Antibiotic stewardship and Infection Prevention: The two sides of the same coin

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Η αντιμικροβιακή αντοχή είναι μια σιωπηλή πανδημία και μια τεράστια παγκόσμια απειλή

AMR is one of the top 10 global health threats[1]

Global Study* estimated 4.95 million deaths associated with bacterial AMR in 2019[2]

- Including 1.27 million deaths attributable to bacterial AMR in 2019
- Lower respiratory infections accounted for more than 1.5 million deaths
- Six leading pathogens for deaths associated with resistance: *Escherichia coli*, *Staphylococcus aureus*, *Klebisella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumanni*, and *Pseudomonas aeruginosa*

Annual deaths projected to exceed 10 million by 2050[3]

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS[4]		
Priority 1: CRITICAL	**Priority 2: HIGH**	**Priority 3: MEDIUM**
Acinetobacter baumannii, carbapenem-resistant ***Pseudomonas aeruginosa***, carbapenem-resistant **Enterobacteracterales**[a], carbapenem-resistant, third-generation cephalosporin-resistant	***Enterococcus faecium***, vancomycin-resistant ***Staphylococcus aureus***, methicillin-resistant, vancomycin-intermediate and -resistant ***Helicobacter pylori***, clarithromycin-resistant ***Campylobacter***, fluoroquinolone-resistant ***Salmonella*** spp., fluoroquinolone-resistant ***Neisseria gonorrhoeae***, third-generation cephalosporin-resistant, fluoroquinolone-resistant	***Streptococcus pneumoniae***, penicillin–non-susceptible ***Haemophilus influenzae***, ampicillin-resistant ***Shigella*** spp., fluoroquinolone-resistant

AMR, antimicrobial resistance; *Global Burden Diseases, Injuries, and Risk Factors Study (GBD 2019) provides age-specific, sex-specific estimates of disease burden for 369 diseases and injuries in 204 countries and territories in 1990-2019; R&D, research and development; [a]Enterobacterales include: *Klebsiella pneumonia*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp, and *Morganella* spp.

1. Ten Threats to Global Health in 2019. Geneva: World Health Organization; 2019 (https://www.who. int/news-room/spotlight/ten-threats-to-globalhealth-in-2019), Accessed 6 October 2022 **2.** Collaborators GBDAR. *Lancet*. Dec 17 2023;400.
3. AMR Review. 2016. Accessed December 22, 2022. Home | AMR Review (amr-review.org) **4**. WHO. February 27, 2017. Accessed December 19, 2022. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis (who.int)

Strong link between antimicrobial use and resistance

Table 2. Antibiotic Use and Antibiotic Resistance Rates for Methicillin-Resistant *Staphylococcus aureus* and Carbapenemase-Producing *Klebsiella* Bacteremia Isolates

Pathogen	Country	Antibiotic Usage[a]	Rate of Resistance
Klebsiella[b]	Greece	38	38%
	The Netherlands	11	0.20%
MRSA[c]	Greece	38	51%
	The Netherlands	11	1.60%

Rates are for 2010–2011, for intensive care units in the Netherlands [19] and Greece [20].

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Daily drug dose per 1000 inhabitants.

[b] Bacteremic *Klebsiella*: rate with carbapenemase-producing strains.

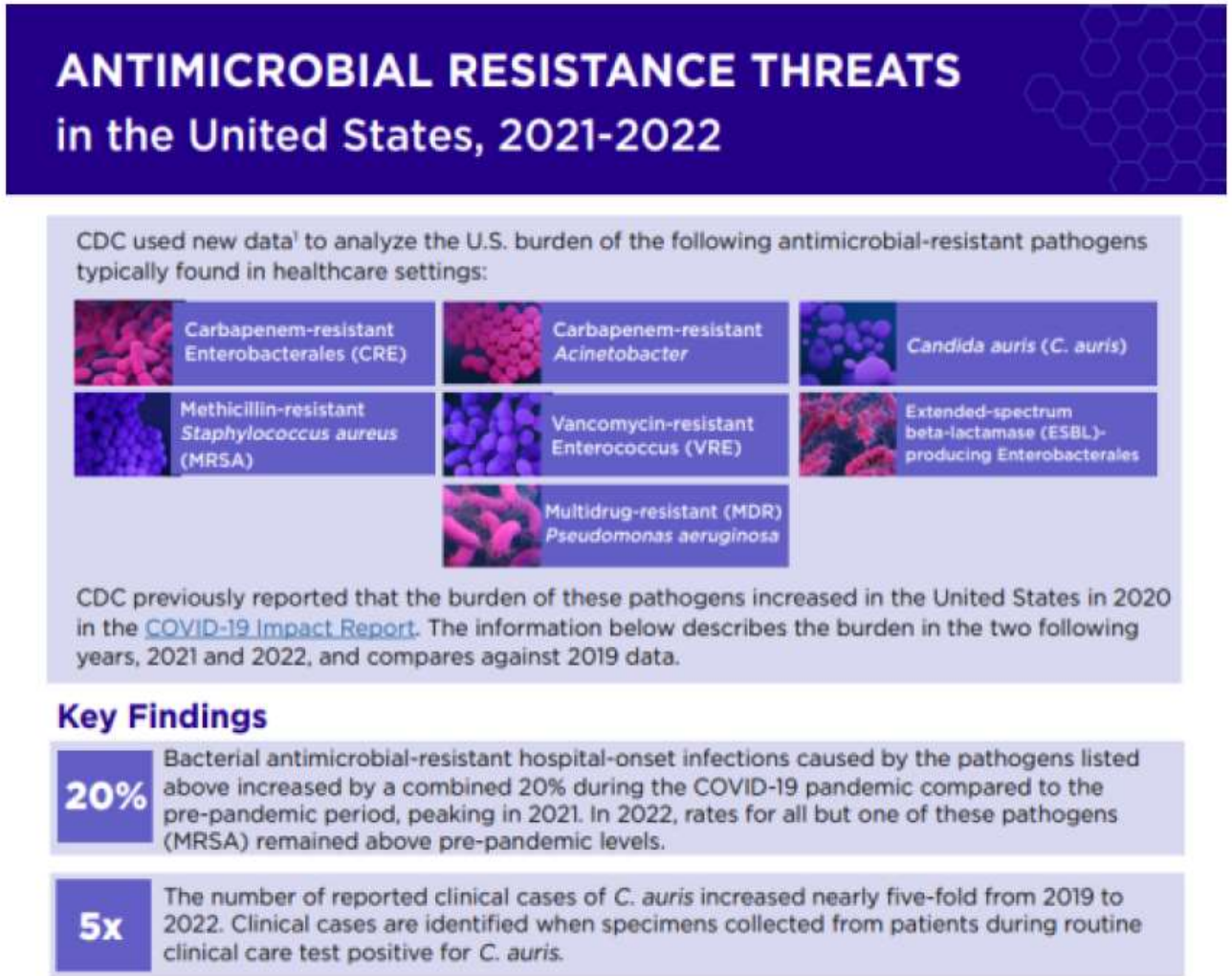
[c] MRSA relative to all *S. aureus* isolates.

