Antibiotic Stewardship and The Pediatrician

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Outline of Discussion

- Rationale for Antimicrobial Stewardship (AMS)
- Clinical approach to antimicrobial stewardship
- Guideline Recommendations
- Researches on Antimicrobial Stewardship
- Research Gaps and Future Plans

Background

- Antimicrobial use has undoubtedly reduced mortalities caused by infections.
- Unnecessary or inappropriate use of antibiotics has increased rates of serious diseases caused by MDROs.

– poor clinical outcomes
– increased lengths of stay
– increased health care costs

Inappropriate use of Antibiotics in Pediatrics

1. Antibacterials for diseases not caused by bacteria;
2. Treatment for culture results that reflect colonization or contamination rather than infection;
3. Use of broad spectrum antibiotics where narrow spectrum agents are equally effective;
4. Prescription of antibiotics longer than necessary; and
5. Prescription of antibiotics at inappropriate doses.

Antimicrobial Prescribing Facts: The 30% Rule

~ 30% of all hospitalized patients receive antibiotics

> 30% of antibiotics are prescribed inappropriately

~ 30% of hospital pharmacy costs are from antibiotics

10-30% of pharmacy costs can be saved by AMS

Hoffman et al, 2007; Wise et al 1999; John et al, 1997

Antimicrobial Stewardship

- Coordinated intervention designed to improve antibiotic use by promoting the selection of optimal drug regimen (dose, duration, route of administration)

- Systematic approach to the use of antimicrobial agents in order to achieve optimal outcomes.

Benefits of Antimicrobial Stewardship

- **Improved patient outcomes:**
  - cure
  - less toxicity
  - reduced adverse events including *C. difficile* infection

- **Improved community outcomes:**
  - decrease antimicrobial resistance
  - reduce health care cost

Very few hospitals have implemented a comprehensive AMS program.

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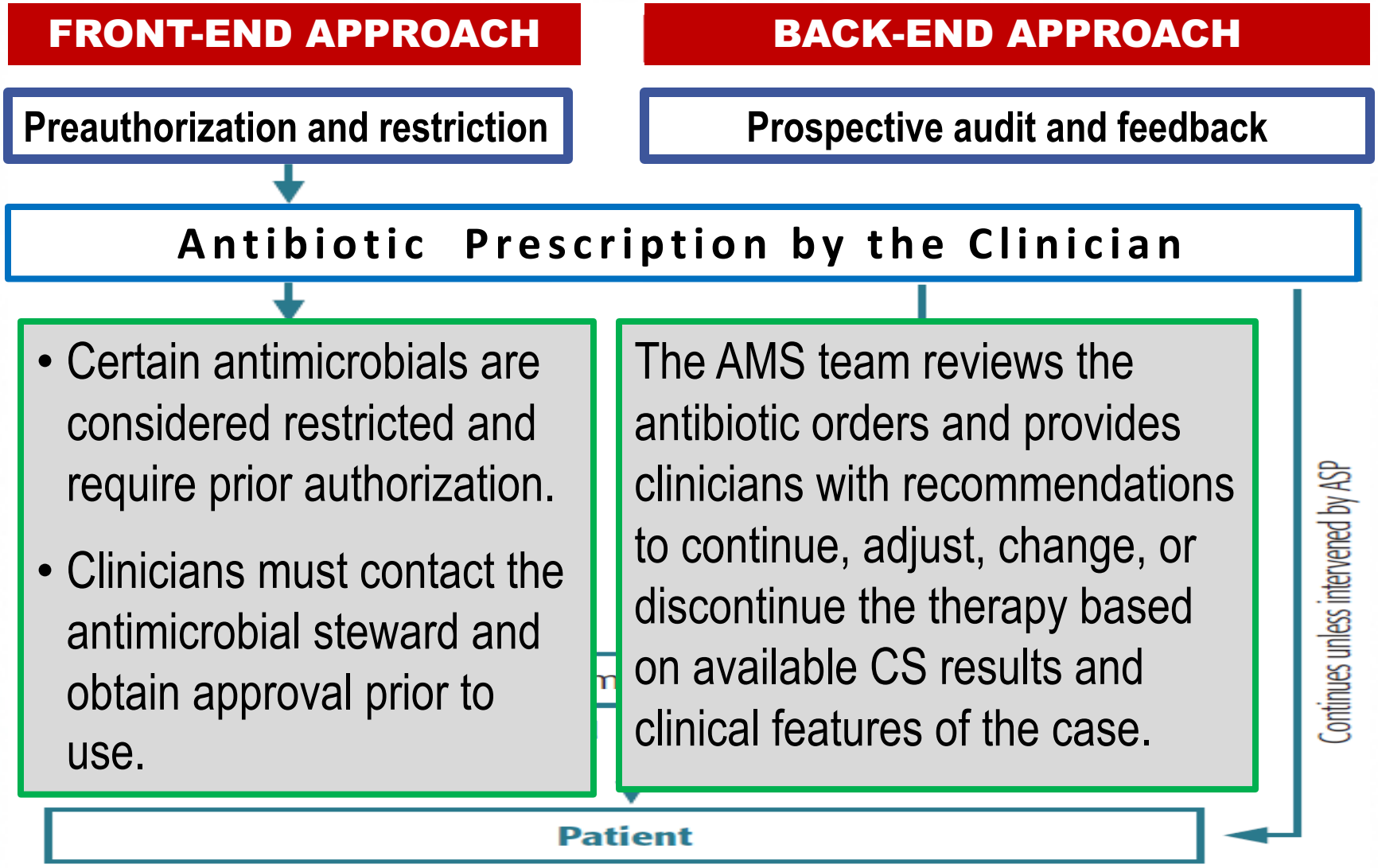
Clinical Approaches to AMS



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

Other Approaches to AMS

1. Education: Essential, but insufficient alone.

2. Guidelines and Clinical Pathways: Can decrease amount of critical thinking.

3. De-escalation or Streamlining: Modify initial empiric regimen to targeted therapy based on culture, discontinue redundant concurrent antimicrobials or stop antibiotics in the absence of infection.

4. Intravenous to Oral Switch: For antimicrobials with excellent oral bioavailability, timely conversion to oral can be done.

Chloramphenicol, Clindamycin, Metronidazole, Macrolides, Fluoroquinolones, Linezolid, Fluconazole

Other Approaches to AMS

5. Dose Optimization: Dose of antimicrobial can be optimized for better microbial kill based on patient characteristics, causative agent, site of infection and drug PK/PD.

- **Prolonged infusion of beta-lactams**
- **Increased frequency dosing of quinolones**
- **OD dosing of aminoglycosides**

6. Computer-Assisted Decision Support: Electronic system to guide clinicians regarding appropriate dosages and administration

7. Order Sets and Treatment Algorithms: Ensure guideline-based appropriate empiric antibiotic choices.

8. Antibiotic Cycling. Scheduled removal or substitution of specific antimicrobials. By removing specific classes of antimicrobials on a regular basis, the development of resistance may be avoided.

Steps in AMS Program Implementation

Assess Current Practices	Establish an AMS Core Team	Plan the Implementation	Evaluate Outcomes/Cost
• Aggregate antibiotic use and pattern of use • Drug resistance rate • Identify common ID syndromes • Identify IT infrastructure • Clinician perception on drug resistance, prescribing and stewardship	• ID Specialist • Clinical Pharmacist • Clinical microbiologist • Infection control representative • Epidemiologist • IT representative • Senior administrator • Group of champion prescribing physicians		

The core team is responsible for developing, implementing, and managing the AMS program.

