

# Antimicrobial stewardship bridging the gap between quality care and Patient Safety



## FACULTY



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Tags: hospital superbugs, antibiotic resistance, measles hysteria

A close-up photograph of a group of young piglets. They are white with pink ears and snouts, huddled together in a cluster. The piglets are looking in various directions, some towards the camera. The background is dark and out of focus.

## Learning Objective:

### Antimicrobial Stewardship

- Discuss the strategies for an effective Antimicrobial Stewardship Program
- The role of infection control and prevention program in antimicrobial stewardship
- Implementation of a stewardship program using a quality improvement methods
- A new novel test in practice for antibiotic escalation
- Improve culture and team dynamics in antimicrobial stewardship
- The Keys to success





## **THE EMERGENCE OF ANTIBIOTIC RESISTANCE: HOW OLD IS RESISTANCE?**









Beginning from the discovery of first antibiotics until the emergence of hard-to-treat multiple antibiotic-resistant infections.....



- First modern antimicrobial was Salvarsan, an arsenic-based magic bullet discovered 1910 by the German infectious disease specialist Paul Ehrlich. Used to treat syphilis

- Quinine became widely used as an antimalarial after it was isolated in 1820 from the bark of the cinchona tree

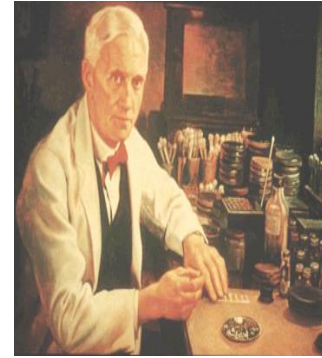
- Sulfonamides were introduced in the 1930s. They are synthetic antimicrobials that block folic acid production in bacteria





Beginning from the discovery of first antibiotics until the emergence of hard-to-treat multiple antibiotic-resistant infections.....

- The first antibiotic (in the original sense of the word) was penicillin
- Alexander Fleming discovered that *Penicillium* kills bacteria in 1928
- Florey and Chain resurrected the work, isolated penicillin, and by WWII were treating millions with antibiotics



Ernst Chain

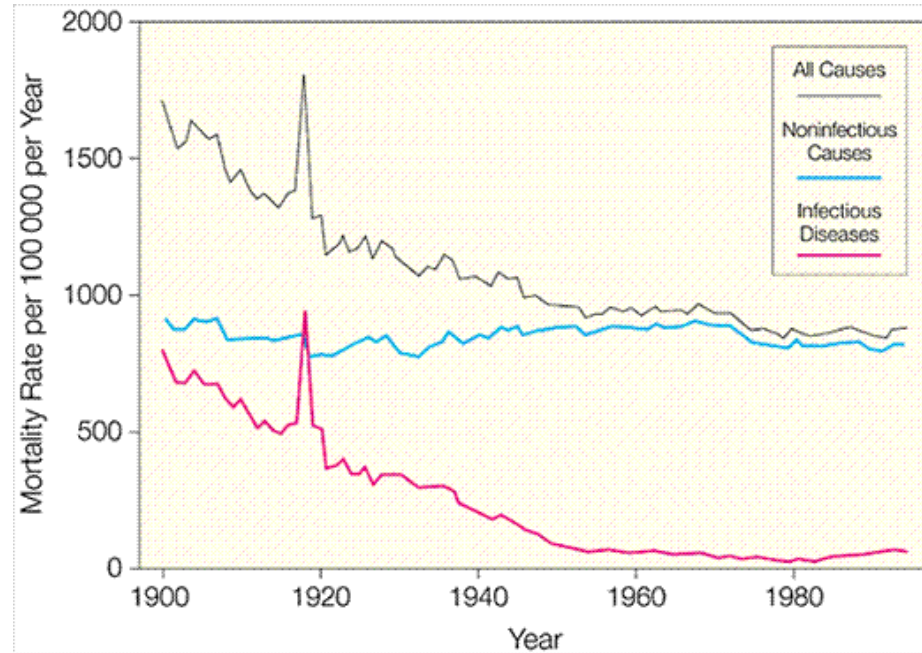


Howard Florey



# The “miracle” of antibiotics

*Crude mortality rates for all causes, noninfectious causes and infectious diseases over the period 1900-1996.*





## Anne Miller, 90, first patient who was saved by penicillin

In 1999, the New York Times published an article about Anne Sheafe Miller... *who made medical history as the first patient ever saved by penicillin...died on May 27 in Salisbury, Conn. She was 90.....*”

- 
- March 1942 - Mrs Miller was near death, suffering from a streptococcal infection. Doctors had tried everything available (sulfa drugs, blood transfusions, surgery). All treatments failed.
  - Desperate, doctors obtained a tiny amount of what was still an obscure, experimental drug and injected Mrs Miller with it.
  - Her hospital chart registered a sharp overnight drop in temperature, and by the next day she was rapidly recovering. **Mrs Miller's life was saved by antibiotics.**



## SCOPE OF PROBLEM



- Up to 50 percent of antimicrobial use in hospitals is unnecessary and inappropriate
- Risk of toxicity, increased length of stay, as well as increased costs to patients, hospitals and payers
- Increasing resistance to antibiotics





## SCOPE OF PROBLEM

- **Developing countries are also hit hard by resistance:** Thailand more than 140,000 antibiotic resistant infections each year causing 30,000 deaths; In Pakistan 71% of infections in neonates are caused by resistant infections.
- The germs that contaminate food can become resistant because of the use of antibiotics in people and in food animals.
- For some germs, like the bacteria *Salmonella* and *Campylobacter*, it is primarily the use of antibiotics in food animals that increases resistance.



## IMPACT OF ANTMICROBIAL RESISTANCE

- When antibiotics fail to work, consequences include extra visits to the doctor, hospitalization or extended hospital stays, a need for more expensive antibiotics to replace the older ineffective ones, lost workdays and, sometimes, death.
- In humans or animals, approximately 80 - 90% of the ingested antibiotics are not broken down, but pass through the body intact and enter the environment as waste. Thus, they retain their ability to affect bacteria and promote antibiotic resistance even after they enter the soil or water as a waste product



## IMPACT OF ANTMICROBIAL RESISTANCE

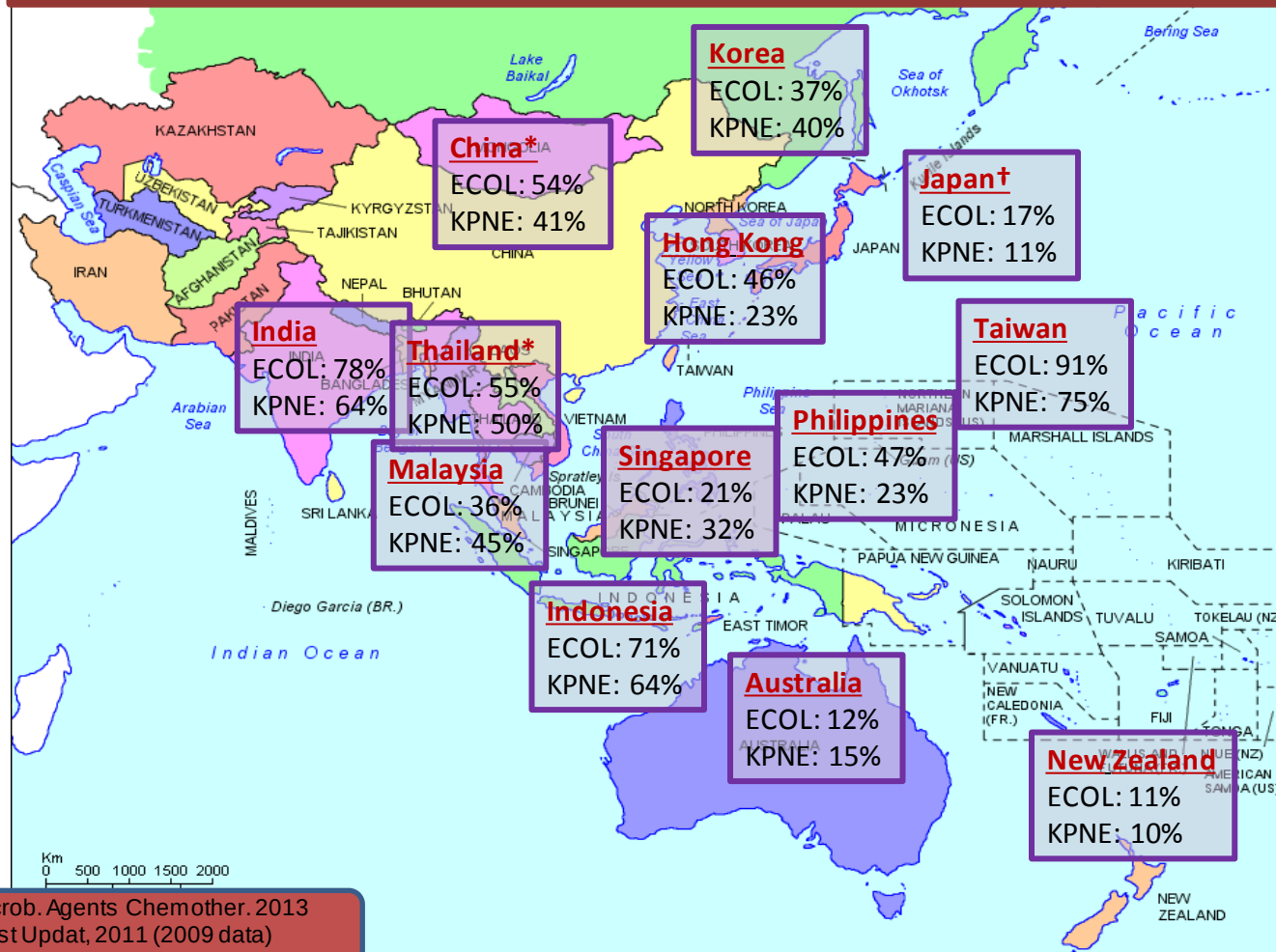
- Just one organism, methicillin-resistant *Staphylococcus aureus* (MRSA), kills more Americans every year than emphysema, HIV/AIDS, Parkinson's disease and homicide combined.
- While antibiotic resistance has predominantly been a clinical problem in hospital settings, recent data show resistant organisms have also been detected in patients in primary care.
- According to the European Centre for Disease Prevention and Control, 25,000 people in Europe die each year as a direct result of resistant infection at a cost of 2.5 million extra hospital days.
- In the USA the large majority of 99,000 deaths each year caused by hospital acquired infections are caused by resistant bacteria and the annual cost of managing these infections \$34 billion per year.