- Excessive and/or inappropriate use leads to
- Increased resistance
- *C. difficile*
- Increased morbidity
- Increased cost
- Reduce quality of life
- Patients infected by drug resistant bacteria have a 2-fold increase in mortality

Bartlett JG et al. Clin Infect Dis 2013

Antimicrobial Resistance (AR) is a public health threat.

- AR is an urgent global public health threat, killing at least 1.27 million people worldwide in 2019.
  - Associated with 5 million deaths.
- In the U.S., more than 2.8 million antimicrobial-resistant infections occur each year.
  - More than 35,000 people die as a result.



Antimicrobial Resistance Facts and Stats | Antimicrobial Resistance | CDC
Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis - The Lancet

Combating antimicrobial resistance

- To overcome the threat of antimicrobial resistance, a three-pillar approach has been advocated:

1. ASP : Optimise the use of existing antimicrobial agents

2. infection control : Prevent the transmission of drug-resistant organisms

3. Improve environmental decontamination

NO ACTION TODAY
NO CURE TOMORROW

Hospital Infection Prevention: Mission & Scope

Mission:

- Surveillance for hospital acquired infections (HAIs) & epidemiologically significant organisms
- Develop strategies to prevent HAIs and organism transmission
- Respond to exposures and outbreaks

Hospital Infection Prevention: Broad Scope

- Central Line Associated Bloodstream Infections (CLABSIs)
- Surgical-site Infection (SSI)
- Ventilator Associated Pneumonia (VAP)
- Catheter-associated Urinary Tract Infection (CAUTI)
- **NEW:** Hospital Onset Bacteremia (HOB)

- Multi-Drug Resistant Organisms (MDRO):
  - MRSA
  - ESBL
  - CRE
  - MDR Gram Negatives
  - *C. auris*
- *C. difficile*
- Respiratory viruses:
  - Influenza
  - Measles
- Pandemic threats: COVID-19, MERS, Zika

Actions to prevent and control antimicrobial resistance and nosocomial infections

Hospital Infection Prevention: Multi-faceted Strategies

Hospital Policy & Practices

- Hand hygiene
- Personal protective equipment (PPE)
- Environmental cleaning/disinfection
- Instrument sterilization & disinfection
- Waste management
- Risk & regulatory

Prevention & Response

- Surveillance & monitoring
- Compliance with policy & practices
- Isolation & cohorting
- Exposure & outbreak response
- Education & training: staff, patients, visitors

ANTIMICROBIAL STEWARDSHIP

- Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting optimal
  - Drug regimen
  - Dose
  - Duration of therapy
  - Route of administration
- For the best clinical outcome for the treatment or prevention of infection
- With minimal toxicity to the patient and minimal impact on resistance and other ecological adverse events such as C. difficile”

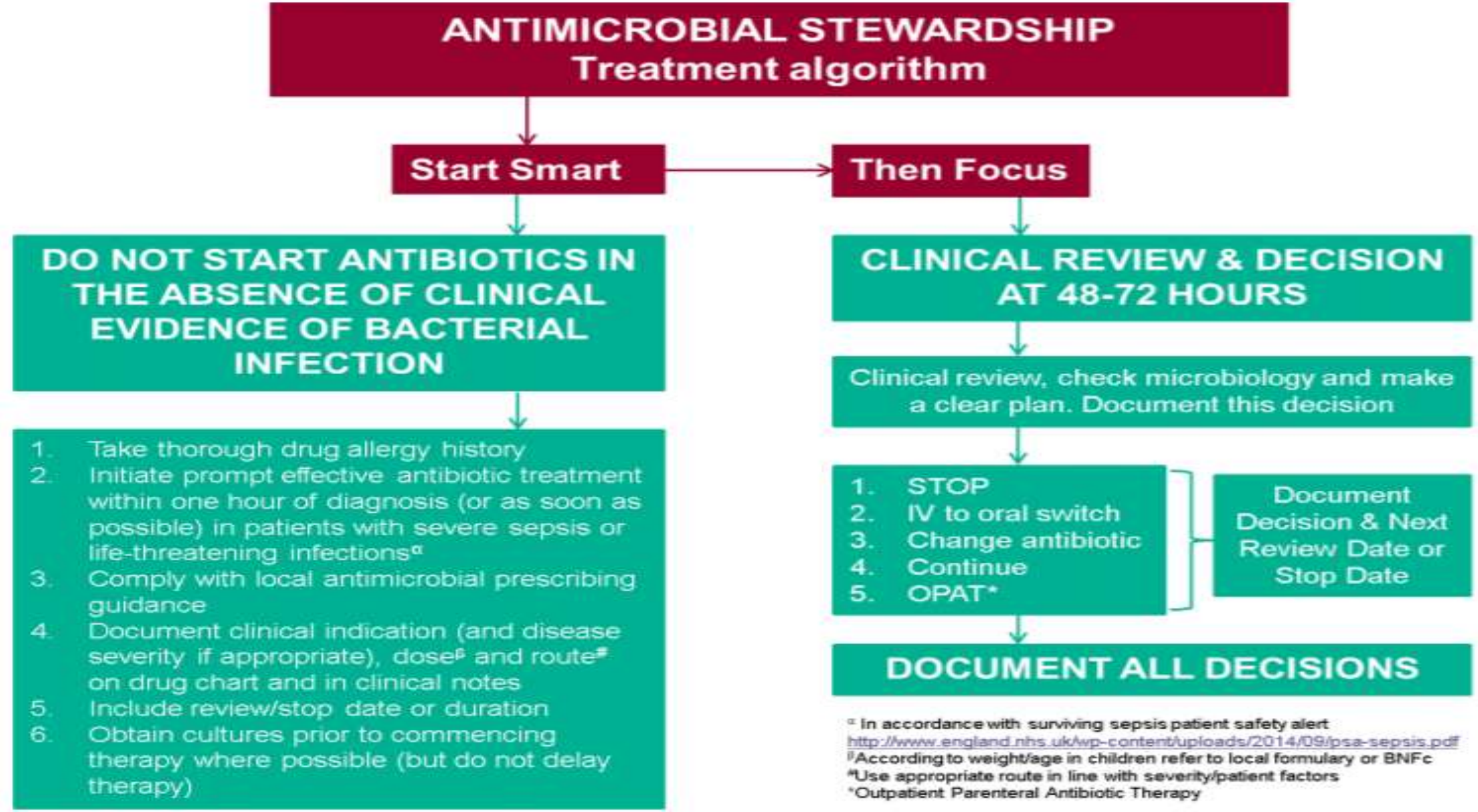
- Right antibiotic
- Right patient
- Right time
- RIght dose
- Right route
- Causing the least harm to the patient and future patients