Identify a group of prescribing pediatricians that can serve as program champions.

Obtaining physician buy-in is crucial to AMS success and sustainability.

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Guidelines for Antimicrobial Stewardship

Centers for Disease Control Guidelines for Multidrug-Resistant Organisms in Healthcare Settings (2006).
Siegel JD. Centers for Disease Control and Prev; 2006: 74

Infectious Disease Society of America Guidelines for Developing Institutional Programs to Enhance Antimicrobial Stewardship
Dellit TH. Clin Infect Dis 2007 Jan 15;44(2):159

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America
Barlam TF, Cosgrove SE, Abbo LM et al. Clin Infect Dis 2016 April 13;

CDC Guidelines for MDROs in Healthcare Settings (2006)

- Developed by experts in infection control in conjunction with CDC's Healthcare Infection Control Practices Advisory Committee
- Stresses the causal relationship between antibiotic use and resistance patterns

Recommendations:

- Staff and fund prevention programs
- Track infection rates
- Use standard infection control practices

Siegel JD. Centers for Disease Control and Prev; 2006: 74

Infectious Disease Society of America
2007 Guidelines for Developing Institutional Programs to Enhance Antimicrobial Stewardship

Elements of a successful stewardship program

- Multidisciplinary team
- Comprehensive program
- Collaboration: Pharmacy, ICC and Therapeutics committee
- Support from hospital administration

Dellit TH. Clin Infect Dis 2007 Jan 15;44(2):159

IDSA 2007 Guidelines: Key Recommendations

Proactive Core Strategies
that lead to reductions in inappropriate antimicrobial use and cost :

1. Preauthorization and formulary restriction (A-II)	Clinicians need to get approval to use restricted antibiotics before they are prescribed *(RD: last-line antibiotics that demand preserving their use to conditions where they are truly indicated)*
2. Prospective audit with intervention and feedback (A-I)	Antibiotic stewards engage the prescribing clinician after antibiotic has been used, typically after 2 to 3 days, to optimize antibiotic treatments.

Dellit TH. Clin Infect Dis 2007 Jan 15;44(2):159

Sample Prospective Audit Strategies

One-on-one patient-specific education by an ID specialist, re: disease epidemiology, local antibiograms, and clinical literature, when the pharmacy receives an order for a restricted drug.

Suggestions from an ID specialist or a clinical pharmacist on a more appropriate agent, route of administration, dosing, discontinuation of the drug, or toxicity monitoring.

Scaled-down model: use of an ID physician or pharmacist with ID training 3 days per week to review patients receiving multiple, prolonged, or high-cost courses of antimicrobial therapy.

IDSA 2007 Guideline: Supplemental Strategies (Level A Recommendation)

1. Education
2. Guidelines and clinical pathways
3. Steamlining and de-escalation
4. Dose optimization
5. IV to oral conversion

Dellit TH. Clin Infect Dis 2007 Jan 15;44(2):159

IDSA/SHEA RECOMMENDATIONS 2016

AMS programs should be led by physicians and pharmacists, including Infectious Disease specialists.

Programs shown to improve patient outcomes, reduce antibiotic resistance and save money:

- Preauthorization and prospective audit
- Syndrome-specific Intervention
- Rapid Diagnostic Testing

IDSA and SHEA Publication in Clinical Infectious Diseases. April 13, 2016

1. Preauthorization or Prospective audit and feedback

Preauthorization of broad-spectrum antibiotics and prospective review after 2 to 3 days of treatment should form the cornerstone of antibiotic stewardship programs to ensure the right drug is prescribed at the right time for the right diagnosis.

Choose one or both of these methods based on local resources and expertise.

IDSA and SHEA Publication in Clinical Infectious Diseases. April 13, 2016

2. Syndrome-specific interventions

- The guideline recommends focused, multifaceted interventions for the treatment of specific syndromes, rather than trying to improve treatment of all infections at once.
- This method makes stewardship more manageable.
- It provides a targeted and clear treatment message rather than trying to disseminate 100 different lessons at the same time.

IDSA and SHEA Publication in Clinical Infectious Diseases. April 13, 2016

3. Rapid diagnostic testing

- Rapid diagnostic testing can help determine if the cause is viral and therefore reduce the inappropriate use of antibiotics.

- Rapid testing of blood cultures in addition to conventional culture is helpful, but should be guided by the AMS team for maximum benefit to the patient.

IDSA and SHEA Publication in Clinical Infectious Diseases. April 13, 2016

IDSA 2016 Guidelines: Other recommendations

4. Reduce the use of antibiotics associated with *Clostridium difficile* infection.
   eg. cephalosporins, fluoroquinolones, clindamycin, extended-spectrum penicillins

5. Implement antibiotic time-outs to encourage prescribers to perform routine reviews of regimens.

6. Use computerized clinical decision support if possible.

IDSA and SHEA Publication in Clinical Infectious Diseases. April 13, 2016

IDSA 2016 Guidelines: Not Recommended for AMS

- Relying solely on passive educational materials is NOT recommended because any improvement will not be sustained.
- Lectures and brochures should only be used to supplement the core strategies. (preauthorization and prospective audit)
- Antimicrobial cycling: insufficient data (Level C)

IDSA and SHEA Publication in Clinical Infectious Diseases. April 13, 2016

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Research on Antibiotic Stewardship

