

# NATIONAL STRATEGIES FOR THE CONTROL OF ANTIMICROBIAL RESISTANCE: THE HELLENIC CHALLENGE

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Antimicrobial resistance (AMR) is a global public health threat with significant social and financial implications. For Greece, the challenge is to control the dissemination of carbapenem-resistant Gram-negatives (CRGNs) in healthcare settings and the use of antibiotics in the community and hospital settings. In August 2013, the Hellenic CDC proposed a holistic strategy to the Ministry of Health. This strategy focuses on strengthening institutional structures through administrative support, the establishment of infection control programmes in every hospital, and awareness promotion and training of healthcare providers. The vision of the new legislative framework is the establishment of institutional bodies and procedures in Greek hospitals that will be effective in dealing with public health issues, like antimicrobial resistance, which pose a serious threat not only to Greece, but to the rest of the world.

Antimicrobial resistance poses an enduring threat to the global community and a major public health risk to developed countries. There is growing use of antimicrobial agents (1), and an increasing prevalence of antibiotic-resistant pathogens (2), that cause community- and hospital-acquired infections as well as neutralizing our most valuable weapons to deal with them, with dramatic consequences for the patients and the health system (3, 4). Even more alarming is the fact that we are heading towards an era of pan-drug resistance (PDR). Already in countries with extensive spread of carbapenem-resistant Enterobacteriaceae (CRE), resistance to all available antibiotics is a reality (5, 6, 7). Only when we estimate the time required for the introduction of new antibiotics to clinical practice do we understand the repercussions it can have for patients' safety and the operation of the health system per se, which basically invalidates itself (8).

Greece faces high levels of antimicrobial resistance, mainly associated with hospital-acquired infections caused by specific Gram-negative pathogens, primarily *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* (CRKP). The incidence of Gram-positive bacterial infections is low and the Methicillin-resistant *Staphylococcus aureus* (MRSA) represents only tenth most common cause of nosocomial infections (data from European Point Prevalence Survey of HAIs and Antimicrobial Use 2012). More specifically, as far

as the *Klebsiella pneumoniae* is concerned, since the beginning of the last decade when the first strains of VIM-producing *Klebsiella pneumoniae* were introduced and spread in Greek hospitals, the high-level resistance of this specific pathogen to carbapenems has significantly increased (9). In 2007, the monoclonal spread of KPC-producing *K. pneumoniae* strains displaced VIM-producing strains and have dominated across the country since (10, 11, 12). In particular, *Klebsiella* appears to be capable of replicating via plasmids maintaining strong resistance mechanisms. Additionally, it appears to have the ability to disseminate widely within a nosocomial environment. Controlling the spread of these specific pathogens has proved a tall order not only for Greece, but also for Europe and the global community (13, 14).

## Initiatives for the control of antimicrobial resistance: The national strategy

Until 2010, there was no data at a national level regarding the extent of the spread of these strains. In October 2010, at the initiative of the Hellenic Centre For Disease Control and Prevention (HCDCP), the "Procrustes Action Plan" was implemented (15), in order to combat the healthcare-associated infections (HAIs) caused by carbapenem-resistant Gram-negatives (CRGNs). The Procrustes Action Plan focused on surveillance of the HAIs caused by the three most significant Gram-negative nosocomial pathogens that are resistant

to carbapenems, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, as well as monitoring the implementation of infection control measures in healthcare settings in accordance with the guidelines issued by HCDCP. Hospital participation in the surveillance was very high and on a voluntary basis. Along with the surveillance of infections, teams of specialized healthcare professionals were set up in all health districts, making site visits to hospitals in order to monitor the implementation of all appropriate infection control measures.

The experience from both the Procrustes Action Plan and the onsite visits resulted in the HCDCP identifying both its intervention goals and the problems and limitations of the implementation of appropriate infection control measures. Significant efforts to combat the increased rates of antimicrobial resistance had also been made in the past, but they were not followed by analogous political commitment. At the end of 2013, the Government, comprehending the significance of the problem, enacted new legislation for the control of antimicrobial resistance and the prevention of healthcare-associated infections in hospital settings, and its implementation concerns all public, military, and private hospitals in Greece with the following aims and objectives:

- ➔ To reduce antimicrobial resistance in healthcare settings and control the dissemination of multidrug-resistant bacteria, focused on carbapenem-resistant Gram-negative pathogens at national level;
- ➔ To promote the rational use of antibiotics in hospitals with a view to improving quantitative and qualitative indicators that relate to their administration;
- ➔ To integrate the prevention of healthcare-associated infections (HAIs) into the routine clinical practice of healthcare professionals so it constitutes a quality index of healthcare services; and
- ➔ To mobilize hospital administrations and reinforce institutional bodies (infection control committees and antibiotic stewardship committees) so that such actions acquire cumulative and timeless value for tackling public health crises.

According to the new legislation, it is imperative that all hospitals apply the following:

- ➔ The establishment of infection control committees and antibiotic stewardship committees;
- ➔ The formulation of an infection control programme and antibiotic stewardship programme, in accordance with instructions issued by the Hellenic Centre for Disease Control and Prevention, which should be approved by the respective health districts;
- ➔ The formulation of an annual action plan for the control of

antimicrobial resistance and the use of antibiotics that will give a detailed account of actions, budget and specific goal setting;

- ➔ The consolidation of mandatory monitoring of eight indicators related to antimicrobial resistance and prevention and control of HAIs (indicators of structure, process and outcome) against which all hospital administrations and the quality of healthcare will be assessed; and
- ➔ The continuous training of all healthcare professionals in the implementation of infection control measures and the proper use of antibiotics. Training is mandatory and will be received annually through the corresponding programmes of HCDCP. The occupation of healthcare professionals with the nosocomial infection control will be assessed and certified by the infection control committees as a separate activity that will enrich their CVs.