Dellit et al. Clin Infect Dis 2007;44:159–77
Nathwani et al., 2012

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.



IV, intravenous; OPAT, outpatient parenteral antibiotic therapy.

Antimicrobial Stewardship Toolkit for English Hospitals, Public Health England. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF. Accessed October 2020.

Infection prevention & antimicrobial stewardship

- **Interestingly, infection control and stewardship interventions appear to be running 'in real life' on two separate paths with limited crosstalk.**
- The infection prevention & antimicrobial stewardship partnership is bidirectional.
  - Where there is no transmission of infection, there is no need for antimicrobial treatment, thus reducing the development of resistance.

- Utilizing antimicrobial stewardship as one of the infection prevention patient safety care bundle strategies to prevent the development of MDROs and *C. difficile* helps healthcare organizations effectively use limited healthcare resources and improve patient outcomes.

Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant *Staphylococcus aureus* infections across a region of Scotland: a non-linear time-series study

- Interventions included
  - Restricting the use of both 4C (cephalosporins, co-amoxiclav, clindamycin, and fluoroquinolones) and macrolide antibiotics, in addition to a
  - Hand hygiene campaign
  - Screening for MRSA upon admission

Laws et al. Lancet Infect Dis 2015

Potential effects of infection control measures and antibiotic stewardship

	Without intervention	With intervention	Marginal difference in MRSA prevalence density associated with successive interventions			MRSA cases prevented per year (95% CI)
			Absolute reduction (95% CI)	p value	Relative reduction† (95% CI)	
Hospitals						
Hand hygiene campaign (January, 2007)	1·890	1·500	0·390 (−0·527 to 1·307)	0·448	21% (−27 to 69)	246 (−316 to 822)
Universal screening (August, 2008)	1·417	1·129	0·288 (−0·725 to 1·53)	0·495	20% (−51 to 92)	180 (−444 to 796)
Hospital antibiotic stewardship (May, 2009)	1·091	0·499	0·592 (0·001 to 1·180)	0·049	54% (1 to 100)	355 (1 to 714)
Combined	1·890	0·947	0·943 (0·267 to 1·619)	0·006	50% (14 to 86)	592 (168 to 1017)
Community						
Indirect effects (hospital interventions)*	0·071	0·045	0·026 (0·008 to 0·038)	0·001	32% (11 to 54)	390 (128 to 652)
Primary care antibiotic stewardship (May, 2009)	0·045	0·028	0·017 (0·004 to 0·029)	0·012	37% (9 to 64)	281 (71 to 491)
Combined	0·071	0·038	0·033 (0·018 to 0·048)	<0·0001	47% (25 to 68)	567 (311 to 822)

Data are MRSA prevalance density in cases per 1000 OBDs (hospital) or cases per 10 000 IDs (community), unless indicated otherwise. Differences are calculated between observed (with intervention) and forecasted (without intervention) scenarios. MRSA=meticillin-resistant *Staphylococcus aureus*. OBDs=occupied bed days. IDs=inhabitants per day. *Effects of hospital-based interventions on community MRSA via reduction in hospital MRSA prevalence density (a predictor of rates in the community). †Described as (MRSA prevalence density without intervention—prevalence density with intervention)/MRSA prevalence density without intervention.

The highest impact was achieved by combined AMS and IPC measures, which reduced the prevalence density of MRSA by 50% in hospitals and by 47% in the community.