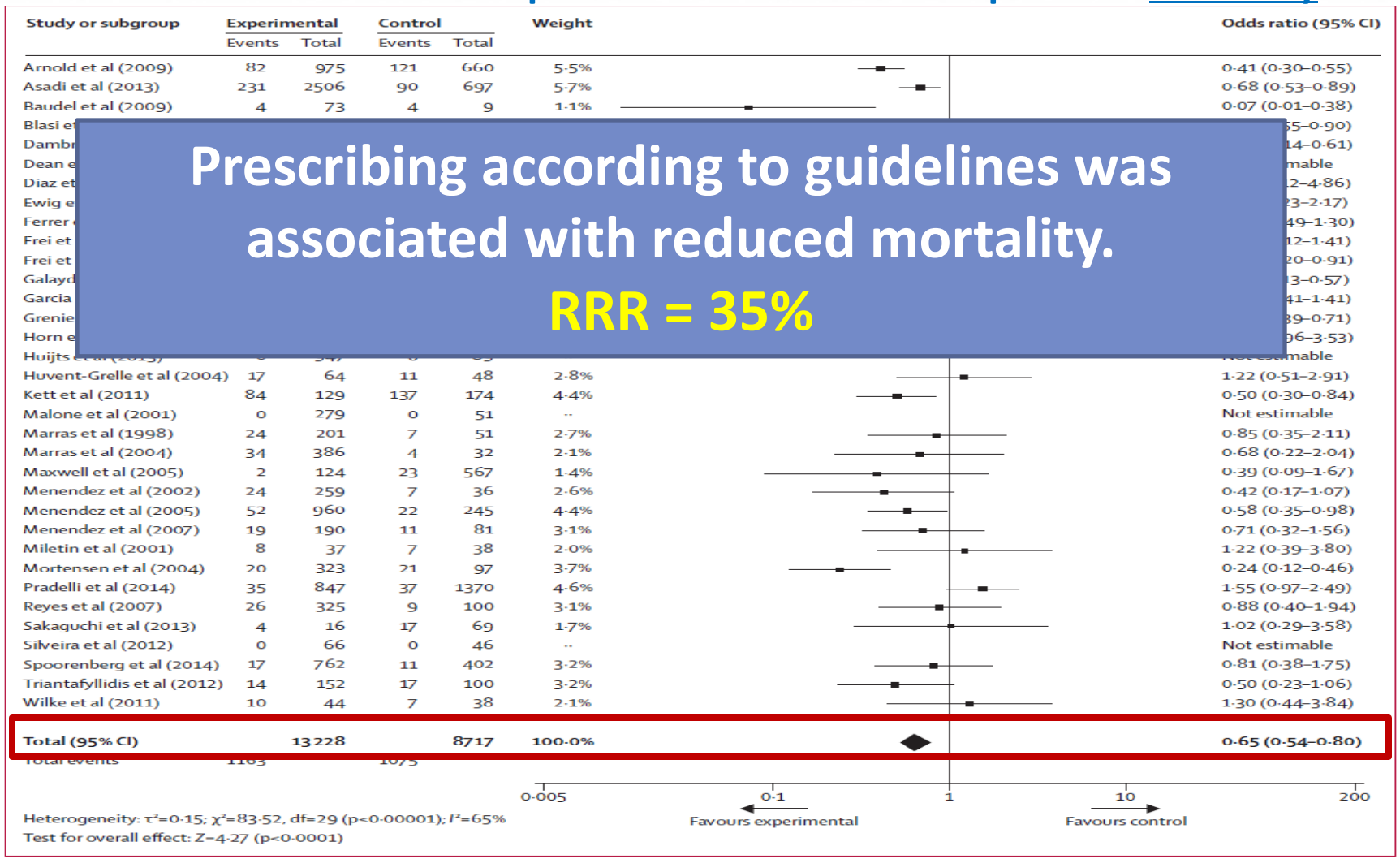
1. What is the effectiveness of AMS programs on:
    a. Primary Outcome: Patient outcomes
    b. Secondary Outcomes: prescribing, costs

2. What are the barriers to implementation and sustainability of AMS programs?

Filice G, Drekonja D et al. Antimicrobial Stewardship Program in Inpatient Settings: Evidence-based Synthesis Program. Sept 2013

1a. What is the effectiveness of AMS program on clinical outcomes?

Effect of CPG-based Empiric Antimicrobial Prescription on Mortality



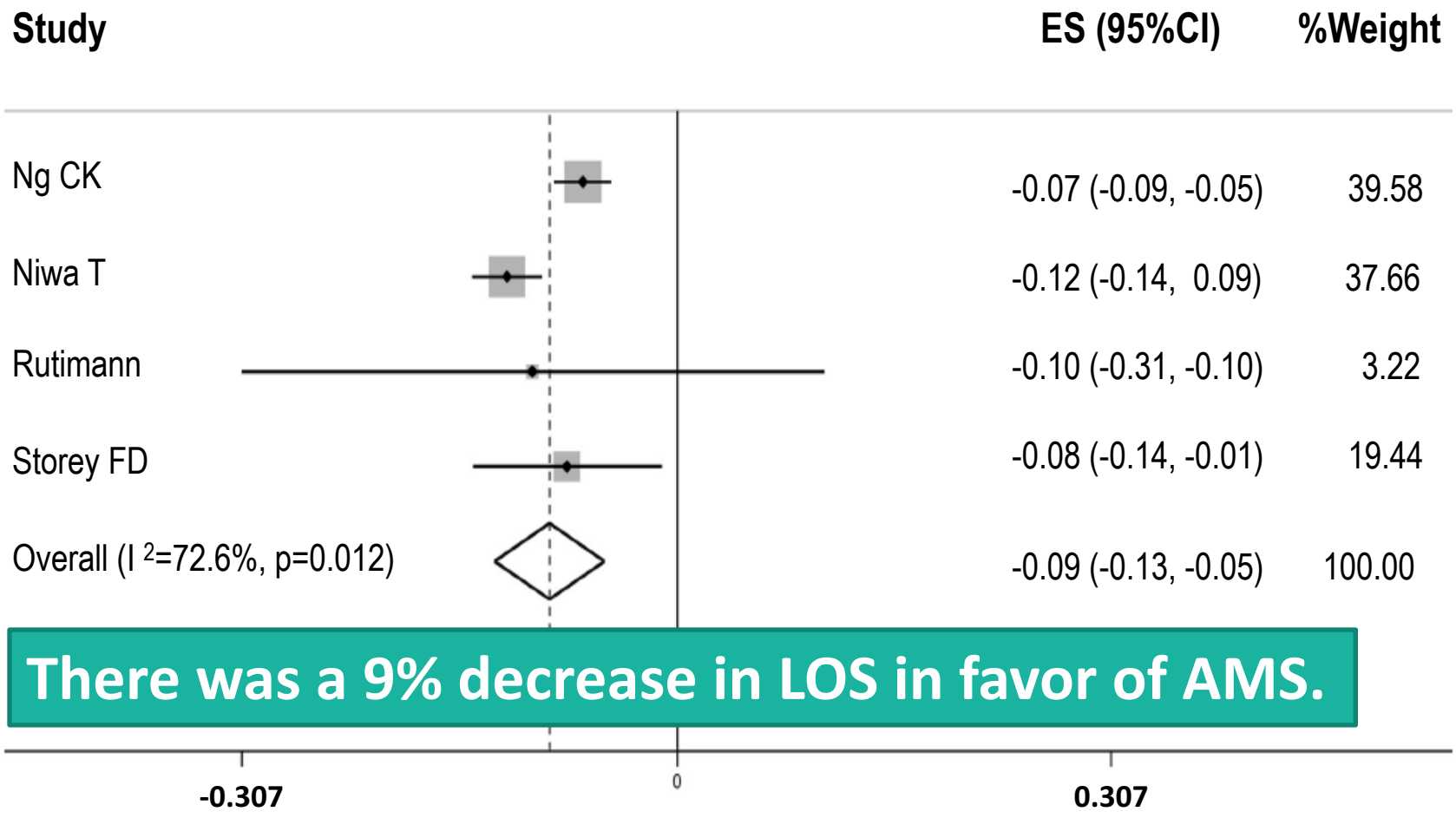
Prescribing according to guidelines was associated with reduced mortality.

RRR = 35%

Schuts EC, Hulscher ME et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Vol 16:July 2016

1a. What is the effectiveness of AMS program on clinical outcomes?

Length of Hospital Stay Outcome



There was a 9% decrease in LOS in favor of AMS.

Karanika S et al. Antimicrob Agents Chemother Aug 2016. 60(8):4840 –4852. doi:10.1128/AAC.00825-16.

1b. What is the effectiveness of AMS programs on antimicrobial prescribing?

Mean Improvement in Antimicrobial Prescribing

Intervention Type	RCT	CRCT	CBA	ITS	CITS
Persuasive	24.7%	3.5%	17.7%	42.3%	31.6%
Dissemination of educational materials	Persuasive methods advise physicians how to p…				
Reminders					
Audit and feedback	or give them feedback about ho… …bed.				
Educational outreach‡					
Restrictive	40.5%		17.1%	34.7%	
Compulsory order forms	…methods put a limit on how physicians				
Expert approval‡	…escribe; Get approval from an ID specialist in order				
Removal b…					
…change	to prescribe a restricted antibiotic.				

