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XIV Seminar - Phd Day

Eppur si muovono: does people mobility enhance global health?

Organized by
the Italian National Institute of Health
and Sapienza University of Rome
Rome, November 6, 2023

Edited by
Bocci S., Brunetti F., Chiovoloni C. and Maddaloni L.

ISTITUTO SUPERIORE DI SANITÀ

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ABSTRACT BOOK

Edited by
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2023, ix, 108 p. ISTISAN Congressi 23/C5

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Keywords: Infectious diseases, microbiology, legal medicine, public health, movements, global health

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Il PhD Day rappresenta un evento ormai tradizionale e di successo nelle attività del Dottorato di ricerca in Advances in infectious diseases, microbiology, legal medicine and public health sciences. Il XIV meeting ha l'obiettivo di indagare come i movimenti delle persone e degli animali abbia contribuito a definire l'evoluzione e la distribuzione delle popolazioni umane, a definire gli scenari di salute globale, ed hanno rappresentato una risposta, oggi come nel passato, all'esigenza di libertà.
Parole chiave: Malattie infettive, microbiologia, medicina legale, sanità pubblica, movimenti delle popolazioni, salute globale.

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Monday, November 6, 2023

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Paolo Villari
Faculty of Pharmacy and Medicine, Sapienza University of Rome, Rome, Italy

Anna Teresa Palamara
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Stefano D'Amelio
Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

Session I

Chairpersons: **Corrado De Vito, Felice Marco Damato, Valerio Capitani**

09.30 Lecture
Sulle tracce dell'uomo
Giorgio Manzi

10.15 Lecture
Marginalità sociale e prossimità sanitaria
Giovanni Baglio

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Laura Donato

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Erika Renzi

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Francesca Cancelli

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Alessandro Lazzaro

PREFACE

The PhD Day represents a traditional, successful event in the activities of the PhD in Advances in infectious diseases, microbiology, legal medicine and public health sciences. The focus of this edition will be on how movements of people and animals have shaped the evolution and actual distribution of human populations, impacted global health, as well as represented the primordial and actual answer to the need of freedom.

The event aims at encouraging sharing and spreading the PhD students' results and research projects. Their works will be presented as either oral communications or abstracts or posters.

This will permit to a wide audience to get in touch with the most updated researches in the field.

As usual, the PhD students of the third year will present orally their results. In this edition, students at the second year will present in a virtual poster session their studies, while the abstracts of first year students studies are included in the "New research topics" section of the abstract book.

The Scientific Staff

Ilaria Bernardini, Camilla Bitossi, Francesca Brunetti,
Claudia Chiovoloni, Nicola Di Fazio,
Maria Greta Di Paola, Luca Maddaloni,
Martina Micocci, Erika Renzi, Eeva Tortellini,
Silvia Venturini, Gianpietro Volonnino

Session I

PhD Candidates' Communications

Chairpersons

Corrado De Vito, Felice Marco Damato, Valerio Capitani

HEALTH DETERMINANTS IN ETHNIC MINORITIES WITH ALZHEIMER'S DISEASE AND IDENTIFICATION OF EARLY DIAGNOSIS STRATEGIES IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT

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(a) Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy
(b) National Centre for Disease Prevention and Health Promotion, Italian National Institute of Health, Rome, Italy

Background: Alzheimer's Disease (AD) is a condition that affects all ethnocultural realities, and AD prevalence is rising more rapidly in low and middle-income countries where life expectancy is increasing. Migration flows are progressively increasing worldwide, and inevitably, healthcare systems are demanded to develop adequate support for the diagnosis, management and treatment of patients that belong to different ethnocultural backgrounds. Mild Cognitive Impairment (MCI) is a clinical condition that occurs before dementia onset and is characterized by cognitive disturbances. These two clinical entities need to be better described in people with a migrant background.

Methods: National surveys, population-based studies and studies on healthcare administrative databases will be essential to comprehend the dementia phenomenon in Italian-born patients as well as in patients with different cultural backgrounds.

Results: Preliminarily, a national survey was conducted in 343 Italian Centres for Cognitive Disorders and Dementia (CCDDs) to obtain information on the number of migrants referred to CCDDs in 2019, the challenges encountered in the diagnostic approach, and potential facilitators in the provision of care. A significant number of migrants are being referred to CCDDs in 2019. However, CCDDs are still not equipped to deliver diversity-sensitive care and support for people with dementia. A population-based, cohort study was also conducted in the Lazio region to identify migrants living with dementia based on data from health administrative databases and to investigate possible differences in the prevalence, clinical correlates, and treatment of dementia between migrant and Italian-born patients. The main results from this study identified that migrants have a lower age-standardized prevalence of dementia and reduced access to dedicated treatments and services than Italians-born patients. Concurrently, to understand the prevalence of use and consumption of Anti-Dementia Drugs (ADDs) (years 2018-2020) among people residing in Italy aged >65 (Italians and migrants), a descriptive study using administrative healthcare databases was conducted. Results from this study identified that 38% of ADDs is not reimbursed by the NHS. This data, together with other results, extends knowledge on the use of ADDs, providing useful comparisons with the prescription pattern of ADDs from other countries.

Discussion: Based on data from health administrative databases, a population-based, cohort study will be conducted in the Umbria region to identify people with MCI and dementia and their ADDs prescription pattern. This study will aim to have a closer look at living people with MCI or dementia with a migration background.

SAFETY AND HEALTH PROTECTION IN MAXI EMERGENCIES

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(b) Sant'Andrea Teaching Hospital, Rome, Italy

Background: The COVID-19 pandemic has severely tested traditional models for healthcare facilities. The initial difficulties faced by the National Health System negatively affected clinical and economic outcomes. Generally speaking, any catastrophic event with unknown characteristics, and which overwhelms the "normal" operational abilities, requires the development of new organizational models. These new models should enable all stakeholders to coordinate their actions and effectively meet health care demands. The primary goal is to increase public health and safety via the development of organizational models which are flexible and can be easily amended based on the organization's specific needs. The secondary goal is to identify/develop real-time clinical pathways able to resolve the emergency, as well as providing a protocol to manage its aftermath.

Methods: The present study was founded on the identification of a methodology for safeguarding the safety of care in the context of maxi-emergencies. Specifically, a five-step process has been implemented for realizing the quality objectives:

1) Operational strategy and strategic time management;
2) Timely processing of available data;
3) Creation of protected paths involving victims and operators;
4) Training for operators involved in the emergency (not only for health professionals);
5) Regular re-training.

In this context, we can look at Disaster management as a multidisciplinary team of experts who rapidly enact solutions for the emergency using the most accurate scientific evidence to best allocate available resources.

Results: The theorized methodology made it possible to develop care models and plan actions for the improvement of clinical and economic outcomes. It was also possible to create a multidisciplinary and transversal organizational system to cope with maxi-emergencies, characterized by a strong preventive perspective for the management of disasters.

Discussion: In the case of maxi emergencies, it is necessary to take actions to reduce public health damage, knowing however that it will be impossible to reduce the risk to zero. Those who deal in public health face a challenge that can be better tackled with a "programming" mindset. The word programming may seem far-removed from the idea of an emergency, yet in our research we aim to demonstrate that it is precisely through a forward-thinking, programming mindset that we can be prepared to face a healthcare maxi emergency and give concrete answers which will allow to protect public health.

IMPLEMENTATION OF TELEMEDICINE ACTIVITIES IN THE LOCAL HEALTH AUTHORITY ROMA 1: FIRST RESULTS

Andrea Barbara (a,b), Leonardo Villani (b,c), Antonella Gemma (b), Claudia Curci (b), Assunta Mammarella (b), Paolo Lombardo (a), Gennaro D'Agostino (b), Paolo Parente (b), Corrado De Vito (a)

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(b) Local Health Authority Roma 1, Rome, Italy

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Background: Telemedicine provides the use of information and communication technologies to deliver healthcare services at a distance. It represents a valuable tool for clinical assessment, monitoring of vital parameters, remote visits and prescription of treatment or hospitalisation in case of clinical worsening. The Local Health Authority (LHA) is the institutions that deliver healthcare assistance to citizens at a local level and it is part of the Regional Health Service (RHS). The study aims to describe the telemedicine activities implemented since 2020 in the LHA Roma 1 with a focus on the Primary Health Care (PHC) field and their first results.

Methods: According to evidence-based practice, opportunities and emergencies intervened (among all the COVID-19 pandemic, most recently the Next Generation EU National Recovery and Resilience Plan - PNRR - and the Ministerial Decree n. 77/2022), different telemedicine solutions have been implemented in the LHA Roma 1 since 2020 in the PHC services.

Results: Activities implemented: (a) Telemonitoring, thanks to the "Lazio ADVICE" platform for remote assistance for COVID-19 patients and heat waves vulnerable over 65 patients, with the aim to monitor and manage patients at home and to facilitate communication between citizens and healthcare professionals. To evaluate the use, barriers and facilitators, strengths and weaknesses of this new platform from the LHA's GPs viewpoint a survey was performed. (b) Teleradiology, i.e. the remote reporting of radiological examinations performed at home or at the Regina Coeli prison. In 2022, around 300 investigations were performed. From a RHS perspective, preliminary results of a cost-minimization analysis estimate that the teleradiology-based approach costs less than the traditional approach applied in both settings. (c) Televisit, in outpatient specialist care, especially in the neurological field for epilepsy and headache follow-up, with more than 200 visits performed. (d) Telerehabilitation: home-based rehabilitation with the remote assistance of healthcare personnel. Approximately 30 patients with cerebral vasculopathy or recent fracture or trauma were treated in 2022, with an average of 12 types of exercises offered per patient, a service's positive evaluation, significant functional recovery and stable outcomes.

Discussion: The pandemic and its regulatory recovery consequences PNRR and DM 70/2022 have accelerated the implementation of telemedicine services around the LHA Roma

1 starting a positive and continuous exchange of experiences, activities and best practices. The first positive data obtained could make it possible to improve resource allocation, both at the territorial level and in a broader Public Health context, offering opportunities for improving the quality of care and cost reduction by increasing accessibility to care, both in territorial care settings and in specific fields of application, such as health care delivered within correctional institute

EVALUATION OF EPIDEMIOLOGICAL TREND OF REPEATED POINT-PREVALENCE STUDIES OF HEALTHCARE-ASSOCIATED INFECTIONS IN A LARGE TEACHING HOSPITAL

Domenico Barbato (a), Giovanna Carluccio (a), Antonio Covelli (a), Mariateresa Ceparano (a), Shadi Orlandi (a), Alessandra Contenti (b), Alessio Dominici (b), Carolina Marzuillo (a), Corrado De Vito (a), Paolo Villari (a), Maria De Giusti (a,b)

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(b) Policlinico Umberto I University Hospital, Rome, Italy

Background: Healthcare-Associated Infections (HAIs) are the most frequent adverse events in healthcare settings. They are associated with increased mortality and Antimicrobial Resistance (AMR), leading to prolonged hospital stays and consistent financial loss for healthcare systems. Similarly, Antimicrobial Use (AMU) and AMR represent a growing threat to global public health and the sustainability of healthcare services.

Methods: The objective of this study is to estimate the burden of HAIs and antimicrobial use in the Teaching Hospital Policlinico Umberto I (THPUI) of Rome describing the trend of prevalence of HAIs across the years, comparing data about: a) patients; b) invasive procedures; c) infections; d) prescribed antimicrobials; e) clinical setting; f) risk factors for HAIs. Data were collected according to ECDC point prevalence survey protocol in the same months of four different years (2018, 2019, 2021, 2022). Descriptive statistics for all variables were calculated. Univariate analysis was used to assess possible associations between variables and HAIs. Variables with a significance level of $p<0.25$ were included in a multiple logistic regression model.

Results: A total of 3086 patients were included in four repeated Point Prevalence studies from 2018 to 2022; 14.0% presented with at least one HAI. The prevalence of patients with HAI was 13.3% (106/799) in 2018, 11.1% (91/818) in 2019, 17.6% (131/745) in 2021, and 14.3% (104/725) in 2022. Bloodstream infections were the most common, accounting for 29.2% of total infections, followed by and pneumonia (26.6%) and urinary tract infections (21.8%). Overall, 502 microorganisms were isolated, with Enterobacteriaceae being the most frequent [39.0% (196/502)]. At the time of the survey, 48.9% (1508/3086) of patients were receiving antimicrobial therapy. The multivariate analysis showed a significant association between HAI and patients' age (OR=1.01; 95% CI:1.00-1.01), hospitalization in intensive care unit (OR=2.39; 95% 1.73-3.30), NHSN surgery (OR=1.37; 95% CI:1.01-1.88), exposure to medical devices (OR=4.55; 95% CI:3.29-6.29), length of stay (OR=1.02; 95% CI:1.01-1.02) and exposure to prophylactic antimicrobial therapy (OR=0.45; 95% CI:0.33-0.62).

Discussion: The ECDC methodology proved to be applicable to THPUI, where HAI prevalence was higher than the European standard. This highlights the need to implement targeted measures to prevent and control HAIs, including continuous monitoring to evaluate the effectiveness of such interventions and economic impact. This methodology

and related tools used in this study could be exported into other local and regional healthcare settings in order to create a standardized approach for the management of HAIs and to compare similar contexts.

DETECTION AND ASSESSMENT OF WORK-RELATED STRESS (WRS) RISK IN AN INFORMATION TECHNOLOGY (IT) SOCIETY: A MIXED THREE STEP APPROACH

Rosario Andrea Cocchiara, David Shaholli, Mariavittoria Manai, Leandro Casini, Giuseppe La Torre
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Background: It has been observed that prolonged Work-Related Stress (WRS), could negatively affect the quality of life of individuals and decrease their performances at job. The aim of this research was to analyze the work reality of an Information Technology (IT) society in order to evaluate the WRS risk and detect causes and possible solutions.

Methods: In order to assess the WRS risk among the employees, between December 2022 and March 2023, a mixed three-step approach was applied: a sentinel event analysis, by the administration of semi-structured interviews to detect context and content indicators; a subjective analysis, to evaluate the perception of the person towards the context and content indicators; a focus group analysis, to highlight the main qualitative themes to be addressed. The investigation strategy was built according to the "INAIL Methodology for assessing and management of WRS risk".

Results: The sentinel event analysis investigated 39 organizational departments and showed a low risk of WRS: a mean score of 4.39 (SD=3.48) was detected and only 2 areas of the IT society reached this value. The preliminary results from the subjective analysis showed a mean job strain value of 0.76 (SD=0.139), in line with the national data of office workers. The focus group analysis reported 5 different themes: personal perceptions about WRS; personal considerations about WRS; presence of WRS within their work environment; possible solutions related to the work environment; possible solutions to be applied in their private lives.

Discussion: The study suggests a wide approach to the assessment of WRS risk among the employees. The three step strategy allows the researchers to deepen their understanding across layers of detail more and more accurate, and to design tailored solutions to prevent the arise of stress among the workers.

THE EXPRESSION OF FOXO3A AS A FORENSIC DIAGNOSTIC TOOL IN CASES OF TRAUMATIC BRAIN INJURY AND IN THE LIGATURE MARK: AN IMMUNOHISTOCHEMICAL STUDY

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Background: The Forkhead box O (FOXO) is a family of transcriptional factors involved in multiple cellular pathways. There are four mammalian FOXO members that share a high protein homology. Among these, FOXO3 induces apoptosis, regulating the transcription of pro-apoptotic or anti-apoptotic genes. This study aims to evaluate the post-mortem Immunohistochemical (IHC) positivity of FOXO3a expression in human cases of Traumatic Brain Injury (TBI) deaths and in the epidermis of ligature marks.

Methods: Autopsy databases from the Institute of Forensic Medicine at "Sapienza" University of Rome were retrospectively reviewed. After analyzing the autopsy reports, 15 cases of death by TBI and 21 cases of death by suicide hanging constituted the study group. Another 15 cases of nontraumatic brain deaths were chosen as the control group. Decomposed bodies or those with initial signs of putrefaction were excluded from both groups. Before staining the study group samples, anti-FOXO3a antibodies were tested on breast cancer samples. For quantitative analysis, 20 observations were made in each immunohistochemical section in different fields/slides at 100-fold magnification. The staining intensity was evaluated using a semi-quantitative scoring scale.

Results: In all 21 cases of hanging, the ligature mark skin samples, obtained at the point of greater compression ("full of the loop"), showed a depletion in FOXO3 in the epidermal layers in correspondence with the epidermal flattening (average value of intensity −2.81, p-value <0.05). In addition, the adjacent non-injured epidermis was positive to FOXO3a (value of intensity 0), which was localized both in the cytoplasm and nucleus.

In all 15 samples of TBI cases, FOXO3a positivity was found in neuronal cells of the brain parenchyma adjacent to the injury (mean intensity value 2.53, p value <0.05).

Discussion: The results presented in this study demonstrate that, in the ligature mark epidermis, there is a depletion in FOXO3 if compared to normal or post-mortem injured skin. FOXO3 depletion was detected both in soft and hard tissue, indicating the same underling ischemia-induced mechanism. Skin compression causes ischemia of the epidermis. This results in the inhibition of protein kinases, such as AKT, that phosphorylate FOXO3. The expression of FOXO3a at the level of the injured brain tissue was significantly increased compared with the control group. This confirmed the existence of a correlation between TBI and FOXO3a expression. Also, it was noted that as the survival time of the subject increased - with the maximum being 6 h - the FOXO3a expression was greater.

EVALUATION OF THE ECOTOXICITY INDUCED BY VETERINARY PHARMACEUTICALS ON THE AQUATIC VERTEBRATE *DANIO RERIO* THROUGH A *ONE HEALTH* APPROACH

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Background: The release of veterinary pharmaceuticals in the aquatic environment is one of the major challenges of the last years. Thousands of different compounds end up daily in the aquatic environment where they pose a threat to human and environmental health. For this reason, a deeper knowledge of the consequences that these products can have on the environmental and human health is necessary, and there is a need for sensitive assays able to identify the risk that these compounds may pose.

Methods: The aim of this study is to highlight and investigate lethal and sub-lethal effects derived from the exposure of fish embryos to veterinary products, in particular the antibiotic amoxicillin, a widely used compound recently integrated in the *watch list* of the European Union for its possible environmental toxicity. For this purpose, the vertebrate *Danio rerio,* a promising and widespread animal model, has been chosen. The starting point is the OECD 236 acute toxicity assay, that allows to detect acute toxicity. This assay is centered on mortality, however sub-lethal endpoints such as shape of the eyes and skeletal deformities have also been quantified in this study to gain additional information on the tested substance. Moreover, the spontaneous coiling activity was also considered: this innovative endpoint detect neurotoxicity starting from the spontaneous movements of the embryo's tail that naturally occur around 24 hours after the fertilization. The data acquisition has been performed with the use of the *Danioscope* software, that allows to acquire images at high resolution.

Results: The results obtained with amoxicillin show low mortality at every tested concentration, with values ranging from 0 to 18%. However, the presence of sub-lethal effects even at low concentrations has been recorded, with values between 10 and 15%. In particular, malformations and premature hatching seem to be the most frequently occurring sub-lethal endpoints. The coiling assay highlights mild dose-dependent neurotoxicity, with effects that show a higher frequency of movement at the higher concentrations.

Discussion: The use of *in vitro* assays based on zebrafish early stages allows to effectively detect acute toxicity, with effects ranging from lethal to sub-lethal endpoints. Moreover, it is possible to investigate the Modes of Action of the single substances, differentiating between effects such as neurotoxicity, cardiotoxicity and developmental toxicity. The results of this study highlights that this kind of approach can play a role in early warning and screening for protection of environmental and human health. In particular, the *coiling assay* is a sensible and promising tool in the detection of neurotoxicity.

MEDICALLY ASSISTED SUICIDE: THE MEDICOLEGAL ANALYSIS REGARDING THE VERIFICATION OF CONDITIONS THAT MAKE THE ACT LEGITIMATE

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Background: Medically Assisted Suicide legislation have been topics of significant ethical, medical, and legal debate worldwide. Italy, a country known for its deep-rooted cultural and religious influences, has grappled with these issues in recent years. This abstract explores the background, methods, results, and discussions surrounding euthanasia and end-of-life legislation in Italy.

Methods: This study employed a comprehensive literature review, legal analysis, and qualitative data collection through analysis of recent cases interviews with healthcare professionals and legal experts. Data were collected between 2020 and 2023 to capture the evolving landscape of Medically Assisted Suicide and End-of-Life legislation in Italy.

Results: Italy has experienced a gradual shift in its approach to end-of-life decisions. In 2017, the Italian Parliament legalized advance directives of treatment, enabling individuals to make informed decisions about their medical treatment in advance. However, euthanasia remains illegal in Italy. Nonetheless, there is growing public discourse and advocacy for the legalization of euthanasia in certain cases, especially in the context of unbearable suffering and terminal illnesses. This tension between individual autonomy and public opinion influences has resulted in a complex legal and ethical landscape.

Discussion: The discussion surrounding Medically Assisted Suicide and End-of-Life legislation in Italy reflects the broader global conversation on individual autonomy, human rights, and moral values. The legalization of advance directives represents a significant step towards respecting patients' autonomy and their right to make decisions about their own lives and deaths. However, the prohibition of euthanasia underscores the enduring influence of conservative ideologies in shaping Italian law and policy.

In conclusion, Italy's approach to euthanasia and end-of-life legislation is characterized by a delicate balance between individual autonomy and religious values. The debate continues to evolve, with ongoing discussions on whether Italy should follow the example of other European countries in legalizing euthanasia under specific circumstances. The outcome of these deliberations will significantly impact the future of end-of-life care and individual decision-making in Italy.

SAN GIOVANNI ADDOLORATA CLAIMS ASSESSMENT COMMITEE: A FIVE- YEAR EXPERIENCE

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Background: San Giovanni Addolorata Hospital is an assisted-living facility with a Level II Emergency and Acceptance Department and a Department of Gynecology and Obstetrics. Since 2012, the San Giovanni Addolorata Hospital has been under self-insurance with regard to damages resulting from medical malpractice. The objective of the study is to compare internal company reporting with the state of the art of "medical liability litigation" and to evaluate the disbursement incurred by the Hospital.

Methods: The present work consisted of a process of unification and normalization of existing data regarding medical malpractice claims in the time frame from January 1, 2018 to June 30, 2023. Thus, a series of indicators were selected for the purely descriptive purposes of the events and to quantify the potential exposure of the hospital's. All the related data were collected in Microsoft Excel and organized based on administrative and personal references of the claim (name, dates of claim, age and gender of the injured party), the proper characteristics of the event (date of the event, department of belonging, brief description) and the ICPS (International Classification for Patient Safety) characterization. The longitudinal assessment of the claim, where possible, describes the occurrence of the judicial drift of the litigation and its progress to the final outcome.

Results A total of 257 claims were indexed between January 1, 2018 and June 30, 2023. For the quantification of the hospital's medical liability, the first figure to be considered is the absolute frequency of claims, which is identified by any form of personal injury claim submission. The analysis of the operating unit of reference for each claim first allowed for a breakdown of the claims by area. Surgical specialties appear to be involved. In terms of event typing, the claims were classified according to the two main descriptive categories indicated by the ICPS.

Discussion: The claims data for the facility under review is in line with the coordinates drawn in the national panorama. The claims ratio is higher than regional and national averages. Until now, the results of the present study confirm the common notion regarding the preferential distribution of claims among operating units, with particular exposure of the surgical. Specialties with a high frequency of litigation are general surgery and orthopedics and traumatology. The other two most represented operating units are: emergency room and neurosurgery. With regard to the economic cost of claims, it is important to reiterate the decisive contribution made by HCAI to the phenomenon of medico-legal litigation. Infact, HCAI absorb most of the cumulative amount although they do not account for the majority of claims.