Laws et al. Lancet Infect Dis 2015

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

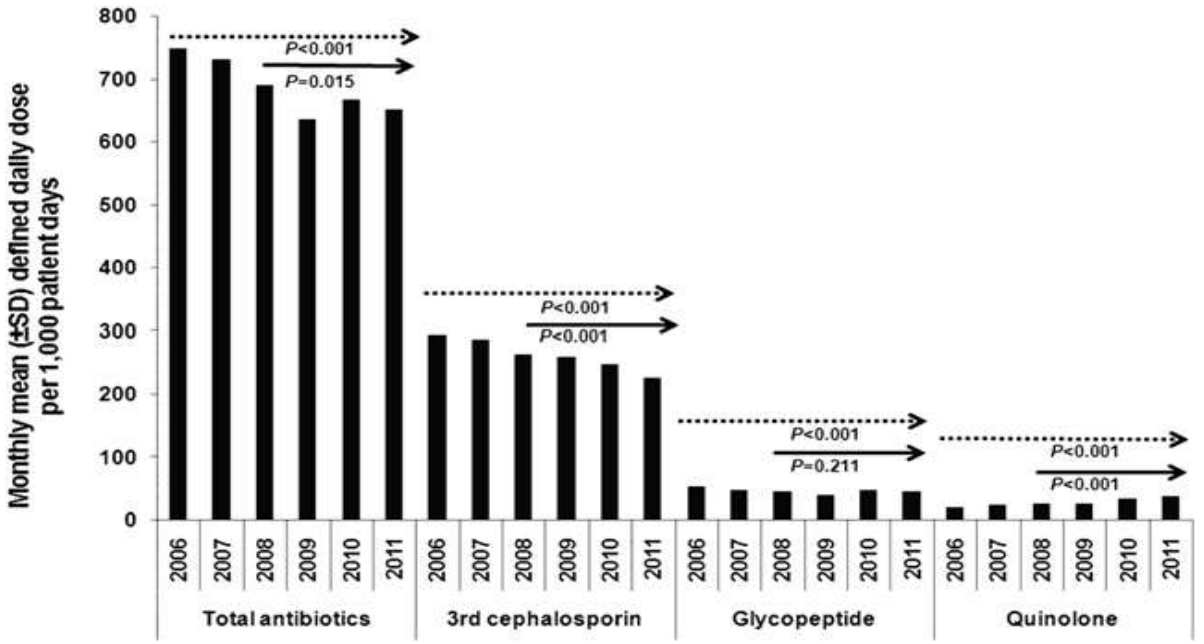
Trend of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in an institution with a high rate of MRSA after the reinforcement of antibiotic stewardship and hand hygiene

- Antibiotic stewardship and hand hygiene programs were reinforced in a 2,000-bed tertiary hospital in South Korea where the MRSA rate is about 65%.
- The computerized prescription restriction was implemented in August 2008.
- "Hand hygiene program," consistent with WHO guideline, was reinforced in December 2008.
- We assessed the effect of the infection control programs on the incidence of MRSA bloodstream infection (BSI) from January 2006 through November 2011

Kim et al. Am J Infect Control 2013;41:e39e43

Trend of MRSA bacteremia in an institution with a high rate of MRSA after the reinforcement of antibiotic stewardship and hand hygiene

- Monthly mean antibiotic consumption decreased from 690.54 ± 28.33 DDD per 1,000 patients-days in 2008 to 652.47 ± 20.77 (P= .015) in 2011.
- The rates of performance in hand hygiene increased from 43% in 2008 to 83% in 2011 (P = .043).
- **Incidence of MRSA BSI was reduced from 0.171 per 1,000 patient-days in 2009 to 0.116 per 1,000 patient-days in 2011 (P = .009)**.

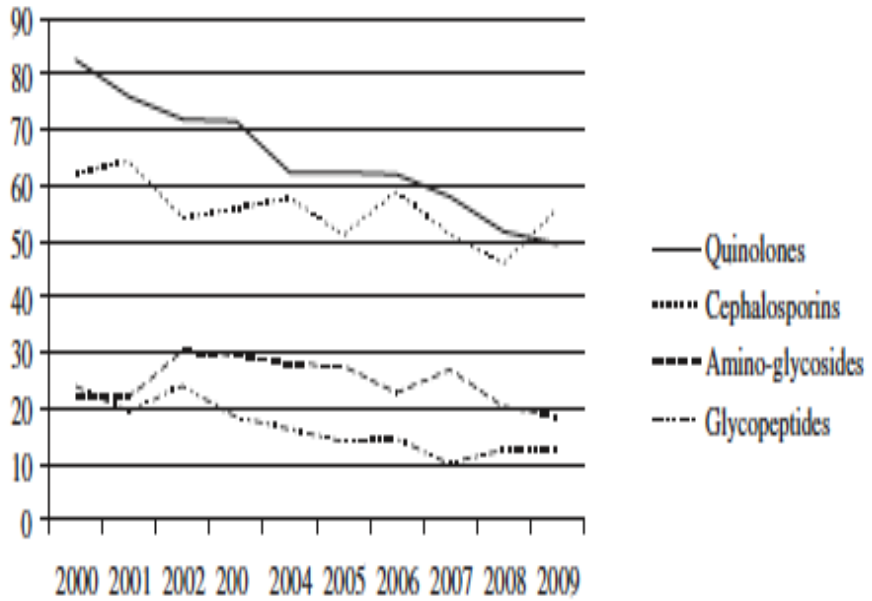


Kim et al. Am J Infect Control 2013;41 (5):e39-43

RESEARCH Open Access

Ten-year decrease of acquired methicillin-resistant Staphylococcus aureus (MRSA) bacteremia at a single institution: the result of a multifaceted program combining cross-transmission prevention and antimicrobial stewardship

- We implemented a multifaceted hospital-wide prevention program and measured the effects on HA-MRSA colonization and bacteremia rates between 2000 and 2009.
- **From 2000 to 2003**, **active screening** and **decontamination of ICU patients**, hospital wide **alcohol based hand rubs** (ABHR) use, **control of specific classes of antibiotics**, **compliance audits, and feed-backs** to the care providers were successively implemented.
- The efficacy of the program was assessed by HA-MRSA colonized and bacteremic patient rates per 1000 patient-days in patients hospitalized for more than 24h



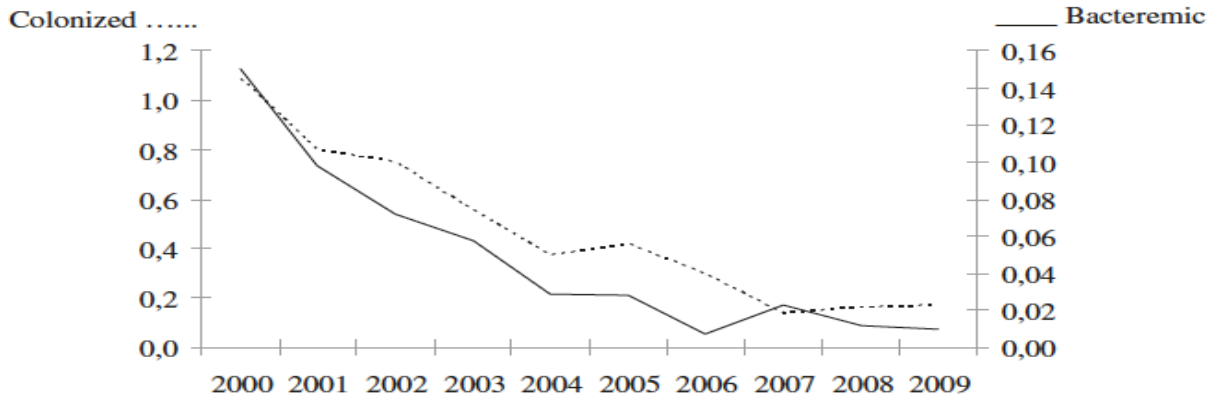
Chalfine et al. Antimicrob Resist Infect Control 2012;18: 1:18

