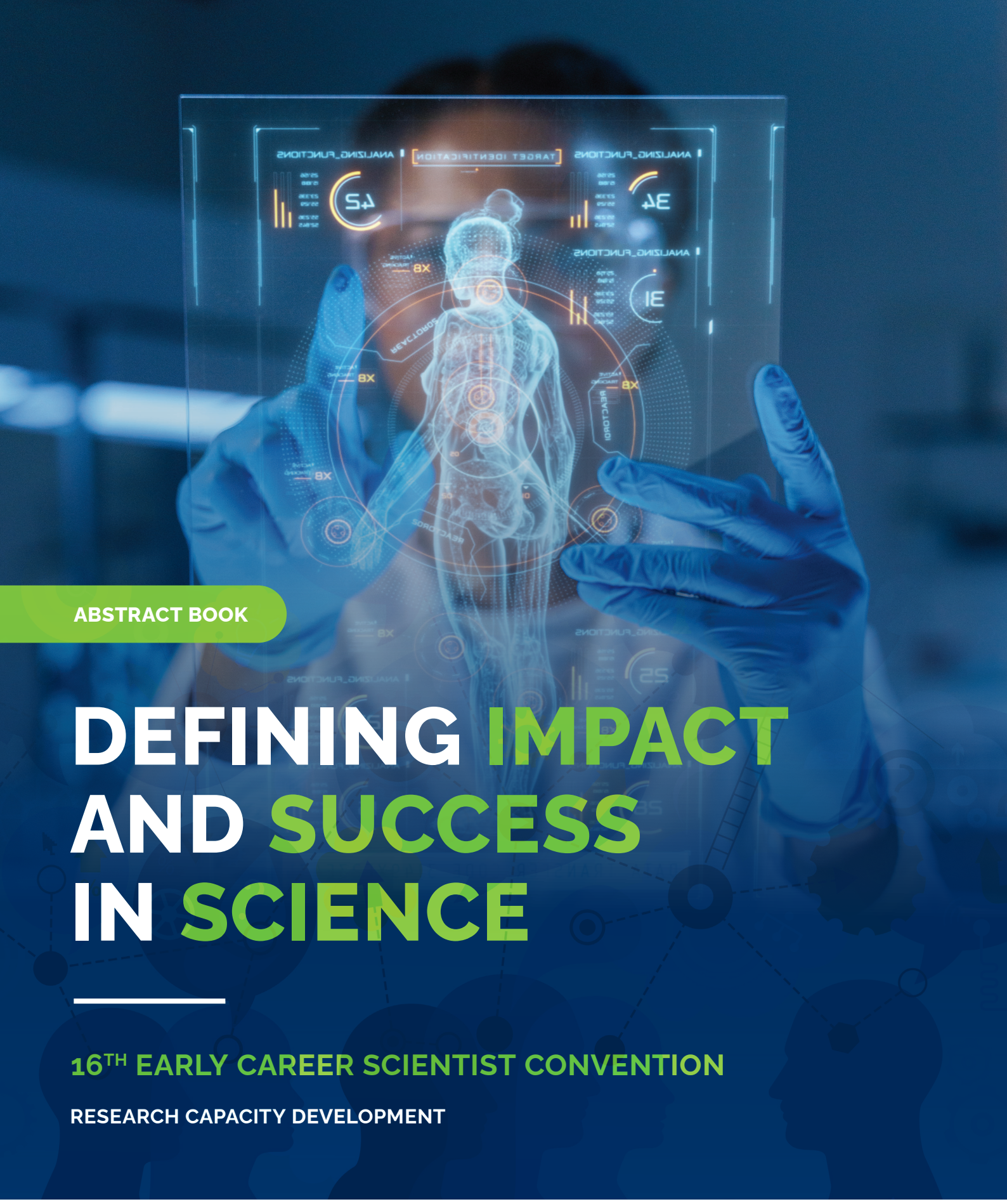

ABSTRACT BOOK

DEFINING IMPACT AND SUCCESS IN SCIENCE

16TH EARLY CAREER SCIENTIST CONVENTION

RESEARCH CAPACITY DEVELOPMENT

saMRC advancinglife

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

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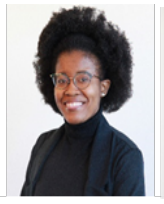