COST ANALYSIS OF HEALTH CARE-ACQUIRED INFECTIONS IN A TEACHING HOSPITAL: A COMPARISON OF METHODS

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Background: Healthcare-Acquired Infections (HAIs) increase costs for medical care. Investigators generally estimate direct additional costs, particularly additional Length Of Stay (LOS), which represents the most expensive element. Aim of this study is to compare internationally used methods, to estimate attributable HAIs extra LOS and economic burden, by applying them to the same population.

Methods: Patients hospitalized at Sant'Andrea Teaching Hospital in Rome (420 beds) developing HAIs, according to CDC criteria, were considered cases. In matched control method, for each infected patient we selected 2 uninfected hospitalized patients according to the following criteria: primary diagnosis (ICD-9-CM) (5 points); same admission ward (5 points); LOS in controls equal at least to the interval from admission to infection in cases (5 points); DRG (4 points), age ± 3 years (4 points); same gender (2 points). Once the pairs were matched, we estimated the number of extra days by subtracting the average LOS of the non-infected patients from that of the infected ones. The Appropriateness Evaluation Protocol (AEP) method is based on a list of objective criteria. The original AEP form was modified adapting some other criteria, finally thirty objective items were incorporated (Full AEP form), ten of which can be met because of HAIs presence (Partial AEP form). All hospitalization days deemed appropriate according to the "full AEP form" but inappropriate according to the "partial AEP form" were defined as extra LOS attributable to the infection.

Results: We enrolled 127 cases. The mean hospital stay in cases was 41.4±26.8 days (median 33), whereas in control group 29.2±23.2 (median 22) ($p<0.001$). The average score for controls was 21.8 (87.3% matching appropriateness). Considering extra-hospital stay for hospital ward, we found for matched comparison 11.9±23.2 (median 7.5) days for medical ward, 16.4±25.6 (median 14) for surgical ward and 14.4±27.3 (median 4.5) for Intensive Care Units (ICUs). AEP method showed respectively 10.2±9.9 (median 9) days for medical ward, 13.9±11.5 (median 11.5) for surgical ward, 6.2±8.4 (median 2) days for ICUs. Extra LOS estimated by matched comparison was 12.5±24.1 (median 7.5) days per patient. Overall, the AEP method showed a lower number of extra LOS with 10.9±10.7 (median 9) days per patient. We did not find a statistically significant difference in the extra LOS estimation by the two methods ($p=0.4$). Applying the single day hospital cost, additional expenditure per patient was € 5,186 estimated by AEP method and € 6,924 with matched comparison.

Discussion: Additional LOS due to HAIs was relevant and consistent, as both methodologies results were similar.

BARRIERS AND SOLUTIONS FOR IMPROVING PAIN MANAGEMENT PRACTICES AT REGIONAL HOSPITALS IN SOUTH ALBANIA

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Background: Proper management of pain is a basic human right, meanwhile this is one of the least known and updated medical fields in Albania. This study aims to increase the standards of Albania's health care system in regards to Pain Management. This goal is meant to be achieved through two objectives: evidence of barriers and solutions on the Albanian Health Care System and experimentation of a Pain Management Protocol.

Methods: This is a mixed cross-sectional and experimental, quantitative study. Population of study includes nurses and patients of Surgery and OBS wards in the regional hospital of Gjirokastër, Vlorë and Fier. We are working with two groups of nurses. One group is trained and the other one is the control group. The instrument we are using is observation of nurses' practices on pain management and experimentation of Pain Management Protocol. We will analyze medical staff's performance regarding pharmacological therapy, non-pharmacological therapy, pain evaluation from nurses and patient satisfaction. Statistical analizys will be done through SPSS.

Results: In the control group of nurses, pain in the majority of patients is considered as a normal simptom and is not given the needed attention neither solutions are adressed at its best options. Non-pharmacological management is barely existent. Pain is evaluated and monitored mainly by subjective and objective evaluation and patients' satisfaction is not pleasing. In the trained group of nurses, pain is being considered fairly and they are also addressing non-pharmacological methods. Pain is being evaluated and continuously monitored by VAS and patients' satisfaction has a remarkable increase.

Discussion: Through this study we clearly demonstrate that improvement in Pain Management is a new higher standard for Albanian Health Care System. Actual barriers to a proper pain management are: public hospitals have limited funds, non-pharmacological pain management randomly is considered as not worthy, lack of physiotherapists and psychologist affiliated to public hospitals, old mentality of medical staff that comes from university curricula lacking Pain Management and actual not updated practices between medical staff that are being inherited to young generations of doctors and nurses. We believe that starting solutions to these barriers are training of medical staff and including pain management in university curricula as soon as possible.

ORAL FLUID AS A NEW INVESTIGATIVE MATRIX TO DETERMINATE IGSR AND OGSR EXPOSURE

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Background: The increased use of ammunition without lead and heavy metals was observed, leading to a growing interest in the detection of Organic Gunshot Residues (OGSR) as evidence of firearms related crimes; however metal determination helps us to determine the type of ammunition used. The purpose of this work is the development of a reliable analytical method by means of ICP-MS for the determination in Oral Fluids (OF) of the most common metals used found in ammunition and gun cleaning oils.

Methods: For this purpose, acid extraction in microwave was used for the OF clean-up and metals extraction before ICP-MS analysis. The method was tested on real samples: a shooting session was performed in an open shooting range; the shooters fired from 2 to 200 rounds with a 9x21 caliber, after which they were sampled. Samples were analyzed confirming that metals explosives may be detected in OF, the use of this matrix may be of great interest for investigative purposes as it is not affected by secondary transfer. and the sampling is fast, not invasive and can be performed by non-medical staff.

Results: The study demonstrates how the most commonly used metals both in the ammunition and in the primer are found in different concentrations depending on the type of cartridge used and the number of shoots. The study also showed that people in close contact with the shooters (example: shooting instructor) still inhaled a large amount of metals and allows us to assess the presence of the risk factors of the exposed subjects. The presented method allows the determination of very low traces of analytes, providing evidence of a direct contact with IGSR.

Discussion: This represents an interesting starting point for the assessment of the potential exposure to IGSR or the use of firearms at a crime scene. In this work also the persistence of IGSRs in OF was investigated. The preliminary results obtained during this trial are very promising, as a close correlation between the concentration of IGSR in saliva and the time elapsed between sampling and exposure was observed.

PUBLIC HEALTH RESPONSE TO THE COVID-19 PANDEMIC IN UNIVERSITY SETTING

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Background: The public health policies involved to mitigate the negative effects of COVID-19 at the individual, community or population level should be evaluated. Assessing risk factors for acquiring SARS-CoV-2 infection and its impact on university students, could guide policy decisions in case of infectious disease epidemic.

Methods: The following studies were conducted during the SARS-CoV-2 testing program of Sapienza University of Rome: a) three case-control studies to identify risk factors associated with SARS-CoV-2 acquiring in unvaccinated and vaccinated university students; Multivariable conditional regression models were built; b) three cross-sectional studies on the impact of COVID-19 pandemic on 11790 university students. Multivariable logistic regression models were built to identify: a) vaccine hesitancy towards anti-SARS-CoV-2 vaccines; b) attitudes of university students towards mandatory COVID-19 vaccination policies; c) predictors of decline in academic performance and COVID-19 anxiety disorders. Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were calculated.

Results: Case-control studies included a total of 639 students (213 cases and 426 controls). The main results highlights that being a non-Italian student (aOR: 8.93, 95% CI: 2.71-29.41), having received only the primary vaccination course (aOR: 2.94, 95% CI: 1.24-6.96) compared to the booster dose, a known exposure to a COVID-19 case or someone with signs/symptoms suggestive of COVID-19 (aOR: 6.51, 95% CI: 3.48-12.18), and visiting discos (aOR: 4.07, 95% CI: 1.52-10.90) in the two weeks before testing increased the likelihood of SARS-CoV-2 infection. Conversely, students attending in-person lectures on campus seemed less likely to become infected (aOR: 0.34, 95% CI: 0.15-0.77). No association was found with other variables. Cross-sectional studies showed that COVID-19 had a strong impact in the daily life of university students, in particular a total of 25.4% of participants reported a decline in academic performance. In addition, Coronavirus Anxiety Scale scores revealed that 133 (11.5%) students had dysfunctional anxiety issues related to COVID-19. The multivariable logistic regression model showed that being non-Italian (aOR: 2.12, 95% CI: 1.29-3.48) and feeling the need for psychological support (aOR: 2.58, 95% CI: 1.87-3.55) were more likely to result in a decline in academic performance. Regarding vaccine hesitancy, university students had more positive attitudes toward the COVID-19 vaccine than the general population.

Discussion: The prolonged closure of universities has brought far-reaching changes in multiple facets of the student experience, including a decline in academic performance, increased levels of psychological distress and anxiety disorders and inequalities in learning opportunities, which particularly affected international students. These studies indicate that in-person learning increases student performance and well-being and can be safely maintained in university settings provided that robust preventive measures are put in place.

Poster Session

MOLECULAR BASIS OF ANTIMICROBIAL PROPERTIES OF GREEN NANOCOATING EFFECTIVE AGAINST VIRUS AND BACTERIA

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Background: Microbial colonisation of surfaces forms a dangerous reservoir for pathogens contributing to spread of infections with impact on human health and a heavy economic burden. Several antimicrobial coatings exist in the market based on the leaching of non-environmentally friendly chemicals or based on formulations hazards to human health and environment. The optimization of disinfection approaches based on metallic nanoparticles, that can remain longer on surfaces, resist to washing and friction and with good safety environment requisites is a challenge. The present project aims to analyze antimicrobial properties of an innovative self-disinfectant nanocoating based on the antimicrobial action by copper nanoparticles drugged with natural peptides effective against a wide range of virus and bacteria.

Methods: Standard procedures to evaluate minimum inhibition doses to distinct substrate were applied. After early exposure to the nanocoating, total RNA was extracted and libraries for transcriptome investigations (RNA-Seq) were prepared. Two NGS platforms, Illumina and MGI, were used. For the bioinformatic analysis an *ad hoc* pipeline was implemented to analyze the sequencing output of each sequencing technology used.

Results: Different monolayers at various concentrations were used to treat distinct microorganisms. Our results indicate that substrates can effectively inhibit the microorganism growth and cause a considerable transcriptome response. In bacteria Reactive Oxygen Species induce a large number of genes related to cell damage, cell membrane repair system, and DNA repair system and genome damages in viruses.

Discussion: The antimicrobial coatings frequently used show serious concerns linked to low product performance, pollution, toxicity and antibiotic resistance. The knowledge of molecular mechanisms that underlie this innovative intervention strategy, could highlight whether one or a combination of several mechanisms at structural, genomic, transcriptomic and proteomic level could trigger possible resistance mechanisms against antimicrobial nanoparticles.

AN INTEGRATED APPROACH TO PREVENT AND CONTROL HEALTHCARE-ASSOCIATED INFECTIONS IN THE INTENSIVE CARE UNITS OF UMBERTO I TEACHING HOSPITAL OF ROME

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Background: Healthcare-Associated Infections (HAIs) are the most frequent and serious adverse event in healthcare. Identifying patients with risk factors for HAI and multidrug-resistant infections is critical to limit the HAI burden.

Methods: For this purpose, the factors associated with the risk of HAIs in the Intensive Care Units (ICUs) of the Umberto I Teaching Hospital of Rome were evaluated thanks to an active surveillance system; the genotypic characterization of the microorganism isolated in the ICU was carried out using the PFGE method, assessment of adherence to good Hand Hygiene (HH) procedures among ICUs Health Care Workers (HCW) was conducted by direct observation.

Results: Using the active HAI surveillance system, data were collected from COVID-19 and non-COVID-19 patients admitted to the adult ICUs. We found little difference between the two cohorts in the cumulative incidence of patients with HAI; in COVID-19 patients, HAIs were mainly caused by *A. baumannii*, while in non-COVID-19 patients *K. pneumoniae* and *P. aeruginosa* were the most frequently pathogens. In this regard, we characterized the clonal spread of *A. baumannii* among COVID-19 and no-COVID-19 patients admitted during two years of the pandemic. Genotypic analysis of isolates in COVID-19 patients revealed two main patterns: pattern "A" (59.4%) and pattern "B" (35.5%). In non-COVID-19 patients, the typed isolates showed more heterogeneous clonal profiles. However, the pattern "A" (47.7%), was the most frequent pulsotype detected. The identification of the pattern "A" in both cohorts of patients, may indicate the possible transfer of related isolates from one ICU to another in the same hospital. We also studied the impact of the pandemic in a neonatal intensive care unit (NICU). Infants were divided into two groups before the pandemic and two during the pandemic. Over the four-year period, a total of 503 infants were included, and 36 infections were recorded. The multivariable analysis showed that being hospitalized during the pandemic years was the main risk factor for HAI acquisition. Finally, as part of the Corporate HH Project, we quantified the compliance with hygiene rules by HCW, within the ICUs for two years. After the second survey, in the NICU, recorded HH compliance was 100% (65.7% in 2021). In the no-COVID-19 ward, it decreased (53.9% *vs* 89.9% in 2021). The COVID-19 ward participated only in 2022 recording 57.7% compliance.

Discussion: Together, these findings suggest that patient management during the pandemic was suboptimal and that HAI surveillance protocols should be implemented in the ICUs setting promptly.

CREUTZFELDT-JAKOB DISEASE (CJD) IN A MAN SURVIVING COVID-19: A CASUAL OR CAUSAL LINK?

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Background: To describe the rare case of a man surviving COVID-19, presenting with ataxia, subsequently associated with a rapidly progressive dementia, eventually diagnosed to have a sporadic Creutzfeldt-Jakob Disease (CJD).

Methods: A 54-year-old man came to our observation for a subacute onset of ataxia, gait disturbance, dizziness, headache, anosmia and hallucinations, followed by rapid cognitive decline, reduced verbal fluency, apathy and urinary incontinence. His past medical history included only hypertension. Two months before, he had contracted SARS-CoV-2 infection, and had remained in home isolation for about 40 days. Diagnostic assessment included blood and Cerebrospinal Fluid (CSF) microbiological testing, onconeural antibodies and neural surface antigens antibodies, brain MRI, EEG studies, chest CT scan, CSF prion Real-Time Quaking-Induced Conversion (RT-QuIC) and 14-3-3 protein analysis, and PRNP sequencing.

Results: Blood and CSF screening and microbiological tests resulted all negative. Chest CT scan documented a mild hypodiafania. Brain MRI showed multiple DWI/FLAIR hyperintensities of caudate and globus pallidus, putamina and thalami. EEG showed short sequences of periodic polyphasic delta waves. Treatment with intravenous steroids and immunoglobulins was promptly tried without any clinical improvement. In the suspicion of CJD, CSF resulted positive for the 14-3-3 protein, and prion seeding activity was demonstrated by the RT-QuIC assay. PRNP sequencing revealed valine homozygosity (VV) at codon 129 and no pathogenic mutations. Our patient progressed up to mutism, akinetic and fully dependent state, and died two months after the discharge. A brain autopsy was performed. The neuropathologic examination revealed spongiform change, gliosis and neuronal loss, predominantly involving the cerebellum, striatum and thalamus. Immunoblotting detected the abnormal, proteinase-K resistant prion protein (type 2 according with Parchi's classification). There were no findings suggesting for COVID-19 related encephalitis.

Discussion: Some recent studies demonstrated that patients surviving COVID-19 can show neuroinflammatory activation of microglia and astrocytes, that might favor the fast development of neurodegenerative diseases, such as CJD. In our case, the neuropathological examination allowed the definite diagnosis of CJD and ruled out a specific neuroinflammatory phenotype related to COVID-19 infection. Further studies will address whether SARS-CoV-2 infection could trigger or enhance susceptibility in individuals already at risk for neurological syndromes. This case expands the spectrum of differential diagnosis of rapidly progressive.

BIO-SUCCESS: BIOMARKERS SUSTAINABLE COLLECTION AND COMPLETE EXTRACTION IN SALIVAOMICS AND FORENSIC SCIENCES

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Background: Among the various biological matrices used for diagnostic purposes or for toxicological investigations, in the last decades Oral Fluid (OF) is an emerging matrix for driving investigations under the effects of drugs, (DUIDs), in the assessment of accidents in the workplace or for doping controls. For diagnostics, it is used in the research of specific salivary biomarkers for pathologies, of hormone levels measurement or to diagnose HIV or COVID-19. Although extremely simple, sample collection is a critical and waste generator step. Sampling devices may also lead to adsorption issues and incomplete extraction is possible especially for lipophilic substances; strong solvents or extremes conditions such as may be required, with the risk of altering the sample itself.

Methods: In this project biodegradable sampling devices will be developed and tested. The materials chosen are chitosan and gellan gum, polymers. The printer is a 3D Bio-Printer BIOX (Cell-Line) based on the extrusion technology. The miniaturized technique parallel artificial liquid membrane extraction was chosen for the clean-up and extraction of the analytes from the sample. High performance liquid chromatography coupled with tandem mass spectrometry allowed the simultaneous identification and quantitation of isoprostanes and several illicit drugs.

Results: The gellan gum has shown some interesting feature; it is a polimer that can be easily dissolved in water with an increasing of temperature. PALME has proven suitable for the purpose of this work; it is a green extraction method which uses small amounts of both organic solvents and sample. The first results are encouraging.

Discussion: The previously tested polymer, PLA, was not suitable especially because did not allow the application of some of the miniaturized techniques considered.

Therefore, water-soluble polymers such as chitosan and gellan gum were chosen. PALME has been applied for the clean-up of the sample and the extraction of selected analytes from a device made of gellan-gum; printing tests and evaluation of recoveries with chitosan will be carried out later.

DATA SCIENCE AND GENOMIC STUDIES ON MAJOR MOSQUITO VECTORS OF HUMAN AND ZOONOTIC DISEASES

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Background: Mosquitoes play a significant public health role due to their relevance in disease transmission. Their ability to transmit pathogens like malaria, dengue fever, and Zika virus poses a considerable health risk worldwide. This PhD project had two main goals: 1) characterize genomic composition, admixture patterns, gene-flow, evolutionary relationships of Afrotropical malaria vector species of the *Anopheles gambiae* complex in Far-West Africa; 2) implement new Information Technology (IT) infrastructure to analyse and disseminate data obtained by the citizen science project "Mosquito Alert Italia", also thanks to the "Avvio alla Terza Missione" 2021 Sapienza grant awarded to develop promotional strategies aimed to raise awareness and engage citizens to use Mosquito Alert app in order to contribute to the monitoring of autochthonous and invasive vectors of arboviruses and their associated nuisance.

Methods: 1) Principal Component Analysis, ADMIXTURE, FST, genetic diversity statistics, TreeMix, Patterson's D statistics, f3-statistics and δaδi are applied to the analysis of genome data from 1,190 *Anopheles gambiae* west-African specimens sequenced by the Ag1000G project; 2) WordPress web server, PostGIS geodatabase, Google News retriever bot and a social media campaign with funnel marketing approach were implemented to enhancing the Mosquito Alert Italia project's IT infrastructure and promote the use of its mobile application.

Results: 1) Findings from genomic analyses revealed distinct genetic signatures in Far-West populations and a complex admixture patterns, indicating the existence of a cryptic taxon characterized by a unique gene pool, provisionally named Bissau molecular form; 2) Results obtained from social media campaign performed in 2022 were: 4,934 website accessed sessions, 11,336 user-generated reports (6,138 mosquito reports, 4,959 mosquito bites, 239 breeding sites), and 188,443 interactions on social media platforms. Data from user reports and social media interactions such as user engagement, click-through rates, and conversion metrics are currently being analysed.

Discussion: 1) Results obtained from the genomic analysis of cryptic taxa in the Far-West region contribute to gaining novel insights into the genomic history of the *An. gambiae* complex and their potential implications for the dynamics of malaria transmission. 2) Results are expected to allow assessment of: i) the impact of the advertising campaign; ii) the presence of invasive species by constructing predictive maps of human-vector contact; iii) the ecology and distribution of invasive species by implementing bioclimatic parameters derived from satellite data. A manuscript on each topic is in progress.

FOUR GAMES – APPLICATION OF A HEALTH PROMOTION PROGRAM AIMED AT REDUCING STRESS AND BURNOUT IN HEALTHCARE WORKERS AFTER THE COVID-19 PANDEMIC

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Background: The COVID-19 pandemic has affected the lives of everyone, especially health workers. Stress and burnout have been the problems that have manifested themselves most in healthcare workers. Stress-related ill health is a growing issue representing major challenges for both the individual and society, as it leads to enormous costs in terms of work disability and puts pressure on the healthcare system.

Methods: The project is divided into four tasks. The first phase involves a systematic review of the literature for assessing whether interventions such as yoga, Mindfulness (MBI), Visual Thinking Strategies (VTS) and Forest Bathing (FB), can reduce stress and burnout in nurses. The second phase involves a Randomized Clinical Trial (RCT) aimed at assessing the effectiveness of an intervention based on four types of techniques in improving mental well-being in nurses. The interventions will be delivered in three different modalities: course in presence, synchronous distance learning, and asynchronous distance learning. The third phase involves the creation of a mobile application that would allow us to examine the efficacy of our interventions on large samples of participants in the healthcare setting. The four phase is the testing of the use of the application, and how it brings benefits in improving the health of nurses. A pre-test and a post-test will be carried out, before and after the use of the application.

Results: The different interventions were created with the aim of implementing the psychological skills of the healthcare staff involved. Employers in the healthcare setting should considered implementing workplace wellness programs that integrate these methods to promote well-being of their staff. MBI, yoga, VTS and FB are an effective intervention can help the psychological functioning of healthcare professionals.

Discussion: Establishing an easy-to-access and remote training program, conducted by experts in the field, through the creation of an application where the lessons will be uploaded, will allow an increase in the psychological well-being of the staff involved, with the aim of decreasing medical errors and increasing standards of care for patients. A tracing network and active and continuous surveillance of all the operators involved could allow companies to prevent their healthcare personnel from being so emotionally exhausted that they leave their profession.

DEEP LEARNING FOR PUBLIC HEALTH: PREDICTING CHRONIC DISEASE PROGRESSION WITH LSTM NETWORKS

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Background: Chronic diseases represent a significant challenge to global public health, considering demographic aspects, e.g. population aging, their economic burden, their impact on the quality of life of millions of individuals.

In order to predict their progression, for an improved prevention and care management, this study examines the application of a specific category of Recurrent Neural Networks (RNN), known as Long Short-Term Memory (LSTM) which are particularly suited to handling sequential or temporal data, thanks to their ability to retain "memories" of previous inputs, thus proving suitable for modeling and projecting the temporal course of chronic diseases in a specific population. The aim is to provide healthcare practitioners and public policy decision-makers with tools based on empirical data for optimal management and prevention of chronic diseases. The ability to project the course of chronic diseases would indeed allow for a timelier interception of changes in the incidence and prevalence of such conditions, enabling the healthcare system to respond in a more agile and targeted manner.

Methods: The study will be conducted on a large database, provided by the UK Biobank, composed of 500,000 units monitored over time, for which genetic, health, and socioeconomic information are available. The data will be preprocessed to handle missing values through imputation techniques and normalize numerical variables to ensure that no variable overshadows others due to its scale.

To model the temporal course of chronic diseases, a variant of Recurrent Neural Networks (RNN) called Long Short-Term Memory (LSTM) will be used. These networks were chosen due to their ability to capture long-term temporal dependencies in data.

Results: The analysis aims at demonstrating the ability of LSTMs to identify long-term relationships between variables such as demographic, climatic, and behavioral data, and the incidence and evolution of chronic diseases. These relationships can be extremely complex and non-linear, eluding more conventional statistical analysis methods.

Discussion: The main aim is to understand how the application of deep learning models, particularly LSTMs, can constitute effective predictive tools for chronic diseases. Once a robust methodology has been established, this could allow for a more efficient allocation of health resources, a crucial element in a context of limited resources and increasing demand for care. Moreover, the identification of specific risk factors could guide prevention strategies and health promotion, contributing to a reduction in the incidence of chronic diseases.