RESEARCH Open Access

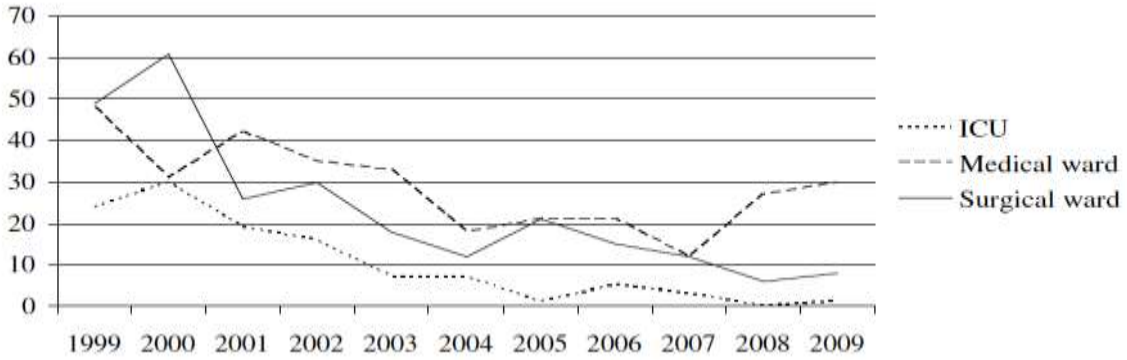
Ten-year decrease of acquired methicillin-resistant Staphylococcus aureus (MRSA) bacteremia at a single institution: the result of a multifaceted program combining cross-transmission prevention and antimicrobial stewardship

- 1 380 MRSA colonized patients including
- 557 HA cases (40.3%), and
- 122 MRSA blood stream infections (BSI) including 56 HA-BSI cases (45.9%).
- Annual rates of **HA-MRSA colonized patients decreased by 84%,** from 1.09 to 0.17 per 1000 patient-days.
- Annual rates **HA-MRSA bacteremic patients decreased by 93%** from 0.15 to 0.01 per 1000 patient-days (p<10−7)

HA-MRSA per 1000 patient-days over time



The numbers of HA-MRSA bacteremic patients decreased in all the categories of wards of the Hospital

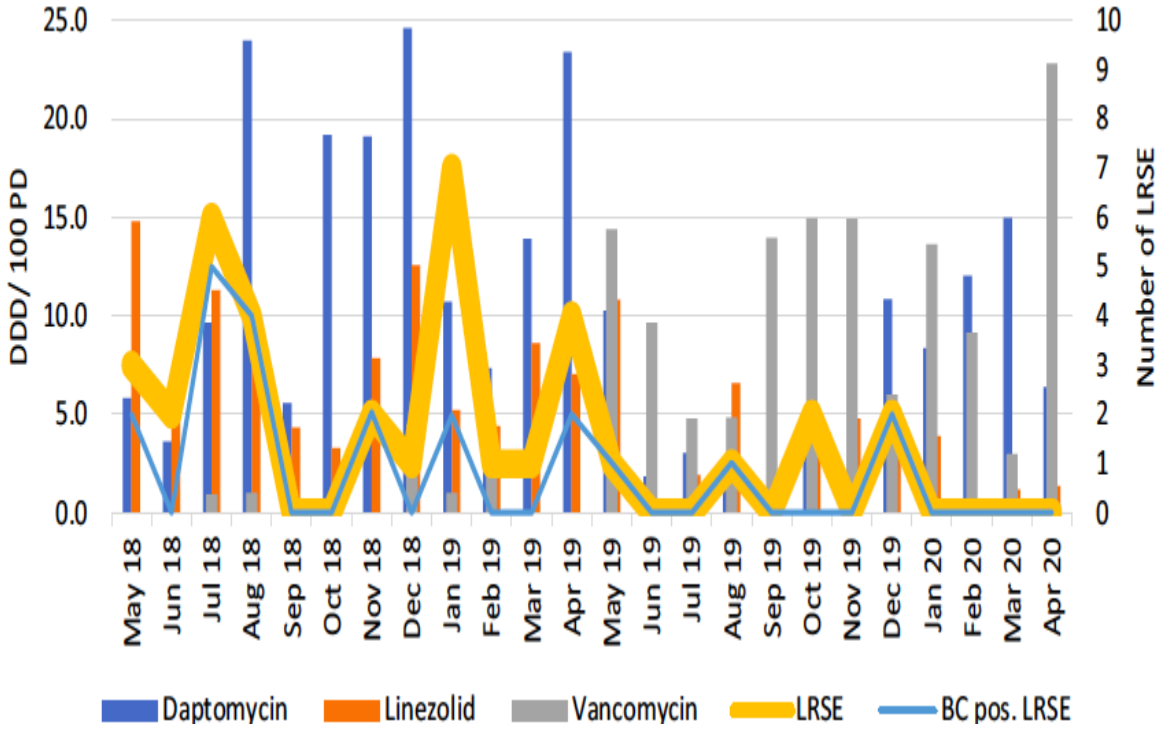


Chalfine et al. Antimicrob Resist Infect Control 2012;18: 1:18

Combined antibiotic stewardship and infection control measures to contain the spread of linezolid-resistant *Staphylococcus epidermidis* in an intensive care unit

- **Infection control measures**
  - Isolation and cohorting of patients
  - Contact precaution
  - A catheter-care bundle
  - Use of chlorhexidine-impregnated dressings
  - Access valve caps with 70% isopropyl alcohol for central Venous catheters, and reinforcing a policy to discourage blood cultures from indwelling arterial catheters.
- **Antibiotic stewardship intervention**
  - Linezolid restriction and promoting vancomycin