## THE GLOBAL BURDENS OF RESISTANCE



# Resistance (%ESBL) in the Asia Pacific region



10. Mendes et al., Antimicrob. Agents Chemother. 2013

11. \*Xiao et al, Drug Resist Updat. 2011 (2009 data)

12. †Chong et al., EJCMID. 2011 (2009 data)



## Risks that have been shown to be associated with overuse of antibiotics.....

- Increase of antimicrobial resistance
- Increase of more severe diseases
- Increase of the length of disease
- Increase of the risk of complications
- Increase of the mortality rate
- Increase of healthcare costs
- Increase of the risk of adverse effects, some being life-threatening
- Increase of re-attendance due to infectious diseases
- Increased medicalization of self-limiting infectious conditions





## PATIENT HARM AND COSTS



- In the United States, according to a 2013 report by the Centers for Disease Control and Prevention, at least 2 million people annually "acquire serious infections with bacteria that are resistant to one or more of the antibiotics designed to treat those infections."
- And at least 23,000 people die annually from antibiotic-resistant infections.



## Ways That Antibiotics Are Misused

- Given when they are not needed
- Continued when they are no longer necessary
- Given at the wrong dose
- Broad spectrum agents are used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection

# Golden age' come to an end

| ANTIBIOTIC RESISTANCE IDENTIFIED           |        | ANTIBIOTIC INTRODUCED |                          |
|--------------------------------------------|--------|-----------------------|--------------------------|
| penicillin-R <i>Staphylococcus</i>         | 1940   | 1943                  | penicillin               |
|                                            |        | 1950                  | tetracycline             |
|                                            |        | 1953                  | erythromycin             |
| tetracycline-R <i>Shigella</i>             | 1959   | 1960                  | methicillin              |
| methicillin-R <i>Staphylococcus</i>        | 1962   |                       |                          |
| penicillin-R pneumococcus                  | 1965   | 1967                  | gentamicin               |
| erythromycin-R <i>Streptococcus</i>        | 1968   | 1972                  | vancomycin               |
|                                            |        |                       |                          |
| gentamicin-R <i>Enterococcus</i>           | 1979   |                       |                          |
|                                            |        | 1985                  | imipenem and ceftazidime |
| ceftazidime-R Enterobacteriaceae           | 1987   |                       |                          |
| vancomycin-R <i>Enterococcus</i>           | 1988   |                       |                          |
|                                            |        | 1996                  | levofloxacin             |
| levofloxacin-R pneumococcus                | 1996   |                       |                          |
| imipenem-R Enterobacteriaceae              | 1998   |                       |                          |
| XDR tuberculosis                           | 2000   | 2000                  | linezolid                |
| linezolid-R <i>Staphylococcus</i>          | 2001   |                       |                          |
| vancomycin-R <i>Staphylococcus</i>         | 2002   |                       |                          |
| PDR-Acinetobacter and Pseudomonas          | 2004/5 | 2003                  | daptomycin               |
|                                            |        |                       |                          |
| ceftriaxone-R <i>Neisseria gonorrhoeae</i> | 2009   | 2010                  | ceftaroline              |
| PDR-Enterobacteriaceae                     |        |                       |                          |
| ceftaroline-R <i>Staphylococcus</i>        | 2011   |                       |                          |

# There's a trickling antibiotic pipeline, but it urgently needs restitution.

## New Antibiotics underdevelopment

| Drug name                                  | Development phase <sup>1</sup> | Company                                                                     | Drug class                                         | Expected activity against resistant Gram-negative ESKAPE pathogens <sup>2</sup> | Expected activity against a CDC urgent threat pathogen <sup>4</sup> | Potential indication(s) <sup>25</sup>                                                                                                                                                                                                                                                                                    |
|--------------------------------------------|--------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nemorosoch <sup>9</sup>                    | Phase 2                        | TaiGen Biotechnology Co., Ltd.                                              | Quinolone                                          | No                                                                              | No                                                                  | Community-acquired bacterial pneumonia, diabetic foot infection, acute bacterial skin and skin structure infections                                                                                                                                                                                                      |
| Radcolid                                   | Phase 2                        | Malenta Therapeutics, Inc.                                                  | Oxazolidinone                                      | No                                                                              | No                                                                  | Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia                                                                                                                                                                                                                               |
| Ramoplanin                                 | Phase 2                        | Nanotherapeutics, Inc.                                                      | Glycolipopeptide                                   | No                                                                              | Yes                                                                 | C. difficile relapse prevention <sup>9</sup>                                                                                                                                                                                                                                                                             |
| Zabofloxacin                               | Phase 2                        | Dong Wila Pharmaceutical Co., Ltd.                                          | Fluoroquinolone                                    | No                                                                              | No                                                                  | Community-acquired bacterial pneumonia                                                                                                                                                                                                                                                                                   |
| SMT 19969                                  | Phase 2                        | Summit Therapeutics, Inc.                                                   |                                                    | No                                                                              | Yes                                                                 | C. difficile-associated diarrhea                                                                                                                                                                                                                                                                                         |
| Omadacycline                               | Phase 3                        | Paratek Pharmaceuticals, Inc.                                               | Tetracycline                                       | Yes                                                                             | Possibly <sup>6</sup>                                               | Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, complicated urinary tract infections                                                                                                                                                                                         |
| Lefamulin (BC-3781)                        | Phase 3                        | Nabriva Therapeutics AG                                                     | Pleuromutilin                                      | No                                                                              | No                                                                  | Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, osteomyelitis, prosthetic joint infections <sup>9</sup>                                                                                    |
| Imipenem/cilastatin-relisibactam (MK-7655) | Phase 3 <sup>9</sup>           | Merck & Co., Inc.                                                           | Carbapenem + novel beta-lactamase inhibitor        | Yes                                                                             | Yes                                                                 | Complicated urinary tract infections, acute pyelonephritis, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia                                                                                                                                      |
| Idaprim                                    | Phase 3 <sup>9</sup>           | Moff Bio plc                                                                | Dihydrofolate reductase (DHFR) inhibitor           | No                                                                              | No                                                                  | Acute bacterial skin and skin structure infections; hospital-acquired bacterial pneumonia                                                                                                                                                                                                                                |
| Cadazolid                                  | Phase 3                        | Actelion Pharmaceuticals Ltd                                                | Quinolony-oxazolidinone                            | No                                                                              | Yes                                                                 | C. difficile-associated diarrhea                                                                                                                                                                                                                                                                                         |
| Takista (Fusidic acid) <sup>9</sup>        | Phase 3                        | Compra, Inc.                                                                | Fusidate                                           | No                                                                              | No                                                                  | Prosthetic joint infections; acute bacterial skin and skin structure infections                                                                                                                                                                                                                                          |
| Carbavanc (BPO7009+meropenem)              | Phase 3                        | Rampen Pharmaceuticals, Inc. (wholly owned subsidiary of The Medicines Co.) | Meropenem + novel boronic beta-lactamase inhibitor | Yes                                                                             | Yes                                                                 | Complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, febrile neutropenia, bacteremia, acute pyelonephritis (some indications specifically target infections caused by carbapenem-resistant Enterobacteriaceae) |

| Drug name                                  | Development phase <sup>2</sup>      | Company                                                                    | Drug class                                     | Expected activity against resistant Gram-negative ESKAPE pathogens <sup>23</sup> | Expected activity against a CDC urgent threat pathogen <sup>24</sup> | Potential indication(s) <sup>25</sup>                                                                                                                                                                                                                         |
|--------------------------------------------|-------------------------------------|----------------------------------------------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ceftolozane+Tazobactam (Zerbaxa)           | Approved Dec. 19, 2014              | Cubist Pharmaceuticals, Inc. (wholly owned subsidiary of Merck & Co.)      | Novel cephalosporin+beta-lactamase inhibitor   | Yes                                                                              | No                                                                   | Approved for: complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infection); other potential indications: hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia             |
| Ceftazidime+Avibactam (Avycaz)             | Approved Feb. 25, 2015 <sup>3</sup> | Allergan plc (formerly Actavis)/AstraZeneca plc                            | Cephalosporin + novel beta-lactamase inhibitor | Yes                                                                              | Yes                                                                  | Approved for: complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infection); other potential indications: hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, bacteremia |
| WCK 4873                                   | Phase 1                             | Wockhardt Ltd.                                                             |                                                | No                                                                               | No                                                                   | Bacterial infections <sup>9</sup>                                                                                                                                                                                                                             |
| MGB-BP-3                                   | Phase 1 <sup>10</sup>               | MGB Biopharma Ltd.                                                         |                                                | No                                                                               | Yes                                                                  | C. difficile infections                                                                                                                                                                                                                                       |
| OP0595 (RG6080)                            | Phase 1 <sup>10</sup>               | Meiji Seika Pharma Co., Ltd./Fedora Pharmaceuticals, Inc. (Roche licensee) | Beta-lactamase inhibitor                       | Possibly                                                                         | Possibly                                                             | Bacterial infections                                                                                                                                                                                                                                          |
| Aztreonam+Avibactam <sup>7</sup> (ATM-AVI) | Phase 1 <sup>10</sup>               | AstraZeneca/Allergan (formerly Actavis)                                    | Monobactam + novel beta-lactamase inhibitor    | Yes                                                                              | Yes                                                                  | Bacterial infections                                                                                                                                                                                                                                          |
| BAL30072                                   | Phase 1                             | Basilea Pharmaceutica Ltd.                                                 | Monosulfactam                                  | Yes                                                                              | Yes                                                                  | Multidrug-resistant Gram-negative bacterial infections <sup>6</sup>                                                                                                                                                                                           |
| CRS3123                                    | Phase 1                             | Crestone, Inc.                                                             | Methionyl-tRNA synthetase (MetRS) inhibitor    | No                                                                               | Yes                                                                  | C. difficile infections                                                                                                                                                                                                                                       |





We could have used our antibiotics better and we should have invested more in research on infectious diseases

You have to remember that the success of those that are in development is not guaranteed



## Jim O'Neill's Review on AMR

Drug resistant infection already kill hundreds of thousands a year globally and by 2050 that figure could be more than 10 million. The economic cost will also be significant with the world economy being hit by up to \$ 100 trillion by 2050 if we do not take action.



- Set up a global AMR innovation fund to ensure that more early stage ideas could actually attract funding.
- Emphasized the importance of conserving the drugs we've got  dosing or combining them with other agents could slow the spread of drug resistance
- Support development of new diagnostic technologies  If we have had the right diagnostic s, more patients would receive the right antibiotics.
- Attract and retain a high caliber skills base. invest in the people who will solve the problem
- Modernize the way surveillance of drug resistance is done and used globally  il scale surveillance organism



*Tackling drug-resistant infections globally*



# What can we do?

- Using antimicrobials properly is the only recourse we have to manage infections and maintain patient outcomes
- When using antibiotics consider:
  - ✓ Why?
  - ✓ Which drug?
  - ✓ What dose?
  - ✓ What duration?



Next

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ANTIMICROBIAL STEWARDSHIP PROGRAM





## What is Antimicrobial stewardship

- Institution-wide comprehensive antimicrobial management program intended to improve patient outcomes from infection while minimizing negative consequences such as healthcare associated infections, and limiting the development of bacterial resistance
- A multidisciplinary approach
- Focuses on: through the optimal diagnosis, drug selection, dosage, de-escalation and duration (the so called 5 “Ds” of antimicrobial





## Reflection

Now consider the following questions:

- ✓ How large is your hospital and how many antibiotics are stocked?
- ✓ Do you have Drugs and Therapeutics Committee and Antibiotic Policy Committee?
- ✓ If yes, are they functioning well? What measures could be taken to improve their functioning?
- ✓ If no, could you initiate the process of starting these committees and how would you do this?



