

# European Strategies to Control Antibiotic Resistance and Use

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Europe has taken many political actions since 1999 to better control antimicrobial resistance and use, including two European Council Recommendations and actions taken by numerous European Union (EU) presidencies. These presidencies triggered many public health and research actions in the EU. Europe developed several very successful surveillance programmes on antimicrobial resistance and antimicrobial use, both currently coordinated by the European Centre for Disease Prevention and Control (ECDC). These surveillance programmes were able to identify emerging problems of antibiotic resistance and targets for quality improvement of antimicrobial use; they also conducted impact assessments of campaigns to reduce antibiotic use and increase hand hygiene. The public antibiotic awareness campaigns were very successful in reducing antibiotic use and resistance in countries like Belgium and France. The successes of these campaigns inspired ECDC to

launch an annual European Antibiotic Awareness Day on November 18, 2008. The hand hygiene campaigns resulted in a dramatic decrease of MRSA infections in many EU Member States. However, ESBL-producing Gram-negative bacteria and Carbapenem-resistant *Enterobacteriaceae* and non-fermenters are increasing in most EU countries. Finally, the EU is investing hundreds of millions of EUROS in a Public Private Partnership (PPP), called the Innovative Medicines Initiative (IMI). An important initiative of IMI is the launch of the Combating Antibiotic Resistance NewDrugs4BadBugs programme. The goal of this new research programme is to create an innovative and collaborative PPP-based approach that will positively impact all aspects of the antimicrobial resistance issue, from the discovery of novel products to Phase 1-3 clinical trials. (**Ann Clin Microbiol 2014;17:1-8**)

**Key Words:** Drug resistance, European union, Microbial

## POLITICAL INITIATIVES

Europe has taken action towards resolving the lack of surveillance of antimicrobial resistance and consumption during an EU conference ‘The Microbial Threat’ back in 1998. This was the first conference at the EU level to discuss antibiotic resistance in humans and animals. The outcome of this conference is referred to as ‘The Copenhagen Recommendations’ that also encompassed the correlation of consumption with resistance [1]. These recommendations paved the way to a number of EU funded projects on antimicrobial consumption, antimicrobial stewardship and antimicrobial resistance.

Less than ten years after ‘The Copenhagen Recommendations’ the EU issued an updated European Council (EC) Recommendation (2009/C 151/01 of 9 June 2009) on patient safety [2]. This

included the prevention and control of Health Care Associated Infections (HAIs) specifically ‘article II.8.c’ i.e., to establish or, where already present, strengthen active surveillance at institution, regional and national level. This EC Recommendation was issued just months after a publication entitled ‘Turning the tide of antimicrobial resistance: Europe shows the way’ was published in Euro-surveillance, the ECDC scientific journal [3]. This publication stated that evidence from some European countries showed that it is possible to reverse the progress of antimicrobial resistance through prudent use of antibiotics, better adherence to infection control practices and immunisation.

Many EU presidencies focussed on antimicrobial resistance and these presidencies triggered many actions in the European Union. Some of the presidencies with the biggest impact were:

- Denmark (September–December 1999): EU Conference on

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the Microbial Threat in Copenhagen, which resulted in the ‘Copenhagen Recommendations’.

- Belgium (July-December 2001): Expert conference, which coincided with the Health Council meeting of Ministers in Brussels on November 15 November 2001, where the Council Recommendations on the prudent of antibiotics in human medicine [2002/77/EC] were unanimously approved. This conference also launched the European Surveillance of Antimicrobial Consumption (ESAC) project.
- Sweden (July-December 2009): Expert Conference ‘Innovative Incentives for Effective Antibacterials’, Stockholm, 17 September 2009, followed by REACT meeting in September 2010. This conference resulted in the Innovative Medicines Initiative, a large Public-Private-Partnership on developing new antibiotics.
- Belgium (July-December 2010): Expert conference ‘European Strategies to Monitor and Control Infection, Antibiotic Use and Resistance in Health-care Facilities’, Brussels 8–10 November 2010. This conference, organised together with the ECDC discussed ‘New strategies to monitor and control infections, antibiotic use and resistance in health-care facilities in the EU Member States’. Experts, representatives of the European Commission and the World Health Organization gathered to discuss common strategies to better manage and control HAI and antibiotic resistance in European hospitals and Long-term Care Facilities (LTCF). Many recommendations and concrete actions were proposed and agreed in four priority areas [4]. The European Commission agreed to fund research on: (i) the development of hand hygiene campaign materials tailored to the Member States, with the involvement of social marketing companies and behaviour scientists with evaluation of hand hygiene campaign materials; (ii) studying the effect on infection rates, either alone or in consort with other actions; and (iii) understanding human factors for compliance. The experts proposed that hospital CEOs should (i) be involved in hand hygiene campaigns; (ii) report on adherence to these campaigns in their hospitals; and (iii) be accountable for adverse events.

