A new member has joined the GABRIEL network in the beginning of 2017: the Health and Environmental Microbiology Laboratory “Laboratoire Microbiologie, Santé et Environnement” in Tripoli, Lebanon. This institution brings new skills to the network and will strengthen ongoing research activities, such as pneumonia study and tuberculosis program.

The Health and Environmental Microbiology Laboratory “Laboratoire Microbiologie, Santé et Environnement” (LMSE), is a research facility affiliated with the Faculty of Public Health and the Doctoral School of Science and Technology of the Lebanese University, the sole public institution for higher education in Lebanon.

LMSE was created in 2011 under the leadership of Prof. Monzer Hamze and is currently staffed by a team of specialists in the field of medical and food microbiology that comprises 3 professors, 6 assistant professors, 1 MD and hospital practitioner, 7 technicians, 1 administrative employee and 9 PhD students. LMSE research activities cover a wide range of fields in microbiology, including tuberculosis, antibiotic resistance, probiotics and antimicrobial peptides, immunity...
and infections, parasitic diseases, molecular typing, applied bioinformatics, and natural bioactive substances. The Laboratory also helps develop scientific expertise by granting fellowships to researchers, entering Master’s students, and PhD graduates.

LMSE enjoys a well-recognized reputation in the field of infectious disease surveillance in Lebanon. Its activities aim at strengthening our understanding of complex microbial diseases and at monitoring their dynamics in the country, so that epidemiological data can be used to help advance the national prevention and healthcare plan. LMSE is accredited by the Lebanese Ministry of Public Health (MoPH) as the reference laboratory for tuberculosis and antibiotic resistance in North Lebanon. It also collaborates actively with several Lebanese hospitals and medical centers to provide advanced diagnostic services. LMSE also helps healthcare professionals through specialized training courses in the field of clinical diagnostic testing.

LMSE operates in strong cooperation with both national and international health authorities/organizations and research institutions, such as the Lebanese MoPH, National Tuberculosis program-related centers, the World Health Organization, the International Organization for Migration, and Fondation Mérieux.

Monzer Hamze, Laboratoire de Microbiologie, Santé et Environnement, Tripoli (Lebanon)

Evaluation of prognostic biomarkers of tuberculosis: a pilot multi-centric study of the GABRIEL network

Tuberculosis (TB), although treatable and curable, is the world’s deadliest infectious disease, especially among vulnerable population groups that include children, patients with multi-drug resistant tuberculosis (MDR-TB), and people infected with HIV. The WHO End TB Strategy states the systematic screening of contacts and high-risk groups, the preventive treatment of persons at high risk, and the development and use of new diagnostic tools. These are topics where GABRIEL network laboratories can effectively make an impact.

At the 8th annual GABRIEL research network meeting in Vientiane, Laos, the TB working group met with healthcare experts and scientists from eight countries (Bangladesh, Laos, Ukraine, Georgia, Lebanon, Mongolia, Italy, and France) to identify the areas where the GABRIEL network can bring added value in TB patient management. Two main points were discussed. First, more reliable diagnostic tests are needed to properly identify latently *M. tuberculosis*-infected
individuals potentially more likely to develop active TB. This would lead to prescribing preventive treatment only to patients who are developing the active form of TB, and to avoiding aggressive and ineffectual treatment to those who are controlling the infection. Second, it is important to distinguish TB patients responding to treatment from those not responding as early as possible. The latter group can thus have its medication adjusted, in order to avoid the consequences of a prolonged and ill-adapted therapy. These recommendations are important to enhance the effectiveness of MDR-TB treatment and thus lead to an improved cure rate.

The detection of blood-based biomarkers is the potential answer to these two requirements, as indicated by Dr. Delia Goletti (from Lazzaro Spallanzani National Institute for Infectious Diseases, Italy). The TB working group has therefore decided to evaluate biomarkers as a supportive diagnostic tool 1) to identify patients progressing from latent to active TB, and 2) to monitor the efficacy of anti-TB treatment.

A seed funding from Fondation Mérieux is financing a 2-year pilot study beginning in 2017 in a limited number of sites that have prior experience in clinical research, TB surveillance, and with adequate capacity/infrastructures. This project is expected to yield significant preliminary data that should lead to further fundraising opportunities through calls for proposals to be gradually expanded to other GABRIEL sites.