SPECIFIC T-CELL RESPONSE TO VACCINATION IN PEOPLE WITH MULTIPLE SCLEROSIS

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Background: People with Multiple Sclerosis (pwMS) are at risk of infections and reactivations partially due to Disease Modifying Therapies (DMTs). Vaccinations to prevent communicable diseases, like SARS-CoV-2 and Varicella-Zoster Virus (VZV), are of key importance. However, DMT immunosuppressive and immunomodulating mechanism of action might alter immune response to vaccination.

Methods: At the Neuroinfectious Unit of Policlinico Umberto I, Sapienza University of Rome mRNA-based vaccine against SARS-CoV-2 (mRNABNT162b2) and recombinant VZV gE vaccine (Shingrix®) has been proposed to pwMS. Specific T-cell responses after Spike (S) and VZV gE peptides stimulations were evaluated, defining "responding" T-cells those producing at least one cytokine among IFNg, IL2 and TNFa, and "triple-positive" those T-cells producing simultaneously all 3 cytokines. For each vaccination, two time-points were considered: before (T0) and after 2 months (T1) from mRNABNT162b2 booster dose; before (T0) and after 1 month (T1) from first Shingrix® dose. In the mRNABNT162b2 evaluation a control group included healthy donors (HDs) were enrolled.

Results: 18 pwMS and 18 HDs that underwent mRNABNT162b2 vaccination were enrolled. At T1, reduced percentage of responding and triple-positive T-cells, as well as a different polarization toward one cytokine production was seen in pwMS compared to HD (responding CD4: p=0.0165 and CD8: p=0.0022; triple-positive CD4: p=0.0007 and CD8: p=0.0422). According to DMTs, differences in T-cells response in immunomodulating- and immunosuppressive-treated pwMS were observed, with a reduction of responding and triple-positive T-cells in the latter one (responding CD4: p=0.0004 and CD8: p=0.0082; triple-positive CD4: p=0.0645 and CD8: p=0.0048). Immunosuppressive-treated pwMS showed a polarization toward TNFa production by T-cells at both time-points, while in immunomodulating-treated pwMS a more heterogeneous cytokine production was seen. Among 12 pwMS who started Shingrix®, no differences in the percentages of responding and triple-positive T-cells were seen between T0 and T1.

Discussion: Vaccination provides additional benefit to pwMS. However, in line with current literature on other vaccine responses, such as influenza, DMTs mechanism of action seem to influence humoral and cellular immune response to vaccination in pwMS.

“CLEAN CARE IS SAFER CARE”. POSTOPERATIVE SEPSIS: ERROR MANAGEMENT AND EVIDENCE OF NON PREVENTABLE EVENTS

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Background: Italy is one of the few countries to have a law (No. 24/2017) that recognizes the safety of care as a fundamental right of every individual accessing health services. The primary objectives of health care safety and quality programs include preventing healthcare-associated infections. The most dangerous complication of infections is sepsis, which implies high morbidity and mortality rate and higher costs. Moreover, it is often difficult to prove the non-preventability of this type of event, with consequent civil proceeding loss in most litigation cases. It means that its monitoring and prevention are critical elements for improving the quality of care. The Agency for Healthcare Research and Quality has proposed a series of quality indicators called Patient Safety Indicators (PSIs), which constitute a screening tool for identifying adverse events using codes present in the hospital discharge forms and represent the current state-of-the-art in measuring the safety of hospital care.

Methods: The study will aim to evaluate the prevalence rate of the adverse event “postoperative sepsis” applying the PSI 13 to the hospital discharge forms of the surgical departments of the “Umberto I General Hospital” in Rome. Medical records selected will be reviewed to identify the adherence to guidelines and existing hospital protocols and the critical issues relating to the correct compilation of the medical record, and to estimate the degree of defensibility in possible litigation. The existing organizational strategies found to be deficient will be implemented; training or refresher courses for medical staff will be programmed; internal audit will be organized, and operational tools that allow the constitution of a defensive file in the eventuality of a legal action will be proposed. At the end of the study the variations obtained will be analyzed.

Results: At present, medical records are being reviewed and corrective measures are being planned.

Discussion: The present study proposes a methodological approach to preventing postoperative sepsis in surgical departments. The wards will benefit from adequate preventive measures for postoperative sepsis and will be able to redesign care based on best evidence-based practices. Consequently, a reduction in this event is expected. The medico-legal team could avail of a valid defence file, helpful in case of hospital litigation.

GENDER DIFFERENCES IN AUTISM DIAGNOSIS. PSYCHOLOGICAL AND SOCIAL MEDICINE REFLECTIONS

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Background: Since its description, autism has been characterized by a predominantly male incidence (the ratio between males and females in the population with autism is equal to 4.3 to 1). This evidence has brought some researcher to question about the existence of different clinical phenotypes or pattern of symptoms in males as compared to females and whether these differences may be due to bias bind to the use of instruments calibrated for the male gender. However, to our knowledge the literature lack of a clear evidence in that regard as far as an explanation of this phenomenon. For example, with reference to restricted and repetitive behaviors, which according to the DSM-5 are one of the two core deficits of autism spectrum disorder, scientific research has obtained contradictory results regarding gender-related differences. The purpose of our study is to verify, using the gold standard tools for the diagnosis of autism, any differences between males and females in the various areas of diagnosis: repetitive and stereotyped behaviors, communication, language.

Methods: This is archival research; the data has been shared by health services that have signed a collaboration protocol with us. The parents of the children and young people have signed, during diagnosis process, the data information and consent to the use of the data for research purposes. Our sample is made up of children and young people who have received an ASD diagnosis. All children were assessed using the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS).

Results: Our preliminary results do not seem to show any significant difference between autistic males and females in terms of social interaction and communication.

Discussion: It is important to assess whether the results will be consistent with the partial ones or will highlight the "camouflage" effect that other studies have underlined: the ability of autistic women to camouflage the typical symptoms of the autistic spectrum.

ITALIAN TRANSLATION, CULTURAL ADAPTATION, AND VALIDATION OF THE STROKE UPPER LIMB CAPACITY SCALE (SULCS) AND ACTION RESEARCH ARM TEST (ARAT) IN PEOPLE AFTER STROKE

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Background: Stroke is the second leading cause of death and the leading cause of disability in Europe. Since the disability of the upper limb is one of the most disabling consequences of stroke, it is essential to have a measuring tool that can specifically evaluate this type of disability, correlating it to activities of daily living. The aim of this study is the cultural adaptation and validation in Italian of the Stroke Upper Limb Capacity Scale (SULCS) on post-stroke patients.

Methods: The original scale was translated and culturally adapted from English to Italian using the "Translation and Cultural Adaptation of Patient Reported Outcomes Measures–Principles of Good Practice" guidelines. Its internal consistency and test–retest reliability were examined. Its concurrent validity was evaluated using Pearson correlation coefficients with the Italian version of the Disability Arm Shoulder and Hand (DASH).

Results: From the results, it can be highlighted how the items translated and adapted in Italian have stability and reliability within and between operators. The Cronbach alpha of 0.904 indicates an excellent internal consistency between the items, and the interclass correlation coefficient is 0.998 for inter-operator reliability and 0.987 for intra-operator reliability. The scales' reliability has been demonstrated by excellent internal consistency and stability. Moderate correlations have confirmed the construct validity with DASH, the gold standard for evaluating UL capacity available in Italian.

Conclusions: The scale is a tool that highlights positive results regarding validity and reliability, allowing applicability at the health level in the diagnosis and/or functional evaluation of the upper limbs in the post-stroke patient. In addition, it can be administered anywhere and does not require special instruments that are difficult to find.

THE MID-LONG TERMS BURDEN OF COVID-19 PANDEMIC ON ITALIAN POPULATION HEALTH STATUS THROUGH THE SURVEILLANCE SYSTEMS PASSI AND PASSI D'ARGENTO

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Background: From August 2020 to December 2022, PASSI and PASSI d'Argento (PdA) - two Italian ongoing population-based surveillance systems coordinated by the Italian National Institute of Health (ISS) on adults and elderly, respectively - have been administering a specific COVID module, in addition to the standard questionnaires, to estimate the mid-long terms burden of COVID-19 pandemic on Italian population health status.

Methods: The COVID-19 module is a set of 17 questions. These preliminary results are on a sample of 59,124 people for PASSI and 29,675 for PdA. Data were appropriately weighted to take into account regional sample sizes and gender and age composition within each region. For both surveillance systems the response rate was over 86%.

Results: The share of 18-69 year old respondents who report that their economic resources have worsened as a result of the COVID-19 pandemic-related crisis remains constant from 2020 to 2022 (32%). Moreover, among the over-65s, 39.8% of respondents in 2020-21 said they had foregone at least one medical examination (or diagnostic test) they would need in the previous 12 months, and 29.3% in 2022.

Discussion: These results suggest a medium-term impact on the population, especially the more disadvantaged by age or socioeconomic conditions, which should be kept in mind in order to limit the increase of inequalities.

SARS-CoV-2 LIFE CYCLE *IN VITRO*

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Background: The emergence of a novel Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) resulted in one of the greatest pandemics of human history. SARS-CoV-2 continues to evolve under immune selective pressure, and while transmission levels remain high, there is an increased likelihood of vaccine escape variants evolving. Given the clinical importance of emerging viral variants with increased transmission, understanding the early stages of viral replication is urgently needed. The aim of this study is to identify the replication kinetics of the virus involved in SARS-CoV-2 infection in the model VERO E6 cells during the first steps of virus replication.

Methods: Viral isolate BetaCov/Italy/CDG1/2020|EPIISL412973|2020-02-20 obtained from a COVID-19 patient, was used to infected VERO E6 cells in Labteck chamber slides and 6-well plates in the certificate BSL-3 Laboratory at Istituto Superiore di Sanità. Indirect Fluorescent antibody assay (IFA) experiments were performed to track the progression of viral protein synthesis during virus life cycle. Transmission Electron Microscopes (TEM) studies of SARS-CoV-2 morphogenesis were performed at different time points, to confirm IFA results.

Results: Infected Vero E6 cells were analysed at different time points that represent very early steps of viral infections (0-30 minutes post virus adsorption). We performed IFAs labelling viral and cellular proteins. The results showed that already after 5 minutes the infected Vero-E6 expressed N and M proteins, localized throughout the cell cytoplasm, together with a strong modification of the cell compartments. The results showed a moderate colocalization with the ER and Golgi of N and M proteins as early as 5 min of infection. Electron microscopy analysis confirmed these modifications at the ultrastructural level and that the host compartment involvement started since the early steps of infection.

Discussion: These results underline the importance of studies concerning the interaction of viral proteins and cellular structures involved in the very early stages of the SARS-CoV-2 viral cycle. Given these promising results, we are going to perform co-localization IFAs of the viral genome with the viral proteins produced and with the cellular host machinery.

HUMORAL AND T-CELL RESPONSE TO THREE DOSES OF SARS-CoV-2 MRNA VACCINE IN SOLID ORGAN TRANSPLANT RECIPIENTS: A ONE-YEAR FOLLOW-UP

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Background: In Solid Organ Transplant Recipients (SOTR), COVID-19 vaccine is strongly recommended as high-risk patients due to their immunocompromised status. We investigated specific humoral and T-cell response to the third dose of mRNA vaccine in this population.

Methods: Humoral and T-cell responses were evaluated in SOTR before(pre) and after 2 months(post) from the third dose of vaccine. By intracellular cytokine flow cytometry assay, upon S peptide libraries stimulation in peripheral blood mononuclear cells, we identified T-cells producing all possible combinations of IFNγ, IL2 and TNFα. We named those producing any of them as "responding" T-cells and those simultaneously producing all 3 as polyfunctional. SOTR were stratified according to transplant into Lung Transplant Recipients (LuTR) and Kidney Transplant Recipient (KTR). As control group, Healthy Donors (HD) were enrolled. For a subgroup of SOTR and HD, the humoral and T-cell response were further assessed with a focus on T-cell response against the S protein of Wild-type (Wt) and Omicron B.1.1.529/BA.5 at 1year from the third dose.

Results: 32 SOTR and 12 HD were enrolled. Overall, 14/32 and 26/32 of SOTR showed a specific humoral response at pre- and post-third dose, with an increase of over 30% maintained at 1year 17/19. Collectively, pre- and post-third dose, significant lower percentage of "responding" T-cells (CD4 $p<0.0001$; $p=0.0005$; CD8 $p=0.0007$; $p=0.0457$) and polyfunctional T-cells (CD4$p<0.0001$; $p=0.0005$; CD8$p=0.0075$; $p<0.0001$) were found in SOTR compared to HD. SOTR were stratified into LuTR and KTR. 1/9 of LuTR and 13/23 of KTR and 4/9 of LuTR and 22/23 of KTR developed a specific humoral response pre- and post-third dose. In both groups, pre third dose, anti-S levels were significantly lower compared to HD ($p<0.0001$ and $p=0.0069$, respectively), while post, only in LuTR group ($p=0.00062$). Pre and post-third dose, a significant lower percentage of "responding" T-cells (CD4 $p<0.0001$; $p=0.0119$; CD8 $p<0.0001$; $p=0.0221$) and polyfunctional T-cells (CD4$p=0.0012$; $p=0.0093$; CD8post: $p=0030$) were found in LuTR compared to HD, as well as in KTR (responding: CD4 $p=0.0004$; $p=0.0002$; CD8$p=0.0073$; $p=0.0691$; polyfunctional: CD4 $p<0.0001$, $p=0.0002$; CD8 $p=0.0002$; $p<0.0001$).

Discussion: In SOTR, the booster dose increased the rate of seroconversion, although anti-S levels remained lower compared to HD. However, vaccine effectiveness in SOTR is suboptimal but improved by boosters. This data showed that T-cell responses in SOTR are worse than those of immunocompetent individuals, but they exhibit T-cell responses without effectiveness humoral responses.

HEALTH LITERACY AS A DETERMINANT OF HEALTH PROMOTING BEHAVIOURS: AN APPLICATION OF EVIDENCE-BASED TOOLS

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Background: Health Literacy (HL) is broadly considered a social determinant of health. Although theoretically its influence on health preventive behaviors is undoubted, evidence is not always in agree of its decisive role in people health choices. For this reason, alongside to general HL, also specific domains have been recently defined and studied as they could be more specifically involved in people decision-making process. Again, the results on the association are mixed and not always in agreement. In this context, the aim of the project is to provide a synthesis of evidence on the topic with an evidence-based medicine approach. We used vaccination behaviours as case-study, and we evaluated the association between both HL and Vaccine Literacy (VL) and vaccination intention and/or status.

Methods: We performed two systematic reviews in which we evaluated the association between HL (i) and VL (ii) and vaccination intention and/or status. In both the cases we included observational studies that provided data of the association between HL (i) and VL (ii) and the outcomes in any population. A narrative synthesis of the main findings was performed for both the reviews. In addition, given the characteristics of the studies on VL, we were able to conduct a meta-analysis using the random-effect model and estimating pooled mean and their 95% Confidence Intervals (CI) for both the outcomes.

Results: In the first review, articles on intention looked at SARS-CoV-2 vaccination whereas studies on vaccination status explored mainly for influenza or pneumococcal vaccines. We found inconsistent results across and within vaccine types, with no clear conclusion for either vaccination intention or status. A weak but positive association was reported between a high HL level and influenza vaccination uptake. By contrast, in the second review the vast majority of the studies investigated COVID-19 vaccination. In general, we found a positive association between higher VL levels and vaccination behaviours. At meta-analysis higher levels of VL seemed to strongly predict vaccination behaviours, especially for vaccination intention.

Discussion: The synthesis of current findings showed that although HL is considered a driver of health choices, its influence has yet to be clearly established when considering a specific health behavior. In fact, it did not seem to significantly influence behavior towards vaccination. Differences in the methods used such as the heterogeneity in tools might explain the results. On the contrary, a promising role seemed to be played by VL that appeared to be a critical factor influencing vaccination behaviours. Future research on the topic should focus on methodological aspects that might be responsible of the findings.

THE ROLE OF IMMUNOTHERAPY IN ONCOHEMATOLOGICAL PATIENTS WITH SARS-CoV-2 INFECTION: A REAL-LIFE EXPERIENCE

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Background: Since the start of the pandemic, numerous drugs have been proposed either to prevent disease progression in patients without pneumonia, the so called "early therapy", or to treat more advanced COVID-19 manifestations. Currently, clinical evidence on the effectiveness and appropriateness of these therapies is lacking for oncohematological patients.

Methods: Patients with SARS-CoV-2 infection were enrolled at SM Goretti Hospital in Latina, and Sant'Andrea Hospital in Rome and divided in two groups according to the final outcome: discharge or death (by any causes). We also considered different factors such as age, hematological disease, vaccination status at the time of hospitalization, severity of infection and type of therapy administered, if any.

Results: A total of 88 patients were enrolled. Of these, 8/88 patients received pre-exposition therapy with tixagevimab/cilgavimab. Considering only early therapy for COVID-19, 75% of total patients did not receive any therapy. These patients developed a more severe form of COVID-19, with an overall higher rate of pneumonia (73.8%) and mortality rate (12 deaths, 85.7%) compared to patients treated with early therapy (2 deaths, 14.3%). For inpatient therapy, patients treated with a combination of drugs had a lower mortality during hospitalization: the combination of both intravenous and oral antiviral (with a 10-days course of remdesivir and a 5 or 10-days course of nirmatrelvir/ritonavir) associated with MAbs is related to a lower mortality rate during the hospitalization (0 out of 7 patients treated).

Discussion: In our real-life experience, early therapy and, or targeted treatment during hospitalization with a combination of antiviral drugs, monoclonal antibodies and immunosuppressive drugs can reduce mortality. The future objective is the use of LIASION®MeMED BV® assay, a new immunodiagnostic solution that will allow us to distinguish a viral *vs* bacterial sepsis through the dosage of TRAIL, IP-10 and CRP, in order to define possibly reversible precipitating factors early.

DEVELOPMENT OF AN INTEGRATIVE APPROACH FOR MONITORING SARS-CoV-2 INFECTION-INDUCED VERSUS VACCINE-ACQUIRED INNATE AND T CELL IMMUNITY IN HIV-1 INFECTED PATIENTS

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Background: Evidence on how HIV infection affects risk of poor outcomes from COVID-19 are still poorly investigated and a clinical and immunological profile due to SARS-CoV-2 infection in People Living With HIV (PLWH) are lacking. Complex immune dysregulation in both interferon and T cell responses has been observed in PLWH as well as in COVID-19 patients. On the light of these, further studies are needed to better understand the impact of SARS-CoV-2 infection on the immunopathogenesis of HIV infection. Furthermore, it is necessary to assess the effectiveness of COVID-19 vaccines, as well as their ability to modify innate and T cell associated immunity PLWH.

Methods: 75 long term treated PLWH were recruited and three peripheral blood draws were collected from all the participants before the first administration of vaccine (T0), the day of second vaccine dose (T1; 21 days from T0) and after the administration of the second dose (T2; 38 days from T1). A quantitative determination of serum specific IgG antibodies against the SARS-CoV-2 spike protein was assessed using a commercial immunoassay. The mRNA levels of type I IFN (IFN-α, IFN-β, IFN-ε and IFN-ω), IFN-I receptor subunits (IFNAR1 and IFNAR2) and ISGs (ISG15, ISG56 and IFI27) and were evaluated using RT/real-time PCR.

Results: Overall, longitudinal increase of anti-Spike IgG titers over the study period was observed ($p<0.0001$). 69 out of 75 individuals (92%) had detectable serum levels of anti-Spike SARS-CoV-2 at T1 and the anti-Spike IgG positivity rate increased to 96% (72/75) at T2. Heterogenous levels of type I IFN genes, IFN-I receptor subunits and ISGs were observed in PLWH over study ($p<0.001$). Although no significant differences of IFN-I genes were observed by among time points, higher IFNAR2 gene expression was detected at T1 in comparison to T0 ($p=0.002$). Furthermore, an upregulation of the mRNA levels of IFNAR1 and IFNAR2 was observed at T2 when compared to respective previous time point ($p<0.05$). Regarding the longitudinal ISGs expression, the amount of ISG56 and IFI27 mRNAs increased progressively over study ($p<0.05$). Likewise, significant differences on ISG15 gene expression were observed between T1 and T2 ($p=0.0001$).

Discussion: These results showed the mRNA-based SARS-CoV-2 vaccine ability in stimulating the anti-S IgG production and IFN pathway genes. Further analysis will be conducted on a larger population to evaluate humoral response, interferon pathways and T cells immune phenotype and frequencies in COVID-19 vaccinated PLWH as well as in SARS-CoV-2/HIV-1 co-infected individuals.

IMMUNOHISTOCHEMICAL ANALYSIS OF HEROIN-RELATED DEATH

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Background: Heroin is a semisynthetic opioid synthesized from morphine. The post-mortem diagnosis of heroin-related death could be difficult and usually bases on various examinations, such as the crime scene investigation, autopsy, histology, and toxicological analysis. Heroin is 2-3 times stronger than morphine and its lethal dose is around 100-200 mg. However, addicts may be able to tolerate up to 10 times those values, and cases of heroin-related death have been described even with doses of 10 mg. Toxicological analysis is fundamental in such cases of death. Nevertheless, when toxicology is not available or its results are not completely clear, the forensic pathologist needs to base his/her considerations on other data. Our study aims to clarify the correlation between blood toxicological results and immunohistochemical features of various tissues through an anti-6-monoacetylmorphine (6-MAM) antibody in cases of heroin-related death.

Methods: Herein, a semi-quantitative analysis of the immunohistochemical reaction is described, testing anti-6-MAM antibodies used on samples of various organs (brain, heart, lung, liver, and kidney) obtained during judicial autopsies. The analysis is conducted on cases of heroin-related death. As control group, cases of death due to other causes, without brain lesions and negative toxicological analysis are selected.

Results: We'll verify if immunohistochemistry could be a valuable tool for the post-mortem diagnosis of acute heroin overdose. The immunohistochemical technique allows us to quantify the expression of the response with a semi-quantitative scale. So far, we found a positive immunohistochemical reaction in the brain, lung, kidney, and vessels of heroin-related death, while the control group showed negative results.

Discussion: Our study suggests a correlation between the immunohistochemical reaction and the toxicological analysis. Indeed, the 6-MAM positive reaction could provide relevant information about the timing of consumption of the drug, especially in the brain samples. A great and intrinsic limit of this study is that is not possible to compare the 6-MAM histological distribution in cases of deadly heroin intoxication with cases of non-fatal heroin consumption, in addition to the small sample size. However, our preliminary results are promising, and it seems that immunohistochemistry with the anti-6-MAM antibody can be a valuable tool for the post-mortem diagnosis of acute heroin overdose.

STUDYING MOSQUITO VECTOR BIONOMICS AND BEHAVIOUR TO BOOST PYRETHROID-FREE INVASIVE MOSQUITO CONTROL IN URBAN AREAS

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Background: *Aedes* invasive mosquitoes are responsible for the global transmission of tropical arboviruses, such as Dengue and Chikungunya - a major public health problem of increasing importance also in temperate regions due to the establishment and spread of *Aedes albopictus*. The control of *Aedes* densities, nuisance and arbovirus transmission is still largely dependent from pyrethroid insecticides, but their environmental impact and the spreading of resistance urge for the need to develop innovative pyrethroid-free control approaches, such as Sterile-Insect Technique (SIT, based on release of irradiated males), Incompatible Insect Technique (IIT, based on the release of males with a different endosymbionts *Wolbachia* strains from those present in wild females capable of inducing cytoplasmic incompatibility) or "auto-dissemination" of Pyriproxyfen (PPF, an Insect Growth Regulator interfering with adult emergence to be exploited to overcome the difficulty in targeting the multiplicity of larval sources). My PhD thesis is focused on studies devoted to better characterize aspects of mosquito bionomics and behaviour (e.g., dispersal, survival, resistance to insecticides) relevant for the design and implementation of integrated management strategies against *Ae. albopictus* in urban areas of temperate regions. Here, I describe the experiments and preliminary results achieved during the 5 month-visit at University of Queensland.

