didactic educational materials for stewardship

Barlam et al. Clin Infect Dis 2016;62(10):e51–e77
Pulcini et al. Virulence. 2013;4:192-202.
Dellit et al. Clin Infect Dis 2007;44:159–77

Guidelines and clinical pathways

- Multidisciplinary development of evidence-based practice guidelines incorporating local microbiology and resistance patterns can improve antimicrobial utilization.

Dellit et al. Clin Infect Dis 2007; 44:159–77

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Streamlining or de-escalation of therapy.

- Empiric antimicrobial regimens are often broad in spectrum
- This strategy refers to narrowing the spectrum of an empiric antimicrobial regimen and can include:
  - Adjusting an empiric antibiotic regimen on the basis of culture results.
  - Discontinuing empiric therapy if testing fails to demonstrate an infectious process.
  - De-escalation reduces the cost of therapy.

Dellit et al. Clin Infect Dis 2007; 44:159–77

Dose optimization

- Includes strategies to ensure that
- Specific characteristics of the drug (e.g., concentration or time-dependent killing, toxicities),
- Infectious agent (minimum inhibitory concentration [MIC]),
- Patient (e.g., weight, renal function), and site of infection are taken into account.

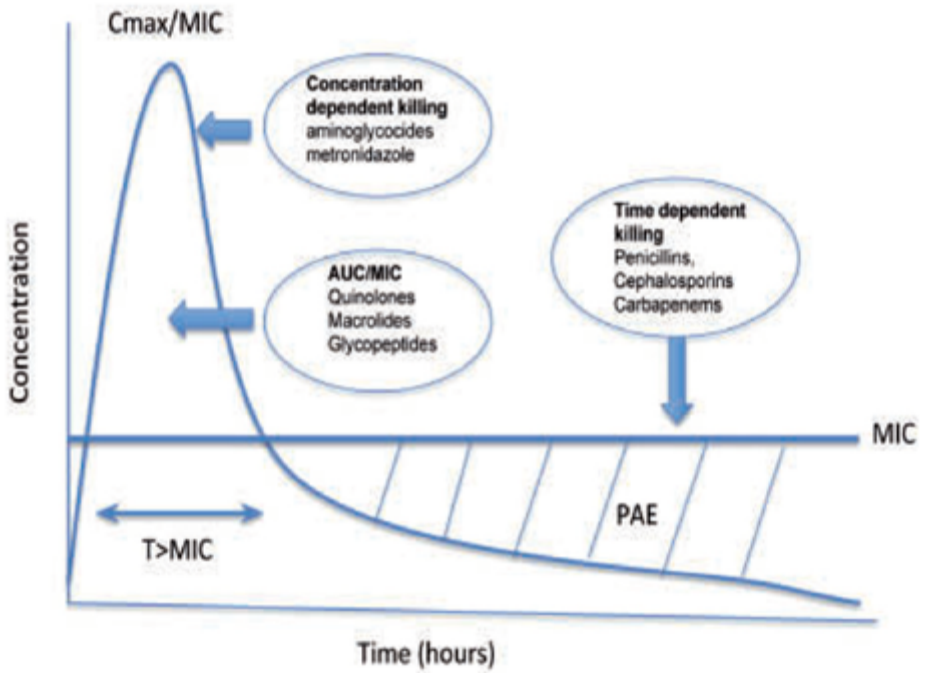

Fig 3 Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration *vs* time curve. Concentration dependent killing—extent of microorganism killing is dependent on the antimicrobial concentration. Time dependant killing—extent of microbe killing remains unchanged providing it is above the MIC. AUC/MIC—exhibit both concentration and time dependent killing. AUC, area under curve; MIC, minimum inhibitory concentration; Cmax, maximum serum antibiotic concentration; PAE, post antibiotic effect.

Dellit et al. Clin Infect Dis 2007; 44:159–77

Parenteral to oral conversion

- Parenteral to oral conversion of antimicrobials with excellent bioavailability, when the patient's condition allows
  - Can decrease the length of hospital stay and health care costs Development of clinical criteria and guidelines allowing switch to use of oral agents can facilitate implementation at the institutional level

TABLE 2. **Highly Bioavailable Antimicrobials That Are Good Candidates for Intravenous to Oral Switch Programs**

Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)
Metronidazole
Macrolides (azithromycin, erythromycin)
Doxycycline
Clindamycin
Rifampin
Linezolid
Fluconazole

Dellit et al. Clin Infect Dis 2007; 44:159–77

Antimicrobial order forms

- Antimicrobial order forms decrease antimicrobial consumption through the use of automatic stop orders and the requirement of physician justification
- The rate of inappropriate initiation of antimicrobial prophylaxis postoperatively decreased from 30% to 11% with use of the order form.

Dellit et al. Clin Infect Dis 2007; 44:159–77

Combination therapy

- There are insufficient data to recommend the routine use of combination therapy to prevent the emergence of resistance.
- Does have a role in empirical therapy for critically ill patients at risk of infection with multidrug-resistant pathogens

Dellit et al. Clin Infect Dis 2007; 44:159–77

Microbiology laboratory

- The microbiology laboratory plays a critical role in AMS by

1. Providing culture and susceptibility data to optimize individual antimicrobial management
2. Resistance surveillance
   - data should be updated at least annually
3. Assisting infection control in molecular epidemiologic investigation of outbreaks

Dellit et al. Clin Infect Dis 2007;44:159–77

Rapid diagnostic Tests

- Rapid diagnostic tests significantly reduce the time for pathogen identification and antimicrobial susceptibility from days to hours compared with conventional techniques
- Can be applied into blood for sepsis, respiratory specimens for CAP, and cerebrospinal fluid CNS infections.
- The RDTs does not necessarily lead to improvements in antimicrobial prescribing.
- Medical staff should be educated on the indications and performance of the new tests

Dellit et al. Clin Infect Dis 2007; 44:159–77

Multiplex RDTs and antimicrobial stewardship

- Systematic review and meta-analysis of 31 studies (5920 patients with BSIs) comparing multiplex RDT with conventional microbiologic methods
  - Significant decreases in mortality risk in the presence of a ASP
  - Decreased time to effective therapy and LOS
  - Greatest benefit of multiplex RDT may be for BSI caused by MDR organisms particularly VRE

Timbrook et al Clin Infect Dis 2017;64:15-23

The Use of Computerized Decision Support Systems (CDSS) to Support Antimicrobial Stewardship Programs (ASPs)

- Support physicians in making decisions on health-care.
- Are potentially useful tools in antibiotic stewardship programs
- Decision support systems range from mobile applications to approval systems, electronic medical records (EMRs), computerized physician order entry (CPOE), and advanced decision support.
- CDSS appear beneficial for improving the quality of prescribing
- Their impact on patient outcome and antimicrobial resistance is less certain

Thursky K. in antimicrobial stewardship book 2017. Elsevier

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Conclusions

- As hospitalized patients become more complex to treat, the increasing prevalence of antimicrobial resistance in both health care and community settings represents a challenge.
- By making antimicrobial stewardship part of our daily practice, we can improve patient safety and care, reduce the unnecessary use of valuable resources, and reduce resistance.

Thank you