## Goals of Antibiotic Stewardship Program

- Optimize antibiotic therapy by ensuring the selection of the most appropriate agent, dose, and duration of therapy
- Screening for significant adverse drug reactions and drug–drug interactions, and
- Modifying initial therapy based on patients' culture and sensitivity reports



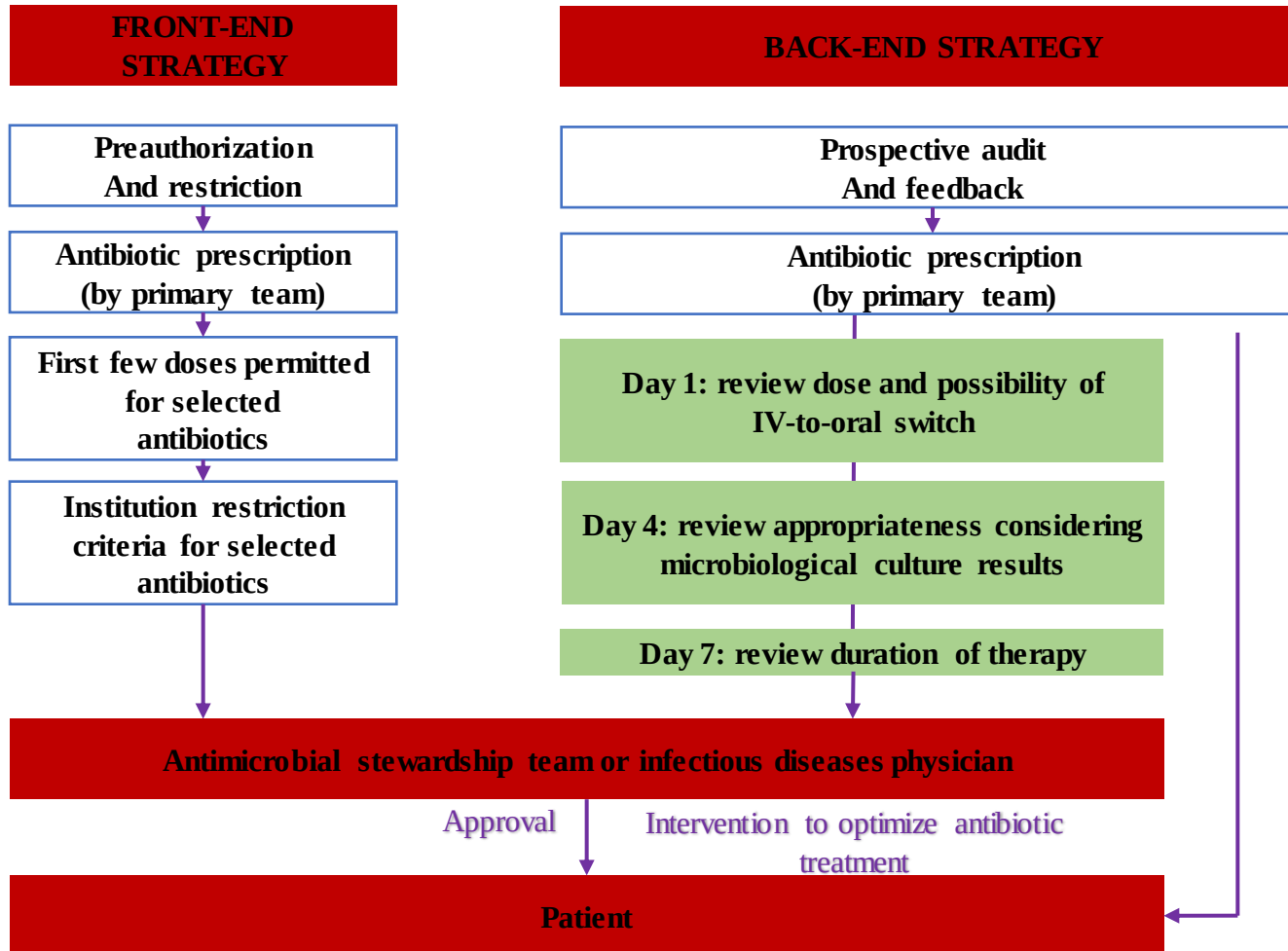
## Strategies To Improve Antimicrobial Prescribing

- 
- 
1. Restrictive strategy uses interventions that either prevent or provide a 'barrier' to prescribing or administering an antibiotic
  2. A persuasive strategy uses interventions that attempt to persuade healthcare professionals to prescribe appropriately by addressing underlying knowledge deficiencies and/or attitudes and/or behavior's

## Restrictive strategy



**Two essential activities for all hospitals**



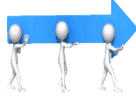
## A persuasive Strategy



**Four antimicrobial stewardship activities that may be considered desirable according to local priorities and resources**



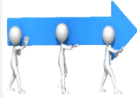
Education of prescribers,  
pharmacists , nurses  
about antimicrobial  
prescribing practice ,  
resistance and Infection  
control



streamlining or timely de-escalation of  
therapy, dose optimization or parenteral (IV)-  
to-oral conversion ,Follow Guide lines



Annually publishing  
facility-specific  
antimicrobial  
susceptibility data



Using information technology such as  
electronic prescribing with clinical decision  
support or online approval systems



# A Multidisciplinary Intervention to Reduce Infections of ESBL- and AmpC-Producing, Gram-Negative Bacteria at a University Hospital

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## Abstract

In response to a considerable increase in the infections caused by ESBL/AmpC-producing *Klebsiella pneumoniae* in 2008, a multidisciplinary intervention, with a main focus on antimicrobial stewardship, was carried out at one university hospital. Four other hospitals were used as controls. Stringent guidelines for antimicrobial treatment and prophylaxis were disseminated throughout the intervention hospital; cephalosporins were restricted for prophylaxis use only, fluoroquinolones for empiric use in septic shock only, and carbapenems were selected for penicillin-allergic patients, infections due to ESBL/AmpC-producing and other resistant bacteria, in addition to their use in severe sepsis/septic shock. Piperacillin-tazobactam ± gentamicin was recommended for empiric treatments of most febrile conditions. The intervention also included education and guidance on infection control, as well as various other surveillances. Two year follow-up data on the incidence rates of patients with selected bacterial infections, outcomes, and antibiotic consumption were assessed, employing before-and-after analysis and segmented regression analysis of interrupted time series, using the other hospitals as controls. The intervention led to a sustained change in antimicrobial consumption, and the incidence of patients infected with ESBL-producing *K. pneumoniae* decreased significantly ( $p < 0.001$ ). The incidences of other hospital-associated infections also declined ( $p's < 0.02$ ), but piperacillin-tazobactam-resistant *Pseudomonas aeruginosa* and *Enterococcus faecium* infections increased ( $p's < 0.033$ ). In wards with high antimicrobial consumption, the patient gut carrier rate of ESBL-producing bacteria significantly decreased ( $p = 0.023$ ). The unadjusted, all-cause 30-day mortality rates of *K. pneumoniae* and *E. coli* were unchanged over the four-year period, with similar results in all five hospitals. Although not statistically significant, the 30-day mortality rate of patients with ESBL-producing *K. pneumoniae* decreased, from 35% in 2008–2009, to 17% in 2010–2011. The two-year follow-up data indicated that this multidisciplinary intervention led to a statistically significant decrease in the incidence of ESBL/AmpC-resistant *K. pneumoniae* infections, as well as in the incidences of other typical hospital-associated bacterial infections.

**Citation:** Knudsen JD, Andersen SE, for the Bispebjerg Intervention Group (2014) A Multidisciplinary Intervention to Reduce Infections of ESBL- and AmpC-Producing, Gram-Negative Bacteria at a University Hospital. PLoS ONE 9(1): e86457. doi:10.1371/journal.pone.0086457

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**Competing Interests:** The authors have declared that no competing interests exist.

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<sup>†</sup> Membership of the Bispebjerg Intervention Group is provided in the Acknowledgments.

- The main focus on antimicrobial stewardship
- Study carried out at one university hospital.
- Four other hospitals were used as controls

## Interventions:

1. Stringent guidelines for antimicrobial treatment and prophylaxis were disseminated throughout the intervention hospital;
2. cephalosporins were restricted for prophylaxis use only
3. fluoroquinolones for empiric use in septic shock only, and
4. carbapenems were selected for penicillin-allergic patients, infections due to ESBL/AmpC-producing and other resistant bacteria, in addition to their use in severe sepsis/septic shock.
5. Piperacillin-tazobactam +/- gentamicin was recommended for empiric treatments of most febrile conditions.
6. Education and guidance on infection control, as well as various other surveillances



## RESULTS.....

### Two year follow-up data on:

The incidence rates of patients with selected bacterial infections, outcomes, and antibiotic consumption

### The intervention led to:

- 
- Sustained change in antimicrobial consumption, and the incidence of patients infected with ESBL-producing *K. pneumoniae* decreased significantly (**p,0.001**).
  - The incidences of hospital associated infections also declined (p's,0.02)
  - In wards with high antimicrobial consumption, the patient gut carrier rate of ESBL-producing bacteria significantly decreased (**p = 0.023**)
  - The 30-day mortality rate of patients with ESBL-producing *K. pneumoniae* decreased, from 35% in 2008–2009, to 17% in 2010–2011.



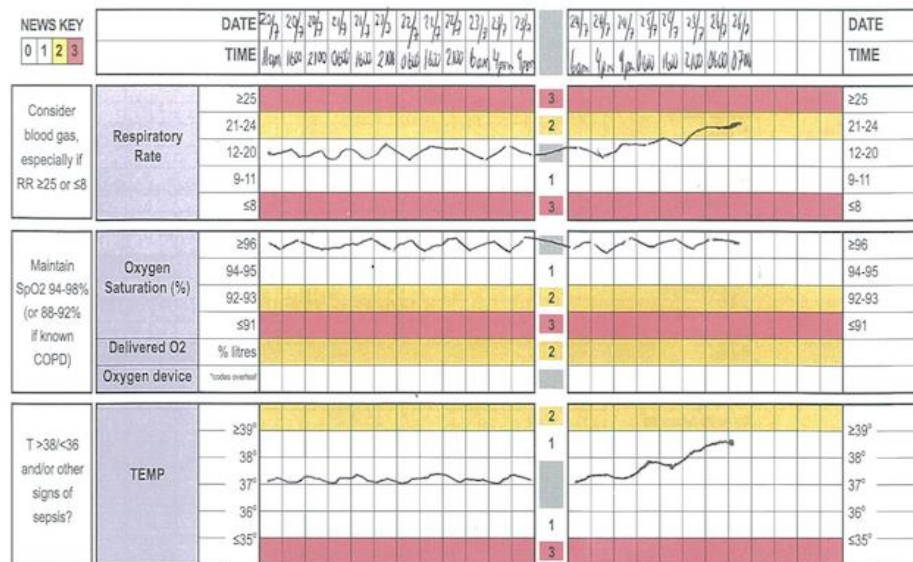
## Antibiotic Stewardship Program Team Members

Who needs to be involved if antimicrobial stewardship ?