Methods: First, a Mark-Release-Recapture (MRR) was carried out: >12,000 *Aedes aegypti* males were reared, marked with 6 fluorescent dusts by a novel marking technique using polystyrene beans, released at daytime and night-time per 3 replicates in about 100-sqm area in Goomeri (QLD), and recaptured daily for 7 days by 40 BG-Sentinel traps. Second, a preliminary experiment was carried out under laboratory conditions to test the hypothesis that feeding males with PPF could bring an increase in population suppression through contamination of females by mating.

Results: Preliminary results of the MRR show significant higher longevity and dispersal than previously assumed, as well as disproved previous indications suggesting that releases during night hours could be more effective than daily ones. Results of PPF test are under analysis.

Discussion: The acquired skills and the expertise developed during the first half of my PhD studies in the group of medical entomology in DSPMI, at Entostudio and at University of Queensland are at the basis of the development of the research activities to be carried out on *Aedes albopictus* in Rome during the second part of the PhD.

EVALUATION OF ANTIBODIES AGAINST SARS-CoV-2 IN A VACCINATED POPULATION

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Background: The continuing spread of COVID-19 caused by SARS-CoV-2 virus has prompted concern worldwide, leading the WHO to declare COVID-19 a pandemic on 11 March 2020. A wide range of immunoassays to detect SARS-CoV-2 Antibodies (Ab) have been developed to complement rRT-PCR, with different antigen targets and formats. Although not well suited for allowing an early diagnosis, serological assays for SARS-CoV-2 play an important role in diagnosing COVID-19 in individuals who present late, in understanding the virus epidemiology in the general population, and in identifying the disease prevalence in categories at higher risk of infection.

Methods: The research project population consists of about 300-600 immunocompetent health workers of the hospital Policlinico Militare of Rome "Celio" vaccinated with Comirnaty (Pfizer/Biontech). For each patient, three different samples will be collected at three different time points (T0=before vaccination; T1=21 days after first injection; T2= 21 days after second injection). This sample will be tested with a commercially available Chemiluminescent Immunoassays (CLIA) Liaison SARS-CoV-2 S1/S2 IgG (ref 311450, insert 200/007-797 v04-2020) (Diasorin, Sallugia-VC, Italy), a fully automated serology test to detect IgG antibodies against SARS-CoV-2. These obtained from Liaison SARS-CoV-2 S1/S2 IgG will be compared to Plaque reduction neutralization test (PRNT50). The Biosafety Level 3 laboratory setting of ISBD will used for PRNT tests. The associations between PRNT50 titers and assays S/CO ratios will be evaluated by multivariate analyses, using SARS-CoV-2 antibody levels, age, gender, commercial brand of vaccines, time from each dose of vaccines as additional predictors.

Results: *Month 1-6***:** up to now we completed the following activities: Sampling patients of different populations, written consent collection, creation of a framework database. *Month 7- now*: samples analysis with Liaison SARS-CoV-2 IgG, Phase 1 of PRNT50 analysis, Evaluation of possible project upgrades. The sample population is 362 workers vaccinated with Comirnaty (Pfizer/Biontech). More precisely we already conducted analysis with Liaison SARS-CoV-2 S1/S2 IgG on all T0 population with a preliminary result of 360 negative samples and 2 positive samples (>33.8 BAU/ml).

Discussion: The selected population is almost all tested negative for SARS-CoV-2 IgG at T0, providing us a good sample for further analysis.

FINGERNAILS ANALYSIS IN TOXICOLOGICAL SCREENING ON CHEMSEX ADDICTED VOLUNTEERS. DIFFERENCES BETWEEN PRE – AND POST – COVID ERA

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Background: Since 2010, at the beginning in LGBTQIA+ community in Great Britain, a phenomenon known as "chemsex" was born, consisting of sexual approach between people who abused illicit drugs before or during sex. Nowadays, chemsex is spreading throughout Europe and is particularly linked to amphetamine, GHB, GBL, cocaine, ketamine. Chemsex poses a health problem due to the risk of overdose and/or the spread of STD. Nails could be a good material for the evaluation of chemsex drugs in Italy.

Methods: Using UHPLC-MS/MS, this study aims to detect the concentration of the most used chemsex drugs. Drug - free nails were donated by volunteers, while chemsex addicted nails were donated by anonymous people who attended raves and sex parties. After calibration and quality control, biological samples were prepared for UHPLC - MS/MS for the detection of opiates, cocaine, THC, amphetamine, MDMA and ketamine.

Results: Nails samples have tested positive for several types of drugs; the most frequently detected drugs were cocaine, MDMA and GHB, sometimes in association with other drugs.

Discussion: Results of our study are little different from the rest of EU: while in Europe people tend to use meth, GHB and mephedrone, Italian chemsex pratictioners choose GHB, MDMA and cocaine. This work also shows the reliability of nails for toxicological analysis, demonstrating that this matrix works as an "archive" for previous drug use, even though we have seen a large difference between fingernails and toenails results. We are developing our study with a new matrix analysis on fingernails collected after COVID lockdown, to see differences between pre - and post - COVID era in Italian chemsex habits.

HOSPITAL ACQUIRED PNEUMONIA IN PATIENTS WITH SARS-CoV-2 ARDS DURING NON-INVASIVE VENTILATION: A RETROSPECTIVE STUDY

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Background: Non-Invasive Ventilation (NIV) can reduce in specific populations the risk of reintubation, mortality, length of stay and occurrence of lung infection. Uncertain results are described in literature in SARS-CoV-2 pneumonia; moreover, Hospital Acquired Pneumoniae (HAP) and superinfections in COVID-19 patients undergoing NIV have not been investigated. The objective of the study was to evaluate occurrence and microbiology of HAP following more than 48h of consecutive NIV in subjects who required sub-intensive care for their severe respiratory failure due to SARS-CoV-2 illness.

Methods: From March 2019 to September 2022, we retrospectively recruited 84 subjects hospitalized in our Sub-intensive Respiratory Unit. All patients with documented SARS-CoV-2 pneumonia at instrumental radiological findings underwent optimized medical therapy, according to current Guidelines and best Scientific evidences. HAP definition was based on Consensus of Guidelines ERS/ESICM/ESCMID/ALAT and defined as a pneumonia developing in subjects after at least of 48h of hospital stay, with an incubation time of at least 2 days. Following clinical suspicion, blood cultures, nasal swabs for MRSA detection and representative samples of lower respiratory tracts, have been collected and broad-spectrum empiric antibiotic therapy was started, Targeted antibiotic therapy was started when the causative pathogen and its antimicrobial susceptibility testings were available.

Results: Thirty-four patients developed HAP (40.5%), with a 30 day mortality of 76.7%, compared to patients with only ARDS-Sars-COV2 (53.7%; p=0.038). Patients at risk of developing HAP had received immunosuppressive therapies or prolonged corticosteroid exposure. Persistent hypercapnia and a high neutrophil / lymphocytes (N/L) ratio were correlated to new pulmonary infection and mortality at multivariate analysis. Twenty subjects (23.8%) had multi drug resistant infections and a high prevalence of extremely drug resistant *Acinetobater baumannii* (12 cases, 35.3%) was found.

Discussion: Our findings showed that 40.5% of COVID19 patients needing NIV for respiratory failure developed HAP during hospitalization with high mortality rates, especially if patients with immunosuppressive or prolonged high doses steroid therapy, and immobilization syndrome, and that a not-negligible rates of HAP were sustained by XDR-Ab. Meticulous strategies to prevent transmission of multi drug resistant germs are needed, especially in high-complexity context such as a Sub-intensive respiratory unit.

DEVELOPING A ONE HEALTH VULNERABILITY ASSESSMENT TOOL FOR UPSTREAM PREVENTION OF WEST NILE VIRUS IN LIBYA

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Background: The risk of epidemic of viruses transmitted by arthropod vectors (arboviruses) is increasing, fuelled by anthropic climate and environmental changes. West Nile Virus (WNV) is a public health concern for humans and animals. It shows a zoonotic transmission cycle between birds and mosquitos, (Culex species), with humans and equines being the dead-end host and potentially manifesting sever disease or death. Upstream prevention of WNV should focus on its multidimensional drivers by integrating a systemic approach like One Health and involving all the relevant sectors and actors. In recent years, sporadic cases and major outbreaks have increased in Europe and neighbouring countries. In Libya, as in other countries, the real burden of WNV is not known, however a seroprevalence study of 950 human blood samples showed a prevalence of WNV of 13.1%. Prevention and anticipatory warning activities for WNV should be promoted in the country by enhancing the collaboration of relevant sectors and actors, especially at local level where governmental and non-governmental stakeholders could implement ongoing and sustainable OH strategies.

Methods: The aim of the study is to develop a OH vulnerability assessment tool in Libya to identify potential upstream drivers of WNV and anticipatory signs leading to animal/human outbreak to adopt appropriate and timely action. The methods would follow a stepwise approach including: 1. Elaboration of a conceptual and measurement framework about WNV multidimensional drivers (literature review and stakeholder consultation). 2. Indicators data collection in Libya based on the measurement framework and community investigation of socio-cultural drivers. 3. Identification of hotspots of vulnerability for WNV in the Libyan context (prediction models). 4. Tool development and validation (composite index creation and validation with local stakeholders).

Results: The literature review and expert consultations highlighted multidimensional domains and associated metrics of vulnerability to WNV. The domains include factors related to the host, vector, pathogen, climate, environment, land use, human and animal mobility, health access, socio-economic factors, and practices. The next step would be the collection of data according to the measurement framework across Libya's 22 districts and community investigation of socio-cultural practices.

Conclusions: The OH vulnerability assessment tool will support the work of governmental officers, community workers and community members of areas at high vulnerability for WNV to enhance the identification of upstream drivers and promote mitigation actions. This would finally support upstream prevention and anticipatory warning of WNV outbreaks in animals and humans in Libya and neighbouring countries.

IMPROVING ACCESS TO IMMUNIZATION FOR NEWLY ARRIVED MIGRANTS IN EUROPEAN COUNTRIES

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Background: Ensuring access to immunization for migrants, particularly Newly Arrived Migrants (NAMs), is of utmost importance in the European Union and the Economic European Area (EU/EEA). Migrants may not be immunized or may be under immunized in their countries of origin and so may be vulnerable to acquire vaccine-preventable diseases. Immunization is a global health intervention that plays a crucial role in saving countless lives and preventing the transmission of infectious diseases. The AcToVax4NAM project aims to improve access to vaccinations for NAMs in European countries. The consortium behind AcToVx4NAM plans to enhance solutions in removing barriers to access vaccination and to improve vaccination literacy within the health system to ensure equal and guaranteed vaccination access for NAMs.

Methods: The project utilizes scientific methods, including participatory approach involving collaboration between stakeholders, healthcare providers, and policymakers within European countries. It includes an updating of the current reception and vaccination systems for NAMs, identification of barriers to vaccination access, and development of strategies to address these barriers. Furthermore, it develops tools to foster stronger networking capacity among organizations and stakeholders to address vaccination literacy and promote migrant-sensitive approaches within healthcare systems. Lastly, the study intends to conduct pilot tests and evaluations of these proposed solutions to enhance vaccination uptake among NAMs.

Results: Preliminary findings provide an updated comprehension of reception and vaccination systems for NAMs in Italy, Spain, Greek, Romania, Germany, Poland, Cyprus and Malta. Moreover, these findings highlight substantial barriers to vaccination access for NAMs. These barriers include professionals' lack of knowledge about the entitlement to health and vaccination for migrants, as well as the lack of specific mention of NAMs as immunization beneficiaries in documents and plans at various levels. The project has successfully developed a General Conceptual Framework to understand how to improve vaccination uptake for NAMs in EU countries, provided country-specific insights into barriers and solutions and strengthened vaccination literacy and migrant-sensitive capacities among healthcare professionals. These outcomes will be involved in a pilot testing of approaches to enhance vaccination uptake of NAMs within countries in this study.

Discussion: Ensuring that migrants have equal access to immunization services reduces the risk of outbreaks and the spread of diseases within communities. Furthermore, it promotes the well-being and integration of migrants, leading to healthier and more inclusive societies. A key objective of this study is to provide tangible and effective practices and recommendations to address the issues.

QUALITY OF T-CELL RESPONSE TO SARS-CoV-2 MRNA VACCINE IN ART-TREATED PLWH

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Background: The quality and duration of immunity to SARS-CoV-2 vaccine in People Living With HIV (PLWH) needs to be clarified. Therefore, we investigated specific humoral and T-cell response to the third dose of mRNA vaccination in this population.

Methods: Humoral and T-cell responses were evaluated in PLWH before (T0), after 2 (T1) and after 6 months (T2) from the third dose of vaccine. By intracellular cytokine flow cytometry assay, upon S peptide libraries stimulation in peripheral blood mononuclear cells, we identified T-cells producing all possible combinations of IFNγ, IL2 and TNFα, naming those producing any of them as *responding* T-cells and those simultaneously producing all 3 as *triple-positive* T-cells. PLWH were stratified according to CD4 T-cell count. As control group, Healthy Donors (HD) were enrolled. An ulterior evaluation of the humoral response was performed at 1 year (T3) from the third dose.

Results: Thirty-seven PLWH (median current CD4 T-cell count [IQR] 547 [308-714] cells/µl) all on Antiretroviral Therapy (ART) and 18 HD were enrolled. Overall, the cross-sectional evaluation of anti-S antibody levels showed no significant differences between PLWH and HD at all time-points, and the longitudinal evaluation revealed a significant increase at T3 compared to T0 in PLWH ($p<0.0001$). Collectively, concerning T-cell response, no statistically significant differences were found in the percentages of *responding* T-cells comparing PLWH to HD at all time points. At T0, stratifying PLWH, lower percentages of responding T-cells in PLWH with <200 cells/µl compared to those with >200 cells/µl were observed (CD4: $p=0.0331$; CD8: $p=0.0055$), as well as compared to HD (CD4: $p=0.0295$; CD8: $p=0.0056$). At T1, the percentages of responding T-cells in PLWH with <200 cells/µl comparable to those with >200 cells/µl as well as to HD, and the same result was found at T2. However, in PLWH, the pattern of co-expression of IFNγ, IL2 and TNFα was characterized, independently of CD4 T-cell count, by a higher expression of TNFα as well as a lower percentage of *triple-positive* T-cells, indicating a persistent immunological signature despite successful ART.

Discussion: In ART-treated PLWH, the third dose increased the rate and the magnitude of the response. However, the cellular one seems to be qualitatively different compared to HD. Therefore, a fundamental understanding of the dynamics of T-cell quality is still needed in order to determine the best vaccination strategy for COVID-19 and in general the capability of immune response in ART-treated PLWH.

PROFESSIONAL RESPONSABILITY PROFILES FOLLOWING COVID-19 PANDEMIC

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Background: Health is a right constitutionally guaranteed by Italian Constitution in Article 32, where to health is raised a fundamental right due to the importance and essentiality that this legal good has for the individual, whether it is considered as single or as part of a community. The state, in fact, has an obligation to protect this right considered as a "perfect subjective right": COVID-19 Pandemic breakdown opens up new medical and legal scenarios in professional liability. Among the dramatic aspects that were highlighted during the pandemic there was also the fear that this emergency could turn into a real accusation against health personnel, already put to the test by the unpredictable extent of this phenomenon. There is no doubt that the COVID-19 pandemic represents a health emergency, difficult to solve and understand. For these reasons, in our country, during the initial phase of the emergency, we discussed about some possible changes to be made to the regulations on medical liability in order to guarantee them to operate with greater serenity in an already critical period. In the criminal field it should be noted that with the L. 76/2021 excludes the punishment of health professionals in cases of: "Criminal liability for administration of the anti-SARS-CoV-2 vaccine" and the non-punishable clause, the so-called "Criminal shield", of health workers in cases of negligent liability.

Methods: An analysis of the evolution of professional health responsibility will be carried out, through the study of the claims of the Policlinico Umberto I.

Results: The trend of complaints is still low, but most of the COVID-19 related clinical cases concern fragile subjects with multiple morbidities

Discussion: The goal aims to standardize a working methodology capable of implementing risk management clinical in reference to the pandemic emergency and, at the same time, aims to analyze the evolution and revolution that COVID-19 will bring in the legal field, to evaluate the effects of pandemic on the over-growing phenomenon of medico-legal litigation.

Session II

PhD Candidates' Communications

Chairpersons

Gianluca Russo, Ilaria Bellini, Martina Micocci, Francesca Brunetti

STUDY CASE OF *PH. PERFILIEWI* (PARROT, 1930) VECTOR POPULATION IN PHLEBOTOMINE-BORNE DISEASES ENDEMIC AREA OF TUSCANY REGION

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Background: Phlebotominae sand flies are small insects worldwide distributed, only female shows hematophagous habits. Due to their broad host range of vertebrate and invertebrate blood sources they may transmit parasites and bacteria belonging to *Leishmania*, *Bartonella* genus respectively and Phleboviruses. In Italy main vector specie is *Phlebotomus perniciosus* present in eighteen regions, followed by *Ph. perfiliewi* especially present along Appenines Adriatic slopes, showing an increasing population density in recent years. Deeping knowledge concerning their biology and ecology is a cornerstone for establishing control measures to prevent phlebotomine-borne diseases and upgrade epidemiological framework. Current monitoring systems are sticky papers and CDC light traps that require cool chain for specimen preservation and pathogen detection, in particular for Phleboviruses. In this contest this work compares a new generation trap (BG-PRO) with standard one (CDC) to collect alive specimens for molecular screening and vector competence studies.

Methods: Samplings were performed from August to October 2022 in Magliano in Toscana (GR). Tests follow Latin squared design: turning traps in two different sites distant ±12m every night. Part of collected *Ph. perfiliewi* specimens was used for *L. infantum* and *Toscana* virus detections by molecular analysis, others for experimental infection with *L. tropica*.

Results: Preliminary results showed a total of 558165 sand flies from 18 replicates. Estimation of data (based on standard volume) shows that BG-PRO is more performing (*n. BG-PRO*=523280; *n. CDC*=34885), with higher survival rate (*n. alive: BG.PRO*=8302; *CDC*=7418) in particular during high density period, but both methods are comparable during low density period. Preliminary *L. infantum* detection indicates a total of 7/91 positive pools (*n*=40±10 females) with average prevalence value of 10% every hundred females. No positive pools were found for *Toscana* virus out of 43 analysed (*n*=30). Results about experimental infections, conducted to determine a transmissible-infection status from T0 to T11, reveal an overall prevalence of 30,6% (*n*=113; *mean*=17.4, *min*=1, *max*=19, *SD*=29.4) with a peak of positivity around one week after feeding and the presence of metacyclic promastigotes in stomodeal valve (between T6 and T8).

Discussion: This encouraging results indicate that BG-PRO seems to be more suitable to collect high density species like *Ph. perfiliewi* during its activity peak and to keep them alive avoiding cool chain for pathogen detections. Additionally, natural infections detection confirm this species as involved in *L. infantum* transmission, and preliminary experimental infections seem to prove *Ph. perfiliewi* as competent vector for *L. tropica*.

Although more analysis is necessary, this study suggests the importance to implement sand flies monitoring systems and to highlight the possibility of non-endemic diseases introduction in Italian context.

THE ROLE OF MICROBIAL TRANSLOCATION IN PATIENTS WITH KPC-PRODUCING *KLEBSIELLA PNEUMONIAE* RECTAL COLONIZATION, AS A RISK FACTOR FOR SUBSEQUENT KPC-KP BLOODSTREAM INFECTIONS

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Background: KPC-producing *Klebsiella pneumoniae* (KPC-Kp) rectal colonization is expression of an altered microbiota caused mainly by previous antimicrobial therapies, inducing detrimental effect on the homeostasis of gut flora. Colonization by KPC-Kp is considered a prerequisite for subsequent infections, especially Bloodstream Infections (BSI).

Methods: We conducted a retrospective observational single-center study of adult patients admitted to the Neurosurgical Intensive Care Unit (NS-ICU) of the AO Policlinico Umberto 1, Sapienza University of Rome: all patients with rectal colonization by Kp-KPC from January 2019 to February 2023 were included.

Results: Of 802 patients admitted to the NS-ICU during the aforementioned period, 129 patients had rectal colonization by Kp-KPC. The incidence of colonization in the total sample was 16.1% and, in most cases (64.4%), Kp-KPC rectal colonization occurred within 14 days after ICU admission. 46/129 colonized patients developed BSI (35.67%). After dividing the population into two groups, group BSI+ (46/129) and group BSI- (83/129), we assessed risk factors for the development of BSI: young age (p=0.020), higher Giannella Risk Score (GRS) (p<0.0001), previous opioid use (p=0.005) and having at least one other site of colonization by Kp-KPC (p<0.0001) have been proven risk factors for BSI. As expected, the presence of BSI correlates with increased length of stay overall (p<0.0001) and in the ICU (p<0.0001). No statistically significant differences were observed about comorbidities, cause of ICU admission, immunosuppressive therapies, and mortality. Multivariate analysis reveals that GRS is independently associated with the occurrence of BSI, whereas the role of opioids, a new finding as a risk factor in this population, appears to have statistical significance only in univariate analysis.

Discussion: Critical NS-ICU patients may have peculiar risk factors for developing BSI, such as opioid use, this could explain the higher incidence of BSI in our subgroup compared with other studies. Our suspicion is that in patients colonized by Kp-KPC there is an intestinal translocation favored by external factors, such as the use of opioids, thus explaining the increased incidence of BSI in our study. The next step of our working group is to analyze the degree of microbial translocation, intestinal damage, and alteration of the gut microbiome in this population by serum markers, to investigate how such markers may predict the development of BSI.

DEVELOPMENT OF MOLECULAR ASSAYS ON *PLASMODIUM FALCIPARUM* GAMETOCYTES FOR FUNCTIONAL ANALYSIS AND NOVEL DIAGNOSTICS ON MALARIA PARASITE TRANSMISSION

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Background: *P. falciparum* transmission from humans to mosquitoes require the sexually dimorphic parasite gametocytes in peripheral blood as both sexes are needed for fertilisation and parasite development in the female *Anopheles* mosquito. An assay was developed here to measure gametocyte sex ratio to assess sex specific effect of compounds on gametocytes *in vitro* and *ex vivo* from natural infections. Comparison of assay results with those of mosquito experimental infections aims to evaluate if measuring sex ratio can predict parasite infectiousness to mosquito.

Methods A multiplex Real time PCR assay with the *pfCCp4* and *pfs25* female- and the *pfMGET* male-specific mRNAs was used to quantify male and female gametocytes in two wild type and one transgenic *P. falciparum* lines and results were compared with sex ratio values from immunofluorescence assays with sex-specific markers. Synthetic RNAs for the above genes were also produced and used with RNAs from serially diluted gametocytes to calculate copy number/gametocyte of these transcripts. The assay was then used on compound treated gametocytes and the data analyzed by the ΔΔCt method.

Results: Copy number/gametocyte of *pfMGET*, *pfCCp4* and *pfs25* differed between the three laboratory lines. A linear relation was determined between the Real time Ct values and the IFA-based sex ratios only in the wild type parasite lines but not in the transgenic line. Real time assays on the compound treated *ex vivo* gametocytes failed to reveal alterations in transcript levels after the 24h treatment (the only time point of the analysis), also for treatments that reduced infectiousness to mosquitoes. Parallel experiments on *in vitro* gametocytes showed that the assay can reveal drops in gene expression and sex ratio alterations only after 48 and 72h treatments.

