



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

National Policy on Restricted Antimicrobial Agents

Health Service Executive

Reference Number		Developed By	On behalf of National Taskforce on HCAI AMR
Version Number	V0.1	Version Date	04/07/2016
Approval Date		Approved By	
Responsibility for Implementation	Hospital Groups	Responsibility for Review and Audit	
Review Date			

Policy Statement

The following, based on the 2009 SARI Guidelines for Antimicrobial Stewardship in Hospitals in Ireland, must be implemented in all acute hospitals in Ireland:

- Each hospital's antimicrobial prescribing guidelines must include a list that stipulates which antimicrobials are unrestricted, restricted (approval of a specialist is required) or only permitted for specific conditions. Criteria for alert antimicrobials include spectrum of activity, potential toxicity, misuse or cost.
- The list of restricted antimicrobials must be reviewed on a regular basis, in light of the hospital's antimicrobial usage data and rates of antimicrobial resistance. Restrictions may have to be reinforced, or applied to additional antimicrobial agents, in the setting of outbreaks caused by antimicrobial-resistant pathogens (e.g. *C. difficile*, VRE, MRSA).
- Restricted antimicrobials should only be available from the hospital pharmacy, and not included in medication ward stocks of those areas where access is restricted. However, hospitals should ensure that there is a mechanism for accessing restricted agents, when required, outside of normal working hours.
- Hospitals should have a process in place to facilitate pre-authorisation for the use of restricted antimicrobials by an infection specialist (Consultant or Specialist Registrar in Clinical Microbiology or Infectious Diseases). An example of such a system is included below.
- Where a Consultant in another discipline considers that a decision to decline approval for use of a specific antimicrobial agent is not consistent with the best interests of their patient, they should attempt to resolve the issue by direct discussion with the responsible Consultant in Clinical Microbiology or Infectious Diseases and, if necessary, make further efforts to resolve the issue by discussion with the local Clinical Director and/or input from other Consultants in Clinical Microbiology or Infectious Diseases. Exceptions to the requirement for pre-authorisation may be made as part of locally-agreed protocols for management of conditions in specific patient groups (e.g. neutropenic sepsis, acute exacerbations of cystic fibrosis). Where restricted agents are prescribed as part of such protocols, this must be clearly documented in the medical notes or prescription record.
- Regardless of whether or not a system of pre-authorisation is in place, hospitals should have a system for identifying when restricted antimicrobials have been prescribed, and early review of such prescriptions by a member of the antimicrobial stewardship team.

Access to following antimicrobial class must be restricted, as per the policy statement above:

- **Carbapenems (e.g. meropenem, imipenem, ertapenem)**

The following antimicrobial classes, or specific agents, should also be considered for inclusion in restricted lists, following local agreement:

- Other specific beta-lactams (e.g. Aztreonam)
- Antipseudomonal penicillins (e.g. piperacillin-tazobactam; ticarcillin-clavulanic acid)
- Third, fourth and fifth generation cephalosporins (e.g. cefotaxime, ceftazidime, cefipime)
- Fluoroquinolones (e.g. ciprofloxacin, ofloxacin, levofloxacin)
- Specialist anti-Gram positive agents (e.g. vancomycin, teicoplanin, linezolid, daptomycin, rifampicin)
- Lincosamides (e.g. clindamycin)
- Aminoglycosides (e.g. amikacin)

The above list is not exhaustive, and hospitals may choose to include other agents on restricted lists such as anti-fungal agents, anti-viral agents, or other antibiotics.

Suggested Procedure for Requesting Restricted Antimicrobials

- i. A member of the medical staff on the antimicrobial stewardship team will be available promptly through a clearly defined pathway 24 hours/seven days a week
- ii. If a consultant or non-consultant hospital doctor is considering prescribing one or more restricted antimicrobial agents, he/she should contact the antimicrobial stewardship team member on-call. The prescriber should be able to provide the following information:
 - a. Patient's name, hospital medical record number and location
 - b. Clinical indication for antimicrobial therapy
 - c. Drug allergies and side effects to previous antimicrobials
 - d. Microbiology culture results, if available
 - e. Renal and hepatic function
 - f. Weight and height of the patient
- iii. The antimicrobial stewardship team member will respond to the prescriber in a timely manner, discuss the case with the prescriber and, on the basis of the above information, may:
 - a. Recommend the use of the restricted agent(s)
 - b. Recommend an alternative therapeutic option
 - c. Recommend further investigations or clinical follow-up
- iv. The prescriber must record the details of the consult in the patient's clinical notes
- v. The antimicrobial stewardship team member will fill out an information card for all restricted antimicrobials requests. The information card contains the following:
 - a. Patient's name, medical record number and location
 - b. Prescriber's name, pager number, clinical service and position
 - c. The prescribing consultant's name and clinical service
 - d. Reason for calling
 - e. If for pre-authorisation, reason for authorisation
 - f. Recommendations given
 - g. Rationale for recommendations given
 - h. Whether or not the infectious diseases or medical microbiology consultant was contacted