## SURVEILLANCE

### 1. European antimicrobial resistance surveillance (EARSS)

The European Union (EU) took a stance on antimicrobial resistance and health-care associated infections in 1999 (2119/98/EC-2000/96/EC) [[http://ec.europa.eu/health/ph\\_threats/com/comm\\_](http://ec.europa.eu/health/ph_threats/com/comm_)

[legislation\\_en.htm](#)]) recognising them as Public Health problems needing surveillance. As a result the European Antimicrobial Resistance Surveillance System (EARSS) was established in 1999 [5]. This network is now fully coordinated by the European Centre for Disease Prevention and Control (ECDC) under the new acronym EARS-Net. For the first decade it was run by the Dutch Institute of Public Health and the Environment (RIVM-*Rijksinstituut voor Volksgezondheid en Milieu*). The aim of EARS-Net is to collect and report valid and comparable data on the resistance of selected bacterial pathogens across European countries. Data on invasive pathogens from sterile sites is collected for: *Enterococcus faecalis*, *E. faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* and *Staphylococcus aureus*. Under RIVM, data were collected from 32 European countries in the final years of EARSS. As from January 2010 under ECDC EARS-Net only EU and European Economic Area (EEA) member countries can participate [6].

Looking at EARS-Net data for MRSA for the past decade major differences in proportion of MRSA in different countries and different trends can be seen: many countries organised hand hygiene campaigns which resulted in dramatic decrease of MRSA infections (e.g. in England, France and Belgium). However, looking at ESBL-producing Gram-negative bacteria and Carbapenem resistant *Enterobacteriaceae* and non-fermenters, trends show the opposite, and resistance is mounting in most EU countries (Source:[http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/table\\_reports.aspx](http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/table_reports.aspx)).

### 2. European surveillance of antimicrobial consumption (ESAC)

Surveillance of antimicrobial resistance cannot be a stand-alone initiative. Surveillance of antimicrobial consumption is an equally important factor in order to determine trends and possible quality indicators. The need for surveillance of antimicrobial consumption was recognised a year later than that of resistance [7]. In 2001 the European Commission Directorate-General Sanco-Health Monitoring Program, issued a Council Recommendation on the prudent use of antimicrobial agents in human medicine [2002/77/EC] [8]. This, in turn, led to the establishment of the European Surveillance of Antimicrobial Consumption (ESAC). Under the University of Antwerp, coordinator of the ESAC project, data were collected from 34 European countries in the final years of ESAC years. As from July 2011 ESAC moved to ECDC under ESAC-Net [6].

The aim of ESAC was to collect comparable and reliable an-

timicrobial consumption data across Europe [9]. Thus the Anatomic Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD) were selected as numerator for national data sets whilst the denominator chosen was the number of inhabitants based on the mid-year population of the country. Back then the DDD values for 2004 were used as these were current at the time of data collection. National antimicrobial consumption was therefore represented as DDD per 1000 inhabitants per day (DID) [10].

The level of total AC antimicrobial use across Europe varied considerably [11,12]. Indeed such differences were also observed for different drug classes, namely: antifungals [13], fluoroquinolones [14]; cephalosporins [15]; penicillins [11]; and ‘macrolides, lincosamides, streptogramins and ketolides’ (MLSK) [16]. Differences were also observed for the level of ‘out-patient parenteral antibiotic treatment’ (OPAT) [17]. However, the overall antimicrobial use in Europe is lower than the US average of 25 DID, with only 3 of 27 European countries showing higher use [18].

One of the main areas where consumption has been studied includes hospitals. However, prior to ESAC, most studies did not use standardised numerator/denominator criteria. For example, quoting total antimicrobial consumption in DDD/100 occupied bed-days (DBD), based on the ATC classification might include only systemic antibacterials (J01) or anti-infective agents (J) thus comparison of results between different studies is hampered [19]. Because there is no consensus on indicators to monitor antimicrobial use over time in hospitals, the ESAC project developed a Point Prevalence Survey (PPS) for antimicrobial use in hospitals. The Web-based method offered a standardised platform that allowed further detailed analysis of the PPS data collected which helped in the identification of targets for quality improvement [20,21]. The ESAC PPS methodology has been adapted for a paediatric specific project ‘Antibiotic Resistance and Prescribing In European Children’ (ARPEC) [22].