Discussion: The observed linear relation between Ct values of sex specific transcripts and number of male and female gametocytes in wild type *P. falciparum* laboratory lines is encouraging towards establishing a molecular assay for gametocyte sex ratios in natural infections, although the observed variable copy number of sex-specific transcripts needs to be addressed. Results of the Real time ΔΔCT method on the *ex vivo* and *in vitro* compound treated gametocytes showed that a 24h treatment is insufficient to lead to a measurable drop in transcript level, even when this successfully reduces gametocyte infectiousness. Nevertheless this work intriguingly suggested an unsuspected preferential susceptibility of female gametocytes to compounds reducing parasite infectiousness to mosquitoes.

NEW ANTIBACTERIAL STRATEGY USING PLASMIDS CARRYING THE CRISPR-CAS9 SYSTEM

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Background: Antibiotic resistance is a global emergency and severely limits the success of antibiotic treatments. Mobilised plasmids carrying the CRISPR-Cas9 system can be designed to induce antibacterial activity in targeted bacterial strains with the gRNA sequence determining specific targeting. The plasmids exploit the bacterial conjugation system encoded by plasmid F in order to be efficiently transferred into strains of *E.coli*, *Salmonella* spp and *Campylobacter* spp.

Methods: The F-Cas9-nsp plasmid was modified with a new spacer by annealing 2 oligonucleotides with complementary sequences at the non-cohesive ends generated by the Sap I restriction. Ligation production between the new spacer fragment and the plasmid backbone was transformed into *Escherichia coli* DH5α strains by thermal shock. The constructs were verified by PCR reaction. Conjugation assays were done with liquid and filter culture and conjugation mixes were vortexed, diluted and spotted on LB agar supplemented with antibiotics to select recipient and transconjugant cells.

Results: The F-Cas9-nsp plasmid was introduced to the LacZ2 gene as a gRNA sequence. The conjugation between the *E. coli* strain F+/TAP-Kn-Cas9-mLacZ2 and an *E. coli* strain containing the LacZ2 gene in its chromosomal make-up showed a conjugation efficiency of 77% and a significant decrease in cell viability of approximately 4 log. The transfer efficiency of the F-Cas9-nsp plasmid, which does not target any specific sequence of the recipient species, using an *E.coli* donor and a *Salmonella infantis* strain was 2% with conjugation in liquid culture and 0.5% with filter mating. No plasmid transfer to *Campylobacter jejuni* and *Campylobacter coli* species was detected under filter mating conditions.

Discussion: In this study, we demonstrate the ability of the plasmids antibacterial strategy to exert efficient, strain-specific antibacterial activity. The TAP design benefits from being versatile and easy to design. Future research will be needed to develop customised plasmids composed of different gRNAs to enable targeted killing of bacteria even within a multispecies population. Furthermore, the future aim will also be to target genes involved in antibiotic resistance in order to achieve antibiotic resensitisation.

CONSERVATIVE OXYGEN SUPPLEMENTATION DURING HELMET CONTINUOUS POSITIVE AIRWAY PRESSURE THERAPY IN PATIENTS WITH COVID-19 AND RESPIRATORY FAILURE: A PILOT STUDY

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Background: Respiratory failure is a severe complication in coronavirus disease 2019 (COVID-19) pneumonia that, in addition to oxygen therapy, may require Continuous Positive Airway Pressure (CPAP) support. It has been postulated that COVID-19 lung injury may share some features with those observed in hyperoxic acute lung injury. Thus, a correct target arterial oxygen tension (PaO_2) during oxygen supplementation may be crucial to protect the lung from further tissue damage. The aims of this study were: 1) to evaluate the effects of conservative oxygen supplementation during helmet CPAP therapy on mortality and Intensive Care Unit (ICU) admission in patients with COVID-19 and respiratory failure, and 2) to evaluate the effect of conservative oxygen supplementation on new-onset organ failure and secondary pulmonary infections.

Methods: This was a single-centre, historically controlled study of patients with severe respiratory failure due to COVID-19 pneumonia, receiving either conservative or nonconservative oxygen supplementation during helmet CPAP. A cohort receiving conservative oxygen supplementation was studied prospectively in which oxygen supplementation was administered with a target PaO_2 <100 mmHg. Results of this cohort were compared with those of a cohort who had received liberal oxygen supplementation.

Results: 71 patients were included in the conservative cohort and 75 in the nonconservative cohort. Mortality rate was lower in the conservative cohort (22.5% *vs* 62.7%; p<0.001). Rates of ICU admission and new-onset organ failure were lower in the conservative cohort (14.1% *vs* 37.3%; p=0.001 and 9.9% *vs* 45.3%; p<0.001, respectively).

Discussion: In patients with COVID-19 and severe respiratory failure, conservative oxygen supplementation during helmet CPAP was associated with improved survival, lower ICU admission rate and less new-onset organ failure.

BEYOND VIROLOGIC CONTROL: DIFFERENT IMMUNOLOGICAL PROPERTIES OF NEW GENERATION ANTIRETROVIRALS. REAL-LIFE DATA FROM CLINICAL COHORTS OF PLWH

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Background: Even under virologic control with ongoing Antiretroviral Therapy (ART), People Living With HIV (PLWH) show chronic immune activation, hyper-inflammation and altered metabolism. The resulting over-inflamed status has been associated to the development of HIV-related non-AIDS-defining comorbidities, such as obesity, insulin resistance and type 2 diabetes, osteoporosis, chronic kidney disease, cardiovascular disease, neuropsychiatric and/or neurocognitive disorders. These comorbidities design a frailer and more aged phenotype which resemble to the one observed with aging in the general population. In this context, we aimed to assess whether and at which extent new generation ARTs impact on immune activation and chronic inflammation focusing on PLWH older than 55.

Methods: We designed two real-life prospective observational clinical cohorts enrolling PLWH after a therapeutic switch from their current ART to a regimen based on a new-generation molecule as anchor drug, namely bictegravir, an integrase strand transfer inhibitor (BICTEL cohort) or doravirine, a non-nucleoside reverse transcriptase inhibitor (DORAGE cohort). Virologic efficacy was the primary outcome; metabolic, immune and inflammatory profiles were the secondary outcomes.

Results: The per protocol analysis (treating missing as excluded) showed a virologic suppression rate of 95.2% (118/124; CIs: 89.8%-98.2%) in the BICTEL-cohort at week96 and 96.3% (129/134; CIs: 91.5%-98.9%) in the DORAGE-cohort at week48 from baseline. In the BICTEL-cohort, a significant increase ($p<.001$) in $CD4^+$ and $CD4^+/CD8^+$ ratio as compared to baseline was observed at both week 48 and week 96, with a median increase in $CD4^+$ cell count by 136 cells/µl. CD4+/CD8+ ratio showed a progressive increase over time (week48 *vs* week96, p .014). Such immune reconstitution showed to be associated to BL immune status in univariate and multivariate linear regression modelling. No significant changes were observed over time. In the DORAGE-cohort, at week 48 from the switch, we recorded a significant decrease in serum fasting glucose (p .019), triglycerides (p. 0.024); not clinically significant differences were detected for the immune (CD4, CD8, CD4/CD8 ratio) and the metabolic (cholesterol, body weight and BMI, hepatic and renal) profiles. Interestingly, a subgroup of about 90 PLWH showed significant reduction in IL-6 (p .019) and PCR (p .019).

Discussion: Both BIC- and DOR-based ART regimens are effective, safe and well tolerated choices for all PLWH, including those older than 55. Differential effects on immune activation and chronic inflammation seem to be associated to specific molecules. Further studies are needed to improve tailored therapeutical approaches to aging PLWH.

INTERPLAY BETWEEN UROPATHOGENIC *ESCHERICHIA COLI* AND BLADDER CELLS AND NEW STRATEGIES TO COUNTERACT BACTERIAL PERSISTENCE

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Background: Urinary Tract Infections (UTIs) are the most frequent community and hospital-acquired infections. Uropathogenic *Escherichia coli* (UPEC) is the major causative agent of UTIs. The high level of same strain recurrences, in which a single bacterial strain causes two or more consecutive UTIs, strongly suggests a reservoir within host. UPEC strains can invade epithelial cells of the urinary tract. Inside the cells, UPEC can replicate to form Intracellular Bacterial Communities (IBCs), aggregates of bacteria with biofilm-like properties, and may persist acting as Quiescent Intracellular bacterial Reservoirs (QIRs). The formation of these structures represents a key event in the development of relapses and is associate with the failure of conventional antibiotic therapies. Nanotechnology has been presented as a promising approach to enhance the activity of antimicrobial agents and to treat intracellular infections. To explore new strategies to induce the bacterial clearance, the study aims to characterize UPEC strains, and evaluate the activity of delivery systems to enhance the effectiveness of available antibiotics.

Methods: Uropathogenic *E. coli* collected from patients suffering from recurrent UTIs and reference strains were used. The whole genome was performed on Illumina platform. Profiles relative to resistance genes, virulence factors, and multilocus sequence typing were determined by querying genomes against dedicated databases. The isolates were phenotypically characterized and assayed to adhere, invade, and persist in bladder cells (T-24 ATCC HTB-4) by gentamicin protection assay. ROS accumulation was detected by 2′,7′-dichlorodihydrofluorescein diacetate (H2DCF). Nanocarriers (NCs), as niosomes and nanoemulsions, loaded with antibiotics, were characterized in term of stability and drug entrapment efficiency. To evaluate potential antiinvasive activity, non-cytotoxic and non-bactericidal concentrations of NCs were added during the UPEC infection in the bladder.

Results: Genotypic characterization of strains evidenced the presence of genes involved in the resistance to a wide spectrum of antimicrobial agents, as well as heterogenous virulence factor profiles. UPEC strains were moderate or strong biofilm producer, non-haemolytic and resistant to heat and acid pH. UPEC strains were able to efficiently adhere, invade and survive in T-24 cell monolayers up to 48/72 hours. UPEC infection promoted the production of ROS in bladder cells. NCs showed nanometric dimensions and a good stability profile and when loaded with antibiotics, significantly inhibited bacteria viability. Antibiotic delivered by NCs decreased UPEC invasion into bladder cells.

Discussion: In conclusion, UPEC infection of bladder cells is likely a complex process and the decrease in invasion rates observed with the use of NCs, leads us to suppose that these delivery systems, by enhancing the release of the antibiotic inside the cell, could represent a very promising tool.

EXPLORING APPLICATIONS AND IDENTIFYING GAPS IN THE IMPLEMENTATION OF THE ONE HEALTH APPROACH FOR ZOONOTIC DISEASE PREVENTION AND PREPAREDNESS STRATEGIES

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Background: The One Health (OH) approach represents a comprehensive paradigm for global health security, recognizing the interconnectedness of humans, animals, and the ecosystem. It emphasizes interdisciplinary collaboration, international cooperation, and integrated disease control and emergence strategies. Within the MediLabSecure Network, OH strategies have been implemented to enhance surveillance and control of arbovirus infections. This thesis investigates the application of the OH approach in strategies aimed at preventing and preparing for zoonotic diseases.

Methods: The research methodology employed encompasses a scoping review, two rapid reviews (one focusing on identifying gaps in the OH approach and the other on Multi-Criteria Decision Analysis (MCDA)), a situational study conducted in Armenia, and spatial modeling of Crimean-Congo Hemorrhagic Fever (CCHF) across Europe.

Results: The study critically examines the practical implementation of the One Health approach within prevention and preparedness strategies for health threats. We identified existing gaps and requirements in current strategies, shedding light on the potential benefits that integration of the One Health approach can bring. We thoroughly analyzed the data sources utilized across various sectors and evaluated the methodologies employed in the development of risk maps for disease outbreak prevention. Furthermore, we assessed the level of integration among diverse sectors involved in preventing and preparing for health threats in Armenia. An integral part of our research entails generating risk maps that prioritize specific diseases, facilitating targeted prevention strategies. These risk maps effectively identify high-risk areas susceptible to the occurrence and spread of targeted zoonotic diseases, enabling the implementation of focused prevention efforts.

Discussion: This doctoral research significantly contributes to advancing the understanding and application of the One Health approach within the context of strategies for preventing and preparing for zoonotic diseases, with a particular emphasis on Armenia. The findings of this study aim to enhance knowledge and foster the effective implementation of the One Health approach in public health interventions, ultimately contributing to the improvement of global health security.

HERPES SIMPLEX VIRUS-1 INFECTION INDUCES COMPLEMENT PROTEIN UPREGULATION IN BRAIN CELLS: POSSIBLE ROLE IN SYNAPTIC DAMAGE

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Background: Several pieces of evidence suggest that recurrent Herpes Simplex Virus-1 (HSV-1) infection reaching the brain is one of the risk factors for Alzheimer's Disease (AD). However, the molecular mechanisms underlying this association have not been fully elucidated. Numerous studies suggest that abnormal upregulation of the complement cascade, a key component of the innate immune system, is involved in the pathogenesis of AD, also concurring to synaptic elimination in the brain. Hence, we investigated if HSV-1 triggers complement cascade activation in brain cells likely leading to synaptic loss.

Methods: Primary neuronal cultures were isolated from the brain of rat or mouse embryos (E18). For triple co-culture experiments, the murine microglial BV2 cell line was added to neuron/glial cocultures before HSV-1 infection (at different multiplicity of infection). Cells were analyzed for the expression of complement components, PSD95 and Synaptophysin (postsynaptic and presynaptic markers, respectively) at protein and mRNA levels with Western Blotting (WB) and RT-PCR. Immunofluorescence analyses (IF) were also carried out to detect specifically C1q and C3 expression. ELISA assay was performed to detect C3 in supernatants. Neutralization assay was performed infecting cells in the presence or absence of an anti-C3 antibody.

Results: We first checked for the effect of HSV-1 infection on the intracellular expression of C1q, C3 and C4, the initial activation components of the classical complement cascade in the primary neuron/glia cocultures. Real-time PCR and WB analyses of cell lysates revealed that HSV-1 infection caused a significant increase of C1q, C3, and C4 at both mRNA and protein levels. Consistently, IF analyses confirmed that HSV-1-infection upregulates intracellular C1q and C3 in HSV-1-infected neuronal cultures, whereas ELISA assay showed an increased amount of C3 in the supernatant of infected cells. We then infected cells in the presence or absence of an anti-C3 antibody to investigate the effect of complement activation on synapses, monitoring the expression levels of PSD95 and synaptophysin. WB analyses revealed that HSV-1 infection induces downregulation of PSD95 and Synaptophysin in not-treated cells, whereas a partial rescue was observed in neurons infected with the anti-C3 antibody. Superimposable results were obtained in HSV-1-infected triple culture of primary mouse neuron/glia and BV2.

Discussion: The HSV-1-induced PSD95 and Synaptophysin downregulation, indicates that the infection induces synaptic dysregulation. The partial rescue observed in cells infected in the presence of the anti-C3 antibody suggests that the HSV-1-induced complement

activation is involved in this process. Our data indicate that complement plays a role in the innate immune response to HSV-1 infection in cultured neuron/glial cells and suggest that it may be involved in the synaptic damage that occurs after infection.

GSTO-1 PRODUCTION DURING *T. GONDII* INFECTION IN RETINAL CELLS AS COMPARED TO RETINA EXPLANTS

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Background: Ocular Toxoplasmosis (OT) is caused by the parasite *Toxoplasma gondii* and it represents the most common cause of eye inflammation in the world. Histopathology information of active OT lesions in humans is difficult to gather, and the majority of data about the inflammatory response and the morphological changes is based on a murine model of congenital OT. With this study we present an *ex vivo* model that facilitates the observation and manipulation of the infected retina. After stabilization of the cultured retina, we have started to analyze the inflammatory response caused by the parasite in this tissue. The marker Glutathione S-Transferase Omega-1 (GSTO1) is the first marker to analyze both in an *ex-vivo* model as compared to an *in vitro* model with retinal cells.

Methods: Explants: Retinas dissected from 3- to 5-week-old C57BL/6J mice were cut into 4 fragments and transferred onto Millicell-CM culture inserts with ganglion cells up. Inserts were placed in 6-well tissue culture plates with 1 mL of culture medium, which was changed every other day. Cell culture: Mio-M1 cells are Muller glial cell lines derived from adult human retina. They are maintained in DMEM supplemented with 10% fetal bovine serum, 1% of D-glutamine and 1% Penicillin-Streptomycin. *T. gondii* (RH strain) were maintained in Vero cells. They were used at a concentration of 2,000/well to infect the retinal explants; and 5:1 ratio to infect cells. Control explants were cultured in an unmodified culture medium. For immunostaining, retinal fragments were fixed with 4% paraformaldehyde, embedded in cryo-gel, and cut into 10-µm-thick sections with a cryostat. For cultured cells they were fixed with 4% paraformaldehyde. The primary antibody was a polyclonal goat anti-*T. gondii* and the secondary antibody was conjugated with Alexa-Fluor-488. The sections were counterstained with DAPI. For Western Blot (WB), fragments were homogenized and processed following standard protocols. Primary antibodies were directed to GSTO-1. Densitometric analysis of the immunoreactive bands was performed using the software ImageLab and statistical evaluation with ANOVA.

Results: Immunofluorescent, putative *T. gondii* cysts were observed at 3D and 7D in the Inner Nuclear Layer (INL), Outer Plexiform Layer (OPL), and in the Photoreceptor Outer Segment (POS). Results from WB showed an increase in GSTO1 levels at 24h, decreasing at 3D and 7D. In cultured cells, GSTO1 was observed around cysts.

Discussion: These results suggest that there might be an initial GSTO1 production in retina and cultured cells as a result of cellular damage and stress during *T. gondii* infection.

POST TRAUMATIC STRESS DISORDER IN A COHORT OF COVID-19 SURVIVORS: THREE-YEAR FOLLOW-UP

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Background: Post-Traumatic Stress Disorder (PTSD) is a severe but treatable mental disorder that develops after a life-threating traumatic event. Coronavirus disease (COVID-19) hospitalization is a potentially traumatic experience, and due to the unprecedented social and cultural context, the life-threating perception of the disease may be amplified even in patients with moderate infection. The aim of our study was to assess the prevalence and risk factors of PTSD in a cohort of patients hospitalised for COVID-19 in the first way of pandemic (March-May 2020) during the observational period.

Methods: We conduct three years observational study at the Division of Infectious Diseases, Department of Public Health and Infectious Diseases, Sapienza University of Rome. Patients were contacted by telephone by trained raters at 3,6,12 and 36 months after hospital discharge and Post-Traumatic Stress Disorder Checklist for DSM-5 and Stress-Related Vulnerability Scale were administered. Multivariate logistic regression models and mixture model analysis were performed to study risk factors and longitudinal course of PTSD symptoms.

Results: To date, our observations are related to the first year of follow-up as we are still analyzing the results of three-year follow-up. For 109 patients who complete the 12 months follow-up, 1-year PTSD period prevalence was 23.9%, peaking at six months and then decrease over the time. 11% of the patients suffered chronic (>6 months) PTSD. Pre- and post-hospitalization factors influenced the onset and course of PTSD over time. These included working status, perception of threat to life and lack of social support. Obesity, pulmonary diseases, a previous psychiatric diagnosis and family cluster infection seem specifically related to PTSD following COVID-19. Inversely, clinical interventions, older age and male gender were protective. Preliminary observations of 36 months follow-up are showing a decreased prevalence of PTSD.

Discussion: In our cohort, one patient out of four has had a diagnosis of PTSD, and a half of them faced a chronic condition. The analysed demographic, social, clinical, and psychological factors predict PTSD symptomatology over time and can modify odds of a chronic course. Clinicians treating COVID-19 should be aware of PTSD risk to better direct screening and treatment efforts. Finally, treatment as usual appeared related to a better outcome and should be proposed to patients with COVID-19 related PTSD.

New Research Topics

ASSESSMENT OF INSECTICIDE RESISTANCE IN *AEDES SPP.* AND *CULEX SPP.* NUISANCE SPECIES AND VECTORS OF HUMAN AND ZOONOTIC DISEASES

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Background: Mosquito vectors are not only a relevant nuisance, but also important health pests causing great damage to human and animal health. With the indulging in the usage of pesticides to control insect vectors of human and zoonotic diseases, as well as agricultural pests, resistance to largely used insecticide molecules is developing and spreading in many species. The focus of this PhD thesis is to contribute to the knowledge on insecticide (pyrethroid and chemical larvicides) resistance in *Aedes spp.* and *Culex spp.* mosquitoes in Italy (and possibly beyond). Phenotypic resistance is studied by performing bioassays on live mosquitoes collected in the field (or on F1 progeny), requiring skills for mosquito manipulation and data analysis. The study of mechanisms underlying phenotypic resistance and the development, validation, and implementation of novel molecular tools for the easy genotyping of insecticide resistance alleles requires skills in molecular biology approaches and genomic analyses.

Objectives: 1) Characterization of target-site-resistance and metabolic resistance mechanisms and identification of known and novel non-synonymous variants associated with reduced susceptibility to pyrethroids and/or larvicides in *Aedes* and *Culex* species; 2) Development and validation of novel molecular tools for easy genotyping of insecticide resistance alleles; 3) Large scale screening of resistance alleles in mosquito field population from Italy and, if possible Iran and other European Countries.

Expected (or preliminary) results: During the first year of this PhD project, I acquired expertise with the morphological and molecular identification of *Aedes* and *Culex* mosquitoes and the molecular genotyping of alleles associated with pyrethroid resistance. In addition, I partially sequenced three domains of the voltage gated sodium channel gene in 121 *Aedes caspius* individuals collected in sympatry with *Aedes albopictus* and *Culex pipiens* specimens showing high levels of resistance to pyrethroids. Sequence analysis is in progress.

Future perspectives: The results obtained in the framework of this PhD project are expected to contribute to increase knowledge on insecticide resistance mechanisms in main nuisance and arbovirus vector species in Europe, to develop new biochemical and molecular approaches to detect insecticide resistance at the genomic level, and to produce evidence necessary for raising awareness on this topic in public health systems and for the development and implementation of resistance management strategies.

LUNG DEFENCE DURING MIXED INFECTIONS AND MODULATOR THERAPIES IN CYSTIC FIBROSIS: DECIPHERING THE KEY ROLE OF HOST INNATE IMMUNITY

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Background: Respiratory infections are the major responsible for morbidity and mortality in Cystic Fibrosis (CF) patients. While the consequences of infection by the most common bacteria such as Pseudomonas aeruginosa and Staphylococcus aureus are best known, a wide range of emerging pathogens in CF have been identified. In addition, evidence is building that fungal pathogens may be playing an important role in lung disease progression. The protracted infections in CF patients and the continuous activation of the innate immunity defenses are combined in an intricate and non-resolving cycle leading to severe host tissue damage. In this scenario, the recent introduction of modulator therapy, whose administration is now approved for nearly 90% of the adult CF population, has completely changed the treatment paradigm towards the correction of the dysfunctional CFTR. While *in vitro* data have shown antimicrobial activities for some CFTR modulators, the real outcome on respiratory bacterial infection and inflammation in CF remains unclear

Objectives: As part of innate immunity, enhanced Interferon (IFN) response can play a critical role in CF disease exerting opposing effects, orchestrating antimicrobial and antiviral response or exhibiting detrimental effects for the host when hyper-stimulated. We will assess multiple cytokines but also IFN pathways expression stratifying for bacterial/Aspergillus infections and patient clinical data. In addition, we will evaluate if modulators are capable of regulating the specific inflammatory profiles and innate immune responses associated with the persistence of CF pathogens.

Expected (or preliminary) results: Pandoraea is an emerging pathogen that can chronically colonized CF patients and alter IFN response likely contributing to immunopathogenesis and disease progression. Heterogeneity in the IFN pathways activation status was recorded in Aspergillus positive CF patients depending on the microbiological and clinical stage, encouraging us to decipher its clinical relevance in CF. In CF adults treated for 3 months with Kaftrio the transcript levels of IFNβ, IL-1β and IL-8 were strongly reduced.