## Prescribing for the scenario

Imagine you are working on the ward during Bill and Fred's initial admission.

During a ward round you see another patient, John who was admitted 5 days prior with urinary retention. John is feeling unwell today and is “shivery”. Look at the observation chart provided. A decision will be made to prescribe an antibiotic for John.

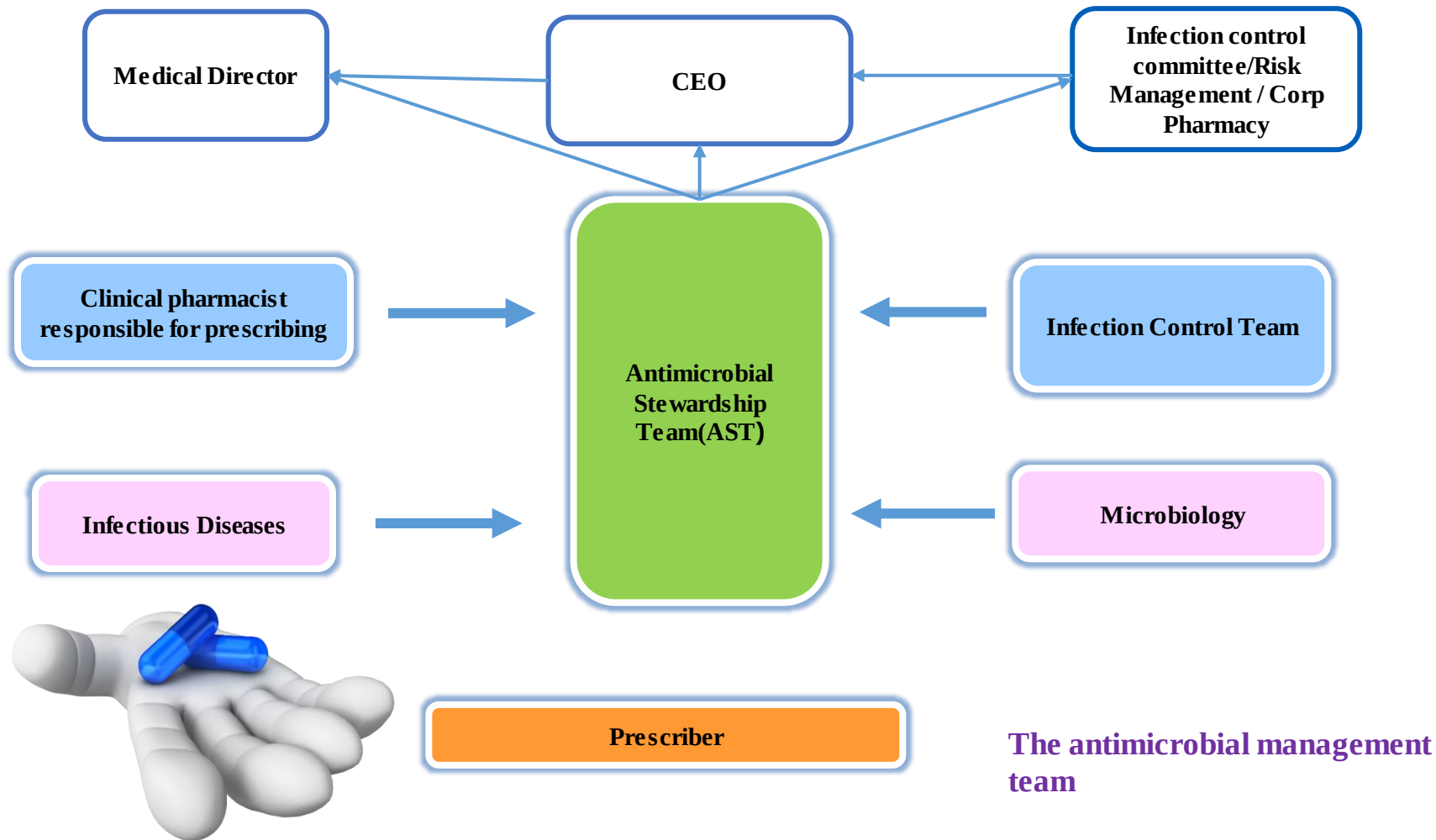




## Consider the following questions

- Who would usually be involved in the prescribing decision for John where you work?
- Are there other healthcare professionals who you think should be involved in the prescribing decision?
- If you already have a team, does it need to be developed further and in what way?







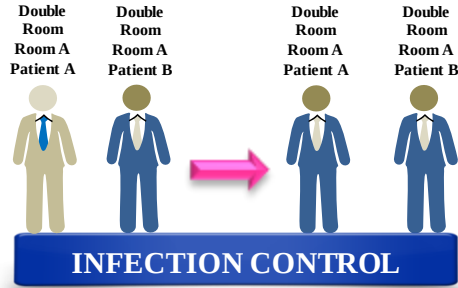


# **The Role Of Infection Control and Prevention Program in Antimicrobial Stewardship**



# Three Pillars Must Be Addresses To Overcome Antibiotic Resistance

Rationale for cohorting, private rooms,  
Hand washing, active surveillance ...



**INFLUENCERS :**

- Hand Hygiene
- Epidemiology
- Outbreak Investigations
- Cohorting
- Active Surveillance

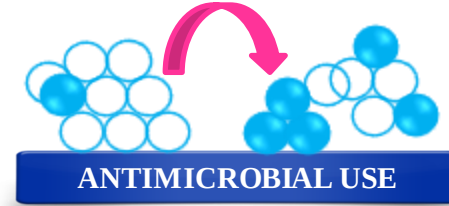


While patients-non infected / non-colonized  
With MDRO



Blue patients – infected or  
Colonized with MDRO

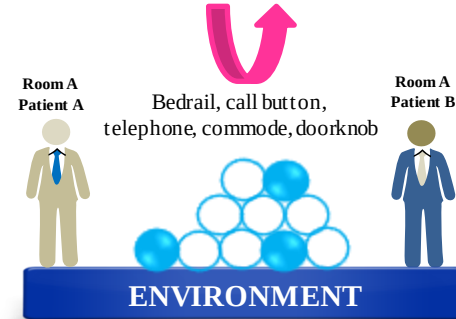
Antimicrobial exposure ( dose, duration, type of antibiotic  
drives selection of resistant bacteria ...



**INFLUENCERS :**

- Human antimicrobial consumption
- Agriculture antimicrobial consumption

Germicides, Sub-MIC residues, ionic surfactants ...



**INFLUENCERS :**

- Germicides
- 10% hypochlorite ( sporicidal ) for C. difficile
- Cleaning Policy & Practice ( What surfaces? How often? )
- Is terminal cleaning enough? ( NO ! )



Resistant  
Organism



Susceptible Organism

# 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

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A series of measures were implemented, in a secondary/tertiary-care hospital in Quebec, to control an epidemic of nosocomial *Clostridium difficile*-associated disease (n-CDAD) caused by a virulent strain; these measures included the development of a nonrestrictive antimicrobial stewardship program. Interrupted time-series analysis was used to evaluate the impact of these measures on n-CDAD incidence. 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%. No change in n-CDAD incidence was noted after strengthening of infection control procedures ( $P = .63$ ), but implementation of the antimicrobial stewardship program was followed by a marked reduction in incidence ( $P = .007$ ). This suggests that nonrestrictive measures to optimize antibiotic usage can yield exceptional results when physicians are motivated and that such measures should be a mandatory component of n-CDAD control. The inefficacy of infection control measures targeting transmission through hospital personnel might be a result of their implementation late in the epidemic, when the environment was heavily contaminated with spores.

*Clostridium difficile*-associated disease (CDAD) is the leading cause of nosocomial diarrhea in industrialized countries. Since the end of 2002, >30 hospitals in the province of Quebec, Canada, have been struggling with an epidemic of CDAD characterized by a high case-fatality rate [1, 2] and an increased risk of recurrence after metronidazole treatment [3]. In Sherbrooke, Quebec, the incidence among individuals  $\geq 65$  years of age increased from 102 cases/100,000 population in 1991–1992 to 866 cases/100,000 population in 2003 [1]. This epidemic has been associated with an emerging strain, NAP1/027, characterized by toxin A and B hyperpro-

duction [4]. Outbreaks due to this same clone have been reported in the United States, the United Kingdom, France, Belgium, and The Netherlands [5].

Receiving antibiotics in the preceding weeks is the most important risk factor for CDAD. Historically, CDAD was associated with a variety of antibiotics, especially third-generation cephalosporins, ampicillin, and clindamycin [6]. Recently, an association between the NAP1/027 clone and fluoroquinolone usage has been consistently reported [7–9]. Before this epidemic, several authors documented how actively restricting the use of high-risk antibiotics led to a reduction in the incidence of CDAD caused by strains other than NAP1/027 [10–12]. As a result, minimizing the inappropriate use of antibiotics is considered to be an important element of CDAD control [13]. A series of measures were implemented at our institution to control the CDAD epidemic, including the development of a nonrestrictive antibiotic control program. To evaluate their impact,

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1058-4838/2007/4505S2-0003\$15.00