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SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

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RCD Portfolio	Contributors
Scholarship Selection Committee	Prof Andre Kengne Prof Shaheen Mowla Prof Kebogile Mokwena Dr Kerry Wilson Prof Teke Apalata Prof Phumla Sinxadi Prof Emily Wong
ECSC Scientific Committee	Dr Nadine Harker Burnhams – Alcohol Tobacco and Other Drug Research Unit (SAMRC-Chair) Dr Jillian Hill – Non-Communicable Disease Research Unit (SAMRC-Deputy Chair) Dr Ebrahim Samodien – Biomedical Research and Innovation Platform (SAMRC) Dr Lawrence Mabasa – Biomedical Research and Innovation Platform (SAMRC) Dr Awelani Mutshembele – TB Platform (SAMRC)
Legal	Ms Sumaya Behardien
Finance	Ms Noluthando Sikhutshwa
Funders	The National Department of Health and Public Health Enhancement Fund

MESSAGE FROM RCD EXECUTIVE LINE MANAGER

It gives me great pleasure to welcome back SAMRC scholars to in-person engagement on our campus as well as those joining us online. The Early Career Scientist Convention (ECSC) provides an important platform for young scientists to network, share experiences, triumphs, and challenges, as well as to engage in healthy competition.

The 16th ECSC's theme, "Defining impact and success in science", is timely and important especially in this time where the traditional narrow definition and/or measurement of success and impact in research is being widely discussed in different academic fields. The COVID-19 pandemic has thrust the scientific community into the forefront globally, changing the speed and manner in which scientists collaborate, scientific results are communicated, and science is translated into new products, practices and guidelines. It has demonstrated the critical role played by research in addressing a global threat, the importance of collaboration, data sharing and rapid dissemination and, most importantly, the visible impact of this. It has also increased the public interest and involvement in the global scientific debates, with activities such as science advocacy, activism and lobbying also coming to the fore. Conventional measurement of impact, based largely on publishing academic journal articles, remains important and one of the most tangible measures of academic success and growth in the scientific body of knowledge; however, at the end of the day, particularly when it comes to health research, it is the lives saves and quality of life improvements that matter. We need to move towards a broader and more outcomes and impact focused way of measuring and rewarding success in science. As young scientists, it is important to keep the end goal in mind as you embark on exciting scientific careers, to define what research impact means for you and your work and to plan how you will achieve this.

This year's ECSC includes a wonderful mix of presentations from young scientists and scholars, but also provides a platform for training, with a broad mix of academic, career and life skills topics addressing science communication and public engagement, career development and tools to improve resilience. I want to encourage all participants (in-person and virtual) to actively engage in the discussions, share their knowledge and experiences, and challenge each other and the other speakers with probing questions to make this a truly interactive and informative event.

I would like to sincerely thank our esteemed invited speakers who have given up their time to share their knowledge with us, the young scientists who will present on their research, the Scientific Committee for their input in organizing the convention and the Research Capacity Development (RCD) team for their time and efforts in making this year's convention a success.

CONTRIBUTERS

Keynote Speakers

Professor Jonathan Jansen- Distinguished Professor at Stellenbosch University and President of the Academy of Science South Africa

Professor Faadiel Essop- Professor and Director, Centre for Cardio-metabolic Research in Africa (CARMA)

Masterclass panelists and facilitators

Masterclass Title	Panelists
1. "The Role of Mental Health in Your Career: Interventions that work" "Ditching the idea of DIY resilience: Multisystemic resources are critical to the wellbeing and success of (early career) scholars"	**Prof Linda Theron, Dr Sibongile Mashaphu, Prof Jason Bantjes and Dr Rehana Kader**
2. "Science communication and public engagement: Reflections on health crisis communication during the Covid-19 pandemic"	**Prof Susan Goldstein, Dr Palesa Sekhejane and Prof Nokwanda Makunga**
3. "Career reinvention and retooling: a resilience strategy"	**Prof Bavesh Kana, Dr Duduzile Ndwandwe and Prof Rabia Johnson**
4. "Scientific career paths for PhDs: How to increase your employability"	**Dr Boitumelo Semete-Makokotlela, Prof Ntobeko Ntusi, Dr Bianca Brider, Prof Maritha Kotze and Dr Maluta Steven Mufamadi**