Future perspectives: Dissection of the innate immune axis associated with the microbial setting and persistence of CF pathogens is essential to better define strategies for counteracting tissue destruction and lung disease progression A deeper knowledge of molecular mechanisms of modulators and correlations between airway microbiota and inflammatory parameters could promote an optimal use of these new therapies.

PROFILES OF BIOETHICS AND COMPARATIVE DEONTOLOGY: A COMPARISON BETWEEN ITALY AND THE UNITED KINGDOM ON THE SUBJECT OF MEDICALLY ASSISTED VOLUNTARY DEATH, USAGE OF BODIES DONATED TO SCIENCE ALSO FOR EXPERIMENTATION, TREATMENT AND SUPPORT FOR WOMEN VICTIMS OF VIOLENCE AND THEIR PROGRESSION OVER THE YEARS

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Background: The Forensic Medicine Section at 'Sapienza' University of Rome has always been devoted to the thorough study of various bioethical and deontological matters which many of whom appear to have reached a critical point in our country, where they require legislator intervention to define precisely the subjects necessitating protection. The reference is mainly, but not limited to, Law No. 219/2017, especially in light of the indications set out in the Constitutional Court ruling 242/2019 regarding assisted suicide. Modern medicine always offers new possibilities to support organ failure and allows the maintenance of vital functions in critical, and sometimes irreversible, clinical conditions, which were incompatible with life until a few years ago. The 'end of life' topic has become increasingly relevant in current medical practice. The point of the discussion focuses on medically assisted voluntary death in the context in which both assisted suicide and active euthanasia can be included. In the field of advance care planning, the post-mortem donation of one's own body is of particular scientific importance, as recently envisaged by the New Law February 10, 2020, no. 10, which, however, needs to be completed by means of an implementing decree. This law has the aim of filling this legislative gap, regulating the various problems underlying the donation of bodies for the purposes in examination, starting from the modalities of providing consent in life, responding to the urgent need to make human bodies available for the purpose of empowerment significantly medical-surgical training and increase scientific progress. One third of the world's women suffer from gender-based violence. The abuse is most commonly inflicted by an intimate partner. It is a social disease, making a government's intervention indispensable.

Objectives: The main objective of this study is to analyse and precisely identify the differences between current legislation (including the deontological legislation) in Italy and in the United Kingdom regarding the medical approach to the delicate issues of medically assisted voluntary death; the practical use of bodies donated to science also for the purpose of experimentation; and the overall treatment and support for women victims of violence.

Expected (or preliminary) results: Upon completion, this study would provide new evidence about how to provide the best tutelage of constitutionally guaranteed rights, guarantee the health of fragile members of society, and support and aid in the difficult choices that the medical profession imposes.

SOCIAL DETERMINANTS IN DEPRESSION, ANXIETY, STRESS, RESILIENCE, JOB SATISFACTION, AND QUALITY OF LIFE AMONG ADULTS AND YOUNG PEOPLE IN CALI, COLOMBIA

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Background: Social determinants of health have been associated with direct effects on health from a causal perspective. However, the causes of these causes are less evident. For example, in the poverty-health link, it is evident that poverty is the cause of many communicable and non-communicable diseases. However, it is less clear how this link between poverty and disease is broken. Therefore, there is a dynamic aspect of social justice that goes beyond determinism and involves changing the measure from absolute to relative, especially in the social gradient. This phenomenon indicates that socioeconomic position has direct health outcomes: better socioeconomic position leads to better health. However, within and between countries, the outcome is relative. Understanding to what extent an individual suffers or is at risk of experiencing the accumulation of cultural, social, environmental, and economic factors that impact health in the short or long term is necessary to reduce the singular disparities within the complex interplay of health and society. The eco-social perspective and social epidemiology allow for a multi-causal and active approach to the individual. Individual and family factors include: biological and physiological aspects, psychological stress, healthy behaviors, social support, and disparities in access to healthcare. Community factors include: housing stability, neighborhood adversity, safe environment, and food insecurity. Social and cultural factors include: discriminatory practices, economic instability, employment and educational opportunities. Resilience is an active characteristic of the individual that modulates the effect of adverse conditions.

Objectives: To assess the relationship between social determinants and depression, anxiety, stress, resilience, job satisfaction, and quality of life in adults and young people in Cali, Colombia. To describe the status of social determinants, depression, anxiety, stress, resilience, job satisfaction, and quality of life in adults and young people in Cali, Colombia.

Expected (or preliminary) results: To describe the prevalence of anxiety, depression, and stress in the adult and young population in Cali, Colombia. To identify the social determinants that impact mental health (depression, anxiety, stress), quality of life, job satisfaction in adults and young people. To establish the role of resilience in the relationship between social determinants and job satisfaction, quality of life, depression, anxiety, and stress in adults and young people. The individual and family factors are related to variations in depression, anxiety, stress, quality of life, and job satisfaction scores among adults and young people.

Future perspectives: Social gradients allow for the focus of public policies and primary care actions on adults and young people in the city of Cali, Colombia, as well as contributing to the understanding of the multidimensional relationship between the individual and society.

MULTI-OMICS CHARACTERIZATION OF THE ORAL MICROBIOTA AND ITS ROLE IN DENTAL CARIES AND PERIODONTAL DISEASE

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Background: Dental Caries (DC) and Periodontal Disease (PD) are the two most common oral diseases worldwide, whose development is known to be associated with microbiota imbalance, defined as dysbiosis. DC is a multifactorial disease, influenced especially by the host diet. This condition is characterized by the production of acidic by-products by endogenous bacteria, such as *Streptococcus mutans* and *Lactobacilli spp*, causing a drop in pH that contributes to the demineralisation of tooth tissues. PD is a chronic inflammatory and progressive disease that affects the tooth-supporting tissues, named periodontium. The disease is characterized by expansion of the microbial biofilm at the gingival margin, where keystones bacteria can orchestrate inflammatory disease and lead the microbiota to dysbiosis. Among the gram-negative proteolytic anaerobic species associated with PD, the major pathogens are *Porphyromonas gingivalis, Treponema denticola* and *Tannerella forsythia*. The association between the two oral diseases and bacterial species is well understood to date, but little is known regarding functional roles of bacteria. Furthermore, previous studies attempted to investigate the linkage between DC and PD, but only few and contradictory information are available so far. Thus, further studies are of crucial importance in order to unravel whether there exists an association between DC and PD.

Objectives: The main objective of this project is to test the existence of association between dental caries and periodontitis, performing a multi-omic analysis (metagenomics and metabolomics) of the oral microbiota and of the salivary metabolites in patients affected either by one or both of the diseases.

Expected (or preliminary) results: Results obtained from the metagenomic analysis are expected to shed light on the structure and on the functional potential of the oral microbiota in the context of dental caries and/or periodontitis. Furthermore, the relationship between microbial communities and salivary metabolites will be elucidated, integrating the metagenomic results with the metabolomic analysis.

Future perspectives: Increasing our knowledge on the communication mechanisms within microbial communities that link dental caries and periodontitis could have a considerable impact on the development of preventive, diagnostic and therapeutic strategies for both of the oral diseases.

THE IMPACT OF SEXUAL ORIENTATION AND HIV-1 INFECTION ON THE COMPOSITION OF THE INTESTINAL MICROBIOTA IN HIV-1 SERODIFFERENT COUPLES

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Background: According to WHO, up to 50% of People Living With HIV (PLWH) in ongoing relationships globally have HIV-negative partners: the so-called serodifferent couples. HIV infection is known to be characterized by the apoptosis of enterocytes and the increase in intestinal permeability, and the main consequence of the structural subversion of the enteric mucosal barrier is the microbial translocation. The alteration of the intestinal mucosa in HIV infection also causes dysbiosis, that contributes to the maintenance of a state of chronic inflammation and immune senescence. Furthermore, a person's sexual behavior can also affect its gut microbiome. Considering the influence of sexual behaviour and HIV infection on the composition of the intestinal microbiota, HIV serodifferent couples could be useful to understand the link between gut microbiota and systemic immune activation.

Objectives: We enrolled 22 serodifferent couples (9 heterosexual and 13 eterosexual). Control groups are characterized by 9 PLWH seroconcordant couples (5 homosexual and 4 eterosexual) and 8 seroconcordant HIV- seroconcordant couples (3 homosexual and 3 eterosexual). All subjects included in this study are in a stable relationship with their respective partners. All study participants were undergone: i) enrollment visit to collect data regarding the clinical history of PLWH. All individuals have completed a food questionnaire and one relating to their sexual habits; ii) blood sampling; iii) fecal sampling. On blood samples we will evaluate the state of activation and senescence of CD4+ and CD8+ lymphocyte subpopulations by flow cytometry, the expression of several genes (IFNs, ISGs, TLRs) by RealTime PCR; the inflammation status (IL-6) and the enterocytes damage markers (I-FABP, sCD14, Zonulin) will be evaluated by ELISA. Moreover, we will perform the analysis of the intestinal microbiota composition on fecal samples by NGS and we will evaluate the metabolome profile by NMR analysis.

Expected (or preliminary) results: The following outputs are expected: i) Characterization of the impact of sexual orientation and HIV infection on the composition of the gut microbiota; ii) Understanding the factor that contributes to intestinal dysbiosis and how it can affect metabolomics systemically; iii) Identification of predictive biomarkers of systemic inflammation and activation of T cells.

Future perspectives: All these results will allow us to set up strategies aimed at identifying specific therapeutic targets on intestinal dysbiosis.

VIRUS-HOST INTERPLAY IN SARS-CoV-2 INFECTION: INSIGHTS INTO INNATE IMMUNE RESPONSES INDUCED BY VARIANTS OF CONCERN IN HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS

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Background: COVID-19 is an infectious disease caused by SARS-CoV-2, which disease severity varies from asymptomatic to severe and life threatening. Virus-host interplay influences the outcome of the disease and favors the emergences of new Variants Of Concern (VOC). SARS-CoV-2 pathogenicity relies on the ability to hamper IFN pathway and to stimulate the production of pro-inflammatory cytokines shifting the balance towards a pro-inflammatory status.

Objectives: We aim at determining whether SARS-CoV-2 evolution has improved its ability to counteract the innate immune response, by investigating the interaction of SARS-CoV-2 VOC with immune cells in an *in vitro* non-permissive PBMC-based experimental model. Thus, we compared cytokines, chemokines and IFN expression following the stimulation with the following VOC at a multiplicity of infection of 0.04: Codogno (D614G), Alpha, Beta, Gamma, Delta and Omicron BA.1.

Expected (or preliminary) results: Data obtained in this first year suggested the existence of a VOC specific response. D614G, Alpha and Omicron showed the strongest ability to induce IFN production by PBMC. In particular, while Omicron BA.1 induced type I IFN signature similarly to D614G, Alpha was the SARS-CoV-2 strain with the highest stimulatory capacity in terms of IFN production and IFN-induced gene expression. A similar trend was also observed for the pro-inflammatory cytokine profile**.**

Future perspectives: Our studies suggested some differences between VOC-induced innate response. In the future, to define the specific contribution of the immune cells to the above observed response, we will study the innate immune transcriptome through single cell analysis in monocytes, macrophages, myeloid and plasmacytoid cells and NK cells stimulated with Omicron BA.1. In addition, we aim to explore the presence of a VOC specific modulation on the oxidative cellular landscape by studying Nrf2-mediated anti-oxidant response and redox sensitive intracellular pathways involved in immune regulation.

VACCEVA: ANALYSIS OF VACCINE HESITANCY AND HEALTH STATUS - A STUDY IN "VULNERABLE" PATIENTS

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Background: A wealth of evidence highlights the benefits of vaccination for the general population, Healthcare Professionals (HCPs), and categories of patients. Despite this, the population has a considerable percentage of vaccine hesitancy. The main reason behind this condition is the belief that vaccines are unsafe and, more specifically, that they can cause severe diseases and side effects, that their long-term effects are unknown, that the risks outweigh the benefits and that they contain dangerous adjuvants.

Objectives: The primary objective of the study is to analyze the level of vaccine hesitancy in an outpatients sample of the "Azienda Ospedaliero-Universitaria Policlinico Umberto I", identified as vulnerable patients (patients suffering from diabetes mellitus, CVDs after risk assessment, COPD and bronchial asthma, patients with congenital/acquired immunodeficiency or under immunosuppressive therapy, subjects with chronic renal insufficiency and on dialysis, subjects with recurrences or severe Herpes Zoster subtypes). The secondary objective is to analyze patients' general health and quality of life and to collect them to evaluate possible associations with the level of vaccine hesitancy and adherence to cancer screening campaigns.

Expected (or preliminary) results: The level of vaccine hesitancy will be assessed in a sample of 500 patients also to identify the main predictors. In addition to this, the study will bring us further information on patients' mental and physical health status and their adherence to the screening campaigns. The analysis will lay the foundations for adapting vaccination and information campaigns and screening programs and could improve healthcare professionals' training and enhance their communication strategies respecting Hospitals' outpatients.

Future perspectives: As evidenced by SARS-CoV-2 vaccine campaign, Hospital Vaccine Centers have been very supportive of the community-based centers in patient care especially with patients already followed by hospital-based specialist centers and it came to light how the hospital represents a fundamental guide to prevent infectious and noninfectious diseases, enabling integrated care especially toward certain at-risk patients' categories. Therefore, we should focus on the relationship between outpatients and health care providers since they appear essential for proper counseling, for increasing patients' Vaccine Confidence and consequently decreasing doubts and fears related to the adverse vaccination's effects.

RAPID PCR-BASED TEST FOR CORRECT MULTI LOCUS SEQUENCE TYPING ASSIGNMENT OF PATHOGENS INVOLVED IN HEALTHCARE ASSOCIATED INFECTION

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Background: The molecular epidemiology of microorganisms responsible for Health care-Associated Infections (HAIs) is becoming increasingly important because of the growing number of HAIs caused by antibiotic-resistant bacteria. Numerous typing methods have been developed for the major opportunistic pathogens. One method that has been particularly successful over time is Multi Locus Sequence Typing (MLST), which on the basis of allelic variants allows the microorganisms under examination to be divided into Sequence Types (STs). However, this method is slowed down by the need to sequence the genes that determine STs.

Objectives: The goal of the project is to develop a PCR-based test that is a valid screening for the identification of main STs. I started with the opportunistic pathogen *Klebsiella pneumoniae*, for which there are suitable genes in the bibliography for the type of screening I intend to perform. In addition, I started by focusing on Italian isolates so that I could contribute as concretely as possible to the epidemiological analysis of Policlinico Umberto I.

Expected (or preliminary) results: The identification of a small number of genes to enable discrimination of the major *K. pneumoniae* STs responsible for hospital infections. Creation of suitable primers and development of multiplex PCR to enable rapid and effective epidemiological pre-screening. Preliminary results indicate feasibility for most STs, but some STs important for the Italian epidemiology of *K. pneumoniae*, belonging to Clonal Group (CG) 258 (ST11, ST258, ST512), are not easily distinguished by such an assay because of their close evolutionary relationship. Further analysis is needed for the correct identification of the components of this CG by this method.

Future perspectives: The same approach can be used for the development of multiplex PCR for the identification of the major STs of other species of opportunistic pathogens cause of HAI and more. Those defined as ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.)*. In addition, the tool through which to carry out the project is evolving. With the refinement of sequencing technology by Oxford Nanopore Technologies, an alternative to multiplex PCR has become possible to accomplish the project's purpose. Currently, a Sapienza research initiation project has been submitted that, if accepted, will allow the feasibility of a new protocol for epidemiological typing of *K. pneumoniae* to be tested.

RESIDUAL SYSTEMIC AND COMPARTMENTAL IMMUNO-INFLAMMATION IN PERSON LIVING WITH HIV: IMPACT OF DAILY AND LONG-ACTING ANTIRETROVIRAL THERAPY

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Background: In recent years, the research has focused on one hand to get easy and safe therapies to administer against HIV and on the other hand on understand the immune dysregulation that persists in people living with HIV despite antiretroviral therapy and virologic suppression. Currently, the first-line therapies consist of a combination of three or two active drugs, administered as single daily tablets for naïve patients; in case of virological undetectability it's possible to administer the new injectable long-acting cabotegravir/rilpivirine therapy, which has a great impact on the improvement of the quality of life. Inflammation dysregulation (systemic and compartmental, as in genital district) results in increased level, for example, of TNFalpha, IFN gamma, IL2, IL 6, IL 10, D-Dimer and shows a change in the monocytic and lymphocytic population. This inflammatory state is related to an increased risk of non-AIDS-defining events, such as cardiovascular disease, chronic kidney disease, cognitive decline, the development of cancers.

Objectives: Herein we analyze the impact of new intramuscular long-acting therapy on immune system and on metabolism, compared to other oral daily therapy. In detail, we study HIV reservoir, monocytic and lymphocytic population, inflammation markers and clinical parameters. In addition, we observe how quality of life change with this new therapy.

Expected (or preliminary) results: At the preliminary results, in people who receive long-acting therapies, we see an increase of CD4+ memory and a decrease of CD4+ naïve and not classical monocytes. We register a decrease of triglycerides, cholesterol and creatinine. Every patient is satisfied with the treatment and reports an improvement of the quality of life. We expect proinflammatory cytokine levels to decrease.

Future perspectives: Our study will help to better interpret the inflammatory dysregulation of the person living with HIV depending on the therapy taken.

INVESTIGATION OF PARASITE-HOST INTERACTIONS THROUGH THE STUDY OF EXTRACELLULAR VESICLES AND *IN VITRO* MODELS

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Background: Helminths are able to install an immunoregulatory environment within their hosts, thus ensuring their survival, an adaption ascribed to long lasting coevolution processes. This modulation of the host's defense system is achieved by several mechanisms such as the induction of apoptosis in immune cells, the manipulation of Pattern Recognition Receptors (PRRs) or the suppression of Th1/Th2 cells and cytokines. In recent years, Extracellular Vesicles (EVs), i.e. membrane-enclosed nanoparticles containing soluble proteins, carbohydrates, lipids and nucleic acids, have been described for playing a central role in parasite-host communication. Many parasite species have shown to be able to release Evs as a strategy to deliver immunomodulatory components involved in immune evasion and pathogenesis, being possibly involved in tumorigenesis.

Objectives: We aim to investigate the cross-talk between a number of nematode species (*Ascaris* sp, *Anisakis* sp, *Dirofilaria* sp) and the human host through genomic, transcriptomic, and proteomic assays, examining, in detail, Evs features, and using *in vitro* cutting-edge models including 2D and 3D human organoids.

Expected (or preliminary) results: Since the full pathogenic potential of parasitic helminths has not been entirely explored, basic knowledge from the characterization of Evs can be of pivotal importance for advancements within this field. Evs may contain bioactive compounds which possibly have a role in the modulation of the expression of host genes involved in immune response, inflammation and pathogenesis.

Future perspectives: The increased understanding of interspecific crosstalk strategies can indeed open up new avenues for vaccine, diagnostic, and therapeutic development for a wide variety of diseases involved with parasite infection, such as cancers and immunological disorders. For instance, in the future, EVs may be explored as vaccine candidates with a potential regulatory effect on the onset and outcome of parasite infections.

TESTING OF A MODEL FOR THE INTEGRATION BETWEEN CLINICAL RISK AND INFECTIOUS RISK AIMED AT THE CONTAINMENT OF HAI

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Background: Hospital-acquired infections, also known as Healthcare-Associated Infections (HAI), are an infection that develops during hospitalization, not present, or in incubation, upon entry into the hospital. HAIs have a significant clinical and economic impact resulting in an extension of the length of stay, long-term disability, increased resistance of microorganisms to antibiotics, an additional economic burden on health systems and patients and their families, and significant excess mortality. Despite the possibility to access new information systems and the large amount of data offered by the automatic warning systems - "big data", the management of information flows related to nosocomial infections is still very compartmentalized. The aggregation of information flows requires a model that involves the construction of a common taxonomic platform where can be placed (merged) data come from different sources (epidemiological clinical and forensic). In the literature, there are some international and national experiences of using reference taxonomies for the classification of events and dangers related to patient safety. The International Classification of Patient Safety (ICPS) developed by the World Health Organization (WHO) appears to be a further important step towards a comprehensive conceptual framework of patient safety, which is able to facilitate the comparison of results from different sources of information, both within health organizations and between institutions, at local, national and international level.

Objectives: The objective of this research project is to test a model for the integration between clinical risk and infectious risk in order to contain adverse events that can be classified as HAI in a third-level Hospital. The project aims at testing a system for integrating information sources previously considered separately. The validation of the ICPS classification system introduced by the WHO within a third-level Hospital, in fact, allows the structuring of a common platform that allows the integration of data from the management of litigation, voluntary reporting systems (IR) of forensic interest, and related to usually serious events (with death or serious injury to patients), with data from health surveillance systems of epidemiological clinical interest.

Expected (or preliminary) result: The identification of a model for correlating clinical risk with infectious risk, through the implementation of a common taxonomy.

Future perspective: Facilitate the analysis of large amounts of data, the evaluation of the effectiveness of the implemented infection prevention and control interventions as well as the optimization of the resources used to reduce the infectious risk.

RISK FACTORS FOR CARBAPENEM-RESISTANT *A. BAUMANNII* (CRAB) BLOODSTREAM INFECTIONS IN CRITICALLY ILL PATIENTS WITH CRAB COLONIZATION: PROPOSAL FOR A CLINICAL SCORE

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Background: The spread of antimicrobial resistance, also referred to as the “hidden pandemic", is a global emergency that threatens public health worldwide. Among multidrug-resistant bacteria, Carbapenem-Resistant *Acinetobacter Baumannii* (CRAB) is a major concern due to the limited therapeutic options. During the COVID-19 pandemic, a worrying increase in the spread of CRAB infections was reported.

Objectives: The primary aim of the study is to evaluate risk factors for developing a CRAB BSI in patients with prior CRAB colonization in ICUs in a multicenter co-hort. Secondary aims are: i) to propose a clinical risk score to develop a CRAB BSI in patients with previous colonization by CRAB in ICUs; ii) to evaluate risk factors associated with mortality in patients with CRAB BSI; iii) to analyze the treatment efficacy in terms of mortality rate, length of hospitalization and recurrence of infection.

Expected (or preliminary) results: The expected results of this multicentric study should be the identification of risk factors and the proposal of a clinical score that could be useful at the bedside of critically ill patients with CRAB colonization and BSI. In the preliminary analysis we included 129 patients from our single center, 57 (44%) out of these developed BSI. At the multivariable analysis the Charlson Comorbidity Index (CCI) ($p=0.026$), COVID-19 ($p<0.001$), multisite colonization ($p=0.016$) and the need for mechanical ventilation ($p=0.024$) were risk factors independently associated with BSI development in CRAB colonized patients.

Future perspectives: Investigating the risk factors of developing an invasive infection in critically ill patients is crucial in clinical management for early risk stratification and more careful treatment choice. The prevalence of CRAB infections in ICUs with their limited therapeutic options makes a thorough understanding of the risk factors for developing bacteremia urgent. Appropriate early therapy is a known protective factor, but identifying additional protective or risk factors within a more comprehensive score is of paramount clinical importance. An advance in scientific knowledge in this regard would set the stage for the development of future validated and established clinical scores that would aid the clinician in the management of these complex infections. Not only that, but the assessment of bacteremia risk is also an advantageous factor in stewardship programs to enable proper assessment of which patients might or might not benefit from a careful evaluation of antibiotic therapy in terms of molecule type and possible subsequent de-escalation, dosages, and duration of therapy.