Performance metrics

The following data should be collected and analysed to assess the performance and impact of the restricted antibiotic policy:

- Number of courses of carbapenem antibiotics dispensed per month (with comparison, via quarterly HPSC pharmacy reports, to carbapenem consumption in other hospitals of similar case-mix and category), and
- Number of courses of carbapenem antibiotics dispensed per month without
 - Prior authorisation by an infection specialist, or
 - Infection specialist review, or
 - Documented compliance with a hospital policy covering exceptional use of these agents
- Proportion of hospital antibiotic consumption accounted for by carbapenems per quarter (included as part of quarterly hospital pharmacy dispensing data reported to HPSC)

The above metrics should also be collected for other classes of antimicrobials included on the hospital's restricted list.

Rationale for Restrictive Antimicrobial Prescribing Policy

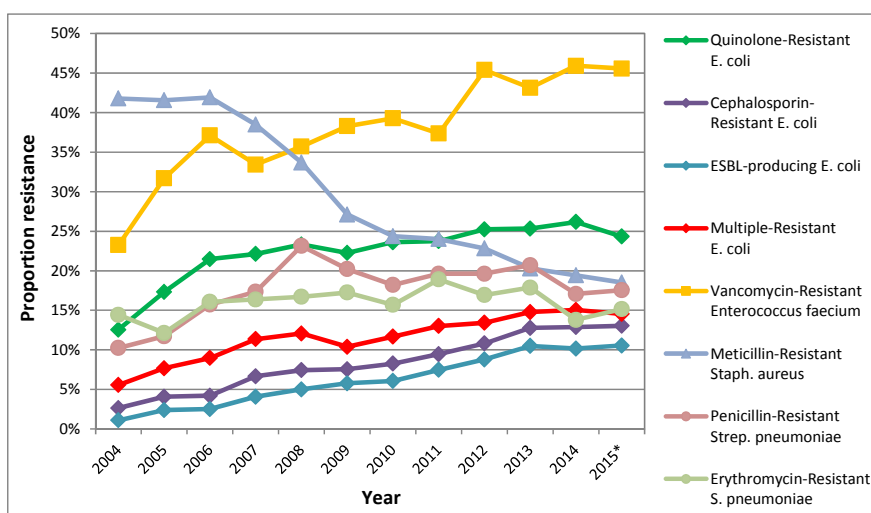
A 2005 Cochrane review of antibiotic stewardship interventions for hospitalised patients found overall rates of success for persuasive interventions (e.g. direct clinical review with intervention and feedback) were 64-75%, and 66-87% for restrictive interventions (e.g. formulary restriction and pre-authorisation requirements for specific agents). However, restrictive interventions had, on average, a more than three-fold greater effect compared to persuasive interventions.¹ In a 2013 update, meta-analysis of 52 interrupted time-series studies was used to compare restrictive versus purely persuasive interventions. Restrictive interventions had significantly greater impact on prescribing outcomes at one month (32%, 95% confidence interval (CI) 2% to 61%, $P = 0.03$) and on microbial outcomes at 6 months (53%, 95% CI 31% to 75%, $P = 0.001$).²

Both formulary restriction and preauthorisation requirements for use of clindamycin during nosocomial outbreaks of *C. difficile* infection have led to prompt cessation of the outbreaks.^{3,4} Pre-approval restriction of broad spectrum antimicrobials has led to increased susceptibilities among Gram-negative pathogens, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*, during a 6–12-month period.^{5,6} In one centre, restriction of vancomycin and third-generation cephalosporins in response to increasing rates of vancomycin-resistant enterococci (VRE) was associated with a decrease in the faecal VRE point prevalence from 47% to 15% during six months.⁴

A guidance document on restriction and preauthorisation of high-risk antimicrobials was produced by the Hospital Antibiotic Stewardship Working Group of the RCPI/HSE Healthcare Associated Infection and Antimicrobial Resistance (HCAI/AMR) Clinical Advisory Group, and was circulated to all acute hospitals via the HSE National Clinical Director in September 2015. This policy document incorporates many of the same recommendations, and complements the guidance document and associated correspondence from the National Clinical Director to acute hospitals.

