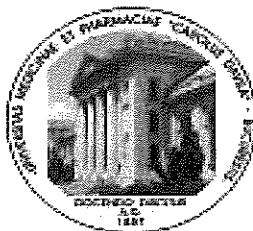


**UNIVERSITY OF MEDICINE AND PHARMACY
„CAROL DAVILA” BUCHAREST**



HABILITATION THESIS

**Contributions in the field of infectious diseases
with impact on public health**

SUMMARY

**ASSOCIATE PROFESSOR
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Habilitation thesis entitled "**Contributions in the field of infectious diseases with impact on public health**" includes the most important research, medical and academic achievements I completed after obtaining a doctoral degree in medicine in 2001.

The thesis was prepared in accordance with the recommendations of the Order issued by the Ministry of Education and Scientific Research regarding the organization and the procedure of obtaining the attestation certificate, 3121 of 27.01.2015, published in M.O, Part I, no.107 / 10.II.2015, and consists of three sections, according to the references of the National council for Titles, Diplomas and Certificates (CNATDCU) and the national legislation.

My scientific, professional and academic activity following the doctoral thesis was conducted in the field of infectious diseases, the special areas of interest being topics with a major impact on public health: tuberculosis, antimicrobial resistance, HIV infection, travel medicine, Lyme disease and other zoonoses. The thesis is a review of the main scientific contributions in the area of the topics covered.

Section 1 covers my professional and scientific achievements until the present. After reviewing the achievements of scientific projects, expressed as publications, both articles in prestigious journals and books or book chapters, which are objectively exposed using indexes of scientometry calculated by various International databases. Thus the Hirsch index in ISI Web of Science Core Collection, Academic Google, Scopus Elsevier was 7, 11 and 9 respectively. Section I continues with the examination of achievements in the main areas of interest.

Tuberculosis

This is an area in which I have published articles on particular clinical aspects (paraplegia secondary to spinal tuberculosis), diagnosis (a score useful to differentiate tuberculous meningitis from viral meningitis) and on the resistance in *M. tuberculosis*. In this field I have extended the research on HIV/tuberculosis

coinfected patients, I have studied factors associated with unfavorable prognosis of tuberculous meningitis and the immune reconstitution inflammatory syndrome.

In the prediction model of tuberculous meningitis, four variables were identified: duration of symptoms before hospitalization >5 days, neurological stage II and III, CSF/blood glucose level <0.5 and protein level in CSF >100 mg/dl. These variables were assigned 3, 3, 2 and 1 points, respectively, and the predictive cut-off for tuberculous meningitis was ≥ 6 . The statistical regression model found that in a given patient, the probability of tuberculous meningitis was 98% (95% CI 94-100) when all four variables were present and 0% when all variables were absent. The sensitivity and specificity of this score were 92% and 94%, and what is important to mention is that this is an easy to use score of prediction, since all variables used are largely available during the patient assessment.

Two of the papers in the field of tuberculosis received the National Scientific Research Council (CNCSIS) Prize in the "Awarding of Research Results" competition in 2008 and in 2012, the importance of these studies being also highlighted by their quoting in 28 publications of the Web of Science Core Collection, including many reviews including one in British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children published in J Infect. 2009 and another in a review on tuberculous meningitis published in Nature Reviews Neurology in 2017.

The experience gained in CNS tuberculosis in HIV-infected patients and multidrug-resistant tuberculosis has been synthesized in a recently published monograph in which I have coordinated specialist doctors and young doctors in training from the neurology and infectious diseases field by compiling a synthesis of information in this area. I was also the co-author of the national treatment guidelines for co-infected HIV/tuberculosis patients, document supervised by a WHO expert. The "TB Guideline for HIV Infected Patients" is presently on the Ministry of Health website for a public debate, following which it will be implemented. To elaborate this document I have worked with a pneumologist

Antimicrobial resistance and health care associated infections

In a postdoctoral program, the project "Supporting research through the training of specialists in the postdoctoral studies program", entitled "Molecular epidemiology of drug-resistant Gram-negative bacterial bloodstream infections in Bucharest", I investigated aspects of resistance of gram negative bacilli, particularly the genetic substrate of ESBL producing microorganisms. During two four-week internships at the University of Berkeley California, in Professor Lee Riley's lab, I conducted bacterial DNA research from antibiotic-resistant strains isolated from patients with blood stream infections admitted to three university hospitals in Bucharest. The research conducted within this program led to the communication of the results in national and international meetings and the publication of four papers, of which three in journals indexed in the Web of Sciences.