OCCUPATIONAL EXPOSURE TO FORMALDEHYDE AND ANTINEOPLASTIC DRUGS IN HEALTHCARE SETTING: FROM SENSITIVE BIOMARKERS TO ASSESS HEALTH RISKS

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Background: Due to the widespread use of Antineoplastic Drugs (AD) and Formaldehyde (FA) in several working environments, there is an interest in the health effects that might be associated with the occupational exposure to these substances. AD are substances used to treat cancer, but some of them are carcinogenic, mutagenic or reprotoxic, therefore they could cause health effects to personnel who handle them. The widespread environmental organic pollutant FA is a chemical used in various industries, including furniture industry and in healthcare sector. Long-term exposure to FA can be harmful to human health, causing an increased risk of cancer. By assessing the risk of exposure to these substances, potential hazards associated with their use can be identified and minimized, protecting the health of workers.

Objectives: The objectives of the research project involve: analysis of data obtained from environmental monitoring strategies; identification of specific sources of exposure to FA and AD (type of handling, used product); assessment of potential health risks. Specifically, the study aims to identify potential cyto-genotoxic, oxidative, inflammatory effects and epigenetic changes in workers exposed to FA and AD. To this end, consistent with timelines related to enrolment, sample availability and experimental phase, several methods will be used: the BMCyt assay; Fpg-modified comet assay on whole blood; proinflammatory cytokine detection; DNA methylation measurement.

Expected (or preliminary) results: Preliminary results obtained during the initial phase of our research on the evaluation of the effects of AD, allowed us to observe early exposure-induced cyto-genotoxic effects, such as cellular and nuclear anomalies and DNA damage in exposed workers. The data obtained will need to be confirmed on a larger number of subjects. Based on the scientific evidence and the chemical properties of FA, we would expect an increased frequency of cells with anomalies and a higher probability of observing DNA damage than in unexposed individuals. For FA, we could also observe a correlation between proinflammatory cytokine levels and global DNA methylation.

Future perspectives: Some possible research directions could involve further investigation on changes in miRNA expression and on key processes that contribute to DNA damage. A longitudinal study could also be included to assess the long-term effects of exposure on DNA integrity. This could be done by monitoring exposed individuals over time to identify potential changes in DNA and possible correlations with genetic disorders or diseases.

EVALUATION OF THE PREVENTIVE AND THERAPEUTIC ADMINISTRATION OF AN INHIBITOR OF THE THIOREDOXIN – THIOREDOXIN REDUCTASE (TRX-TRXR) ENZYME COMPLEX (EBSELEN) IN HUMAN BOTULISM

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Background: Botulinum Toxins (BoNTs), produced by various bacterial species belonging to the Clostridium genus, are one of the biological agents potentially available in the event of war and/or terrorist attack. The BoNTs are produced as a biologically inactive form. Activation takes place within the nerve cells following the action of the Thioredoxin - Thioredoxin Reductase (Trx-TrxR) system. The active toxin works by blocking the SNARE complex responsible for the release of the neurotransmitter causing flaccid paralysis. To date, the only therapy is post-exposure based on the production and administration of specific antisera related to the involved BoNTs serotype. However, the administration of these antisera could induce individual hypersensitivity reactions and requires long preparation times. To reduce/eliminate the pathogenic effects of BoNTs, Ebselen has been shown to be able to inhibit the Trx-TrxR redox complex system.

Objectives: The present project aims to confirm the efficacy of Ebselen also in humans. Based on the results of the preclinical studies of pharmacodynamics, pharmacokinetics and toxicity, performed in primary cultures of neurons, in muscle cells and in mice, we will proceed with: 1) the synthesis and manufacture of the drug, in compliance with Good Manufacturing Practice; 2) phase I human clinical trial, in compliance with Good Clinical Practice.

Expected (or preliminary) results: In order to proceed with the clinical trial, an experimental protocol will be set up that will involve healthy volunteers. The protocol will be approved by the Ethics Committee and AIFA in order to ensure the rights, welfare and protection of the trial subjects. The ability of Ebselen to prevent local paralysis induced by BoNT type A will be measured using the Compound Action Muscle Activity electromyographic technique.

Future perspectives: This project will offer the possibility of post-exposure preventive and/or therapeutic treatment of botulism in its various clinical forms and also for a potential war/terrorist threat. The drug based on Ebselen will have the advantage of being administered, being easily available, since its mechanism of action is independent of the BoNTs serotype involved. Furthermore, the costs of long-term supportive therapies and individual hypersensitivity reactions could be eliminated and/or reduced.

FUNCTIONAL STUDY OF *AEDES ALBOPICTUS* MOSQUITO GENES INVOLVED IN CHIKUNGUNYA VIRUS (CHIKV) TRANSMISSION TO HUMAN HOSTS

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Background: *Aedes albopictus* becomes infected with CHIKV after the ingestion of a viraemic blood meal. The virus starts a journey inside the mosquito, that involves the overcome of immune barriers (midgut and haemocoel), to reach the salivary glands and to be transmitted to new hosts. Few years ago, at DSPMI of Sapienza University, in collaboration with ISS, a research project started with the aim to study the molecular interaction between *Ae. albopictus* and CHIKV. Indeed, RNAseq approach was used, sequencing transcriptomic repertoires of midguts and carcasses collected from CHIKV-infected/not-infected *Ae. albopictus* at 1- and 5-days post infection, as indicative of important viral infection stages in the mosquito. The reads were then assembled in a transcriptome using a recently released genomic dataset (FPA, Foshan strain) as reference, Differentially Expressed (DE) genes were identified, Pfam and Gene Onthology enrichment analyses were performed. Trascriptional profiles of a group of RNAseq-selected genes were validated by RTqPCR on different *Aedes albopictus*'immune tissues/organs.

Objectives: This project has the aim to carry out a functional study of *Ae. albopictus* genes modulated by CHIKV to discover their role during mosquito infection, and to identify possible strategies to limit/inhibit CHIKV transmission by *Ae. albopictus* mosquito. Molecular function of selected genes will be studied in CHIKV infected/not infected conditions by: 1) transient gene silencing through RNA interference performed both: i) *in vivo*, by systemic intrathoracic microinjection of dsRNA in *Ae. albopictus* mosquito, and ii) *in vitro*, by transfection of dsRNA in *Ae. albopictus* C636 cell line. 2) genome editing by CRISPR/CAS 9, to evaluate effects of permanent knock-out of the most promising candidates, as resulted from the above described procedures, in order to create transgenic lines of *Aedes albopictus* mosquitoes unable/less competent to transmit CHIKV.

Expected (or preliminary) results: This work could bring to light immune pathways activated by *Aedes albopictus* following arboviral infection and CHIKV strategies to survive inside the vector and to increase its transmission to the next host.

Future perspectives: The knowledge of what happens inside *Ae. albopictus* during infection with CHIKV could lay the basis to manipulate mosquito and to impair its ability to transmit CHIKV, suggesting possible future application strategies to stem the spread of this virus in the regions of the world where it represents a public health problem.

THE ELDERLY IN KORCA REGION, THEIR NEEDS, LEGAL ASPECTS AND GERIARTRIC CARE PRIORITIES

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Background: In the city of Korça, as in many other Albanian cities, elderly occupy a large number of patients in Primary Health Service. Visits with elderly patients are characterized by some specific principles that should be kept in mind by doctors and nurses. One of the most important priorities is to maintain patient autonomy and functional ability, not to cure their disease, but to ensure well-being and quality of life. Discussion among health personnel is advisable to choose the best strategy and provide a comprehensive geriatric assessment. The main aim of this project is to identify health problems in elderly patients and to design a care and monitoring plan at certain time intervals, 1, 3, 6 and 12 months. The plan will be based on the needs, preferences and goals of each elderly person included in the study group; the plan will be integrated where the different measures interact with each other and are viewed not separately but as a whole.

Objectives: Presentation of a comprehensive sociodemographic and economic profile of the elderly; Monthly in-depth screening and assessment of at least one or two areas of geriatric assessment; Active search for symptoms that are underestimated; Identification of factors related to the quality of life in selected study group; Establishing a relationship of trust and open communication between nurses and elderly/ their family; Counseling and informing elderly patients/family members from the nurses; Collaborative and coordinating work with doctors, physiotherapists and other medical and social workers involved in elderly care.

Expected (or preliminary) results: The primary outcomes will be the change in life quality and self-care. Secondary outcomes measures will include the care of chronic diseases, and necessary nursing procedures. Outcomes will be assessed both in experiment group from the nurse group through repeated measures over 12 months follow–up period (baseline, 1, 3,6, 12 month)

Future perspectives: The project will contribute to: better identifying elderly needs and providing nursing care at home for better chronic disease management; improving nurses skills in elderly patients care in Primary Service; indicators of quality geriatric care in Primary Health Service are means that measure the quality of family nurses service at Health Centers.

PHENOTYPIC AND GENOTYPIC CHARACTERIZATION OF *ACINETOBACTER BAUMANNII* CLINICAL ISOLATES: YESTERDAY AND TODAY

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Background: *Acinetobacter baumannii* are highly adaptable bacteria that are able to change their lifestyle deeply to conquer and persist within nosocomial environments. As a consequence, A. *baumannii* clinical isolates undergo local clonal expansion showing a wide range of different phenotypes to quickly adapt to environmental/host changes.

Objectives: This study aims to compare the phenotypic and genotypic traits of *A. baumannii* clinical isolates collected in the last decade as a step forward in understanding their changing under antibiotic selective pressure. Herein, 30 clinical *A. baumannii* isolates, mainly from respiratory and urine specimens, were collected from Policlinico Tor Vergata, during 2010-2023.

Expected (or preliminary) results: All isolates were extensive drug resistance (XDR) but were sensitive to colistin. 60% of strains isolated from respiratory infections displayed moderate to strong biofilm-forming activity compared to those from urinary sites. Only 20% of the isolates exhibited marked twitching motility, 53% had some degree of motility, whereas the remaining 27% were not motile. All strains showed no protease activity. The ability to invade human A549 epithelial cells varied among all strains, whereas 17% of respiratory isolates have greater colony-forming units/ml after 48 h of incubation compared to control cells.

Future perspectives: Current work with whole-genome sequencing is ongoing; these analyses will provide the genomic profile associated with antimicrobial resistance, virulence factors, multi-locus sequence types, and the relationship among isolates. Characterizing their chromosomal and plasmid-encoded resistance and virulence traits could help us understand the mechanisms behind the genetic mobilization and spread of these genes among these opportunistic pathogens and clues about their changing as a response to environmental stress conditions. This comparative study could spotlight valuable information on preventing transmission in a healthcare environment.

VALIDATION OF INTRABODIES AGAINST THE E6 AND E7 ONCOPROTEINS: A TARGETED THERAPEUTIC APPROACH FOR THE TREATMENT OF HUMAN PAPILLOMAVIRUS 16 - ASSOCIATED LESIONS

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Background: Human Papillomavirus 16 (HPV16) is the most spread high-risk HPV genotype. It is the cause of almost all cervical cancer and is responsible for a substantial fraction of other anogenital and oropharyngeal cancers in both sexes. Currently available HPV vaccines are efficacious for prevention of the infection but ineffective on pre-existing infections and associated tumor lesions. The only therapies in use today are surgery and chemotherapy, which are deleterious especially in young women. The E6 and E7 viral oncoproteins, expressed early in HPV infection and only in infected tissues, alter cell homeostasis by interacting with hundreds of different proteins and are necessary to both induce and maintain the transformed state of the cell. Therefore, they are optimal targets for tumour therapy. The approach for HPV tumor therapy based on the use of single-chain variable fragment antibodies (scFvs) directed against HPV16 oncoproteins, expressed as intrabodies in specific cellular compartments, has led not only to inhibit cell proliferation but also to delay or even hinder tumor onset in mouse models. We currently know that one effect of the anti-E6 antibody is the rescue of its main target p53, and that the anti-E7 intrabody hinders the binding of E7 to its main target, the tumor suppressor pRB.

Objectives: The project aims to unravel which of the cellular pathways involved in the 16E6 and 16E7 oncogenic activity are most influenced by the expression of oncoprotein-targeting intrabodies. This will be pursued through transcriptomic analysis of HPV16-positive cells expressing the anti-E6 and anti-E7 intrabodies. The network analysis of the cell pathways undergoing differential gene expression will possibly allow unravelling new mechanisms underlying intrabody activity, with implications for the knowledge of their efficacy and safety. Furthermore, it could help to highlight the relevant mediators of tumorigenicity associated with HPV16 infection, and consequently the identification of useful targets for the search of new chemotherapeutics.

Expected (or preliminary) results: Since E6 and E7 interact with more than 200 cellular proteins involved in key cancer hallmarks, intrabodies are predicted to subvert many other pathways besides pRb and p53, an expectation also supported by the demonstrated delocalization of E6 and E7 proteins by intrabodies, which necessarily prevents their interaction with the expected targets in the natural cellular compartment.

Future perspectives: Investigation of the antitumor effect of scFv intrabodies delivered in 3D cultures to evaluate molecular and biochemical changes during tumor growth in cell systems mimicking human tumors.

FREQUENT USERS IN THE EMERGENCY DEPARTMENT: ANALYSIS OF THE CONTEXT AND THE EFFICACY OF NEW ORGANIZATIONAL MODELS TO CONTRAST THE PHENOMENON THROUGH THE NRRP

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Background: Frequent Users (FU) are patients who repeatedly and inappropriately access the emergency room, with low grade symptoms that could be treated outside the hospital setting. Individual and personalized care programs for these patients can reduce the organizational and economic impact on hospitals, as well as improve the clinical and social outcomes of patients. The Health District Centers and the new digital platforms, born during the COVID-19 pandemic to quickly integrate all the organizational and professional structures and to meet the emergency needs, can represent new tools to implement local prevention policies and strengthen the primary care services. This project assess the impact of the frequent users phenomenon in Rome and describe the interventions that a Local Health Authority can implement through new information technologies and new chronic management models.

Objectives: The project will be divided into 3 phases. The first one is a literature review, the second one is the definition of the Roman FU profile analysing the FU attendances in the Local Health Authority Roma 1 (LHA Roma 1) and the FU clinical and social characteristics. The third one is a pre-post analysis of FU attendances in LHA Roma 1 after the implementation of new organizational model through the new National Recovery and Resilience Plan (NRPP) and the Health District Centers.

Expected (or preliminary) results: The frequent users have chronic and exacerbating conditions, associated with serious social dynamics. They contribute to increase the boarding in the emergency rooms and the health care costs. Cost savings are expected from the implementation of new organizational models and a more efficient use of resources planning.

Future perspectives: The phenomenon of FU in the Emergency Department is widely recognized and studied but no strategies and customized programs on individual users would seem to be described. This projects describe targeted interventions that a Local Health Authority can implement through new information technologies and new chronic management models.

EPIDEMIOLOGY AND CHARACTERISTICS OF VARICELLA (CHICKENPOX), IN PEDIATRIC AGE GROUPS

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Background: Varicella (chickenpox) is an acute infectious disease. It is caused by Varicella-Zoster Virus (VZV), which is a DNA virus, member of the herpesvirus group. After the primary infection causing varicella, VZV stays in the body (in the sensory nerve ganglia) as a latent infection. Varicella vaccine is not included in the routine childhood vaccination scheme in Albania. The aim of this study was to estimate the baseline of national varicella disease burden in pediatric age.

Objectives: A descriptive analysis with regards to number of cases and incidence, severity, and seasonality will be carried out covering the time period 2022 to 2025. Use of available health care registers and national communicable disease notification databases: hospitalizations and primary health consultations in specialist and primary care, using diagnosis of varicella (ICD-10).

Expected (or preliminary) results: Total cases and annual hospitalization, complication and death rates by age group, gender and seasonality. Death rate and duration of hospitalization by age group, gender and the range of clinical features. Estimation of the risk factors for complications. This study will estimate the association of young age, co-morbidity, recent positive history for COVID-19, abnormalities in laboratory examinations, referral to a certain type of clinic, not starting acyclovir on time in cases with a predisposition to severe forms, lack of vaccination and/or other factors with the progress, complications, length of hospitalization and fatalities among children developing varicella.

Future perspectives: Review of the treatment and follow-up protocols to prevent complications. Study findings will provide insights for future cost-effectiveness studies regarding the implementation of the vaccine in the mandatory vaccination calendar.

RISK HEALTH BEHAVIORS ENCOUNTERED IN SECONDARY SCHOOL YOUNG PEOPLE IN KOSOVO: THE ROLE OF EDUCATION IN DISEASE PREVENTION AND QUALITY OF LIFE

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Background: Adolescents are the most delicate and vulnerable age group to risky behaviors that negatively affect physical, social, mental and spiritual health. Risky behaviors also affect the personality of young people, negatively influencing the formation of the future. Adolescents are more likely to engage in risky health behaviors compared to older individuals.

Objectives: The purpose of this project is to evaluate dangerous behaviors among teenagers, such as the impact and level of violence, the use of tobacco, the use of alcohol and drugs, unprotected sexual behaviors, the way of eating and inadequate physical activity, in the teenagers of high schools in the city of Kosovo.

Expected (or preliminary) results: The identification of risk factors, problems or dangerous phenomena is essential to then lead to the identification, addressing or solving of problems arising from these factors.

Future perspectives: This project is important because after the identification of dangerous behaviors for health and the provision of didactic materials, it is expected that we will have a positive approach of young people towards healthy behaviors, reduction of the consequences and therefore a future generation with a positive expectation towards life. Given that these dangerous health behaviors are established more often during childhood and early adolescence, assessment and intervention are key elements to orientate adolescents in this way for the benefit of the individual, the family and society.

OCCUPATIONAL INFECTIONS IN THE HEALTHCARE SECTOR: ACCIDENTS TREND, SEX-DISAGGREGATED VACCINATION EFFECTIVENESS DATA AND INFECTIONS PREVENTION POLICIES

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Background: In the healthcare setting, a vast array of infections that cause substantial illnesses and occasional deaths can occur. The COVID-19 pandemic has highlighted the importance of public health interventions. According to EU strategic framework on health and safety at work, Healthcare Workers (HCWs) are at high risk of exposure to Biological Agents (BA). Insufficient data on accidents due to BA exposure and their causes is a challenge. Vaccination coverage are crucial for effective vaccination strategies and measure the efficiency of the system. Vaccination data are mainly focused on the general population, making it necessary to implement data regarding HCWs and address gender dimension, workforce data, and causes of vaccination hesitancy to target health surveillance interventions. Several factors can affect the immune response to vaccines, among which sex/gender is an important factor. It is known that females develop stronger immune responses to vaccines than males, however sex disaggregated analysis of humoral response to vaccines is rarely available.

Objectives: The proposed activities aim to increase knowledge of emerging infectious diseases in the health sector, raise employee's awareness of occupational infection factors, develop personalized risk management pathways considering gender diversity, and promote patient and occupational health protection. Moreover, antibody levels related to different vaccinations in HCW will be evaluated and mechanisms underlying the different immunological responses between male and female disclosed, with the aim of identifying potential sex-specific biomarkers.

Expected (or preliminary) results: The anticipated results will shed light on prevalence and distribution of occupational infections among healthcare workers, with a focus on gender differences. They will improve knowledge on biological risk in healthcare facilities, addressing critical issues in risk management and implementing prevention plans and training. The project will follow the sex/gender approach, evaluating biological, environmental, and social variables to improve the appropriateness of preventive interventions. Surveys will assess HCWs prevention measures, training, vaccination coverage, and predict vaccine response and adverse effects.

Future perspectives: This research will contribute to better understand occupational infections in healthcare sector, and will stimulate the development of targeted policies and guidelines. The outcomes will help to create a safer working environment, will improve the quality of care, and mitigate risks associated with infections.

POST-MORTEM BRAIN MAGNETIC RESONANCE (PMBMR) ON FORMALIN-FIXED ORGANS: A NEW PERSPECTIVE FOR APPLICATION IN THE FORENSIC SCENARIO

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Background: Forensic radiology is a widely spread and rapidly expanding branch of post-mortem diagnostics. The use of conventional radiology and Computed Tomography (CT) has, in fact, made it possible to integrate the more classical autoptic investigations in a now considerable range of cases. However, the use of Magnetic Resonance Imaging (MRI) in post-mortem diagnostics has not known an equally satisfactory development and diffusion, as its use is currently reserved for a restricted number of selected cases, more frequently related to deaths in the fetal and neonatological-pediatric age. As it concerns the study of the formalin-fixed brain, the currently available evidence mainly regards post-mortem study of neurological diseases in neurosciences, in which MRI is usually performed on brain coronal slices providing a valid diagnostic support.

Objectives: The project sets a series of objectives related, at first, to the validation of an effective methodology and, secondly, to the evaluation of its possible use in the field of forensic medicine investigations. In the first place, the clarification of the artifacts and the signal modifications induced by formalin-fixation plays a fundamental preliminary role in elaborating a dedicated acquisition protocol and in training physicians to interpret findings. Secondly, the project will focus on the definition of the properties of specificity and sensitivity of the technique in the study of lesions of forensic interest. Finally, further studies will evaluate the effective cost-benefit ratio of different technical and logistical repercussions compared to the current applications.

Expected (or preliminary) results: The application of this method on formalin-fixed whole brains could allow the resolution of many of the issues which predominantly limit the application of PMBMR on a large scale, such as the conservation of samples, the transport of corpses, the overlap with clinical routine exams, and the difficulties of interpretation introduced by low-temperature storage.

Future perspectives: In consideration of the demonstrated high sensitivity and specificity of MRI in the diagnostics conducted on brain parenchyma, as well as the encouraging results of the initial investigations on post-mortem samples, it seems reasonable to expect that PMBMR will constitute one of the main research fields in the forensic radiology field. Finally, the proposal of a standardized methodology supported by an adequate level of evidence would favor the multicentric sharing of the same protocol, with all the desirable consequences in terms of both diagnostic and evidential purposes.

EVALUATION OF THE CONTRIBUTION OF DOMESTIC HEATING TO AIR QUALITY AND HEALTH FOR ANALYSIS OF THE EFFECTIVENESS OF THE LAZIO AIR QUALITY REMEDIATION PLAN

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Background: In recent decades, there has been a strong increase in the combustion of biomass for domestic heating due to various factors. The woody biomass represents a less expensive fuel and in the common imagination, the use of biomass is perceived as a renewable source and, consequently, is considered less threatening to the environment than the generally used fossil fuels. However, many studies have shown the significant impact of this source on air quality, especially related to atmospheric Particulate Matter (PM) emissions.

Objectives: Experimental measurements will be carried out through monitoring campaigns in well-known critical areas of the Lazio: the Rome area and the Sacco Valley, with the support of the air quality monitoring network of the Regional Environmental Protection Agency (ARPA Lazio). The aims are the definition of the contribution of this source to PM emissions, the chemical characterization of the produced dust, and the assessment of health risk due to the inhalation of toxic compounds. In addition, the research and the monitoring of actions aimed at mitigating the problem will be investigated, in order to give a significant contribution to the protection of public health and to the environmental remediation.

Expected (or preliminary) results: The thorough knowledge of the chemical and toxicological characteristics of the contribution linked to the combustion of biomass for domestic use will provide useful information to support the evaluation of the effectiveness of the measures that will be introduced with the Update of the Air Quality Remediation Plan (A-PRQA) of the Lazio.

Future perspectives: The research project will provide the knowledge bases necessary for the evaluation of the effectiveness of the measures of the A-PRQA. In fact, the monitoring of the implementation of A-PRQA actions will be based on the use of indicators that evaluate the effects directly attributable to the measures and actions of the Plan itself.

Finally, it will be possible to evaluate how much the abatements related to the mentioned intervention can affect the reduction of PM concentration on the ground, through simulations with pollutant dispersion models, using as input for the models the estimates of emissions reduced with the implementation of the actions.

CEREBROSPINAL FLUID AND PLASMA BIOMARKERS IN PATIENTS WITH COVID-19: A RETROSPECTIVE STUDY

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Background: COVID-19 is a systemic disease which involved Central Nervous System (CNS). Evaluation of Neurofilament Light chain (NfL), a specific biomarker of neuro-axonal damage, and Matrix Metalloproteinases (MMPs), zinc-dependent enzymes involved in Blood–Brain Barrier (BBB) integrity may correlate with the severity of the disease and with long-COVID.