Antibiotic consumption and the incidence of LRSE over time for each month



Papan et al. Antimicrob Resist Infect Control (2021) 10:99

Combined antibiotic stewardship and infection control measures to contain the spread of linezolid-resistant *Staphylococcus epidermidis* in an intensive care unit

- In the pre-intervention period, LRSE were isolated from 31 patients (17 in blood cultures).
- The average consumption of linezolid and daptomycin decreased from 7.5 DDD/100 PD and 12.3 DDD/100 PD per month in the preintervention period to 2.5 DDD/100 PD and 5.7 DDD/100 PD per month in the post-intervention period ($p = 0.0022$ and 0.0205), respectively.
- Conversely, vancomycin consumption increased from 0.2 DDD/100 PD per month to 4.7 DDD/100 PD per month ($p < 0.0001$). In the post-intervention period, LRSE were detected in 6 patients (4 in blood cultures) ($p = 0.0065$).
- Complementing infection control measures by targeted antibiotic stewardship interventions was beneficial in containing the spread of LRSE in an ICU.

Papan et al. Antimicrob Resist Infect Control (2021) 10:99

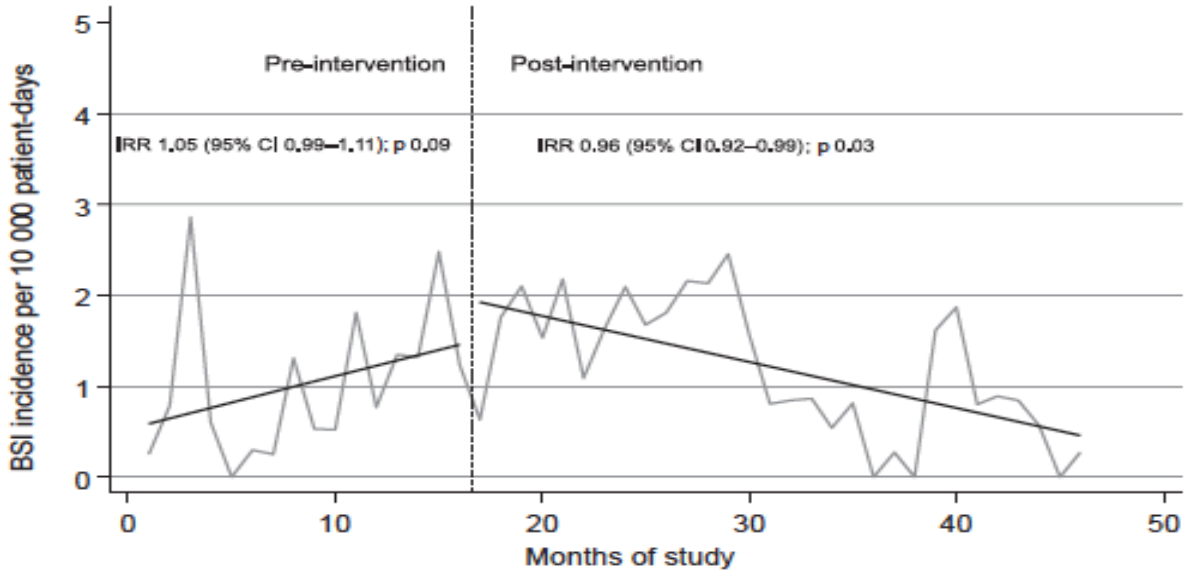
Impact of a hospital-wide multifaceted programme for reducing carbapenem-resistant *Enterobacteriaceae* infections in a large teaching hospital in northern Italy

- The interventions implemented included
  - Screening in all patients admitted to any high-risk unit
  - Cohorting of carriers
  - Intensification of education
  - Cleaning, and hand-washing programmes
  - AMS carbapenem-sparing regimen

Vialle et al. Clin Microbiol Infect 2015; 21: 242–247

Impact of a hospital-wide multifaceted programme for reducing carbapenem-resistant *Enterobacteriaceae* infections in a large teaching hospital in northern Italy

- Following the intervention
- The incidence rate of CRE BSI (risk reduction 0.96, 95% CI 0.92–0.99, p 0.03) and CRE colonization (risk reduction 0.96, 95% CI 0.95–0.97, p <0.0001) significantly decreased over a period of 30 months.
- The average institutional monthly rate of compliance with CRE screening procedures was the only independent variable associated with a declining monthly incidence of CRE colonization (p 0.002).
- The monthly incidence of CRE carriage was predictive of BSI (p 0.01).



A significant decline in the monthly incidence rate ratio (IRR) of CRE BSI during the 30-month post-intervention period was found