Interventions to improve antibiotic prescribing have been successful.

RCT = randomized controlled trial; CRCT = cluster randomized controlled trial; CCT = controlled clinical trial; CBA = controlled before and after study; ITS = interrupted time series; CITS = controlled interrupted time series; k = number of studies

*Positive change is a change in the direction of the intended change

#Includes at least 1 trial of prophylactic antimicrobials

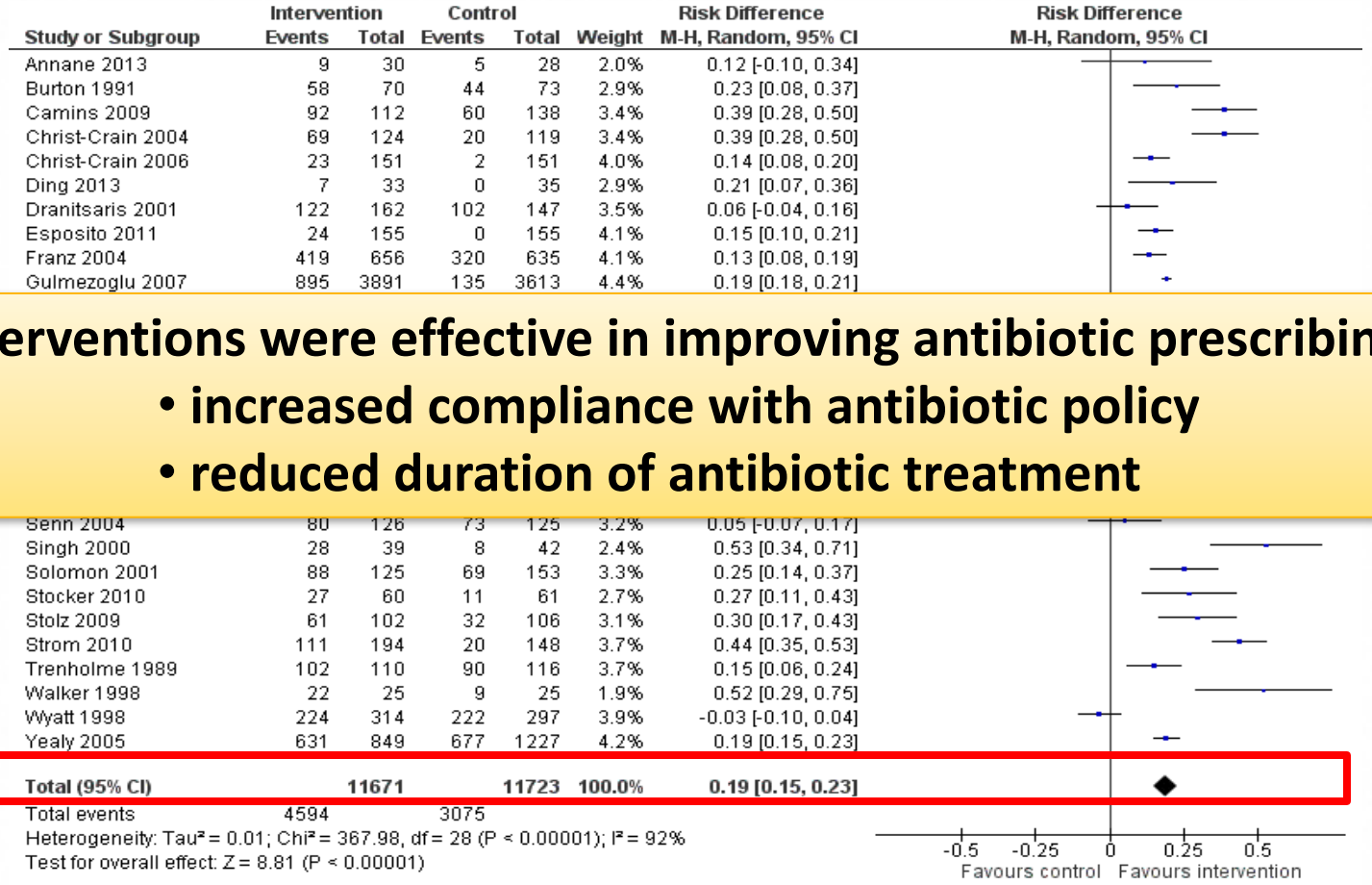
^Includes at least 1 trial from neonatal or pediatric setting

‡One additional study of this intervention type was not included in calculation of median change

†Includes one study from nursing home setting

Filice G, Drekonja D et al. Antimicrobial Stewardship Program in Inpatient Settings: Evidence-based Synthesis Program. Sept 2013

Interventions to improve antibiotic prescribing practices for hospital inpatients



Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Annane 2013	9	30	5	28	2.0%	0.12 [-0.10, 0.34]
Burton 1991	58	70	44	73	2.9%	0.23 [0.08, 0.37]
Camins 2009	92	112	60	138	3.4%	0.39 [0.28, 0.50]
Christ-Crain 2004	69	124	20	119	3.4%	0.39 [0.28, 0.50]
Christ-Crain 2006	23	151	2	151	4.0%	0.14 [0.08, 0.20]
Ding 2013	7	33	0	35	2.9%	0.21 [0.07, 0.36]
Dranitsaris 2001	122	162	102	147	3.5%	0.06 [-0.04, 0.16]
Esposito 2011	24	155	0	155	4.1%	0.15 [0.10, 0.21]
Franz 2004	419	656	320	635	4.1%	0.13 [0.08, 0.19]
Gulmezoglu 2007	895	3891	135	3613	4.4%	0.19 [0.18, 0.21]
Senn 2004	80	126	73	125	3.2%	0.05 [-0.07, 0.17]
Singh 2000	28	39	8	42	2.4%	0.53 [0.34, 0.71]
Solomon 2001	88	125	69	153	3.3%	0.25 [0.14, 0.37]
Stocker 2010	27	60	11	61	2.7%	0.27 [0.11, 0.43]
Stolz 2009	61	102	32	106	3.1%	0.30 [0.17, 0.43]
Strom 2010	111	194	20	148	3.7%	0.44 [0.35, 0.53]
Trenholme 1989	102	110	90	116	3.7%	0.15 [0.06, 0.24]
Walker 1998	22	25	9	25	1.9%	0.52 [0.29, 0.75]
Wyatt 1998	224	314	222	297	3.9%	-0.03 [-0.10, 0.04]
Yealy 2005	631	849	677	1227	4.2%	0.19 [0.15, 0.23]
Total (95% CI)		**11671**		**11723**	**100.0%**	**0.19 [0.15, 0.23]**
Total events	4594		3075			

Heterogeneity: Tau² = 0.01; Chi² = 367.98, df = 28 (P < 0.00001); I² = 92%
Test for overall effect: Z = 8.81 (P < 0.00001)