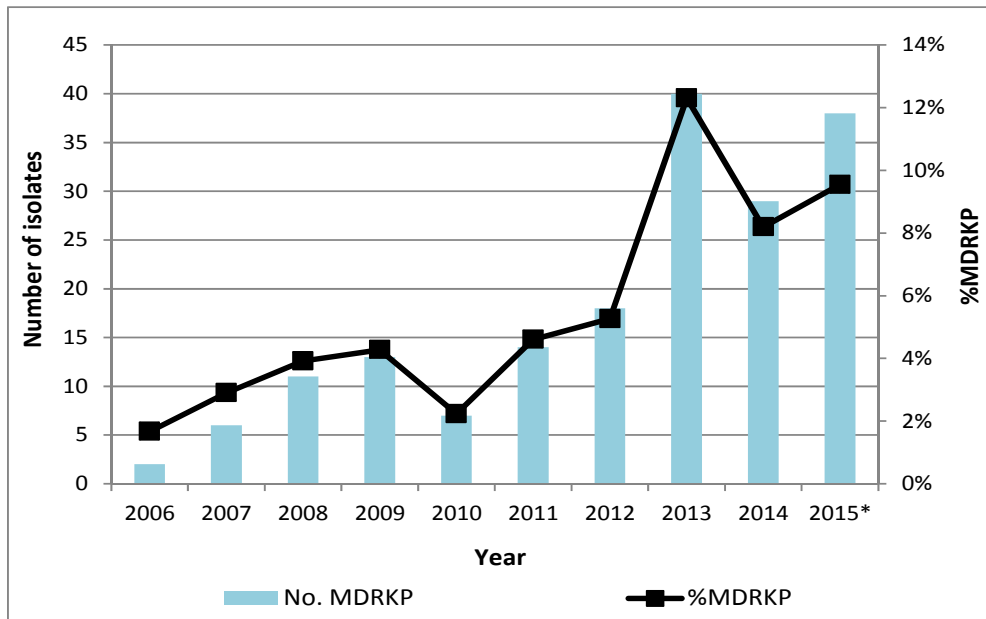
There is an increasing prevalence of antimicrobial resistant pathogens causing invasive infection in Ireland (figure 1). In addition, an extensive national outbreak caused by multiple drug-resistant clones of *Klebsiella pneumoniae* has been identified (figure 2), along with increasing reports of infections caused by carbapenem-resistant enterobacteriaceae (CRE).

Figure 1: Proportion of resistance to selected antimicrobials among key bloodstream infection isolates in Ireland, 2004 – 2015 (data source: HPSC; *2015 data provisional)



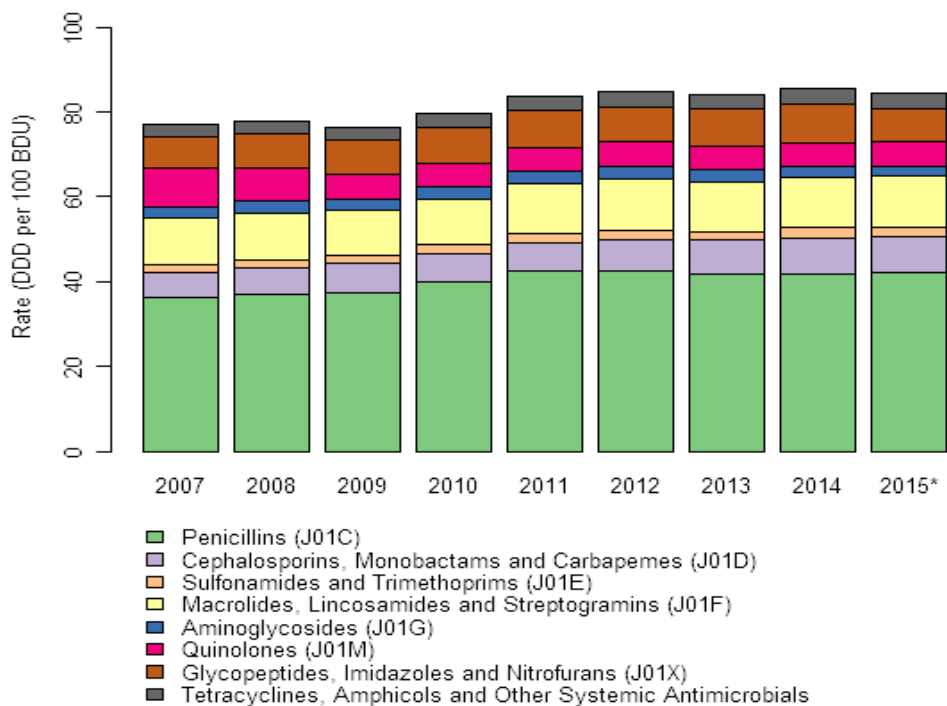
Notes: "Multiple-Resistant E. coli" refers to blood culture isolates resistant to three or more classes of antibiotics; "Cephalosporin-Resistant E. coli" refers to blood culture isolates resistant to third generation cephalosporins