Scientific Committee

Dr Nadine Harker Burnhams- Alcohol Tobacco and Other Drugs Research Unit (SAMRC)

Dr Jillian Hill- Non-Communicable Disease Research Unit (SAMRC)

Dr Ebrahim Samodien- Corporate and Marketing Communications (SAMRC)

Dr Lawrence Mabasa- Biomedical Research and Innovation Platform (SAMRC)

Dr Awelani Mutshembele- TB Platform (SAMRC)

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

RESEARCH CAPACITY DEVELOPMENT (RCD) FUNDING CATEGORIES 2022/23
RCD SCHOLARSHIPS

PROGRAMME	BONGANI MAYOSI NATIONAL HEALTH SCHOLARS PROGRAMME	CLINICIAN-RESEARCHER (MBChB-PhD) DEVELOPMENT PROGRAMME	SAMRC INTERNSHIP SCHOLARSHIP PROGRAMME	VACCINOLOGY PROGRAMME	RESEARCHER DEVELOPMENT PROGRAMME
OBJECTIVE	Develop a vibrant and a transformed health research academic pipeline in SA that is adequately equipped to train healthcare workers and inspire a new generation of health/clinical researchers	Develop a cadre of highly trained clinician-scientists who are likely to be attracted to and excel in careers in academic medicine. MBChB/BChD holders	Contribute towards the SAMRC's transformation agenda to increase the representation of quality postgraduate scientists from designated groups (African, Coloured, Indian and Asian)	Develop the next generation of leaders in the field of Vaccinology. The focus is on early career researchers specializing in the various research areas within the broad field of Vaccinology	Support employees in academic institutions or SAMRC units who are engaged in clinical/health research and wish to complete their doctoral degrees.
KEY PARTNERSHIPS	NDoH PHEF NHRC	SA Medical Schools	SAMRC Intramural and Extramural Units	University of Lausanne Wits alive and other institutions that specialize in Vaccinology	Academic and research institutions
SCHOLARSHIP VALUE	No set amount, the scholarship value is equivalent to the after-tax take-home pay of the candidate, based on the salary scales of the relevant post (or equivalent) in the National Department of Health.	500K per annum	PhD 200K per annum MSc 160K per annum		Up to 250K once-off funding

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

RESEARCH CAPACITY DEVELOPMENT (RCD) FUNDING CATEGORIES 2022/23
RCD GRANTS AND FELLOWSHIPS

PROGRAMME	SAMRC RESEARCH CAPACITY DEVELOPMENT INITIATIVE (RCDI) PROGRAMME	SAMRC RCDI-NESTED POSTDOCTORAL FELLOWSHIP AND POSTGRADUATE PROGRAMME	SAMRC MID-CAREER SCIENTIST PROGRAMME (MCSP)	SAMRC INTRAMURAL POSTDOCTORAL FELLOWSHIP PROGRAMME	SAMRC CLINICIAN POSTDOCTORAL CAREER DEVELOPMENT PROGRAMME	SAMRC EARLY INVESTIGATORS PROGRAMME (EIP)
OBJECTIVE	Provide an opportunity for funding researchers at universities and research institutions previously constrained by inadequate access to resources. The aim of the RCDI grant is to contribute and assist in accelerating research capacity building and scientific leadership at the selected universities.	Accelerate research capacity building and scientific leadership by strengthening research teams and improving supervision experience of RCDI- principal investigators. Postdoctoral fellows and scholars are identified and nominated by RCDI PIs	Accelerate research standing of funded Mid-Career Scientists and facilitate their retention in the public sector in areas of strategic interest to both the National Department of Health (NDoH) and the SAMRC. Transition from MCS to research leaders.	Contribute and assist in accelerating research capacity development and scientific leadership by creating opportunities to host and retain postdoctoral scientists that have demonstrated the potential to become independent researchers.	Build research capacity and scientific leadership of early-career clinician-scientists who have demonstrated a potential to become excellent clinician-researchers. Post-PhD developmental programme.	Support the career development of scientists who are at the end of their early postdoctoral stage and facilitate their transition to established research (i.e., MCS)
KEY PARTNERSHIPS	HDIs	HDIs	Nominations by the SAMRC President	SAMRC Intramural Units	SA Medical Schools	SA Academic Institutions
VALUE OF AWARD	Each university is awarded one million rand per financial year for five years	R350 000.00 pa for postdoctoral researcher R200 000.00 pa for PhD scholar R160 000.00 pa for MSc scholar	The funding period is two years renewable for a further third year, subject to satisfactory performance and availability of funding.	R350 000.00 pa for postdoctoral researcher	Equivalent to the after-tax take-home package for the qualification according to the DPSA remuneration scales.	Value of the award is up to R500 000.00 pa for five years comprising the first two years renewable for a further period of three years