The next step is to develop a global PPS. The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (GLOBAL-PPS) is an ambitious project funded by BioMérieux to develop further on the point-prevalence surveys (PPS) carried out by the ESAC project. This ESAC PPS tool has illustrated many benefits; 1] the web based tool provides ease of access of data entry and analysis and an opportunity for rapid feedback of results to participating centres; 2] the tool is simple and requires a small amount of training and can be used by a range of professionals- there is evidence of consistency and reproducibility

with the data entry; 3] the PPS protocol/tool allows to link PPS data to other indicators (e.g link of PPS data to local antibiotic guidelines and compliance); 4] identification of current hospital clinical practice and showing significant variation and deficiencies in the quality of antibiotic prophylaxis and treatment; 5] the data has informed the development of quality indicators as well as performance targets for the improvement of antibiotic prescribing in hospitals; 6] participation in the survey has encouraged, thorough engagement and feedback, a sense of ownership and learning between the prescriber’s and the local infection community. The aim is to pilot the GLOBAL-PPS in about 30-40 hospitals during the Fall of 2014 and a global PPS in hundreds of hospitals during the Spring of 2015. Results would be reported on the 18 November 2015 for the European Antibiotic Awareness Day.

## AWARENESS CAMPAIGNS

Back in November 2001, during Belgium’s past presidency of the EU-Council, the Belgian Antibiotic Policy Coordination Committee (BAPCOC) [23] organised its first European Conference focusing on antibiotic use and resistance in Europe. The conference marked the launch of the ESAC project and coincided with the approval of the 2001 Health Council recommendations on the prudent use of antimicrobial agents in human medicine. Since then, the prudent use of antibiotics and the prevention of healthcare associated infections (HAI) have become priorities in all EU Member States. The success of the Belgian (since 1999) [23,24], French (since 2003) [24-26] and many other public awareness campaigns [27] inspired the European Centre for Disease prevention and Control (ECDC) in 2008 to launch an annual European Antibiotic Awareness Day (EAAD) on November 18 [28]. For instance, Belgium’s national campaigns from 1999 to 2010 reduced the total number of antibiotic packages per 1000 inhabitants from 3.6 in 1999-2000 to 2.4 in 2009-2010 (-33%). Resistance of *S. pneumoniae* to penicillin decreased from 18% in 2000 to 7% in 2009. Moreover, the total cost for reimbursement of antibiotics decreased with 21 million Euro (-16.7%) from 125,555,454 Euro in 2002-03 to 104,529,213 Euro in 2008-09. The cumulative savings between 2002 and 2009 were 90,154,345 Euro (two thirds were due to reduced prescribing; one third was due to reduction in price of antibiotics). Because the costs of the six campaigns between 2002 and 2009 was 2.4 million Euro, we can conclude that for every EUR invested in the campaign, 25 EUR were saved. France’s

national campaign from 2002 to 2007 reduced the total number of antibiotic prescriptions per 100 inhabitants by 26.5% overall, with the greatest reduction (35.8%) in antibiotic consumers aged 6-15 years old [24-26].

## RESEARCH

Since 1999, the EU has spent EUR 800 Million on AMR Research. Two new research tools were developed:

### 1. Joint Programming Initiative (JPI)

The aim of Joint Programming Initiative is to pool national research efforts in order to make better use of Europe's public R&D resources and to tackle common European challenges more effectively in a few key areas. With the JPIs Europe hopes to overcome the fragmentation of national research programmes to address global challenges. European Member States agreed, on a voluntary basis and in a partnership approach, on a common Strategic Research Agenda (SRA) to address major societal challenges which will be implemented jointly. So far, ten JPIs have been agreed by the European Commission; the JPI-Antimicrobial Resistance (AMR) was the last one to be launched in 2011.