C. difficile infection is an emerging infection associated with the health care system, which has occurred and has spread on the background of excessive antimicrobial use. The severe or relapsing *C. difficile* infection is occasionally difficult to treat and off-label use of tigecycline is seen in this context. Therefore, we conducted a retrospective cohort study that analyzed the prognosis of vancomycin and tigecycline vs vancomycin-treated patients during 2014-2015, according to the severity and recurrences of *C. difficile* infection. The statistical analysis was done through logistic regression and the propensity score, which allowed us to obtain important results that have been published in one of the most prestigious European journals on infectious diseases and microbiology, namely *Clinical Microbiology and Infection*. For the statistical analysis we have worked with colleagues from the Medical University of Seville, Spain.

Zoonoses and travel medicine

The interest in Lyme disease started with the PhD thesis, and the research done on this occasion was subsequently published in 2001, in an

article, which is my most cited publication, a total of 30 times in the Web of Science. The study sought to describe the seroprevalence of *Borrelia burgdorferi* infection and to find the factors associated with it in a prospective transversal study in 13 counties in 1999. A number of 1598 sera from donors and 1048 sera from the foresters were collected. Seroprevalence of *B. burgdorferi* infection in donors was 4.3% overall, but the importance of this study lies in the identification of regions with high prevalence, because this prevalence is the pre-test probability whose knowledge is important in interpreting the result of a serology that often results false positive. Seroprevalence among donors varied between 1.4% and 8.7%, with the highest seroprevalence in Maramures. In forest workers seroprevalence was 9.3%, but varied between 2.8% and 31.7%, with the highest seroprevalence in Arad County, where previous studies showed the highest density of *Ixodes ricinus* ticks, the vector of Lyme disease in Europe. Studies on Lyme disease have also been published and communicated in international meetings, including a monograph published in 1999, as a result of the research funded by a grant from the National Scientific Research Council (CNCSIS), 5D-UMF Carol Davila project, "Seroprevalence of *B. burgdorferi* infection in Romania". I have also contributed, together with an infectious diseases colleague and a neurologist, to a chapter on Lyme neuroborreliosis, Central Nervous System involvement in Lyme disease – Making the diagnosis and choosing the correct treatment, in *Miscellanea on Encephalopathies/ Book 1*, edited by Radu Tanasescu, published in an online book, edited by InTech Books and Journals (www.intechopen.com).

Other studies were reported as articles or abstracts on zoonoses including Mediterranean spotted fever, anthrax, leptospirosis, *Streptococcus suis* meningitis, Q fever.

In the field of travel medicine, I have published a number of articles in journals indexed in international databases, I had communications at national and international conferences. In 2017 I obtained the Certificate of Knowledge of the International Society of Travel Medicine, which is a recognition of the knowledge in the field. The "Infectious diseases associated with international

travel" monograph published in 2010 answered a need for information in the field. The chapter on infectious diseases associated with the international travels, in the book "Travel Medicine and Survival Manual in Extreme Conditions. Medical-Aeronautical Implications", a book that received the National Prize of the journal "Gândirea Militară Românească" General de Brigadă Constantin Hîrjeu further contributed to the field of travel medicine.

HIV infection

HIV infection research has focused on the epidemiology of HIV infection, various opportunistic infections other than tuberculosis, Kaposi sarcoma, the consequences of antiretroviral therapy, persistent low level viremia, metabolic and bone abnormalities.

Some of the researches were funded through grants awarded following a competitive selection process. In these researches I was a member of the research team and directly involved in the process.

Section 2 presents the evolution of my academic career in the University of Medicine and Pharmacy Carol Davila since 1991. I have been involved in teaching activities for both students and doctors in the infectious disease residency program but also didactic activities for physicians from other specialties in pre-congress courses, symposiums and educational courses under the patronage of the College of Physicians across several counties in Romania.

I have directed over 50 students in the development of their bachelor thesis and research work and countless other residents in their professional and research work. I was also a lecturer at summer schools organized by other universities such as Ovidius University of Constanta, University of Medicine and Pharmacy Iasi, in partnership with Carol Davila University of Medicine and Pharmacy and lecturer invited to national conferences and international congresses.

I was involved in organizing several scientific events, including three satellite symposiums of Salzburg Seminars organized by the American Austrian Foundation.

Section 3 presents my individual capacity to coordinate research teams, organize and manage teaching activities as well as the development directions of my professional, academic and scientific careers. I was the director of a National Council of Scientific Research (CNCSIS) project selected for funding via a competitive process. The project brought together both researchers from the Molecular Techniques Laboratory of the National Institute for Infectious Diseases Prof Dr Matei Balș and clinicians from the same institution. The research in tuberculosis field has led to solid interdisciplinary research teams, which is of paramount importance in the field.