Vialle et al. Clin Microbiol Infect 2015; 21: 242–247

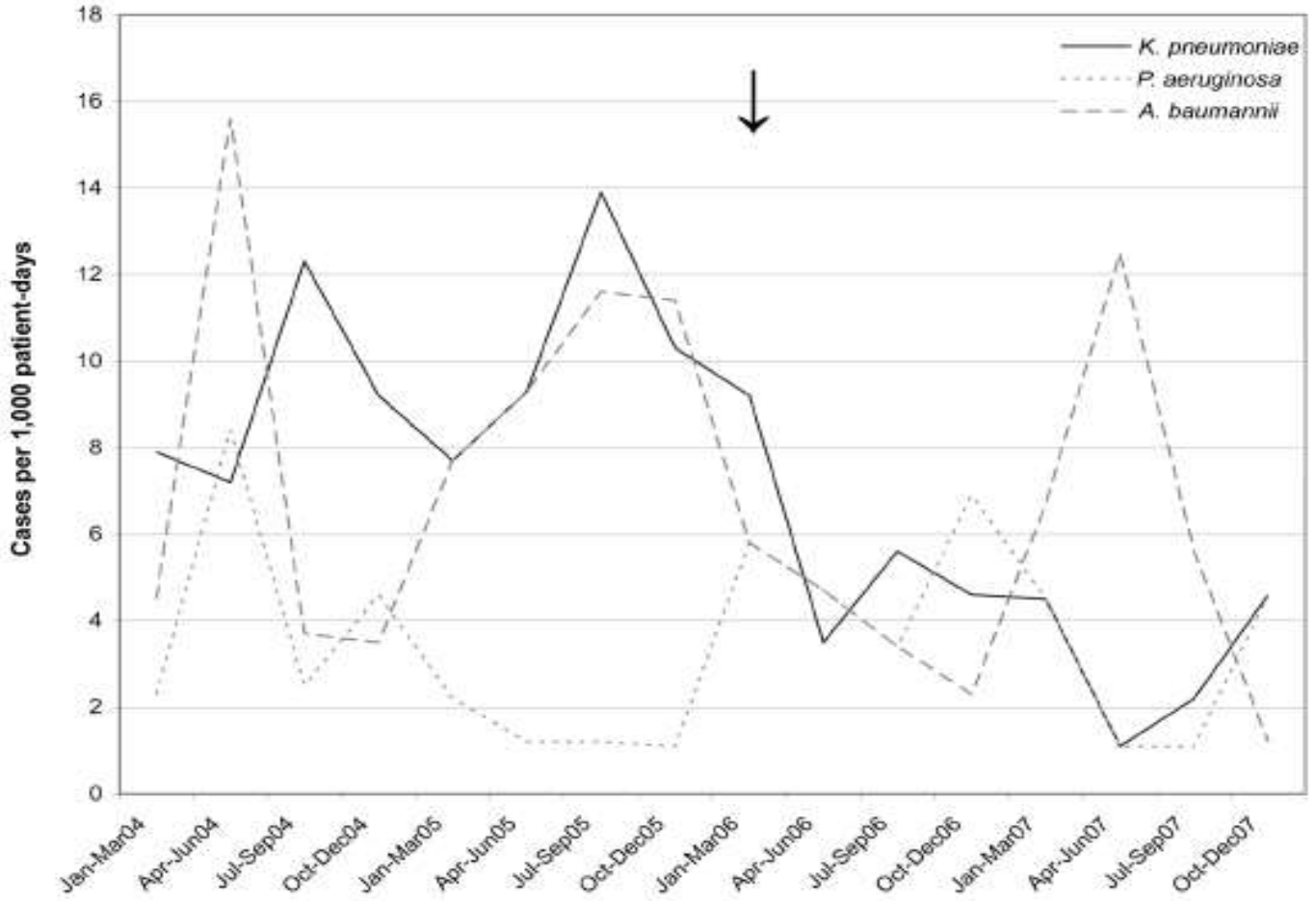
Success of an Infection Control Program to Reduce the Spread of Carbapenem-Resistant Klebsiella pneumoniae

- Beginning in 2006, a comprehensive **infection control program** was instituted in a 10-bed medical and surgical intensive care unit at a university-based medical center.
- All patients colonized or infected with carbapenem resistant gram-negative bacilli, VRE, or MRSA
  - Were placed in contact isolation
  - Cohorted to one end of the unit
  - Improved decontamination of hands and environmental surfaces
  - Rectal surveillance cultures for the presence of carbapenem-resistant pathogens.
- The number of patients per quarter with clinical cultures positive for carbapenem-resistant *K. pneumoniae* was compared during the approximately 2-year periods before and after the intervention.

Kochar et al. Infect Control Hosp Epidemiol. 2009;30:447-52

Success of an Infection Control Program to Reduce the Spread of Carbapenem-Resistant *Klebsiella pneumoniae*

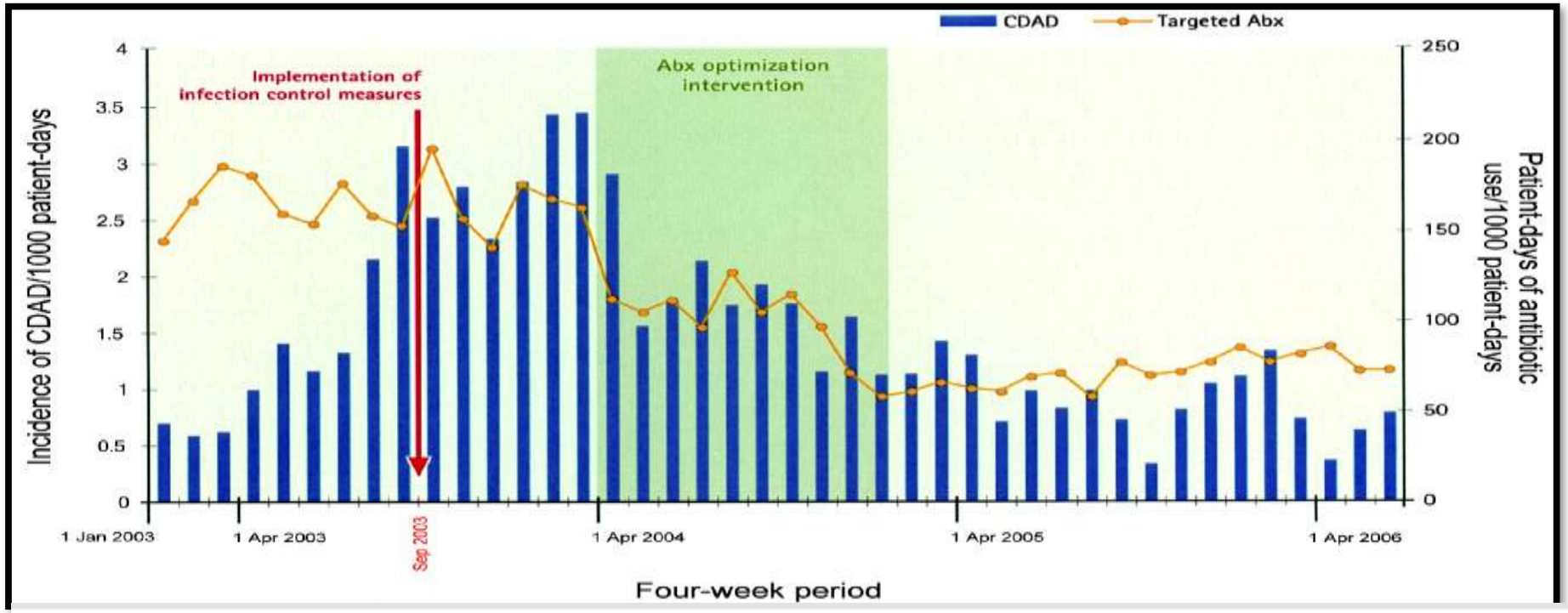
- The mean number (± SD) of new patients per 1,000 patient-days per quarter with cultures yielding carbapenem-resistant *K. pneumoniae* decreased from 9.7 ± 2.2 before the intervention to 3.7 ± 1.6 after the intervention (P < .001).
- There was no association between antibiotic usage patterns and carbapenem-resistant *K. pneumoniae*



Number of clinical cultures positive for carbapenem-resistant gram-negative bacilli per 1,000 patient-days per quarter. Arrow, start of intervention.