Figure 2: Number and proportion of *K. pneumoniae* bloodstream infections caused by multiple drug-resistant clones (i.e. isolates of *K. pneumoniae* which are either ESBL-producers and non-susceptible to both ciprofloxacin and gentamicin AND/OR carbapenemase-producers), 2006 – 2015 (data source: HPSC; *2015 data provisional)



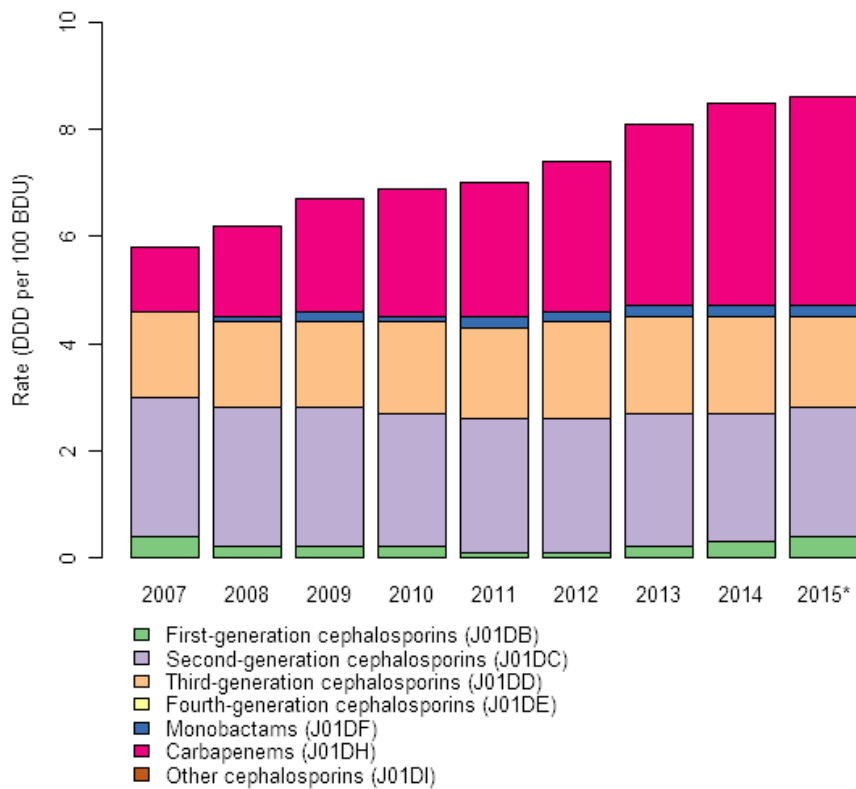
In parallel with the increasing levels of antimicrobial resistance, there has been an upward trend in antimicrobial consumption in hospitals in recent years (figure 3).

Figure 3: Consumption of antibiotics in acute hospitals, 2007 – Q2 2015* (data source: HPSC)



Of particular concern is the increasing consumption of broad-spectrum antibiotics. For example, carbapenem consumption in hospitals has steadily increased over the past number of years, and this increase appears to be occurring in addition to (rather than instead of) consumption of other broad-spectrum antibiotics (figure 4).

Figure 4: Consumption of selected broad-spectrum antibiotics in acute hospitals, 2007 – Q2 2015* (data source: HPSC)



References

1. Davey P, Brown E, Fenelon L, Finch R, Gould I, Hartman G *et al.* Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev.* 2005 Oct 19; (4):CD003543.
2. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev.* 2013 Apr 30; 4:CD003543.
3. Pear SM, Williamson TH, Bettin KM, Gerding DN, Galgiani JN. Decrease in nosocomial *Clostridium difficile*-associated diarrhea by restricting clindamycin use. *Ann Intern Med* 1994 Feb 15; 120(4):272-7.
4. Quale J, Landman D, Saurina G, Atwood E, DiTore V, Patel K. Manipulation of a hospital antimicrobial formulary to control an outbreak of vancomycin-resistant enterococci. *Clin Infect Dis* 1996 Nov; 23(5):1020-5.
5. White AC Jr, Atmar RL, Wilson J, Cate TR, Stager CE, Greenberg SB. Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities, and clinical outcomes. *Clin Infect Dis* 1997 Aug; 25(2):230-9.
6. Bamberger DM, Dahl SL. Impact of voluntary vs enforced compliance of third-generation cephalosporin use in a teaching hospital. *Arch Intern Med* 1992 Mar; 152(3):554-7.