Risk Difference M-H, Random, 95% CI

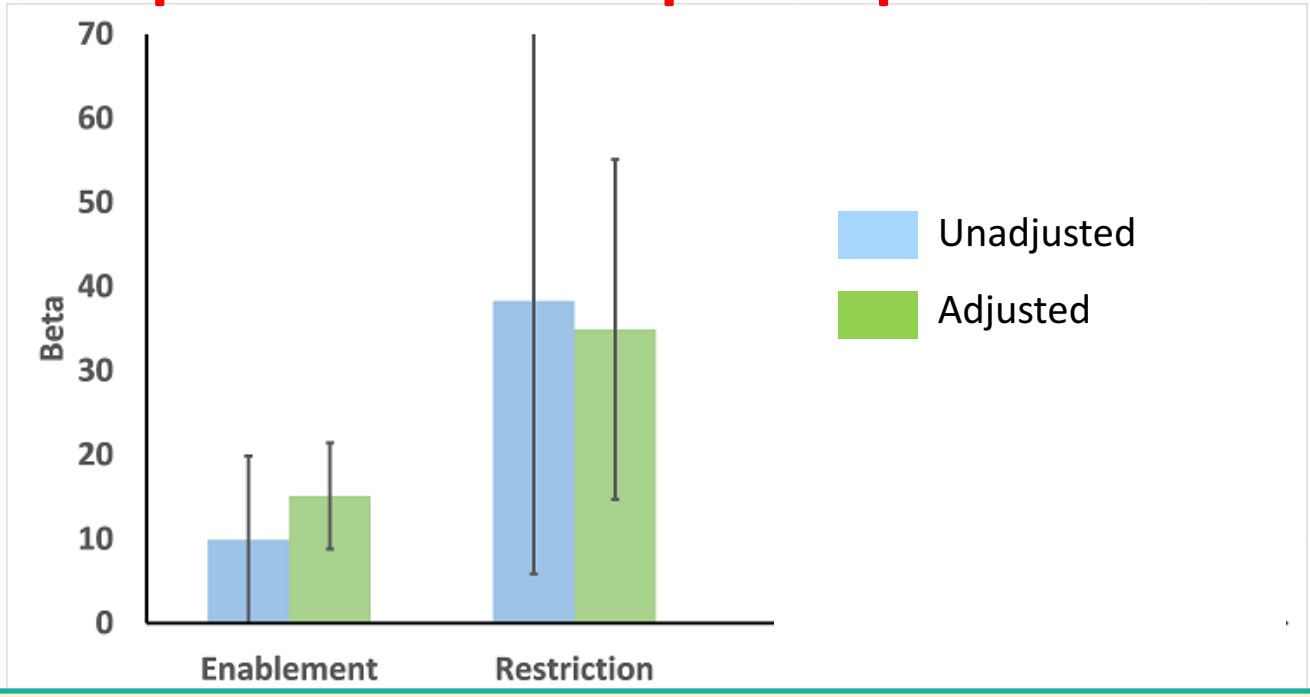
-0.5 -0.25 0 0.25 0.5
Favours control Favours intervention

Interventions were effective in improving antibiotic prescribing:

- **increased compliance with antibiotic policy**
- **reduced duration of antibiotic treatment**

Cochrane Database of Systematic Reviews
9 FEB 2017 DOI: 10.1002/14651858.CD003543.pub4
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003543.pub4/full#CD003543-fig-0003

Interventions to improve antibiotic prescribing practices for hospital inpatients



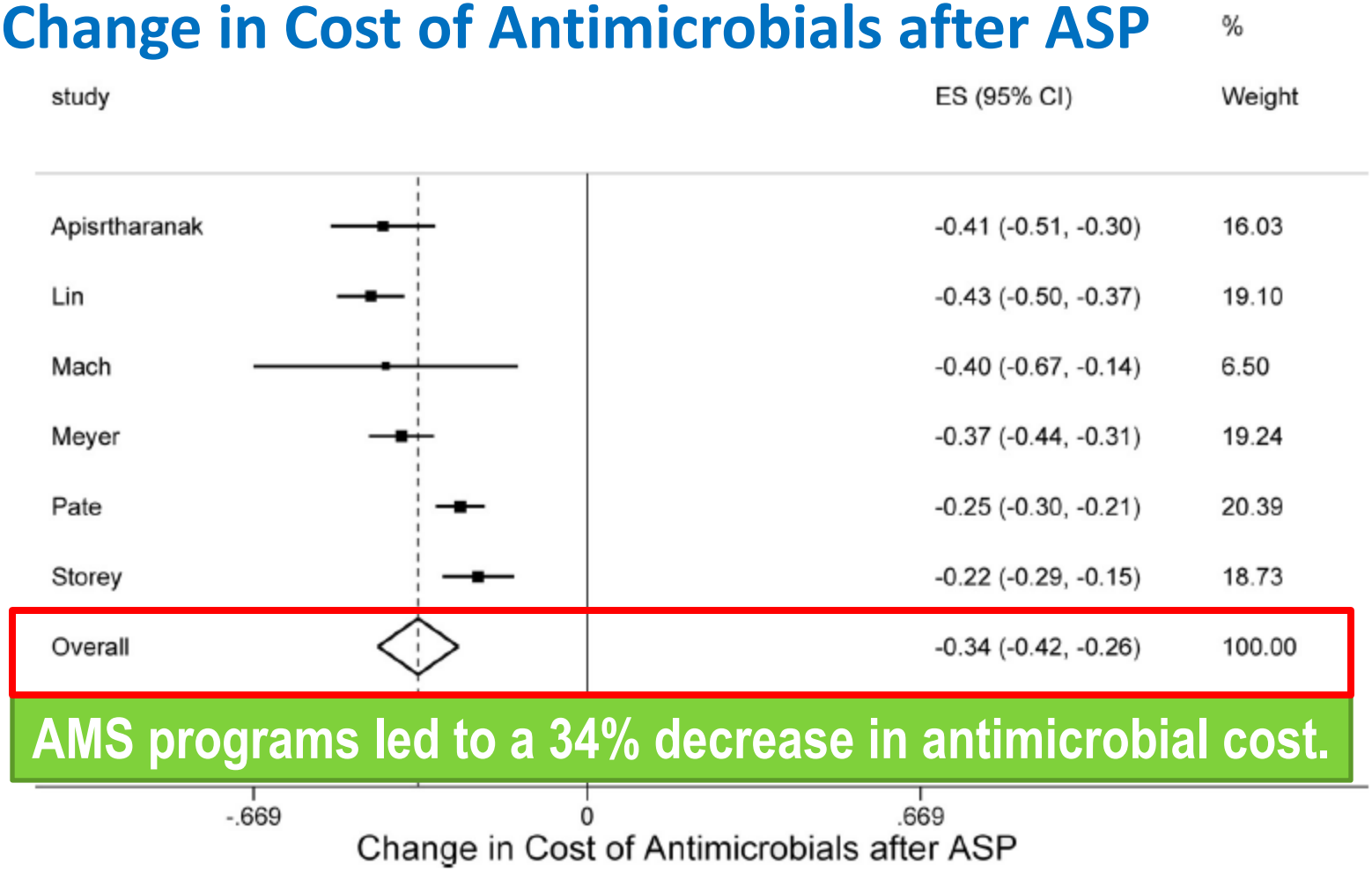
Enablement increased the effect of interventions, including those with a restrictive component.

Those that provided advice or feedback and restriction to physicians were effective in improving prescribing practices than those that did not.