Kochar et al. Infect Control Hosp Epidemiol. 2009

Impact of a Reduction in the Use of High-Risk Antibiotics on the Course of an Epidemic of *Clostridium difficile*–Associated Disease Caused by the Hypervirulent NAP1/027 Strain



Valiquette et al [20], 2007	Secondary/tertiary-care hospital, Quebec, Canada	Audit and feedback strategy focused on appropriate use of second- and third-generation cephalosporins, ciprofloxacin, clindamycin, and macrolides	• Decreased total antimicrobial consumption by 23% • Decreased targeted antimicrobial consumption by 54% • Incidence of *C. difficile* infection decreased by 60% ($P = .007$)

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

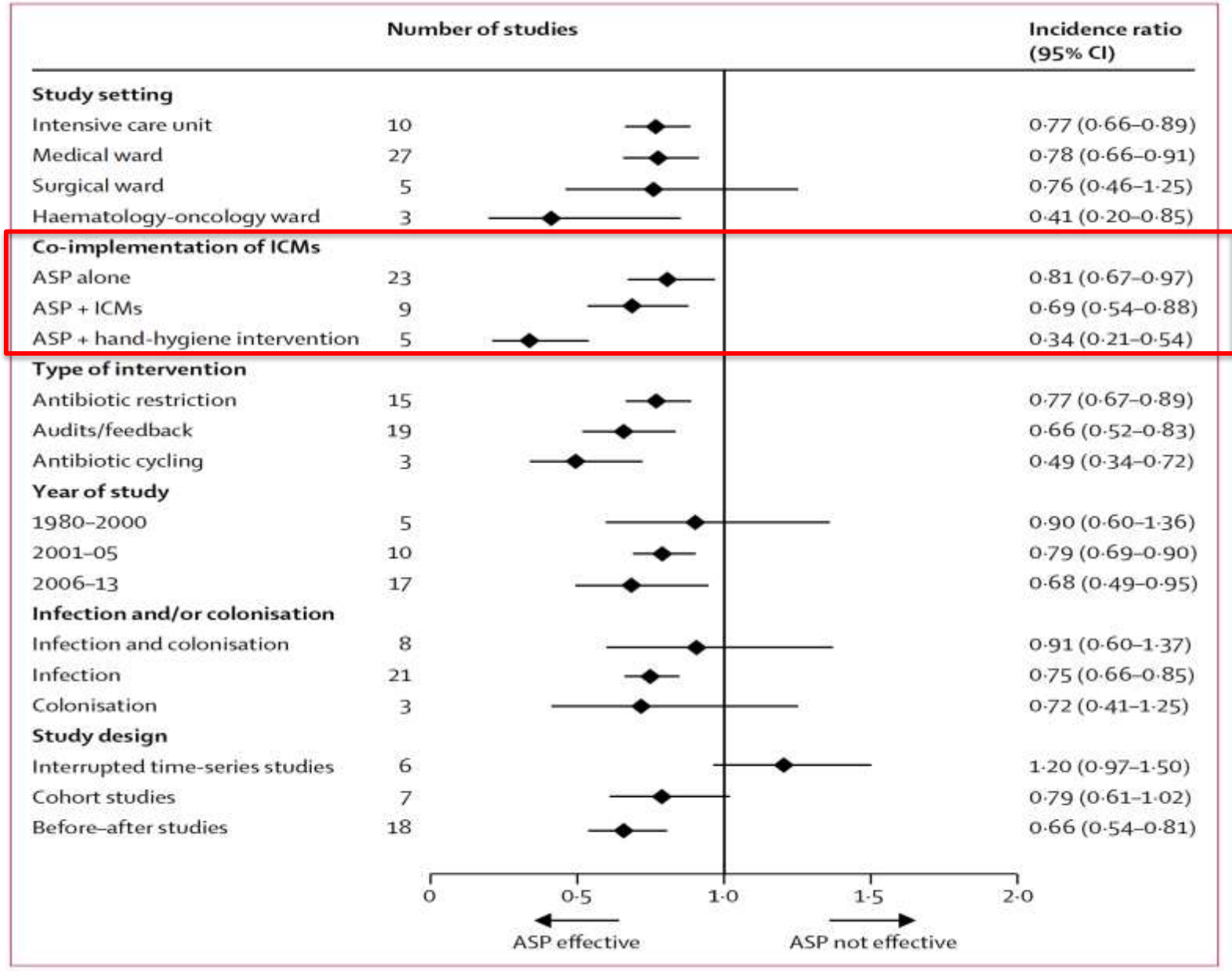
META-ANALYSES OF STEWARDSHIP PROGRAMS AND ANTIBIOTIC RESISTANCE

- Several meta-analyses and systematic reviews of antimicrobial stewardship programs have recently been published.
- All found that stewardship programs were effective in reducing the nosocomial occurrence of infections caused by resistant bacteria

Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis

- AMS programmes significantly decrease the incidence of both infections and colonization with
  - MDR Gram-negative bacteria by 51%
  - ESBL Gram negative bacteria by 48%
  - MRSA by 37%
  - *C. difficile* by 32%
- AMS programmes were also significantly more effective when implemented with infection control measures, and especially hand hygiene compared to AMS by itself.

Summary of the incidence ratios for studies investigating the effect of ASPs on antibiotic resistance, according to study characteristics



Baur et al. Lancet infect Dis 2017;17:990

Conclusions

- Recently published studies, meta-analysis or systematic reviews have shown that ASP interventions in combination with IC measures can have an important impact on resistance rates in individual institutions