Publishable summary

Impact of Specific Antibiotic Therapies on the prevalence of hUman host ResistaNt bacteria

Project context and objectives

The emergence and spread of human pathogenic bacteria resistant to antibiotics has become a major problem in the past fifty years. Antimicrobial resistance (AMR) is rampant among bacteria that cause healthcare- and community-acquired infections, driving up costs and increasing the difficulty of therapeutic management. Molecular and patient-level investigations are necessary to better elucidate the time-varying and heterogeneous role of antibiotic selection pressure on emergence and selection of AMR.

SATURN aims at defining strategies to improve the knowledge about antibiotic selection pressure and judicious antibiotic use.

The SATURN program will provide a comprehensive knowledge base on the effect of various antibiotic classes, duration of treatment, order of treatment and dosage on AMR in the community, general hospital wards and in intensive care units. This comprehensive data will be generated at the individual level for both colonised and non-colonised patients and at the ecological (i.e. ward) level.

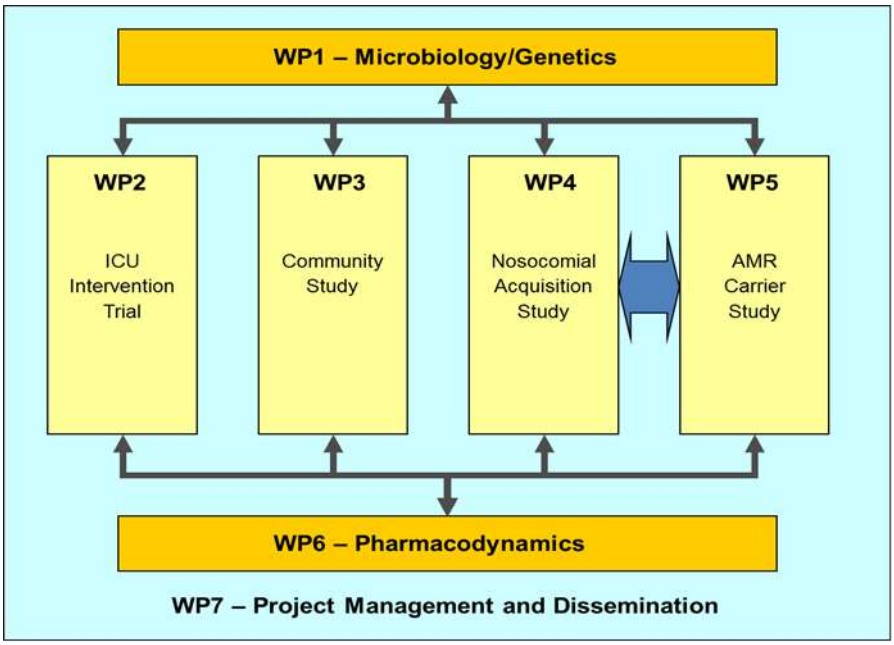
Moreover, SATURN will provide data on the effects of antibiotics on resistance both at the human host level and at the bacteria level. Combining the results of epidemiological investigations with microbiological and molecular studies on epidemicity, virulence and fitness of strains will provide data for action.

The aims of SATURN are selected on the basis of important clinical and public health needs and hitherto unmet methodological challenges. The different components of the programme will help to better define strategies to improve the knowledge about antibiotic selection pressure and judicious antibiotic use. Although each component has clear stand-alone objectives, the components will inform and complement each other in a translational programme of clinical and laboratory research with a number of added value elements in order to guide clinicians in their decision making and to prevent spread of AMR.

One *intervention study* (WP2) and three *observational clinical studies* (WPs 3-5) are conducted that will produce demonstrable improvements over previously generated evidence regarding the effect of antibiotic exposure and selection pressure on acquisition, selection and transmission of ARB within hospital and community settings. *Molecular* (WP1) and *pharmacologic* (WP6) issues generated by the four clinical studies are addressed by two additional studies. The latter two project components are essential elements of the research project and will interrelate synergistically with the clinical studies.

An additional work-package (WP7 - Project management and dissemination) assures the coordination of the work, its dissemination outside the consortium, proper exploitation and transfer.

The workplan structure is shown here after:



SATURN partners

SATURN objectives will be achieved in a five-year multidisciplinary collaboration of leading European researchers in antimicrobial resistance.

The SATURN project, coordinated by Prof. Stephan Harbarth (University of Geneva) unites the best expertise in the field of antimicrobial resistance in Europe. The consortium brings together 14 partners from 11 countries which are members or associated states of the EU. In addition to these partners, the project interacts with hospitals (subcontractors) throughout Europe for the SATURN ICU-trial.

- **University of Geneva** – S. Harbarth (Switzerland)
- **Medical University of Lodz** – M. Godycki-Cwirko (Poland)
- **Tel-Aviv Sourasky Medical Center** – Y. Carmeli (Israel)
- **Universiteit Antwerpen** – H. Goossens, S. Malhotra (Belgium)
- **Università Cattolica Sacro Cuore** – E. Tacconelli (Italy)
- **University Medical Centre Utrecht** – M. Bonten (Netherlands)
- **ARTTIC** – C. Triay (France)
- **Institut D'Investigacions Biomediques August Pi i Sunyer** – J. Vila (Spain)
- **Assistance Publique – Hôpitaux de Paris (Hôpital G Pompidou)** – L. Gutmann (France)
- **Universität Würzburg** – K. Ohlsen (Germany)
- **Clinical Centre of Serbia** – B. Carevic (Serbia)
- **Institute for Infectious Diseases 'Matei Bals'** – L. Preotescu (Romania)
- **Radboud University Nijmegen Medical Center** – J. Mouton (Netherlands)
- **University of Tübingen** – E. Tacconelli (Germany)

Work performed since the beginning of the project

During the 54 months of the SATURN programme, our effort focused on the logistics, implementation and analysis of the clinical studies.