The JPI on Antimicrobial Resistance (AMR) provides an excellent opportunity for joint research of the EU Member States addressing the emerging problem of antibiotic resistance. Indeed, the currently funded research projects in national or trans-national programs are commonly the result of an open competition for grants with projects from other research areas rather than a result of competition in a research programme specifically focusing on AMR. Consequently, the variable and non-permanent resources of trans-national organisations and individual countries are insufficient to provide long-term funding opportunities that are required to solve the major research questions concerning AMR. In addition, research activities on AMR are not harmonized between countries; which may lead to duplications in the research being performed in different countries. This JPI aims to accomplish the coordination of European research on AMR in close collaboration with the funding instruments of the EU; specifically Framework Programme 8 (Horizon 2020), Innovative Medicines Initiative (IMI) and the ERA-NET scheme.

A Strategic Research Agenda “2020 and Beyond” has been developed to prioritize research on AMR in Europe and beyond. The 6 pillars of this SRA are:

- Development of novel antibiotics and alternatives for anti-

biotics - from basic research to the market

- Design strategies to improve treatment and prevention of infections by developing new diagnostics.
- Implementation of a publicly funded global antibiotic resistance surveillance program.
- Transmission Dynamics
- The role of the environment and sewage as a source for the emergence and spread of antimicrobial resistance
- Designing and testing interventions to prevent acquisition, transmission and infection caused by antibiotic-resistant bacteria.

Nineteen Member states and Canada have joined forces in the Joint Programme Initiative on Antimicrobial Resistance (JPIAMR) to coordinate the research, in order to allow greater impact and avoid duplication. The JPI-AMR Strategic Research Agenda will be launched on 3 April 2014 in Brussels. The first call will be published in early 2014 with Canada (about EUR 20 million on topic A: discovery of a new pipeline).

### 2. ERC

Set up in 2007 by the European Union, the European Research Council (ERC) aims to stimulate scientific excellence in Europe by encouraging competition for funding between the very best, creative researchers of any nationality and age from anywhere in the world.

The ERC is part of the EU's Seventh Research Framework Programme (FP7) and has a total budget of €7.5 billion from 2007 to 2013. Its budget will increase by around 70% under the new EU research programme 'Horizon 2020' (2014-2020).

A new initiative has been launched in November 2013 to boost opportunities for early-career Korean scientists to come to Europe to join the research teams of European Research Council (ERC) grantees. The agreement was signed on 8 November 2013 by Minister of Science, ICT and Future Planning of the Republic of Korea, Choi Mun Kee, and – on behalf of the ERC – the European Commissioner for Research, Innovation and Science, Máire Geoghegan-Quinn. Young and talented Korean researchers will have the opportunity to join the teams of ERC grant holders, thus building new links between Korea and Europe bottom-up, in the ERC way.

The objective of the agreement is to stimulate cooperation by bringing the best researchers together to exchange ideas and experiences, and to enhance their international profile and knowledge. The initiative will make it easier for early-career Korean top scientists to be part of ERC-funded research teams for six

to twelve months.

### 3. Public Private Partnership (PPP): Innovative Medicines Initiative (IMI)

Unlike drugs used in the treatment of chronic non-communicable diseases, which do not become ineffective with usage, antibiotics do become ineffective within a few years of clinical use. This implies that antibiotic development is not as profitable so the Pharma-industry is deserting the anti-infective branch of R&D making the antibiotic pipeline drier [29]. From an industry point of view antibiotics are not as interesting because these cure and not control the condition so treatment is not prolonged. Indeed, most antibiotics in most indications are used for 1-2 weeks only [30]. In recent decades the pharmaceutical industry has decreased the research and development (R&D) budget into antimicrobials as these are usually used on a short term basis and therefore the developers do not make enough turnover before the expiry of the patent [31,32]. This could be partly attributable to the fact that commercially available antibiotics are cheap, broad spectrum effective and safe. Furthermore, antibiotics are used for a short period of time unlike chronic medication. We are currently using derivatives of the original drugs that were originally put in clinical use decades ago.

The importance of tackling the drought in the antibiotic pipeline, especially for infections caused by resistant bacteria, was first recognised in a report from the World Health Organization in 2004 as the number one therapeutic area requiring priority medicines based on the potential public health impact [33].

The safeguards to restrict antibiotics for future use by delaying the development of resistance is seen as a deterrent for the industry as the return on investment is highly compromised in the first few years of a product's launch. For other drugs (non-antibiotic) these years are the most profitable years even in short term use drugs such as anti-cancer chemotherapeutic agents and even more so in drugs intended for long term use such as antihypertensive agents.

Various ways of stimulating R&D have been proposed, including amongst others, safeguarding currently available drugs, extending the patent period, and public-private or academic-industrial partnerships in the development process.