We anticipate this project to strengthen the capacities of each GABRIEL network member to manage collaborative research projects, to create and monitor cohorts, to use immunological diagnostic tools and to conduct clinical trials. The long-term direct beneficiaries will be the children and adults with a suspected, latent, or active TB infection.

Jonathan Hoffmann and Jean-Luc Berland, Emerging Pathogens Laboratory, Fondation Mérieux (France)

Polymyxin B resistance in multidrug-resistant Klebsiella pneumoniae involves multiple regulatory elements and intracellular targets

Polymyxins, including Polymyxin B (PB) and colistin, are cationic antimicrobial lipopeptides which act like antibiotics. Despite being available for decades, their use has greatly diminished because of their nephrotoxicity and the lack of pharmacodynamics and pharmacokinetics data. The mode of action of these drugs has not yet been fully established, but generally involves interaction with lipopolysaccharides (LPS) in the outer membrane of Gram-negative bacteria through competition with the calcium and the magnetic ions that stabilize LPS, thus allowing for drug uptake.
into the interior of the bacterial cell. Recently, polymyxins have re-emerged, now as ‘last resort’ drugs administered to patients with difficult-to-treat infections caused by MDR Gram-negative bacteria including Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii. Bacterial resistance to polymyxin has been reported across the world. We previously reported our work on the complete genome of a clinical K. pneumoniae strain carrying a truncated mgrB gene, consistent with recent reports that mutations in this gene represent one of the various mechanisms for acquired polymyxin resistance. Although that isolate already displayed PB resistance, our project consisted in inducting additional adaptive responses by culturing the bacterium in high PB concentrations, and obtaining whole transcriptome data under various environmental conditions and PB treatments. We gave special attention to the functional transcriptomic aspects governed by PB treatment and the regulatory responses that may relate to resistance to this antibiotic. We identified intracellular targets that appear linked to the response elicited by PB exposure, such as the ArcA-ArcB system, previously shown to be unlinked to polymyxin response. Also, we revealed that PB exposure induces a metabolic shift into fermentative growth in the K. pneumoniae isolate under study.

The full article can be found in BMC Genomics, volume 17, supplement 8, page 737.

Marisa Nicolas and Ana Tereza Ribeiro de Vasconcelos, National Laboratory for Scientific Computing (Brazil)

Lung ultrasound is comparable to chest radiography for diagnosis of community-acquired pneumonia among hospitalized children

The study objective was to evaluate the accuracy of lung ultrasound (LUS) compared to that of chest radiography (CXR) among hospitalized children with community-acquired pneumonia (CAP), the leading cause of death in children under 5 years of age in India. We conducted a hospital-based prospective observational study in 2014. After ethics committee approval and written informed consent of parents, we recruited hospitalized children aged 2 to 59 months with CAP. We excluded those clinically diagnosed with asthma, cystic fibrosis, congenital heart disease, immunodeficiency disorder, malignancy, and those being hemodynamically unstable. Anterior-posterior chest radiography and a LUS were performed within 24 hours of hospital admission.

We recruited 118 cases, of which 65 were boys (55.1%) with a mean age in months of ± SD 26.22 ± 19.60. Abnormal CXR was found in 101 (85.6%) and abnormal LUS in 105 (89%). LUS had high sensitivity (98.02%) and reasonable specificity (64.71%) for diagnosing radiologically proven CAP. In diagnosing a specific radiological type of CAP or pleural effusion, a very good concordance was observed between CXR and LUS. We conclude and recommend that, whenever possible, LUS should be substituted for CXR in children with suspected CAP, so that exposure to radiation can be minimized.

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Assessment of the prevalence of multi-resistant bacteria in hospitals: a pilot project in a surgical intensive care unit

Bacterial resistance to antibiotics has become a severe public health problem worldwide, because appropriate therapy has now reached an impasse. In Madagascar, the epidemiology of multi-resistant bacteria (MRB) in hospitals and in the community is still poorly documented. Studies in other countries have reported that intensive care units are the facilities primarily implicated in nosocomial infections often associated with MRB. In fact, the diverse and broad spectrum of healthcare, the steady stream of patients and healthcare givers, and the frequent transfer of patients to and from other locations make these wards an ideal reservoir for the transmission of pathogens. An assessment of MRB prevalence in an intensive care unit is an absolute prerequisite if a comprehensive in-depth study on nosocomial infections is to be conclusive. It should be emphasized that bacterial transmission does not originate solely from infected patients, but also from asymptomatic carriers. Even when considering the true risk of transmission from an unidentified source of infection, the relevance of systematically screening patients for MRB carriage upon admission is debatable in view of the cost, the logistics, and the feasibility of such an undertaking in resource-limited countries.