The implementation of this legislation began in the second semester of 2014 and the gradual monitoring of the indicators has begun. HCDCP has completed and dispatched the common surveillance methodology to all hospitals and 75% of public and military hospitals and a significant number of private hospitals have been participating in the mandatory surveillance thus far. Infection control committees have been reconstituted in all hospitals and antibiotic stewardship committees are being set up. All health districts have established committees for the approval of the infection control programmes and hospitals' annual action plans based on national guidelines. HCDCP has also dispatched updated guidelines for controlling the spread of multidrug-resistant pathogens in healthcare settings, with a focus on carbapenem-resistant Enterobacteriaceae (CRE) isolates, and updated guidelines on the use of antibiotics in the community and hospital settings in 2015.

From October 2014 until May 2015, the first cycle of nationwide training of trainers in prevention and control measures for the spread of multidrug-resistant organisms (MDRO) in the hospital setting was concluded. In total, 864 healthcare professionals from all the hospitals (both public and private) of every health district were trained in specific materials and tools developed by HCDCP. The training will continue with hospital administrators and pharmacists.

From the participation of hospitals in the process and monitoring of training so far, there seems to be a growing awareness among healthcare professionals in terms of the prevention of HAIs and antimicrobial resistance. The results of the first indicators also suggest that despite limiting resources, no effort is spared to implement control measures. In 2013, the upward rise in the incidence of bacteremia caused by CRGN pathogens under surveillance was halted and, in

2014, it began to decrease for the first time (16), nevertheless, it is still too early to assess the implementation of the national strategy.

Another challenge that Greece faces is the proper use of antibiotics in healthcare settings as well as in the community. In hospitals, efforts are focused on the effective implementation of antibiotic stewardship programmes whose main objectives are the rational use of broad spectrum antimicrobial agents and surgical prophylaxis. The salvage of the last available antibiotics for treating infections caused by CRGN pathogens disseminating even through the food chain is a major issue at a time when resistance even to colistin appears to be on the increase worldwide (17, 18). In the community, the publication of guidelines on infection treatment in 2007 was a significant step that was met with broad acceptance by clinicians. The continuing training of primary care physicians, the promotion of public and healthcare professionals' awareness through the actions of European Antibiotics Awareness Day (EAAD) and finally, the introduction of e-prescribing, are the main factors that have contributed to the decrease in the use of antibiotics in the community over the last five years (19).

### Expectations and limitations

The implementation of this national strategy has to overcome several limitations before it achieves its objectives. These limitations are related to the health system structure, its organizational culture and the available human and financial resources. As regards the health system structure, a critical issue is that in Greek hospitals, a significant proportion of the patients are chronically ill with long-term and/or multiple hospitalizations and at risk of infection or colonization with multidrug-resistant bacteria, thus these patients are a major source of the spread of nosocomial pathogens. Additionally, a significant number of these patients are constantly recycled in the same or different hospitals. The shortage of nursing staff, and the limited number of isolation units available in hospitals make it all the more difficult to control the spread of CRE. Early detection of high-risk patients, especially those with CRKP colonization, and their isolation/cohorting are the most basic measures, the implementation of which is constantly increasing.

The key for the effective implementation of the new national strategy is the change of organizational culture, although it needs time to transform even in an advanced health system (19). Prevention is of great significance, not only for patient safety, but also because it saves resources that are channelled into improving the performance of the health system (20, 21). With these two aims, and the opportunity offered by the new national strategy, prevention of HAIs will be incorporated into routine clinical practice, which is an essential element of both

the organizational and the staff culture. A major step towards improving the organizational culture is the strengthening of the infection control committees' (ICCs) role. An inhibitory factor for the implementation of the preventive measures has been that ICCs have not had the corresponding administrative support, and, as a result, their role is constantly weakened. With the new legislative framework, the domains of ICCs are strengthened. The desideratum is to mobilize hospital administrators to promote the implementation of cost-effective measures and support the efforts made by the infection control committees.

At the current time, however, the main problem we face in implementing the new legislative framework is that all the aforementioned have to be implemented in an environment of limited resources and research conduct. Moreover, changing the culture of the health profession to enforce compliance with procedures, which is of vital importance to the effective implementation of health strategies under these circumstances, is best achieved through intensive intervention and training.

The role of education here is highly significant because not only does it aim at presenting and consolidating proper procedures, but also at properly assessing and prioritizing needs so as to allow maximum utilization of available resources. Therefore, the process of education includes hospital executives who are now actively involved with the implementation of the prevention of healthcare-associated infections programmes. Another important step in the training process of physicians is the recent launch of mandatory courses on the prevention of nosocomial infections, antimicrobial resistance and the appropriate use of antibiotics for medical students at undergraduate level.

### The Hellenic challenge

For Greece, despite the major public health challenges it faces, antimicrobial resistance is a top priority. The implementation of the policy that has been formed at national level calls for radical changes and time. Nonetheless, it is an important innovation for our health system that will revise old structures and values by promoting its development and improvement. Tackling antimicrobial resistance is not a simple task; it requires a holistic approach not only at the legislative level, but also at a clinical level with the appropriate support of the health system and institutional bodies, like the infection control and antibiotic stewardship committees. It demands strong political commitment with continuous monitoring and evaluation, provision of necessary resources and development of international cooperation, because antimicrobial resistance knows no bounds. International efforts to address antimicrobial resistance should take

account of the peculiarities of each health system so as to develop tools that are capable of helping countries effectively, especially those with significant problems and limited resources. ■

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