DOI: 10.1093/cid/csl258

## Wave.1

Strict adherence to infection control policies

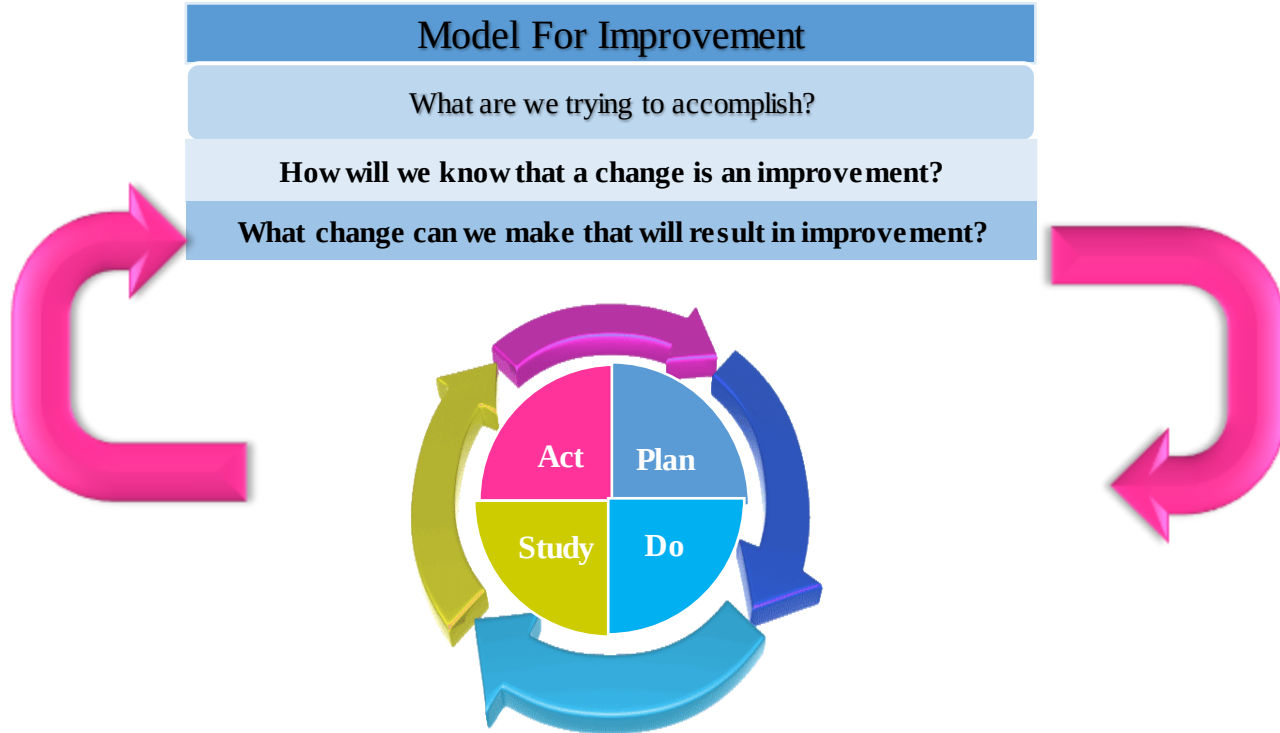
## Wave.2

Antimicrobial stewardship program:

1. Guidelines
2. Education
3. Prospective Audit
4. Feedback

- Reducing the use of antimicrobials that were highly associated with CDI (e.g., cephalosporins, most fluoroquinolones, and macrolides).
- The combined approach of infection control with environmental and antimicrobial stewardship significantly resulted in reduced rates of CDI.
- This was accomplished without the implementation of antimicrobial restrictions.

# Implementation of a stewardship program using a quality improvement model



# Antibiotic Stewardship Driver Diagram



INSTITUTE FOR  
HEALTHCARE  
IMPROVEMENT

## Timely and appropriate antibiotic utilization in the acute care setting

↓

Decreased incidence of antibiotic-related adverse drug events (ADEs)

Decreased prevalence of antibiotic resistant healthcare-associated pathogens

Decreased incidence of healthcare-associated *C. difficile* infection

Decreased pharmacy cost for antibiotics

### Primary Drivers

Timely and appropriate initiation of antibiotics

Appropriate administration and de-escalation

Data monitoring, transparency, and stewardship infrastructure

Availability of expertise at the point of care

### Secondary Drivers

- Promptly identify patients who require antibiotics
- Obtain cultures prior to starting antibiotics
- Do not give antibiotics with overlapping activity or combinations not supported by evidence or guidelines
- Determine and verify antibiotic allergies and tailor therapy accordingly
- Consider local antibiotic susceptibility patterns in selecting therapy
- Start treatment promptly
- Specify expected duration of therapy based on evidence and national and hospital guidelines

- Make antibiotics patient is receiving and start dates visible at point of care
- Give antibiotics at the right dose and interval
- Stop or de-escalate therapy promptly based on the culture and sensitivity results
- Reconcile and adjust antibiotics at all transitions and changes in patient's condition
- Monitor for toxicity reliably and adjust agent and dose promptly

- Monitor, feedback, and make visible data regarding antibiotic utilization, antibiotic resistance, ADEs, *C. difficile*, cost, and adherence to the organization's recommended culturing and prescribing practices

- Develop and make available expertise in antibiotic use
- Ensure expertise is available at the point of care

Leadership and Culture

## Specific Change Ideas

- Specify expected duration of treatment based on evidence and national and hospital guidelines
- Make antibiotics patient is receiving and start dates visible at the point of care
- Give antibiotics at the right dose and interval
- Stop or de-escalate therapy promptly based on the culture and sensitivity results
- Reconcile and adjust antibiotics at all transitions and changes in patient condition
- Monitor for toxicity and adjust agent and dose promptly



## Specific Change Ideas

- Identify clinical providers as champions to be thought leaders about antibiotic stewardship.
- Work with administrators to ensure that they understand the rationale and goals for stewardship programs and interventions so that they can provide support (financial and non-financial).
- Engage a physician champion and core team to enhance the focus of antimicrobial stewardship into the current process of care.





## Measurements

- **Monitoring antibiotic prescribing**
- **Antibiotic Use Process measures**
  1. accurately applied diagnostic criteria for infections
  2. prescribed recommended agents for a particular indication
  3. documented the indication and planned duration of antibiotic therapy
  4. obtained cultures and relevant tests prior to treatment; and
  5. modified antibiotic choices appropriately to microbiological findings



## Measures

- Days of therapy per 1000 patient-days.
- Number of patients with specific organisms that are drug resistant.
- Mortality related to antimicrobial-resistant organisms.
- Conservable days of therapy among patients with community-acquired pneumonia (CAP), skin and soft-tissue infections (SSTI), or sepsis and bloodstream infections (BSI); and
- Unplanned hospital readmission within 30 days after discharge from the hospital in which the most responsible diagnosis was one of CAP, SSTI, sepsis or BSI. The first and second indicators were also identified as useful for accountability purposes, such as public reporting.



# IHI Checklist for Implementation



## DIAGNOSIS AND INFECTIONS SPECIFIC INTERVENTIONS

*Does your facility have specific interventions in place to ensure optimal use of antibiotics to treat the following common infections?*

**ACTION  
PERFORMED**

K. Community-acquired pneumonia

☐ Yes ☐ No

L. Urinary tract infection

☐ Yes ☐ No

M. Skin and soft tissue infections

☐ Yes ☐ No

N. Surgical prophylaxis

☐ Yes ☐ No

O. Empiric treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA)

☐ Yes ☐ No

**LEADERSHIP SUPPORT****ESTABLISHED  
AT FACILITY**

A. Does your facility have a formal, written statement of support from leadership that supports efforts to improve antibiotic use (antibiotic stewardship)?

☐ Yes ☐ No

B. Does your facility receive any budgeted financial support for antibiotic stewardship activities (e.g., support for salary, training, or IT support)?

☐ Yes ☐ No

**ACCOUNTABILITY**

A. Is there a physician leader responsible for program outcomes of stewardship activities at your facility?

☐ Yes ☐ No

**DRUG EXPERTISE**

A. Is there a pharmacist leader responsible for working to improve antibiotic use at your facility?

☐ Yes ☐ No

**KEY SUPPORT FOR THE ANTIBIOTIC STEWARDSHIP PROGRAM**

*Does any of the staff below work with the stewardship leaders to improve antibiotic use?*

B. Clinicians

☐ Yes ☐ No

C. Infection Prevention and Healthcare Epidemiology

☐ Yes ☐ No

D. Quality Improvement

☐ Yes ☐ No

E. Microbiology (Laboratory)

☐ Yes ☐ No

F. Information Technology (IT)

☐ Yes ☐ No

G. Nursing

☐ Yes ☐ No

**LEADERSHIP SUPPORT****ESTABLISHED  
AT FACILITY**

- A. Does your facility have a formal, written statement of support from leadership that supports efforts to improve antibiotic use (antibiotic stewardship)?
- B. Does your facility receive any budgeted financial support for antibiotic stewardship activities (e.g., support for salary, training, or IT support)?

☐ Yes ☐ No☐ Yes ☐ No**ACCOUNTABILITY**

- A. Is there a physician leader responsible for program outcomes of stewardship activities at your facility?

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- C. Infection Prevention and Healthcare Epidemiology

☐ Yes ☐ No

- D. Quality Improvement

☐ Yes ☐ No

- E. Microbiology (Laboratory)

☐ Yes ☐ No

- F. Information Technology (IT)

☐ Yes ☐ No

- G. Nursing

☐ Yes ☐ No

## Ideas to improve antibiotic prescribing





Step.2 Aim : Right drug, right dose, right time, right duration for Surgical patients

Review in line with HMC guidelines with H.H OR

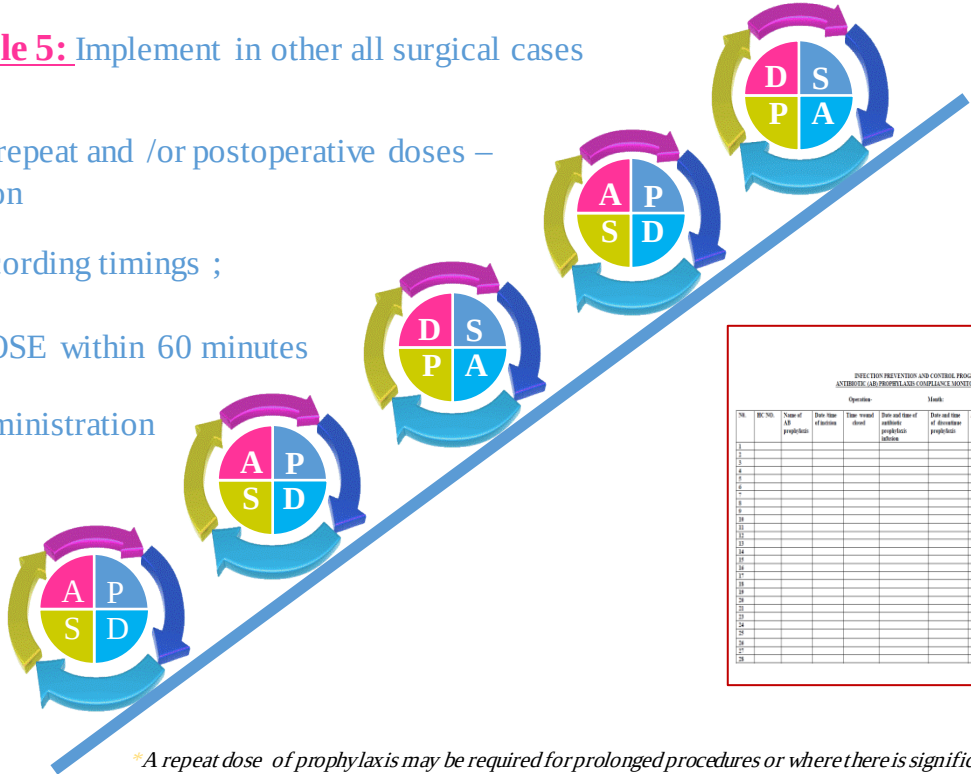
Cycle 5: Implement in other all surgical cases

Cycle 4: Testing repeat and /or postoperative doses – pharmacist /surgeon

Cycle 3: Testing recording timings ; Surgical prophylaxis ONE DOSE within 60 minutes before knife to skin