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

LIST OF SCHOLAR ABSTRACTS 2022/2023				
SAMRC CLINICIAN RESEARCHER (M.D PHD) DEVELOPMENT PROGRAMME				
No.	**Initials**	**Surname**	**University/ Research Unit**	**Abstract Title**
1.	T	Amoa	University of Cape Town	Ameliorating the foreign body response to polymeric implants using helminth-derived extracellular vesicles.
2.	I	Beesham	University of Witwatersrand	Post-trial oral pre-exposure prophylaxis access among women from Durban, South Africa
3.	L	Farrant	University of Cape Town	Integrating palliative care into primary care for patients with chronic lung disease.
4.	G	Hyman	University of Witwatersrand	Surgical health service capacity and utilisation in Gauteng and Mpumalanga
5.	I	Francis	University of Cape Town	Clinical Factors, Environmental Risk factors and Microbiome signatures of Helicobacter Pylori in a South African cohort
6.	F	Mabena	University of Witwatersrand	ESKAPE plus Candida Colonisation among Neonates in a Regional South African Hospital
7.	N	Mboweni	University of Witwatersrand	The clinical and biochemical effects of atrial fibrillation on HFrEF; a Sub-Saharan African perspective
8.	T	Molefi	University of Pretoria	Profiling molecular pathways and therapeutic targets in endometrial cancers occurring in Black South African women
9.	Y	Moosa	University of Kwa-Zulu Natal	TB genomes, disease, and transmission in an HIV-endemic rural South African district
10.	P	Namale	University of Cape Town	Investigation of novel strategies for treatment of patients with HIV-associated disseminated TB

11.	I	Roomaney	University of Western Cape	Facial Imaging in FASD screening by Oral Health practitioners in South Africa
12.	L	Rametse	University of Cape Town	Penile Barrier Integrity; a mechanistic search for the effectiveness of Medical Male Circumcision in HIV prevention
13.	P	Rose	University of Stellenbosch	Decreased hepatic steatosis in adolescents with perinatal HIV switching to dolutegravir-containing regimens
14.	S	Simelane	University of Cape Town	Strengthening Child & Adolescent Mental Health Systems and Services in the Western Cape of South Africa.
15.	C	Snyders	University of Pretoria	Symptom number and reduced pre-infection training predict prolonged return to training after SARS-CoV-2 in athletes: AWARE IV

SAMRC INTERNSHIP SCHOLARSHIP PROGRAMME (ISP)

No.	Initials	Surname	University/ Research Unit	Abstract Title
1.	F	Barmania	University of Pretoria	Host genetic variant analysis for COVID-19 outcomes in the African population
2.	A	Hellebo	University of Cape Town	The Economic Burden, Well-Being, And Social Determinants Of Diabetes In South Africa
3.	S	Khoza	University of Western Cape	The in vitro approach to identify CatS-inhibitor compound(s) from Hypericum perforatum plant
4.	M	Kuali	University of Kwa-Zulu Natal	Effect of endo/exogenous female sex hormones on HIV-1C latent reservoir reactivation
5.	T	Lopes	Stellenbosch University	Association between PBD adherence and cardiometabolic risk profile in commercial taxi drivers.
6.	S	Madlala	University of Western Cape	Nutrient density relative to cost of commonly consumed foods