Cochrane Database of Systematic Reviews. 9 FEB 2017 DOI: 10.1002/14651858.CD003543.pub4

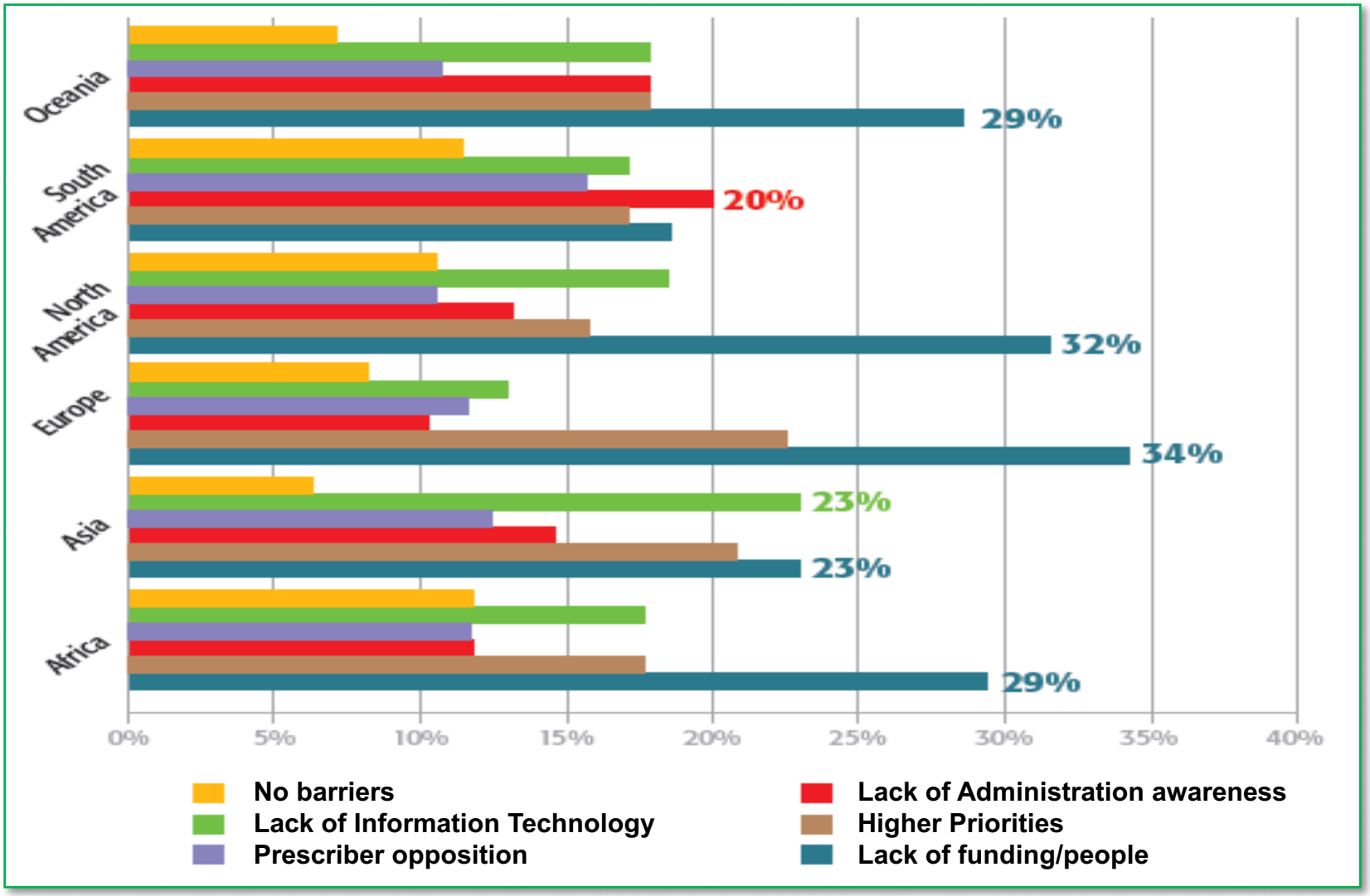
1c. What is the effectiveness of AMS programs on cost of antimicrobials?

Change in Cost of Antimicrobials after ASP



Karanika S et al. Antimicrob Agents Chemother Aug 2016. 60(8):4840 –4852.

2. What are the barriers to implementation and sustainability of inpatient AMS programs?



First global survey of antimicrobial stewardship (AMS), Howard P. et al., ESCMID Study Group for Antimicrobial Policies (ESGAP) & ISC Group on Antimicrobial Stewardship ECCMID 2013, Berlin Presentation Nr. 2448.

AMS in Pediatrics:
Focusing on the challenges clinicians face

Parameters with GREATEST IMPACT in decreasing antimicrobial use	Staff Pediatrician	Pediatric Resident
Decreasing the length of antimicrobial therapy	2 (4.4)	4 (12.9)
Discontinuing antimicrobials if there is no documented infection	28 (60.9)	11 (35.5)
Early conversion from intravenous to oral therapy	3 (6.5)	1 (3.2)
Narrow spectrum antibiotics versus broad spectrum antibiotics	9 (19.6)	15 (48.4)
Antimicrobial stewardship parameter MOST DIFFICULT TO ACHIEVE		
Decreasing the length of antimicrobial therapy	9 (20.9)	6 (19.4)
Discontinuing antimicrobials if there is no documented infection	21 (48.8)	9 (29.0)
Early conversion from intravenous to oral therapy	5 (11.6)	5 (16.1)
Narrow spectrum antibiotics versus broad spectrum antibiotics	8 (18.6)	11 (35.5)

Pediatricians perceived that discontinuing empiric antimicrobials was the most difficult to achieve.

Bowes et al. *BMC Pediatrics* 2014. 14:212

Bowes *et al. BMC Pediatrics* 2014, **14**:212
http://www.biomedcentral.com/1471-2431/14/212

BMC Pediatrics

RESEARCH ARTICLE Open Access

Antimicrobial stewardship in pediatrics: focusing on the challenges clinicians face

Jennifer Bowes[1], Abdool S Yasseen III[1], Nicholas Barrowman[1], Barbara Murchison[1], Judy Dennis[2], Katherine A Moreau[1], Nisha Varughese[2] and Nicole Le Saux[1,2*]

In a pediatric setting, diagnostic uncertainty plays an important role in starting empiric antimicrobials.