The objective of our prospective study is to evaluate, in the shortest possible time, MRB prevalence in a surgical intensive care unit and to follow the kinetics of inter-human transmission on D2 and D7, and possibly D14. We will examine nasal swabs for MRSA (methicillin-resistant \textit{Staphylococcus aureus}) and rectal swabs for ESBL (extended-spectrum beta-lactamase) producing Enterobacteriaceae, CPE (carbapenemase-producing Enterobacteriaceae), IRAB (imipenem-resistant \textit{Acinetobacter baumannii}), and extended spectrum beta-lactamase-producing or ceftazidime-resistant \textit{Pseudomonas aeruginosa}.

Ultimately, this study will allow us to: i) measure the prevalence of MRB in a surgical intensive care unit, ii) determine the phenotype(s) of antibiotic resistance, iii) identify resistance genes, and (iv) preliminarily evaluate the frequency of MRB associated with signs of infection in the context of nosocomial infections.

Zakasoa Mbololona RAVAOARISAINA (Centre d’Infectiologie Charles Mérieux), Lalaina Vonintsoa RAHAJAMANANA (Centre Hospitalier Universitaire Mère-Enfant Tsaralalâna), Saïda RASOANANDRASANA (Hôpital Universitaire Joseph Raseta Befelatanana), Sidonie RAKOTONOMENJANAHARY (Hôpital Universitaire Joseph Ravoahangy Ampefiloha), Mala RAKOTO ANDRIANARIVELO (Centre d’Infectiologie Charles Mérieux), Antananarivo, (Madagascar)
A Training of Malian scientists was held at Christophe Mérieux Laboratory in Beijing

In accordance with the Cooperative Framework Agreement signed in 2015 by the Centre d’Infectiologie Charles Mérieux (CICM) in Mali, the Chinese Academy of Medical Sciences (CAMS), and Fondation Mérieux, two collaborative research projects will be launched in Mali in 2017 to develop greater research capabilities on emerging infectious diseases in Africa: “Identification of the Respiratory Virus Spectrum in Mali”, and “Characterization of the Wildlife (Bat and Rodent) Virome in Mali”. To effectively plan for these two projects, the Christophe Mérieux Laboratory (CML), the Institute of Pathogen Biology (IPB), and CAMS, organized intensive training sessions in Beijing for the benefit of four scientists from CICM between January 9 and 19, 2017.

This course provided instruction on the technical protocols and regulations of the two projects, as well as operational considerations. It included the criteria for case recruitment, the template for case report form, statements of informed consent, sample collection and storage, nucleic acid extraction, detection of pathogens, data analysis, lab management, and biosafety issues. These topics were presented with a hands-on approach.

The instructors were senior technicians, researchers, and physicians highly experienced in their field, working at IPB, Peking Union Medical College Hospital, Beijing Children’s Hospital, Ecohealth Alliance, and East China Normal University. Dr. Florence Komurian-Pradel from Fondation Mérieux lent her support for the training course and shared her experience on the organizational and managerial aspects of running a multi-centric study.

After the course, Dr. Jianwei Wang, director of Christophe Mérieux Laboratory, together with Dr. Florence Komurian–Pradel, handed over to the participants certificates that state that they are course instructors and qualified practitioners for the projects in Mali. Professor Chen Wu, Deputy Director of the Department of International Cooperation, Professor Jianwei Wang, Director of the Department of Science and Technology Management of CAMS, and Professor Haiying Liu, Deputy Secretary General of the Institute of Pathogen Biology (IPB) of CAMS attended the welcoming reception and presented background information on
CAMS, IPB, and CML.

Jianwei Wang and Lili Ren, Christophe Mérieux Laboratory, Beijing (China)

Publications from GABRIEL Members since January 2017