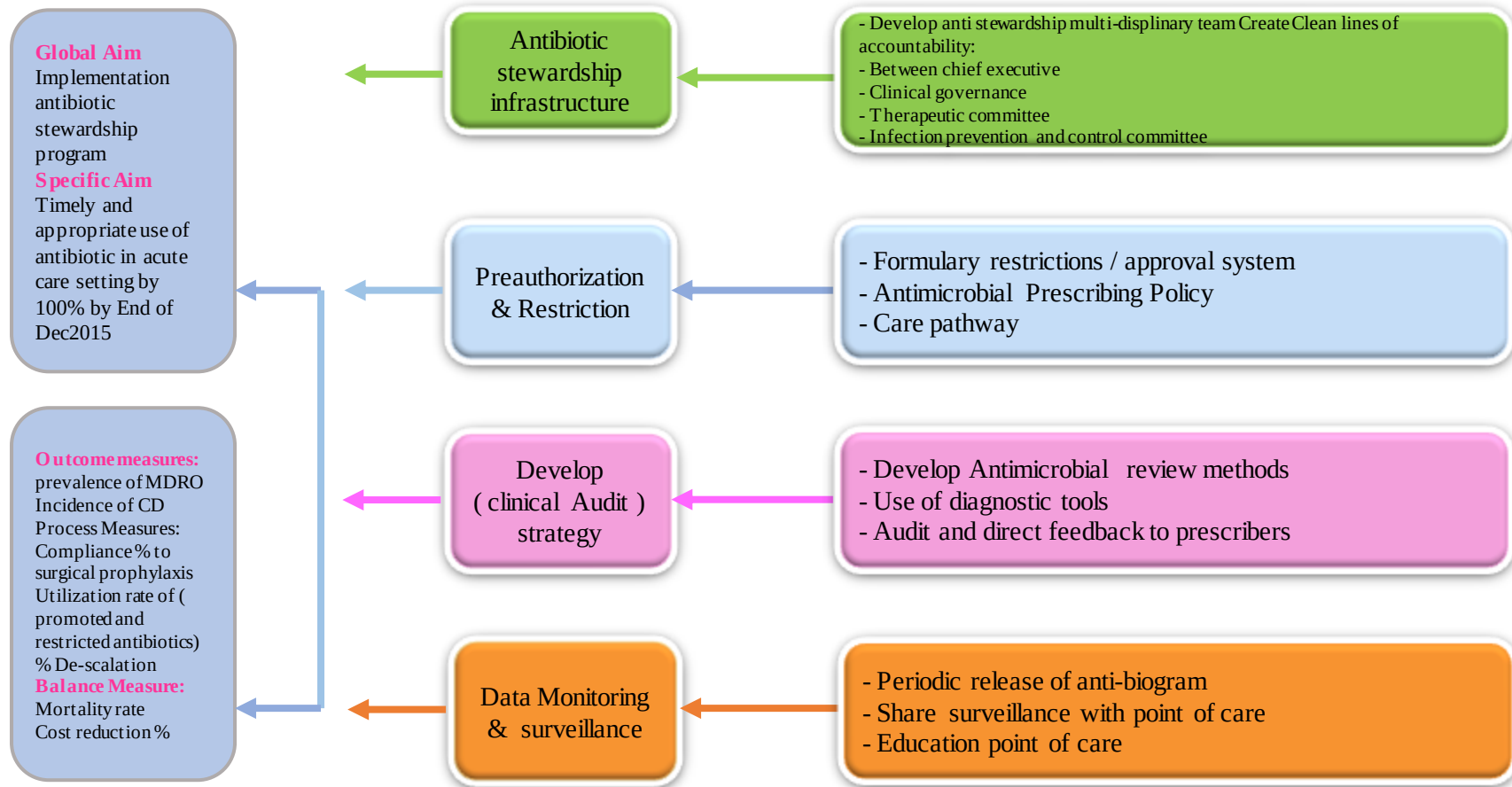
Cycle 2: Testing administration in anesthetic room

Cycle 1: Testing prescribing in CABG pilot population based on local policy



| INFECTION PREVENTION AND CONTROL PROGRAM<br>ANTIBIOTIC AND PROPHYLAXIS COMPLIANCE MONITORING TOOL |        |                    |                                     |                   |                                                  |                                         |         |
|---------------------------------------------------------------------------------------------------|--------|--------------------|-------------------------------------|-------------------|--------------------------------------------------|-----------------------------------------|---------|
| Operation                                                                                         |        |                    | Month                               |                   | Year                                             |                                         |         |
| Sl.                                                                                               | BC No. | Name of antibiotic | Date time of antibiotic prophylaxis | Date wound closed | Date and time of antibiotic prophylaxis delivery | Date and time of antibiotic prophylaxis | Remarks |
| 1                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 2                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 3                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 4                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 5                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 6                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 7                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 8                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 9                                                                                                 |        |                    |                                     |                   |                                                  |                                         |         |
| 10                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 11                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 12                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 13                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 14                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 15                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 16                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 17                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 18                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 19                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 20                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 21                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 22                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 23                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 24                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 25                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 26                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 27                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 28                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 29                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |
| 30                                                                                                |        |                    |                                     |                   |                                                  |                                         |         |

\*A repeat dose of prophylaxis may be required for prolonged procedures or where there is significant blood loss. A treatment course of antibiotics may also need to be given in cases of dirty surgery or infected wounds.



# The role of quality measurement in AMS program and Infection Control .Why measure?

## Outcome Measures

- C. difficile infection rate
- Surgical Site Infection (SSI) rates post surgery
  - Surveillance of resistance

## Process Measures

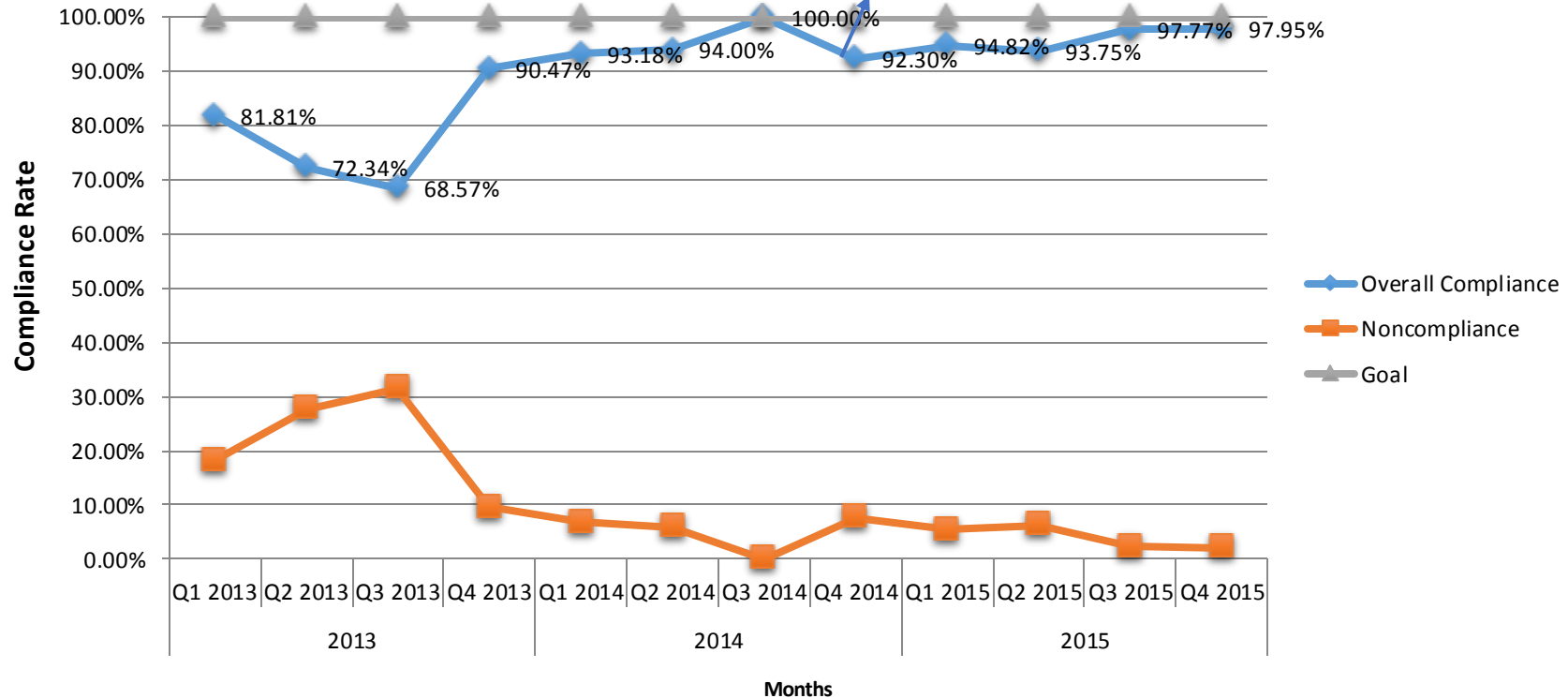
- Compliance with surgical prophylaxis (<60 min from incision)
  - Compliance with care “bundles” – all or nothing

## Balance Measures

- (ventilator-associated pneumonia, CLABSI)



# Overall Antibiotic Prophylaxis Compliance Versus Noncompliance in CABG Surgeries, Year 2013-2015



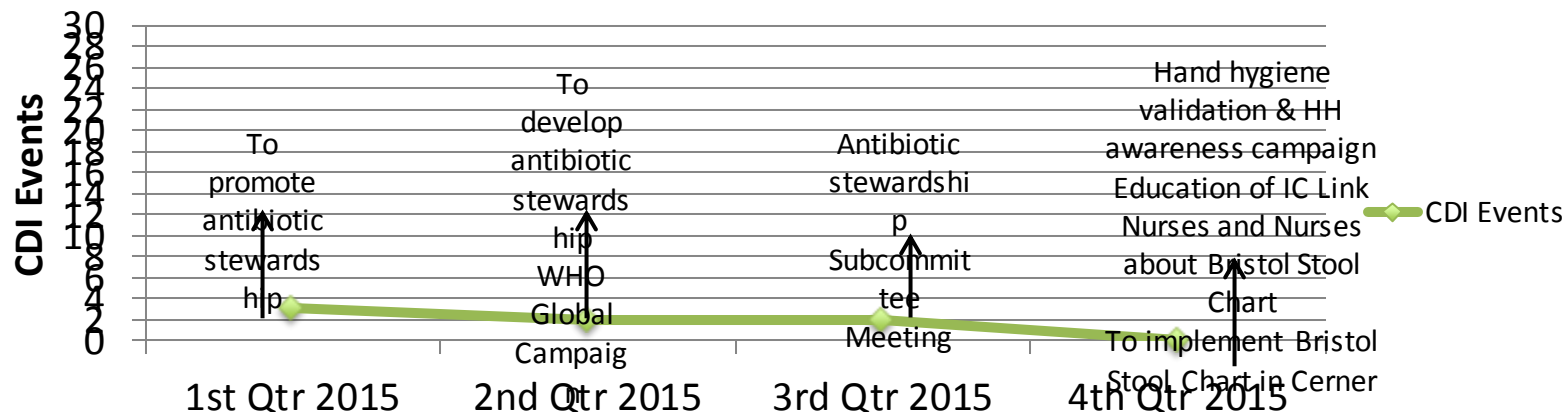
# Clostridium Difficile Infections (CDI) in Heart Hospital

**Standard PCI 6:** The hospital uses a risk-based approach in establishing the focus of the health care associated infection prevention and reduction program.