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is a unique pan-European public private partnership between the European Commission and European Federation for Pharmaceutical Industry Association (EFPIA) driving collaboration between all relevant stakeholders including large and

small biopharmaceutical and healthcare companies, regulators, academia, and patients.

The aim of IMI is to propose a coordinated approach to overcome identified research bottlenecks in the drug development process, in order to accelerate the development of safe and more effective medicines for patients, by fostering collaboration between all stakeholders such as industry, public authorities (including regulators), organisations of patients, academia and clinical centres, and enhancing Europe's competitiveness.

An important initiative of IMI is the launch of the Combating Antibiotic Resistance NewDrugs4BadBugs (ND4BB) programme. The goal of this new research programme is to create an innovative and collaborative PPP-based approach that will positively impact all aspects of antimicrobial resistance, from the discovery of novel products to Phase 1, Phase 2, and Phase 3 clinical trials. This will increase the probability of success of developing new and effective antibiotics for the treatment or prevention of infections caused by resistant pathogens as well as the consequences of those infections.

The focus of the work in the current topics will be on products targeting treatment, prevention, or management of the sequelae of infections due to resistant priority bacterial pathogens (e.g. one or more of the following: *Enterobacteriaceae* (specifically *E. coli*, *K. pneumoniae* and *Enterobacter* species), *Acinetobacter*, *Pseudomonas*, *Clostridium difficile*, or methicillin-resistant *Staphylococcus aureus* (MRSA)). So far, 5 topics have been published and two are in the pipeline (Fig. 1).

An important aim of ND4BB is also to develop a data repository that is sustainable beyond the life of the current programme, so that ND4BB will provide a key information base for research projects focused on antibiotic resistance. All consortia participating in topics running under the ND4BB research programme will be expected to deposit data in the ND4BB data hub and work together to share data and experience as widely as possible amongst all programme members and the antibiotic community as a whole.

Finally, ND4BB will establish a network of investigators that will exist beyond the life of these particular IMI calls.

Since 2009 the concept of globalisation of antibiotic drug development has started taking shape with various initiatives from various organisations. Collaboration between the two sides of the Atlantic was seen in the Transatlantic Task Force on Antimicrobial resistance (TATFAR) between the ECDC and CDC Atlanta which was set up in 2009 and in 2011 recommended five strategies to improve the antibiotic pipeline [34].