Challenges identified include:

- Improving knowledge on local antibiogram
- Focusing on discontinuation of antimicrobials

Bowes et al. *BMC Pediatrics* 2014. 14:212

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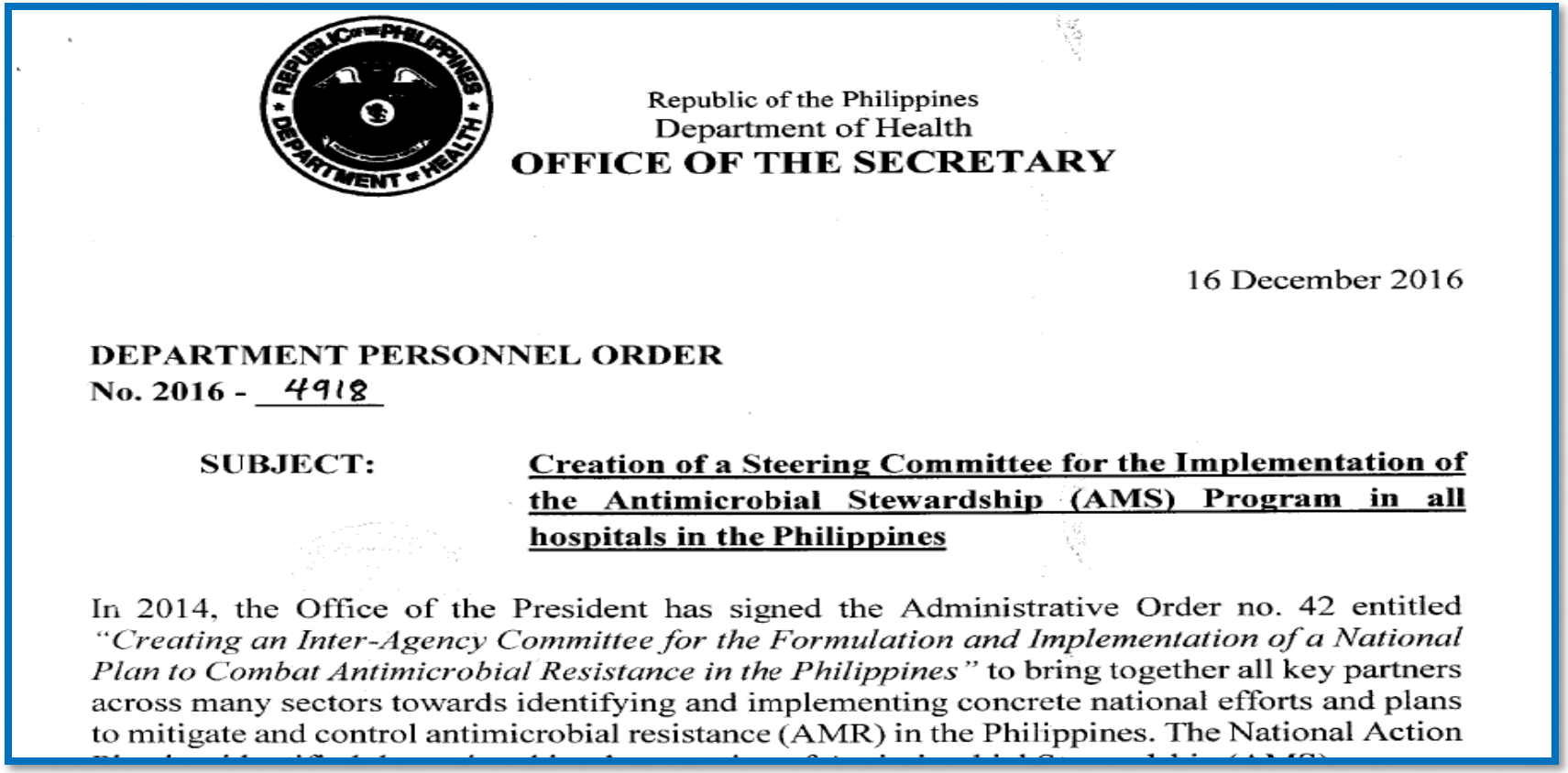
Research Gaps: What are missing?

- Potential harms, sustainability, and costs of AMS
- Comparative effectiveness trials to identify the most effective approach.
- Cluster RCTs may be the most feasible way to provide high-quality evidence. *Contamination may exist in studies randomized at the subject level.*

Large healthcare organizations could play a role by providing a venue for multiple sites but with shared data.

What has been done by the DOH?

Dec 2016: Creation of a steering committee to oversee the implementation of AMS program in all hospitals in the Philippines.



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

16 December 2016

DEPARTMENT PERSONNEL ORDER
No. 2016 - 4918

SUBJECT: **Creation of a Steering Committee for the Implementation of the Antimicrobial Stewardship (AMS) Program in all hospitals in the Philippines**

In 2014, the Office of the President has signed the Administrative Order no. 42 entitled *"Creating an Inter-Agency Committee for the Formulation and Implementation of a National Plan to Combat Antimicrobial Resistance in the Philippines"* to bring together all key partners across many sectors towards identifying and implementing concrete national efforts and plans to mitigate and control antimicrobial resistance (AMR) in the Philippines. The National Action

Steering Committee Members from DOH Units

Chairperson: **Regina Berba, MD**

Name	Position	Office
Faye Diana C. Chua, RPh	Devt Mgt Office IV	Health Facilities Development Bureau
Maria Rosa Abad, MD	Medical Specialist II	Health Facilities / Services Regulatory Br.
Lyndon Lee Suy, MD	Director III	Disease Prevention and Control Bureau
Genesis Samonte, MD	MS III, OIC-PSHD	Epidemiology Bureau
Celia C. Carlos, MD	Director III	
	Head, ARSP	RITM
Charmian Hufano, MD	MS II	RITM
Jonathan Michael Ele, MD	MS III	PHIC
Mediadora C. Saniel, MD	Chairperson	National Antibiotic Guidelines Committee
Mary Ann D. Lansang, MD	Member	National Antibiotic Guidelines Committee

Steering Committee Member Societies

- Philippine Medical Association (PMA)
- **Pediatric Infectious Disease Society of the Philippines (PIDSP)**
- Philippine Society for Microbiology and Infectious Disease (PSMID)
- **Philippine Pediatric Society, Inc. (PPS)**
- Philippine College of Physicians (PCP)
- Philippine Hospital Infection Control Society (PHICS), Inc.
- Philippine Hospital Infection Control Nurses (PHICNA), Inc.
- Philippine Society of Pathologist (PSP)
- Philippine Pharmacists Association (PPhA)
- Philippine Society of Hospital Pharmacist (PSHP)
- Philippine Association of Medical Technologist (PAMET)
- Philippine Hospital Association (PHA)
- Private Hospital Association of the Philippines (PHAPi)

AMS PROGRAM in the Philippines:
Where are we now and where are we heading?

Training status	Public Hospitals		Private Hospitals
Level III	DOH-retained	LGU	
Trained	14	1	1 (TMC)
For Training	22	12	2 (SLH, MMC)
Level II			
For Training	48		314 (Level II and III)
Level I			
For Training	320		454

PLANNED ROLL-OUT	
April 2017	Level III Pilot hospitals
August 2017	Level III DOH-retained and LGU hospitals
November 2017	Level III Private hospitals
2018	Level I and II Private hospitals