7.	PZ	Mahlobo	Stellenbosch University	Tuberculosis (TB) infectiousness and transmission (TITAN)
8.	N	Malaza	University of Pretoria	Association between microRNAs, glucose control and outcomes in diabetic pregnancies
9.	N	Mangwana	Stellenbosch University	Prevalence of Norovirus and Rotavirus in wastewater in the City of Cape Town metropolitan
10.	M	Masiza	University of Western Cape	Child and adolescents sexual abuse interventions in developing countries: A scoping review protocol
11.	S	Minnies	Stellenbosch University	Novel and rapid tests for diagnosis of tuberculosis using non-sputum specimens
12.	M	Mokoatle	University of Pretoria	Discriminatory Gleason grade group signatures of prostate cancer: An application of machine learning methods
13.	L	Montewa	University of Cape Town	Knowledge and attitudes regarding feedback of individual genetic results findings in Genomics research: A baseline survey.
14.	LB	Moyakhe	University of Cape Town	Genetic and epigenetic associations with child development and mental health
15.	N	Mthembu	University of Cape Town	Transcriptomic approach on the early development of severe asthma
16.	S	Mthembu	North West University	Role of dyslipidemia in modulating coenzyme-Q10 and mitochondrial function in cardiac muscle
17.	A	Mzukwa	University of Cape Town	A pilot study to document Schistosoma mansoni infection in Chinese rhesus macaque
18.	G	Ndlangalavu	Stellenbosch University	Novel sputum and non-sputum-based TB diagnostics in unselected ART-naïve HIV-positive outpatients

19.	L	Ndou	University of Cape Town	Investigation of Cancer Risk and Survival for Lynch Syndrome Patients Carrying the Same Pathogenic Variant MLH1 c.1528T>C
20.	T	Nkonyane	University of Cape Town	Utilization of CRISPR-interference to elucidate hierarchies of DNA repair mechanisms in Mycobacterium tuberculosis
21.	N	Ntlapo	University of Kwa-Zulu Natal	Anxiety and depression in new-onset atrial fibrillation among men and women.
22.	OV	Oyekunle	University of Kwa-Zulu Natal	Cluster randomized controlled trial of Stepping Stones and Creating Futures to reduce mental health challenges among young men in informal settlement in KwaZulu-Natal Province, South Africa
23.	S	Poswayo	University of Cape Town	Role of CysLTR1 during Mycobacterium tuberculosis and Listeria monocytogenes infection in mice
24.	D	Ralefeta	University of Cape Town	Investigating the impact of mycobacterial cell-cell heterogeneity on susceptibility to antituberculosis (TB) chemotherapy.
25.	ML	Raphela	University of Cape Town	Morphological phenoprinting of essential genes in mycobacteria using inducible CRISPR interference.
26.	L	Rockman	Stellenbosch University	Novel methods for the oral-based diagnosis of tuberculosis in an HIV-endemic setting
27.	R	Roomaney	University of Western Cape	One in five South Africans are multimorbid.
28.	B	Shabangu	University of Witwatersrand	Genomic characterisation of Acinetobacter baumannii associated with neonatal sepsis and stillbirths in a South African population
29.	K	Ziqubu	North West University	Effect of age on brown adipose tissue and batokines gene expression in type 2 diabetic (db/db) mice
30.	A	Scott	University of Cape Town	Novel biomarkers, including computer-aided radiological screening, for the community-based detection of tuberculosis

31.	E	Makanza	University of Johannesburg	COVID-19 impact on provision of pre-exposure prophylaxis among key populations: a review
32.	J	Choshi	University of Limpopo	The effect of HAART on renal function in HIV-infected patients
33.	M	Masete	University of Pretoria	Exploring the potential of DNA methylation as biomarkers for screening gestational diabetes mellitus
34.	R	Sebati	University of Johannesburg	The impact of COVID-19 on HIV treatment services among key populations: a review
35.	S	Jacobs	University of Cape Town	Common risk for epilepsy identified by GWAS: A systematic review
36.	S	Ngoto	University of the Western Cape	Assessing the effect of imbalance correction through oversampling in the prediction of injury prevalence in distance runners
37.	T	Maila	Stellenbosch University	Identification of Mycobacterium tuberculosis essential genes that potentiate the efficacy of anti-TB drugs

BONGANI MAYOSI NATIONAL HEALTH SCHOLARS PROGRAMME (BM-NHSP)

No.	Initials	Surname	University/ Research Unit	Abstract Title
1.	I	Basson	University of Cape Town	Proteomic profiling and biomarker discovery in acral lentiginous melanoma using FFPE tissue
2.	P	Bhengu	University of Cape Town	Behavioural and social drivers of human papillomavirus vaccination in eThekwini District (KwaZulu-Natal)
3.	E	Bröcker	Stellenbosch University	Preliminary findings for a PTSD Coach intervention in a resource constrained setting.