Objectives: The primary objective is to explore CSF and plasma NfL levels, as well as CSF MMP-2 and MMP-9 levels in COVID-19 patients with severe neurological symptoms. The secondary objective is to evaluate plasma NfL levels longitudinally in COVID-19 patients during the acute phase of the disease and three months after discharge. Furthermore, we evaluate the presence of SARS-CoV-2 RNA in CSF and blood samples by dd-PCR and RT-PCR.

Preliminary results: COVID-19 patients(n=55) showed elevated plasma levels of NfL compared to HDs (n=31) ($p<0.0001$). NfL plasma levels increased in COVID-19 patients with acute respiratory syndrome (ARDS) compared with those without (n=23) ($p=0.0005$). Longitudinal evaluation showed decreased plasma NfL levels three months after the acute phase of COVID-19 compared to baseline levels. NfL Plasma levels increased in patients with neuro-COVID (n=12) compared with patients without neurological symptoms (n=43) ($p=0.0346$). Among patients with neuro-COVID, CSF and plasma NfL levels are higher in the ARDS group than in the non-ARDS group. A positive correlation was observed between CSF and plasma NfL levels ($p=0.0218$). In the neuro-COVID group, SARS-CoV-2 RNA was detected in the CSF of 4/12 and in the plasma of 2/8 patients. Detection of SARS-CoV-2 RNA in CSF or plasma was not associated with increased CSF NfL, MMP-2, MMP-9 levels.

Future perspectives: COVID-19 patients reported many neurologic symptoms during the acute stage of the disease as well as several neurological sequelae following COVID-19 recovery. Our data showed that SARS-CoV-2 can affect central nervous system and lead to a damage of BBB integrity in the absence of viral RNA detection in CSF or plasma. Biomarkers of neuronal and astrocyte damage or inflammation may vary during COVID-19 infections and can help the clinician to evaluate the prognosis. The prognostic value of these biomarkers needs to be assessed in prospective studies.

INVESTIGATION OF THE ROLE OF THE NEUROTROPIC JC VIRUS IN ONCOGENESIS OF BRAIN TUMORS

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Background: To date, about 20% of all cancers are linked to infectious agents, therefore, understanding the potential role of viral infection in tumor development remains a very active area of research. JC Polyomavirus (JCPyV) represents the etiological agent of Progressive Multifocal Leukoencephalopathy (PML), but it has also been found implicated in carcinogenesis. Indeed, evidences about transforming activities in non-permissive cells as well as brain tumor formation in non-human primates inoculated with JCPyV, led to the hypothesis that this virus plays a role in Central Nervous System (CNS) neoplasms. The molecular mechanisms involved in JCPyV oncogenesis are still a topic of debate. The Large T Antigen (LTAg) seems to be essential in the process of cell transformation since it is able to bind cellular factors as Retinoblastoma (Rb), p53 and β-catenin, thus deregulating the cell cycle. Viral sequences and protein expression have been found also in human brain tumors, supporting JCPyV as a causative factor in brain cancers.

Objectives: Since there is no clear association between JCPyV infection and tumor formation in humans, the goal of this study will be to investigate a series of pediatric gliomas for the presence of JCPyV DNA, transcripts, miRNAs and proteins, as well as for cellular pathways involved in carcinogenesis and interacting with JCPyV, in order to elucidate the potential role of JCPyV in tumorigenesis.

Expected (or preliminary) results: The results obtained from this study will add new insights about a possible correlation between JCPyV and tumor development, and contribute to better understand the role of this virus as potential causal agent in CNS malignancies. Understanding the role of a viral infection in the etiology of cancer opens up the opportunity for developing preventive measures and targeted therapies. In addition, establishing an association may also lead to identify viral specific targets for diagnosis and biomarkers to evaluate prognosis. Current evidences suggest that JCPyV miRNAs may serve as *biomarkers* since they are stable, robustly detected, and their levels in body fluids reflect viral perturbations in tissue sites. This study will be one of the first to address the JCPyV miRNA expression in brain tumors, adding new insights about the diagnostic potential of viral miRNA in JCPyV infection and CNS cancers.

Future perspectives: Moreover, in order to clarify JCPyV molecular biology and oncogenic mechanisms in CNS tumors, a cellular model *in vitro*, will be also carried out in future experimental studies.

AN ETHICAL FRAMEWORK WITHIN WHICH TO UPHOLD EPISTEMIC STANDARDS DURING A PUBLIC HEALTH CRISIS: LESSONS LEARNED DURING COVID-19

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Background: The COVID-19 pandemic has brought to light the lack of comprehensive ethical frameworks within which to communicate science between all relevant stakeholders during a public health crisis. Important questions should be address at the governmental level to better prepare for future crises. For example: Whose opinion matters when it comes to science in a public health crisis? How can decision makers ensure that a plurality of views informs policy without allowing erroneous and ultimately harmful knowledge to shape government action? Should every scientific claim be given a platform during a public health crisis? What should the limits to free speech and epistemic pluralism be during a pandemic? How can we distinguish between misinformation/fake news and valid claims that do not conform to a particular orthodoxy?

Objectives: This exploratory, qualitative study will use the overarching questions presented above as an interpretative framework to analyse COVID-19-related case studies as the main narrative context. The aim of the study will be to develop an ethical framework that attempts to determine which epistemic standards: (1) Should be fulfilled for scientific claims to enter political conversations in the context of a public health crisis; (2) Should be adhered to by politicians and governmental institutions when communicating science to the public during a public health crisis; and (3) Should be enforced/promoted on traditional and social media platform.

Expected (or preliminary) results: A detailed analysis of the ethical issues surrounding science communication during the COVID-19 pandemic will reveal the mechanism and character of key dysfunctional systems in today's public health landscape.

Future perspectives: One of the key predictors of future success is the ability to learn from past mistakes. By defining epistemic standards, analysing some of the dysfunctions in the transfer and use of scientific claims during the COVID-19 pandemic and using them to create an ethical framework within which to uphold those standards during a public health crisis, a conversation on the importance of their formalisation, academic and otherwise, will hopefully continue. Projects such as these have the potential to directly influence policy in future pandemics as well as in wider issues of health and science by providing much needed guidance on how to navigate and set epistemic standards in real-world settings.

HUMANOID ROBOTS FOR ENHANCING WORKPLACE SAFETY AND PREVENTING WORK-RELATED ACCIDENTS AND ILLNESSES IN HOSPITAL SETTINGS

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Background: The project, promoted by INAIL and the Italian Institute of Technology, aims to utilize digitization, the Internet of Things, and robotic elements introduced in production processes under Industry 4.0 to prevent accidents and occupational diseases. A humanoid robot prototype will be trained in a realistic hospital scenario, where frequent movement of bedridden patients poses a high risk of accidents and occupational illnesses.

Objectives: The interaction between humans and robots aims to facilitate work activities by implementing perception systems that monitor workers' movements and analyze data related to physical stress. Existing wearable technologies will be further developed and integrated for interaction with robots. The project aims to devise humanoid robots that improve work ergonomics and technological acceptability in future healthcare environments, thereby enhancing the prevention of work-related accidents and occupational diseases, ultimately reducing risks faced by workers.

Expected (or preliminary) results: The prototype will learn to replicate the movements of human operators and replace them in performing more dangerous and physically demanding tasks. It will serve as a collaborative "robot workmate" capable of sensing abnormal situations through advanced systems that perceive the physical state of humans, intervening to support and anticipate the risk of errors and injuries caused by continuous and repetitive movements. Workers will wear a non-invasive sensor system to provide the robot with information about their psychophysical health, including heart rate, respiratory rate, and temperature, enabling the robot to execute the most appropriate movements accordingly.

Future perspectives: The ultimate goal is to reduce or eliminate the risk of accidents and musculoskeletal disorders among healthcare workers. When implementing these intelligent systems in work environments, it will be essential to evaluate the short-term and long-term effects of robot workmate presence, including the potential risk of perceiving the robot as an intruder rather than a helper. Further studies will be conducted to anticipate and address the inevitable ethical and medicolegal implications associated with the routine use of robot workmates in healthcare activities.

GEOSTATISTICAL ANALYSIS OF ENTOMOLOGICAL FACTORS AFFECTING MALARIA TRANSMISSION IN THE VILLAGE OF GODEN (BURKINA FASO)

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Background: Burkina Faso is among the ten malaria-endemic countries with the highest morbidity and mortality worldwide. Following WHO's directive strategy to control malaria, Long-Lasting Insecticide-treated bed Nets (LLINs) have been massively applied throughout the country since 2010. Despite the efforts and an initial decrease in cases, the number of infected people and deaths has remained almost constant over the last 13 years. Several studies have revealed multiple mosquito resistance mechanisms (behavioral and physiological) to LLINs in the country. In particular, the rural village of Goden (central Burkina Faso) has been studied since 2011 for its high transmission intensity, mainly sustained by *Anopheles coluzzii* and *Anopheles arabiensis*. Entomological surveys were conducted in 2019, 2020, and 2022, in which indoor-resting mosquitoes were collected in different houses and compounds in the Goden village. The sampled mosquitoes were identified at the species level, subjected to blood meal analysis, tested for resistance, and for the presence of *Plasmodium* sp. Along with entomological information, data on human and other potential hosts availability, bed net usage, and environmental parameters were collected and georeferenced.

Objectives: The project aims to perform a geostatistical analysis of the data collected during the tree years survey period. The analysis will allow us to identify how mosquito distribution trends, human blood indices, and sporozoite rates relate to the ecological parameters (i.e., presence/absence of water, distance from water etc.) of the village.

Expected (or preliminary) results: The results of the geostatistical analysis will identify the main distribution patterns characterizing the transmission dynamics of malaria in the village. The identified pattern will also represent a reference model that could be used for comparable eco-epidemiological situations.

Future perspectives: The present study will allow to identify potential targets for control strategies complementary to current ones, useful to tackle malaria in this hyper-endemic context.

VALIDATION OF AN INTERNAL METHOD AND A PGS (PROBABILISTIC GENOTYPING SOFTWARE) FOR THE INTERPRETATION OF MIXED GENETIC PROFILES

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Background: Evidence are taken from the crime scenes and hopefully will give rise to genetic profiles useful for the identification of the subjects involved in the crimes being investigated. The high sensitivity achieved by genetic-forensic analyses currently makes it possible to obtain genetic profiles even from very low quantities of DNA, but,in the most part of the cases, mixed genetic and/or degraded profiles of increasing complexity are obtained. For the interpretation and subsequent bio-statistical evaluation of these profiles, it is no longer sufficient the only experience of forensic geneticist, but it is necessary the use of PGS (Probabilistic Genotyping Software), which must undergo a process of validation in your own laboratory.

Objectives: Here, we describe a study concerning the analysis of mixed genetic profiles of 2 and 3 contributors obtained from two different sets of stains, a first set, consisting of traces built *ad hoc* in the laboratory, and a second set, represented by in silico genetic mixtures, whose raw data are available online and collected in the public database PROVEDIt. All the mixtures produced will have variable proportions of the different contributors, various amount of total DNA input, degradation, and the presence of stochastic effects (such as drop-out, increase in the heights of the stutter peaks, presence of drop-in alleles). The first goal will be the evaluation of the best analytical threshold to apply for the interpretation of the electropherograms obtained from the mixed genetic profiles. The second one will be the evaluation of different PGS (continuous *vs* semi-continuous approach) to select the more suitable to be submitted to the validation phase.

Expected (or preliminary) results: The supplementary information exploited by fully continuous PGS, essentially represented by quantitative information (in terms of peak height), make them probably the best solution for studying complex DNA mixtures.

Future prospects: The study could in the future also be extended to more complex genetic mixtures (i.e.with a greater number of contributors and/or greater stochastic effects) for the evaluation of possible limits and further applications.

COCAINE-RELATED DEATHS: A COMPARATIVE STUDY ON IMMUNOHISTOCHEMISTRY AND MOLECULAR BIOLOGY AS INNOVATIVE DIAGNOSTIC TOOLS

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Background: Cocaine-related deaths have increased steadily through the years with 19,447 deaths reported in 2020. Many of the severe pathological effects induced by cocaine could be attributed to chronic consumption (neurodegeneration, premature brain aging, depression). Other effects, such as hyperthermia, seizures, headaches, muscle hyperactivity, and multiorgan failure, arise with acute abuse (even after a single dose). Drug-associated histopathological findings are widely studied and substance-related histopathological findings are usually the result of chronic consumption. All the above mentioned morphological and histopathological changes, although frequent, are not pathognomonic for cocaine-abuse, and histology alone cannot confirm the post-mortem correlation with drug abuse. Toxicological data are of greater importance for the diagnosis of cocaine-related deaths, but framing the postmortem diagnosis of such cases could be a problem when blood, bile or/and urine are absent. In this context, recent researches are focusing on new methods to investigate the distributive physiopathological response to drugs, especially immunohistochemistry and molecular biology, focusing on the role of miRNAs.

Objectives: The aim of this study is to evaluate the correlation between cocaine concentration in blood, bile and urine in cocaine-related deaths and the immunohistochemical study with anti-cocaine antibody on brain, heart, lungs, liver and kidney samples. A second aim is to assess the expression of three specific miRNAs (directly involved in cocaine exposure) in blood and brain samples of subjects tested positive to cocaine at classic toxicological analysis.

Expected (or preliminary) results: At the end of the research, it will first be possible to assess whether the immunohistochemical and the biochemical markers actually respond to qualitative and quantitative criteria useful to allow a scientifically reliable diagnosis of cocaine-related death, thus allowing its use in the forensic routine.

Future perspectives: Forensic pathology could benefit from the use of immunohistochemistry: in fact, there are numerous cases in which the forensic investigation - albeit conducted with the most valid autoptic, histological and toxicological procedures - does not lead to a certain diagnosis. In addition, through the results of this research, it will be possible to evaluate the utility and reliability of tested miRNAs, and their use in the diagnosis of drug-related death, favoring their possible use in the forensic setting.

EXPOSURE TO *ALTERNARIA* TOXINS IN THE ITALIAN POPULATION

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Background: *Alternaria* toxins are secondary metabolites produced by fungi that can contaminate cereals, oilseeds, fruits, and vegetables. The most common *Alternaria* toxins in food products are Alternariol (AOH), Alternariol Monomethyl Ether (AME) and Tenuazonic Acid (TeA). In 2011, the European Food Safety Authority (EFSA) published the first risk assessment at the European level in which, due to the limited number of toxicity data, the Threshold of Toxicological Concern (TTC) approach was used to assess the level of concern for dietary exposure. Under the TTC approach, substances are classified depending on their chemical structure and associated to defined TTC levels. Because of the *in vivo* experimental evidence of genotoxicity, AOH and AME are associated to the TTC value of 2.5 ng/kg bw per day. TeA is classified as a Cramer structural class III and it is associated to the TTC level of 1500 ng/kg bw per day. In 2016, EFSA published a dietary exposure assessment for *Alternaria* toxins in which the higher exposures are reported for toddler and infants. Recently, the European Commission published the Recommendation (EU) 2022/553 on monitoring the presence of *Alternaria* toxins in food in which the need for additional toxicity and occurrence data is reported.

Objectives: The objective of the study is to verify the scenario of dietary exposure to this group of toxins by two complementary survey methods. The first combines occurrence data monitored at national level and daily consumption information to determine dietary exposure of different groups of population; the second approach exploits the measure of biomarkers into biological fluids to determine the internal exposure to which individuals are subjected.

Expected (or preliminary) results: A sensitive analytical method (HPLC-MS/MS) will be set up and validated for the analysis of biomarkers considered in this study. Special effort will be put in defining appropriate Limit of Quantification (LOQ) of the method to minimize the influence of censored data affecting the uncertainty of exposure estimates. In addition, the comparison of the results obtained by both survey methods will elucidate the status and levels of exposure to *Alternaria* toxins and the appropriateness of the national monitoring.

Future perspectives: By interpreting the level of dietary exposure and internal exposure, the competent authorities will gather useful information to direct appropriate actions in official control. All occurrence data will feed EFSA database on *Alternaria* toxins contamination which is the base for the setting of possible maximum limit in food products.

TECHNICAL CONSULTANCY IN THE DIGITAL AGE

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Background: The technological evolution will produce radical changes, subjective, structural, functional, and morphological in the whole world of civil liability. As is well known, in fact, digital progress will involve a profound metamorphosis of what are now considered the traditional structures of civil liability, both in terms of the audience of subjects who, abstractly, may be called to answer for "new" prejudices, and from the point of view of the empirical unraveling of individual cases, profoundly innovated by the spread of digital tools.

Objectives: The research will be divided into two distinct levels: the one attentive to the positive figure (*de iure condito*); the other one, programmatic (*de iure condendo*), aimed at outlining certain proposals of reform of the current discipline. This axiological separation derives from the uncertain action of the legislator, both community and domestic.

Expected (or preliminary) results: To propose an interpretation of the current legislation to offer acceptable solutions to the problems that technological innovation involves**.**

Future perspectives: The role of the coroner will necessarily be conditioned by the “new damages” that technological progress will produce (e.g.: medical devices). My research project aims to investigate the desirable regulatory changes so that the transition takes place in the best possible way.

DEFINE A NEW METHODOLOGY TO PROVIDE EACH "COMMUNITY HOME" WITH HEALTH SERVICES TAILORED TO THE HEALTH NEEDS OF THE POPULATION

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Background: The territory of the local health care service of Avezzano-Sulmona-L'Aquila includes the entire L'Aquila province with a population density of 57.92 ab/Kmq VS regional average value equal to 118,66 ab/Kmq and its area is 5.047 Kmq - and corresponding to the mountain and inland region areas – and covers about a half (47%) of Abruzzo areas, while the remaining part (53%). The total health distribution point is 73. Initiative health, i.e. the assistential model for the management of chronic diseases. Community Homes, which include one hub every 40,000-50,000 inhabitants and several spokes to be defined taking into account the orographic and demographic characteristics of the territory to favor capillarity of services and greater equity of access according to proximity principle, specifically in inland and rural areas.

Objectives: In the light of the programmatic plan as defined in MD 77/2022 and with the analytical knowledge of the needs of the population (see stratification and chronicity), the problem shifts to the organizational-functional level and shows unprecedented complexity. The question is what the allocation criteria are for the specialist healthcare offer in the CH, as regards the quantitative and qualitative-disciplinary distribution, staff recruitment and contracting, response times, fair geographic distribution, etc. The goal is to develop specific algorithms to optimize the functional distribution of the specialistic territorial assistance offer, based on the above "terms".

Expected (or preliminary) results: To elaborate the model, a study of the needs of the population will be carried out through the stratification of the population as well as the demographic conditions of the territories. Population stratification will be conducted by risk profiles, through predictive algorithms, which will allow to differentiate of the intervention strategies based on risk level, need for health, and consumption of resources. A personalized organization model for L'Aquila province will be developed based on the location of CH, and in case CH cannot grant concrete proximity assistance, itinerant teams will be set up and organized so that they can really reach the entire population. In consideration of the vastness of its territory, digital healthcare and telemedicine will be applied and organized with various services such as specialist video consultation, tele-care, tele-monitoring, tele-rehabilitation.

Future perspectives: Evaluation of the epidemiological profile of the reference population and of the intervention priority will allow the define an integrated and multidisciplinary model of social welfare services, that will be more appropriate to the specific conditions of the L'Aquila province population and territory. This method can be used for the entire Italian healthcare system.

INFECTIONS BY CEFTAZIDIME-AVIBACTAM RESISTANT *KLEBSIELLA PNEUMONIAE*: RISK FACTORS AND CLINICAL IMPACT

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Background: WHO defined Multi-Drug-Resistant Organisms (MDROs) as one of the biggest threats to global health. KPC carbapenemase producing Klebsiella pneumoniae (KPC-Kp) is the most widespread MDRO in Southern Europe and United States. Nowadays, the treatment of KPC-Kp infections mainly relies on Ceftazidime/Avibactam (CZA), which contributed to the reduction of mortality. Unfortunately, CZA-resistant strains are slowly emerging, especially in countries with endemic KPC-Kp like Italy. So far, little is known regarding clinical outcomes and optimal therapeutic regimens of infections caused by KPC-Kp exhibiting resistance to CZA, especially those exhibiting in-vitro susceptibility to meropenem.

Objectives: We aim to answer the question whether infections caused by KPC-Kp exhibiting resistance to CZA are associated with higher mortality, length of hospitalization and super-infection rates than those caused by CZA-susceptible strains. Furthermore, we aim to evaluate the different therapeutic regimens and outcomes in the subgroup of patients with KPC-producing CZA-resistant and MEM-susceptible KPC-Kp.

Expected (or preliminary) results: This project starts from the preliminary results of a study conducted at our Institution including patients with KPC-Kp bloodstream infections treated with CZA, alone or in combination with other antimicrobials, showing an overall 30-day mortality rate of 19.4% and a rate of CZA-resistance development of 3.7%. Furthermore, we are currently experiencing an increasing rate of CZA-resistant KPC-Kp infections. Therefore, we believe that the clarification of the clinical impact of these infections will be crucial for the appropriate therapeutic management and the reasoned use of the new available armamentarium towards KPC-Kp, according to antimicrobial stewardship principles. Our project will elucidate the clinical impact of CZA-resistant KPC-Kp infections in the real-life and address the question whether these infections are associated with worse outcomes than those sustained by CZA-susceptible strains. Finally, it may be possible to identify strategies to contain the phenomenon, including studies of antibiotic synergism to protect CZA from resistance.

Future perspectives: Preliminary results seem to indicate that treatment with Meropenem/Vaborbactam (MVB), a new carbapenem/inhibitor association with activity against KPC-Kp, may be associated with a better clinical outcome. We aim to confirm these findings and ascertain whether specific populations (e.g., critically ill ones) may benefit from MVB administration.

COMPARATIVE ANALYSIS OF THE GUT MICROBIOME OF HIV-EXPOSED UNINFECTED AND HIV-UNEXPOSED CHILDREN IN CAMEROON

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Background: PMTCT (Preventing Mother-To-Child Transmission) has significantly reduced the rate of vertical transmission, leading to the setting up of a new cohort of HIV-Exposed Uninfected children (HEU) in Cameroon and around the world. 14.8 million HEU children were estimated, where 90 % of whom lived in SSA showed the highest vulnerability to severe infections such as pneumonia and gastroenteritis, and increased mortality rates in infancy compared to children HUU. Considering the huge role played by the Gut microbiome in the maintenance of health status, mainly in immune and metabolic homeostasis, it has been hypothesized that the vulnerability of these children faced with severe infections can be related to dysbiosis of the gut microbiota which would cause an alteration of the immune system. The Gut microbiome has been associated with multiple diseases including HIV infection and this latter is characterized by gut microbiota dysbiosis, with a high level of immune activation induced in the human organism and differs between treated and antiretroviral therapy-naïve.

Objectives: To evaluate the effect of HIV/ART exposure on the quality of the microbiome of HEU children in Cameroon by characterizing the diversity of the gut microbiome of HEU and HUU children, Assessing the microbial translocation (sCD14 and LPS level) and Inflammatory cytokines (IL-12p70, TNF, IL-10, IL-6, IL-1β, and IL-8) and correlating the quality of the microbiome with the degree of morbidity in this HEU children comparing with the appropriate HUU control children.

Expected (or preliminary) results: Establish the difference between the microbiota of HEU children and that of HUU children living in Cameroon finding the correlation between the microbiome and morbidity.

Future perspectives: The need to understand the mechanisms of increased morbidity and mortality in HEU infants and children, a longitudinal study would be ideal to better determine the dynamicity of the microbiome of these children comparing them also with infected children.

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