**Definition:** Healthcare Associated Clostridium difficile infection (CDI) Facility Onset

CDI Incidence Rate =  $\frac{\text{Number of healthcare associated CDI per month} > 3 \text{ days after admission to the location}}{\text{No. of patient days for the same period in a given unit}} \times 10000$

## Healthcare Associated Clostridium Difficile Events in Heart Hospital, Year 2015

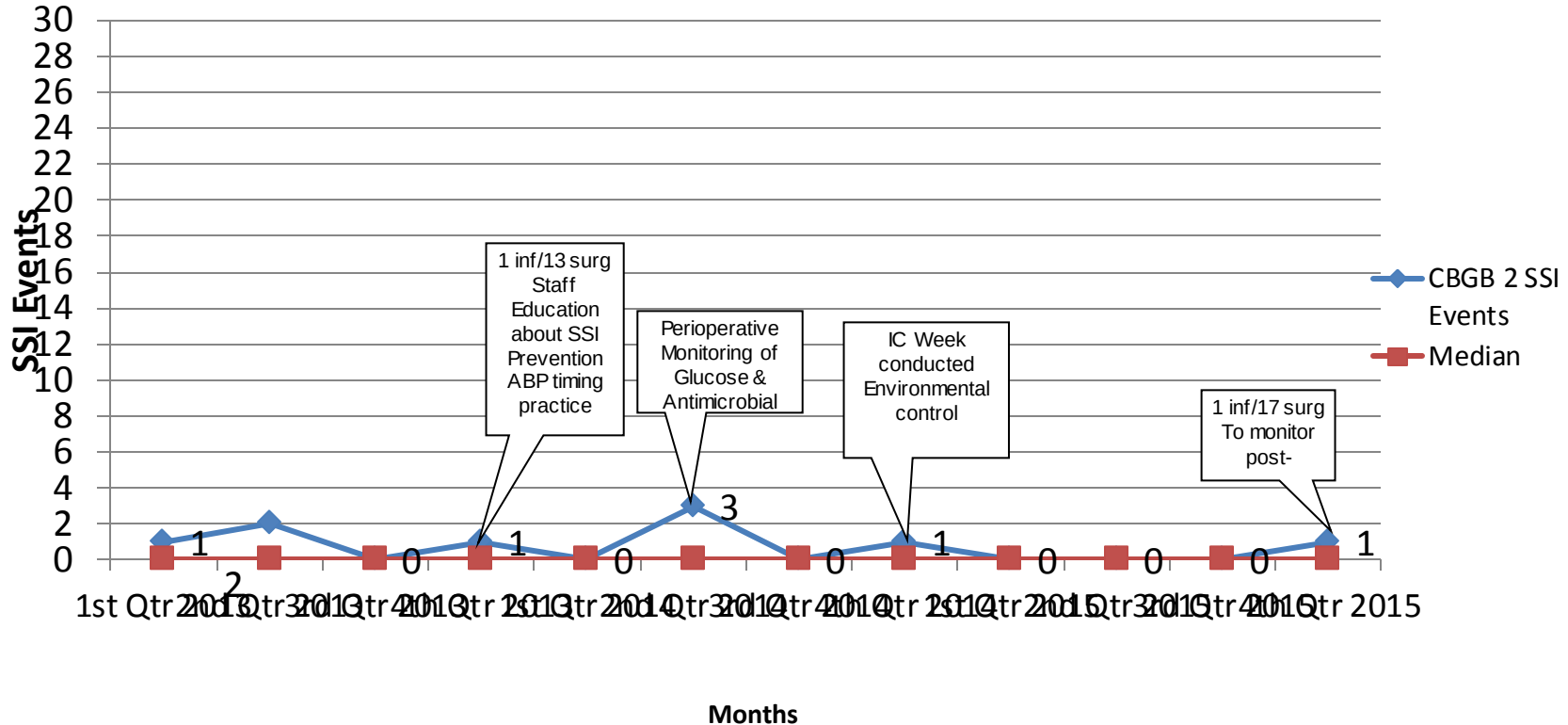


# Coronary Artery Bypass Graft Chest and Donor Incisions (CBGB 2) SSI , Year 2013 - 2015

**Standard PCI 6:** The hospital uses a risk-based approach in establishing the focus of the health care associated infection prevention and reduction program.

**Definition:** Surgical Site Infections for Coronary Artery By pass Graft (CBGB)

**Indicator:**  $\frac{\text{Number of infections}}{\text{Number of operations}} \times 100$





## Alternative methods for monitoring prescribing antimicrobial use





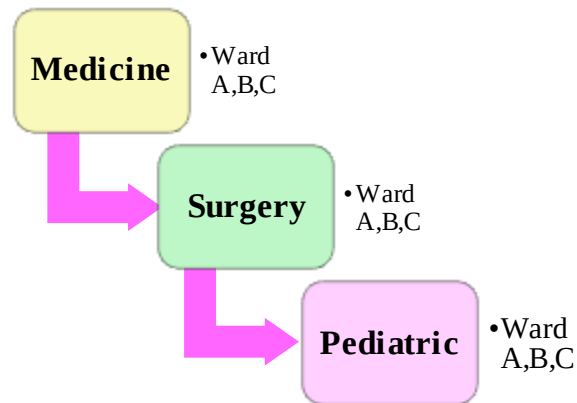
## Point Prevalence survey :

Key to qualitative measurement of antibiotic prescribing in your hospital

### Questions 1- What are you interested in measuring?

Identified any areas of concern

| Data element                     | Data options                                                                                    |
|----------------------------------|-------------------------------------------------------------------------------------------------|
| Name of drug                     | From filtered WHO Drug list                                                                     |
| Route                            | Parenteral, Oral, Rectal, Inhalation                                                            |
| Unit dose                        | Grams or MU, to three decimal places                                                            |
| Dosage frequency                 | 1-12 per day, every (18,36,48) hours, twice per week, three times per week, continuous infusion |
| Indication                       | Coded list of indications                                                                       |
| Indication group                 | Indication Group                                                                                |
| Prophylaxis                      | Surgical, Medic                                                                                 |
| Diagnosis                        | Coded list of diagnoses                                                                         |
| Day of therapy                   | 1-28,29+,Long Term, Unknown                                                                     |
| Is Review / Stop Date Documented | y/n/unknown                                                                                     |
| Reason in notes                  | y/n/unknown                                                                                     |
| Complies with (local) guidance   | y/n/unknown                                                                                     |
| Date start Indication            | DD/MM/YY (the date first antimicrobial was prescribed for indication)                           |



## Who Is a Good candidate for ASP Review?

- High-cost agents (eg, linezolid, daptomycin, echinocandins)
- Broad-spectrum agents (eg, carbapenems, piperacillin/tazobactam)
- High risk of adverse effects (eg, aminoglycosides)
- Cases for surgical procedures
- High-use agents (facility dependent)
- Double coverage of organisms (eg, anaerobes)
- 3 or more anti-Infectives for >3 days



# The Impact Of Rapid Diagnostic Test in Antimicrobial Stewardship

In 2015 a paper, [“Randomized Trial of Rapid Multiplex Polymerase Chain Reaction-Based Blood Culture Identification and Susceptibility Testing”](#) by Banerjee et al,

A new novel test in practice, The trial included:

- A conventional blood culture work-up arm
  - A new rapid test arm and
  - The combination of the new rapid test and direct communication with the antimicrobial stewardship team.
- 
- The time to identify pathogen was significantly decreased in the arms in which the new rapid test applied to positive blood culture bottles compared to the conventional arm.
  - Streamlining was accomplished significantly when rapid diagnostic testing was combined with the antimicrobial stewardship intervention such as de-escalation antimicrobial drugs





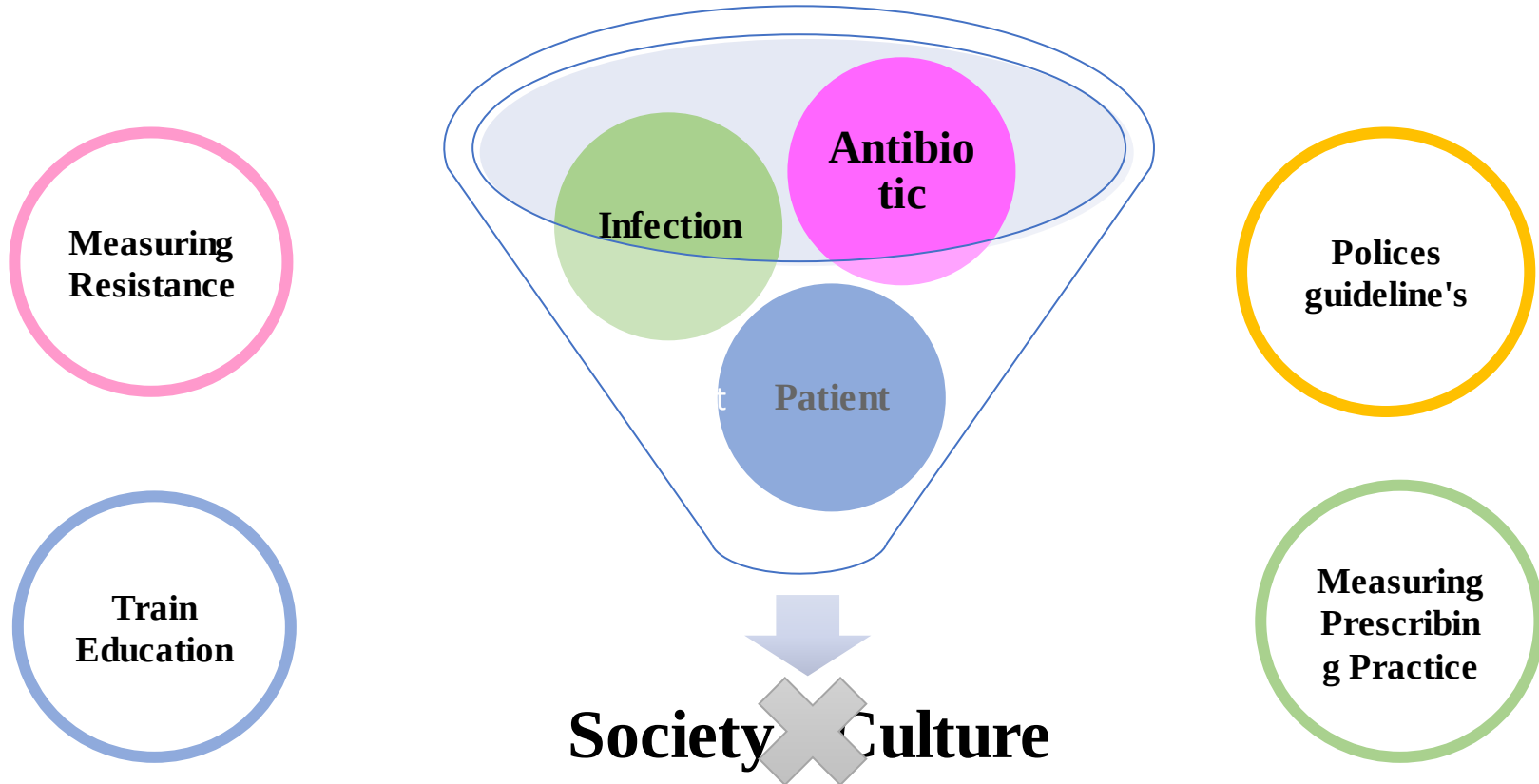
**Why change an already  
winning team?**

-Accurate microbiological diagnosis does not always lead to appropriate antimicrobial prescribing?