Additionally, I was the director of an European-funded education program and won by contest, contracted with the Ministry of National Education, the National Center for Vocational Training Program, Leonardo da Vinci in the field of travel medicine in the 2000-2002 Community call. The program was carried out within the framework of Mobility projects 2001. The promoter was the Romanian Society of Travel Medicine (SRMV), the partner was the Institute d'Etude Epidemiologiques et Prophylactiques Villeneuve St Georges, Villeneuve St Georges, France and 15 doctors were included in the program, which further have developed activities in this field.

As part of the discipline development strategy, I also had activities related to the development of travel medicine through the SRMV, whose chair I have been since its founding in 2001. We set up and developed a site with information for medical staff, we organized in 2016 and in 2017 conferences where SRMV was partner with the Carol Davila University of Medicine and Pharmacy, Ovidius University from Constanța and other institutions which are involved in public health activities.

My ability to coordinate research teams is also illustrated by the role as a principal investigator in various clinical trials. I was a principal investigator in Combatting Bacterial Resistance in Europe, a core component of the Innovation Medicines Initiative, a partnership between academic media and pharmaceutical companies that aims to acquire clinical and epidemiological information essential to the development of antimicrobials through optimizing coordination between

clinical trials and scientific research sites, and expanding the network of researchers and research laboratories.

There are three consortia within this partnership dedicated to building clinical and laboratory research networks: COMBACTE NET COMBACTE CARE andS, COMBACTES AND MAGNET COMBACTS. Of the 15 studies that are underway or under preparation by the COMBACTE consortia, together with my team, I have been involved in three studies. In one of these studies I worked as a national coordinator of the seven sites activated in Romania. All collaborations within the COMBACTE consortia created the conditions for collaboration with prestigious European institutions involved in the research: University Medical Center Utrecht, FISEVI (Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla), Hospital Universitario Virgen Macarena.

The coordination of the teams involved in the research was also achieved in the three clinical studies in which I was the principal investigator but also in other studies where the research was not funded by a competition but collaborative contracts such as Groupe d'Etude Epidemiologique et Prophylactiques Villeneuve St Georges, France (1998), or with Professor Richard B. Roberts, Rockefeller University New York, USA (2002-2004).

I coordinated the training and training courses in infectious diseases for many residents and encouraged their training in research by involving them in the development of databases, but also by developing their skills in the field of medical statistics and their involvement in the publication of articles, chapters, posters, and oral communications at national and international conferences.

The development of scientific, professional and didactic career will be achieved in the areas in which I have already had research projects, but also in new research fields. The research topics addressed so far were various and I have always been interested in subjects, which are also public health issues. The main directions of research in which I will continue to develop projects are tuberculosis, travel medicine, antimicrobial resistance and zoonoses.

The team I am coordinating is currently working with researchers from Radboud University Nijmegen, the Netherlands, in a prospective, randomized,

open-label cohort study to determine whether BCG vaccination reduces the number and severity of infections in people with over 60 years of age by stimulating the immune system.

During the skills exchange program that took place in January 2018 in London, I set new collaborations in tuberculosis and HIV field with colleagues from the Royal Free Hospital (JUSTRI). Until present I participated in programs coordinated by JUSTRI team in Romania: Immune reconstitution inflammatory syndrome-part 2 JUSTRI TB Training, Constanta, Romania, 27.09. 2014, and Where are we with TB. Putting the patient first <http://justri.org/justri-where-are-we-with-tb-bucharest-romania/> HIV Academy, Matei Balş Institute, Bucharest, 4th-5th November 2016

In the field of travel medicine I have started questionnaire studies, which will allow the database to be expanded in this field, in partnership with other institutions in the country. In order to improve the management of health problems after international travels, with the agreement of the manager of the National Institute for Infectious Diseases Prof Dr Matei Bals, I intend to set up in the unit I have been running since 2014 a tropical medicine unit.

Moreover, I have started the activities of setting up a certificate of complementary studies in the field of prevention of pathologies associated with international travel, acknowledged by the Ministry of Health. The program includes all those educational elements necessary for acquiring the ability to offer a consultation before international travel in order to prevent the diseases that may be acquired during the travel. The program is designed especially for doctors in the specialties of infectious diseases, epidemiology, family medicine, internal medicine, pediatric. Structure and content are based on recently published data in the field. The program is designed to have a four-week duration over a four-month period, counting 60 hours (15 hours/week).

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