During the first 18 months (Period 1), SATURN partners set up microbiological techniques and manuals, finalised the study protocols and data collection tools, obtained approval by ethical committees, registered the clinical studies on official trial registers, completed the enrolment of hospitals (WP2), trained personnel for data collection and observations, started the collection of bacterial isolates, and validated microbiological sampling techniques and methods for detection of the antibiotic-resistant bacteria targeted by the clinical studies.

During the following 18-month period (Period 2), the clinical studies progressed nicely and achieved most of the milestones as initially scheduled, with some minor delays and deviations from the initial work plans. In parallel to the progress of the clinical studies, WP1 and WP6 started their work related to clinical WP2-5 studies; in collaboration with the WP leaders of the corresponding clinical studies.

In the last 18-month period (Period 3), the clinical teams focused on the finalization and analysis of their clinical studies, in collaboration with the microbiologic team (WP1) and the pharmacokinetic/pharmacodynamic partner (WP6).

The primary analyses of the completed clinical databases are in an advanced stage, but final results cannot be reported yet. Nevertheless, several interesting side projects including 2 metagenomic projects based on substudies at UniGe and UA have been conducted and submitted for publication. Furthermore, several WPs have already generated interesting publications related to results related to molecular and epidemiologic studies. For instance, methodological advances in reliable detection of multiresistant Gram-negative bacteria have been achieved. Furthermore, WP5 (AMR carrier study) has submitted and published papers on several topics:

- Different aspects of carriage of KPC-producing CRE were completed and published: a study on the duration of carriage and the risk factors for persistency, a study on the risk for carriage on a second admission and a study on the risk factors to develop a clinical infection.
- Two studies describing the unique epidemiology of OXA-48 producing CREs in Israel have been published or submitted to publication.
- One study concerning the epidemiology of the KPC-negative ST-258 *K. pneumoniae* strain was published. This paper also assessed the effects of different infection control and antibiotic prescription practices on the dissemination of these strains.

The activities of all WPs were closely monitored by the coordinator. Cooperation between the WPs has been ensured and supported. The kick-off meeting was held in February 2010, followed by regular teleconferences and numerous bilateral contacts between partners. The follow-up meetings of the consortium were held in June 2011 (Rome), June 2012 (Barcelona), June 2013 (Leuven) and May 2014 (Warsaw). We have paid particularly attention to the flow of information between partners in order to ensure that despite the size, geographic dispersion and diverse expertise of this study team, we efficiently and successfully address our study objectives.

Finally, the SATURN project has continued promoting the project through its dissemination work-package (WP7.2) by creating a project website (http://www.saturn-project.eu), a leaflet which presents the project to be distributed by the partners to create the adequate interest among stakeholders at this stage of the project, and a poster for visibility during events. Both leaflet and poster reference the website, which among other things contains a section which collects the SATURN related scientific publications as they become available for public exposure. The first results of the project have been presented in 2 SATURN Newsletters, issued in August 2011 and April 2013.

The expected final results and their potential impact and use (including the socio-economic impact and the wider societal implications of the project so far

The gaps between scientific knowledge and current practices of misuse of antimicrobial agents are enormous. AMR represents a particular challenge, because it touches upon several aspects of care, from basic knowledge to antibiotic prescribing. The continuing emergence of new resistance traits or their spread to new species permanently challenges our ability to contain AMR. SATURN addresses this knowledge gap through a variety of research platforms focusing on the effect of various antibiotic agents and prescribing patterns on selection and spread of antibiotic-resistant bacteria. The ultimate aim is therefore to develop an educational knowledge base for better antibiotic prescribing practices reflecting the best of current knowledge. Links to the resources of the European professional societies relevant to the objectives (ESCMID, ESICM, ESPRM) and the existing networks (ESAC, EARSS) will allow to develop educational material. An integrated and structured repertoire of educational and training activities will be developed that will be made available for the training of clinicians, infection control personnel and other relevant health care professionals, as well as for the public.

Results of the SATURN project should be generalised and applied to settings and healthcare institutions in other European countries. Practical recommendations might be used by others, after taking into account differences in baseline resistance rates and patient case-mix. Furthermore, this

program should provide a sound basis for improved antibiotic prescribing practices in the future and may generate a direct impact on clinical practice and appropriate administration of broad-spectrum antimicrobial agents. Finally, the results of this project will be of value to policy makers, by providing data useful for evaluation of different national antibiotic stewardship strategies. Ultimately, this work will contribute to the prevention of antibiotic-resistant infections and improve quality of patient care in Europe.

Contact details

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SATURN project public website

A public website on the SATURN project is available at: www.saturn-project.eu.

The website contains an overview of SATURN, more detailed information on its objectives, innovative aspects and work structure, as well as the research domain and main applications, the groups involved and their contributions, downloadable publications and links to other related information sources on the web and a contact email.