-Why modify antimicrobial therapy if the patient is having a favorable clinical course with broad-spectrum antimicrobials?



## Improve culture and team dynamics in antimicrobial stewardship





# Understanding the Determinants of Antimicrobial Prescribing Within Hospitals: The Role of “Prescribing Etiquette”

E. Charani,<sup>1</sup> E. Castro-Sanchez,<sup>1</sup> N. Sevdalis,<sup>2,3</sup> Y. Kyratsis,<sup>1</sup> L. Drumright,<sup>1</sup> N. Shah,<sup>1</sup> and A. Holmes<sup>1</sup>

<sup>1</sup>The National Centre for Infection Prevention and Management, Hammersmith Hospital; and <sup>2</sup>Department of Surgery and Cancer, and <sup>3</sup>Imperial Centre for Patient Safety and Service Quality, St Mary's Hospital, Imperial College London, United Kingdom

**Background.** There is limited knowledge of the key determinants of antimicrobial prescribing behavior (APB) in hospitals. An understanding of these determinants is required for the successful design, adoption, and implementation of quality improvement interventions in antimicrobial stewardship programs.

**Methods.** Qualitative semistructured interviews were conducted with doctors (n = 10), pharmacists (n = 10), and nurses and midwives (n = 19) in 4 hospitals in London. Interviews were conducted until thematic saturation was reached. Thematic analysis was applied to the data to identify the key determinants of antimicrobial prescribing behaviors.

**Results.** The APB of healthcare professionals is governed by a set of cultural rules. Antimicrobial prescribing is performed in an environment where the behavior of clinical leaders or seniors influences practice of junior doctors. Senior doctors consider themselves exempt from following policy and practice within a culture of perceived autonomous decision making that relies more on personal knowledge and experience than formal policy. Prescribers identify with the clinical groups in which they work and adjust their APB according to the prevailing practice within these groups. A culture of “noninterference” in the antimicrobial prescribing practice of peers prevents intervention into prescribing of colleagues. These sets of cultural rules demonstrate the existence of a “prescribing etiquette,” which dominates the APB of healthcare professionals. Prescribing etiquette creates an environment in which professional hierarchy and clinical groups act as key determinants of APB.

**Conclusions.** To influence the antimicrobial prescribing of individual healthcare professionals, interventions need to address prescribing etiquette and use clinical leadership within existing clinical groups to influence practice.

**Keywords.** prescribing etiquette; antimicrobial prescribing; prescribing behavior.

1. A systematic review-2011  
Qualitative and quantitative  
research

→ found very little evidence of  
using social science research in  
antibiotic stewardship program

2. This systematic review was  
followed up with a qualitative  
study, where 39 health care  
professionals from nursing,  
medical, and pharmacy professions  
across three hospitals were  
interviewed



The study explored their perceived self-reported determinants on antibiotic prescribing behaviors

### **What was identified in UK :**

- 
- The existence of tacit rules governing prescribing.
  - Hierarchy and prescribing etiquette overruled policy and guidelines.
  - Senior clinicians wielded significant influence on the prescribing choices and decisions of junior doctors.

### **When study replicated in Norway:**

- It was interesting to find differing results, with hierarchy not emerging as a key determinant.
- For example, in Norwegian hospitals, all hospital staff wear the same white uniform. And these activities may have inadvertently helped them overcome some of the barriers.



## Influence on Prescribing

- Including cultural aspects related to the country background,
- Sociocultural and socio-economic factors, and
- The cultural beliefs of the patient and the prescriber,
- Patient demand, and
- Clinical autonomy
- Diagnostic uncertainty plays an important role in antibiotic overprescribing



## Improving Antibiotic Use Saves Money

Comprehensive programs have consistently demonstrated a decrease in antimicrobial use with annual savings of \$200,000 - \$900,000”





## Role of Clinical and Administrative Leaders



Promote a culture of optimal antibiotic use within the facility, How:

→ Engage administrative and clinical leadership to champion stewardship effort



**The importance of culture and team dynamics in  
antimicrobial stewardship  
Higher order goals**

We were in a position where we had to reduce our health-care-associated infections ( MRSA, CDI, AMS)

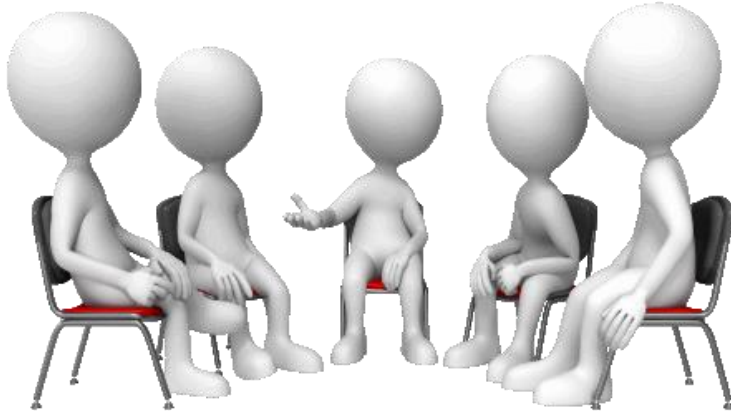
We'd been collecting our data for several years on a number of different infections and antibiotics misuse



Dr. Mike Cooper



Feedback to the senior managers and all consultants being sent a monthly email showing the trends, the number of infections, and the attributions of these infections to individual wards and clinical areas.



The staff were encouraged to share these results with all their colleagues, and to put them on display for the patients and the public.



Sense of shared responsibilities if the performance was less good

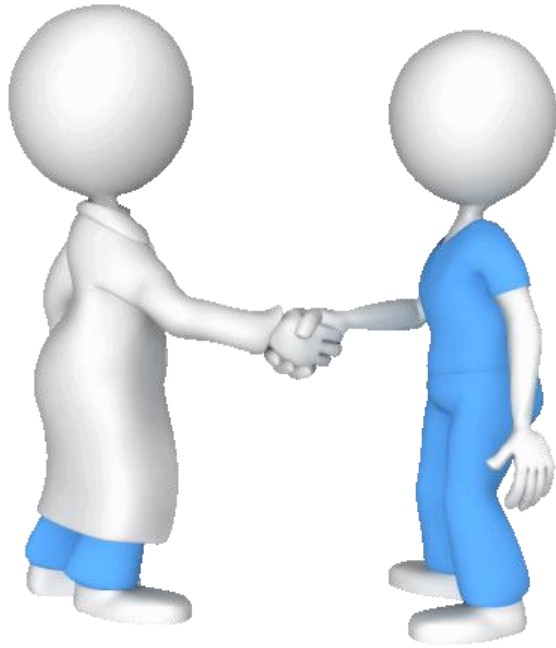
if a ward did well, it was recognized as being due to their local actions and for taking ownership of the issue.

if a ward did badly, this was seen as the failure of everyone involved, including the infection prevention team, and also possibly the wider structures of the hospital.



When we compared our more recent data with the historical figures, we could demonstrate the difference in the mortality numbers and the mortality rates from before and after the improvements. So this was fed back to the medical staff.





The infection prevention team were being stopped in the corridor and congratulated and quizzed about what more they could do.



one consultant said the day he first saw the mortality data, he had been due to teach the junior doctors about hypertension, but changed his plans and actually talked about antibiotic resistance & infection control because he said he realized that this was more important.



# Patient Engagement



Centers for Disease Control and Prevention  
CDC 24/7: Saving Lives, Protecting People™



CDC A-Z INDEX ▾

## Get Smart Programs & Observances



In Doctors' Offices

[More >](#)



In Healthcare Facilities

[More >](#)



On the Farm

[More >](#)



Get Smart Week

[More >](#)



## Role of Patient and Family:

1. Use antibiotics only as prescribed by your doctor.
2. Take the appropriate daily dosage and complete the entire course of treatment.
3. If you have an antibiotic prescription, ask your doctor what you should do if you forget to take a dose.
4. If for some reason you have leftover antibiotics, throw them away. Never take leftover antibiotics for a later illness. They may not be the correct antibiotic and would not be a full course of treatment.
5. Never take antibiotics prescribed for another person



## Role of Patient and Family

- 
- Don't pressure your doctor to give you an antibiotic prescription. Ask your doctor for advice on how to treat symptoms.
  - Practice good hygiene. Wash your hands regularly with soap and water, especially after using the toilet, before eating, before preparing food and after handling fresh meat. Wash fruits and vegetables thoroughly, and keep kitchen work surfaces clean.
  - Make sure you or your children receive recommended vaccinations. Some recommended vaccines protect against bacterial infections, such as diphtheria and whooping cough (pertussis).

# THE KEY TO SUCCESS

- Establish a clear aim/vision that is shared by all the stakeholders
- Assemble a strong coalition including a multi-professional antimicrobial stewardship team with a strong influential clinical leader.
- Establish effective communication structures within your hospital.
- Start with core evidence-based stewardship interventions depending on local needs, geography and resources and plan measurement to demonstrate their impact.
- Ensure all healthcare staff are aware of the importance of stewardship. Empower them to act and support with education using a range of effective strategies.
- Ensure early or short term wins and then consolidate success/gains while progressing with more change or innovation.



# SAVE OUR ANTIBIOTICS

1. So are we really approaching the post-antibiotic era?



2. Have we abused this precious resource so badly that we soon won't have these most valuable of drugs?



3. Will what are now considered to be trivial infections once again become killers?



4. Have we come a full circle back to before penicillin became available to use in the 1940s?



## RESOURCES

### **-Core Elements of Hospital Antibiotic Stewardship Programs**

<http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>

### **-Antimicrobial Stewardship Toolkit**

<http://www.ahaphysicianforum.org/resources/appropriate-use/antimicrobial/index.shtml>

### **-Antimicrobial Stewardship (Society for Healthcare Epidemiology of America)**

<http://www.shea-online.org/PriorityTopics/AntimicrobialStewardship.aspx>



1. What deficiencies in infection control and clinical practice are depicted in the video?
2. What are the key drivers for resistance?