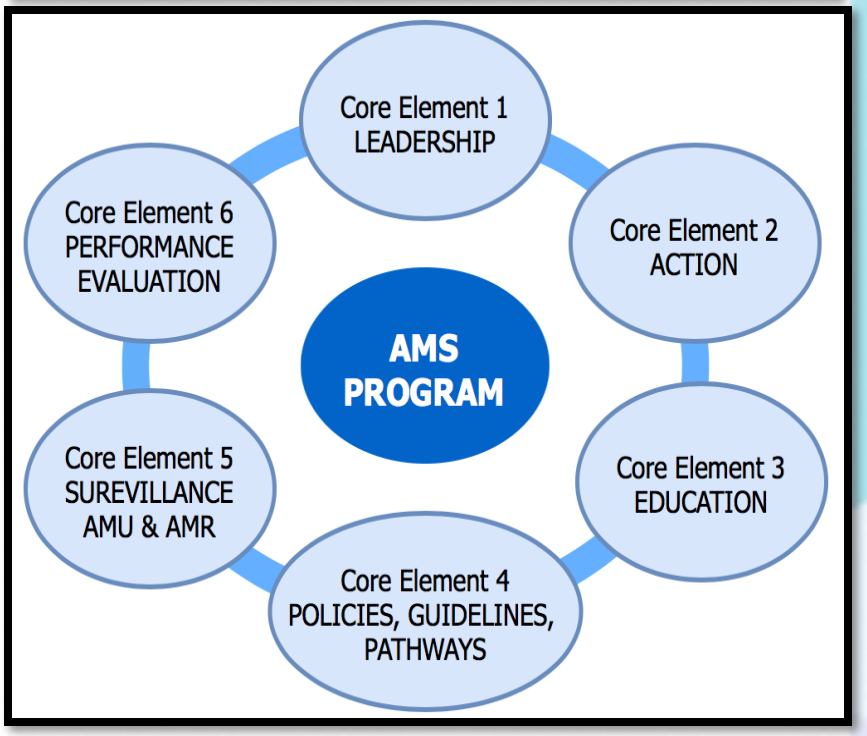
AMS PROGRAM in the Philippines:

Where are we now and where are we heading?

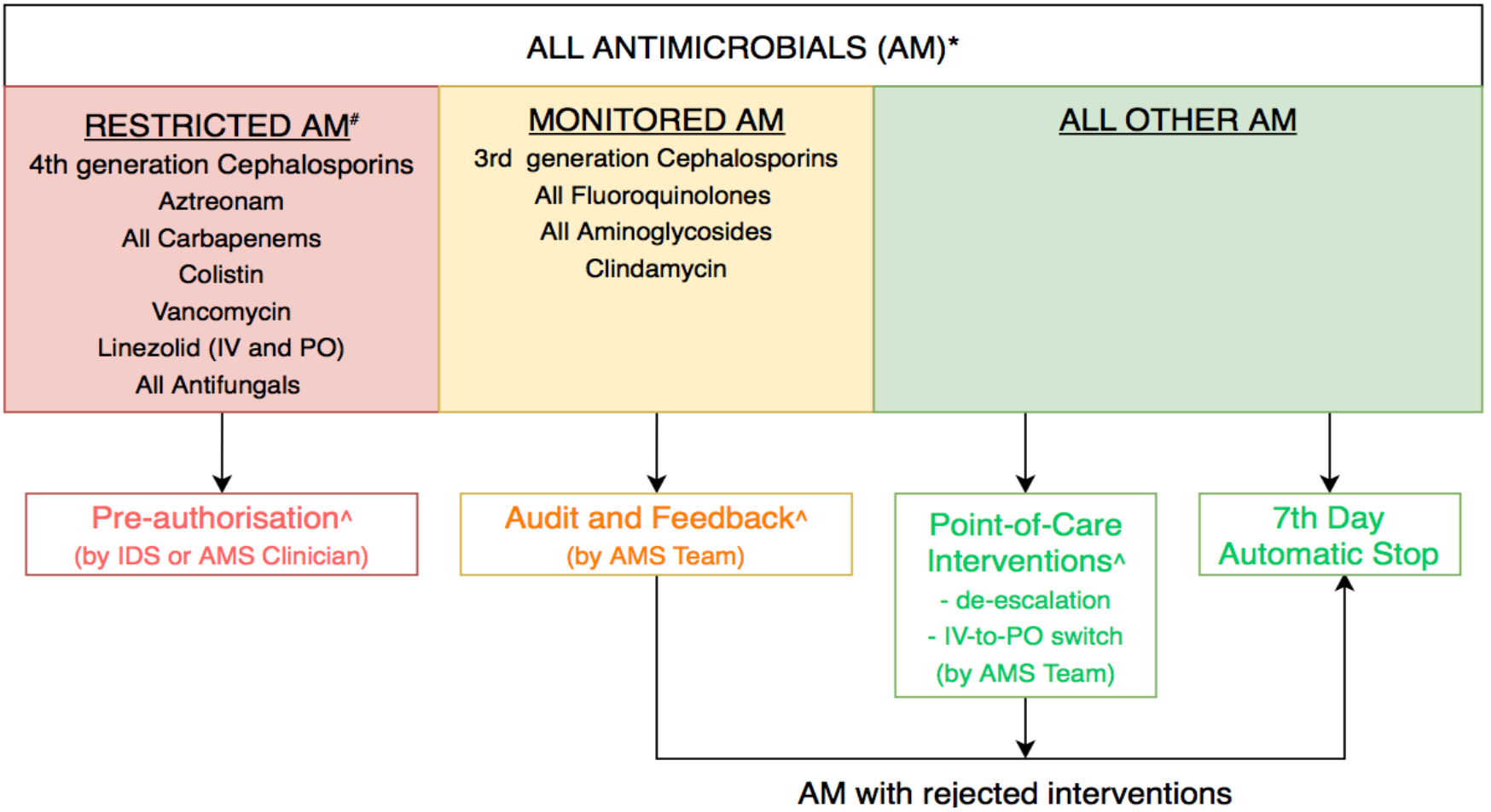
MANUAL OF PROCEDURES FOR IMPLEMENTING ANTIMICROBIAL STEWARDSHIP PROGRAMS IN HOSPITALS

Department of Health
2016

Core Elements of an AMS Program



AMS Actions based on the DOH Manual of Procedures



* AM prescribed by IDS are not subjected to the above AM Action strategies, provided IDS states approved duration of use. Dosing POC interventions are to performed for all AM.

Restriction and Pre-authorisation applies to both inpatient and outpatient prescriptions.

^ All recommendations by IDS, designated approver and AMS Team must be accompanied by duration of use. Subsequent extension of duration will require approval by the relevant IDS, designated approver or AMS Team.

PIDSP AMS Program Initiative

EVALUATION OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM IN THE DEPT OF PEDIATRICS IN SELECTED PRIVATE HOSPITALS IN THE PHILIPPINES

Controlled clinical trial
with mixed methods of intermittent time series data collection.

- Baseline data collection:
  - Point Prevalence survey (antibiotic use, antibiotic resistance)
  - Perception Survey, Situational assessment (KAP on AMS, situation in the hospitals, existing hospital AMS activities)
- Intervention: site-specific AMS program
- Evaluation: based on specific outcome measures

Golden Rules of Antimicrobial Prescribing

M - Microbiology should guide therapy whenever possible.

I - Indications should be evidence-based.

N - Narrowest spectrum must be ordered.

D - Dosage must be appropriate to site / type of infection.

M - Minimum duration of therapy must be given.

E - Ensure monotherapy in most cases.

Summary

- AMS improves patient outcomes and antimicrobial prescribing.
- The 2016 IDSA guideline recommends:
  - **preauthorization and prospective audit of antibiotics**
  - **syndrome-specific Intervention**
  - **rapid diagnostic testing**
- The recommended supplemental approaches to AMS are:
  - **Education**
  - **Guidelines and clinical pathways**
  - **De-escalation**
  - **Dose optimization**
  - **Parenteral to oral switch**
- The DOH and PIDSP are one in promoting AMS.

Take Home Message:

Antimicrobial stewardship is a team game with the patient at the center and it is our teamwork that will make the dream work.

"If we use antibiotics when not needed,
we may not have them when they are most needed."

Dr. Tom Frieden
Director U.S. CDC