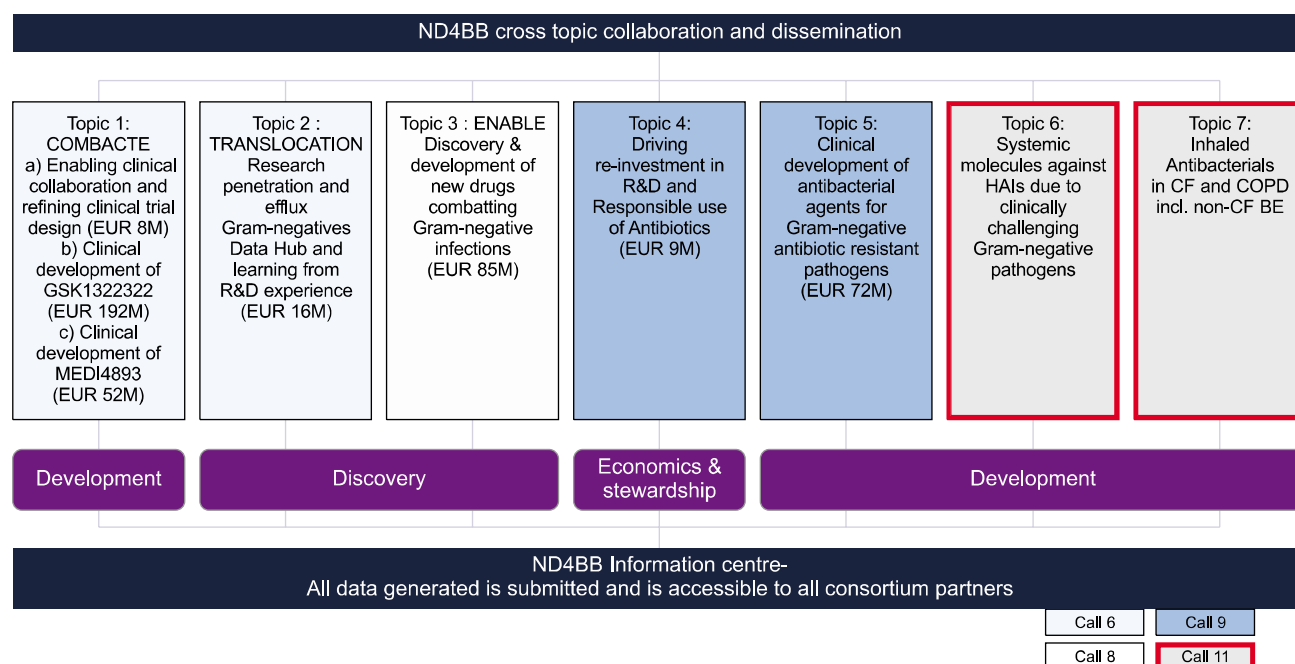


Fig. 1. ND4BB: Proposed Program, from 2014.

## CONCLUSION

The fact that antimicrobials are different from any other drug class makes surveillance of their consumption a much needed Public Health measure. They are unlike any other medication in that their use in one patient has a direct consequences by increasing the likelihood of the micro-organisms developing resistance to antimicrobial agents to which they have been exposed. Often resistance also develops to unrelated agents as well. This issue of resistance has to be seen from the perspective that antimicrobials are used to treat communicable diseases. Thus, inappropriate prescribing both in the community but especially in the hospital affects not only the specific boundaries of that community or institution. It will have an impact both on the population in question as well as a global effect as has been seen with the spread of any ‘novel’ resistance pattern identified. Once established, resistance is not always easily reversible. Furthermore, the hospital setting is the optimal environment for proliferation of resistance because there is higher antibiotic exposure and close proximity of vulnerable patients giving the perfect recipe for development of resistance and cross-infection.

## SUMMARY

Finally, the EU has been partially successful in controlling

antibiotic use and resistance by:

- Bottom up Member States initiatives (e.g. rotating European presidencies) resulting in top down political support and commitment at European level (e.g. Council recommendations);
- Successful surveillance programmes on antimicrobial use and resistance
- Strong leadership with close link between opinion leaders, policy makers and politicians
- Support of AMR research projects by the EC, providing evidence for public health interventions
- European antibiotic awareness day (EAAD), built on success stories of countries;

The biggest current challenge remains resistance among Gram-negative bacteria.

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=국문초록=

## 유럽의 항균제 내성 및 투여 관리 전략

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유럽은 1999년 이후 항균제 사용과 내성을 조절하기 위해 다수의 유럽 연합 의장들이 선택한 두가지 유럽의회 지침 등 많은 정책적인 활동을 취했고, 다수의 공중보건 및 연구 활동들을 시작하였다. 현재 유럽 질병관리본부는 다수의 항균제 내성(EARS-Net)과 사용(ESAC-Net)에 대한 감시 프로그램을 성공적으로 개발했다. 이 감시 프로그램들의 목적은 항균제 내성 검출과 항균제 사용의 질적 향상이다. 항균제 사용 감소와 손 위생 캠페인의 영향평가를 시행하였다. 이러한 공공 캠페인은 벨기에와 프랑스 등의 나라에서 항균제 사용과 내성을 줄이는데 큰 역할을 하였다. 이러한 캠페인들의 성공으로, 유럽 질병관리본부에서는 2008년 11월 8일을 유럽항균제 주의의 날로 지정하였다. 손 위생 캠페인은 여러 유럽 국가들에서 메티실린 내성 황색포도알균(MRSA) 감염의 큰 감소를 가져왔다. 그러나 대부분의 유럽 국가에서 광범위 베타 락탐 분해효소 생성 그람 음성세균, 카바페넴 내성 장내세균과 포도당 비발효균들은 증가 추세에 있다. 유럽 연합은 수억 유로를 의료혁신계획(Innovative Medicines Initiative)으로도 불리는 공공 민간 파트너십(Public Private Partnership)에 투자하고 있다. 의료혁신계획 중 하나는 항균제 내성에 대항하는 NewDrugs4BadBugs (ND4BB) 프로그램의 실행이다. 이 프로그램의 목표는 새로운 항균제 개발에서부터 1~3 단계의 임상시험들을 포함한 모든 항균제 내성 현안에 긍정적인 영향을 줄 혁신적인 공공 민간파트너십에 기반한 공동접근을 수행하는 것이다. [Ann Clin Microbiol 2014;17:1-8]

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