4.	L	Chetty	University of Kwa-Zulu Natal	The perceptions of older people living with HIV/AIDS towards physical activity and exercise
5.	B	Chisholm	University of Cape Town	Designing a WhatsApp-based training intervention for nurses and community health workers: research proposal.
6.	T	Elloker	University of Western Cape	Physical activity in community dwelling persons with traumatic spinal cord injuries
7.	N	Gontse	University of Kwa-Zulu Natal	Developing Practice Guideline for Enhancing Communication in Hearing Families with Deaf Children
8.	G	Inglis-Jassiem	Stellenbosch University	Descriptive Review of Online Information Resources for Stroke: A Scoping Review
9.	N	Jama	University of Western Cape	An exploration of emerging collaboration models between Traditional Health Practitioners and Mental Health Practitioners in South Africa
10.	N	Kitchin	Stellenbosch University	Investigating the gut microbiome in Foetal Alcohol Spectrum Disorders
11.	T	Mabuda	University of Western Cape	Molecular & histological effects of a novel aptamer on diet-induced obesity and steatohepatitis.
12.	R	Maharajh	University of Kwa-Zulu Natal	Identification of Mycobacterium tuberculosis immunogenic adhesin proteins as diagnostic and vaccine candidate
13.	K	Mahlatsi	University of Venda	A communal Holistic Therapeutic Approach for Psychosocial Health Management Among Southern African Indigenous Communities
14.	DG	Mashala	University of Limpopo	Socioeconomic Status and Related Sociodemography Of Unpaid Family Caregivers For The Visually Impaired Patients: A Systematic Review
15.	U	Matodzi	University of Pretoria	Detection of drug resistant tuberculosis to first-line, second-line and newer anti-tuberculosis drugs

16.	M	Mavhungu	University of Witwatersrand	SARS-CoV-2 antibody kinetics in adults and pregnant women after natural infection
17.	C	Mlandu	University of Witwatersrand	Trends and determinants of late antenatal care initiation in three East African countries. A population based cross-sectional analysis.
18.	K	Mngomezulu	University of Kwa-Zulu Natal	Investigating the potential of traditional medicine in reactivation of latent HIV-1
19.	K	Moabelo	University of Western Cape	Development of aptamer-based drug delivery systems for the treatment of obesity
20.	Tr	Mudau	University of Pretoria	Allergic rhinitis, rhinoconjunctivitis and hayfever symptoms among pre-schoolers are associated with school transport mode
21.	A	Ndadza	University of Cape Town	Pharmacogenomics of warfarin: unique profiles important for an African-specific dosing algorithm
22.	S	Ndlovu	University of Witwatersrand	Association of maternal vaginal microbiome and adverse foetal birth outcomes
23.	S	Ngobese	Sefako Makgatho Health Sciences University	Traditional And Modern Intercept of Smokeless Tobacco Use in South Africa
24.	SM	Oelofse	University of Cape Town	Unfavourable outcomes and transmission dynamics in patients with drug-resistant tuberculosis receiving bedaquiline
25.	SM	Pheeha	Stellenbosch University	Associating gut-microbiota profiles with HbA1C and immunity in type-2 diabetics/non-diabetics, with/without COVID-19
26.	A	Saferdien	University of Cape Town	Anti-Cancer effects of Dodonaea Viscosa, a Herbal Medicine used by traditional healers.
27.	MC	Salane	Sefako Makgatho Health Sciences University	Maternal depression and infant nutritional status in rural areas of Thulamela local municipality in Limpopo province

28.	D	Senthebane	University of Cape Town	The Role of The Tumour Microenvironment Components in Cancer Cell Behaviour and Drug Response.
29.	J	Shaw	Stellenbosch University	Epidemiologic And Immunologic Interactions Between COVID-19 And Tuberculosis.
30.	N	Sikhosana	University of Witwatersrand	Nano-embedded 3D-bioplatforms for Ocular Tissue Regeneration
31.	A	Thiba	University of Witwatersrand	Differences in the gut microbiome in rat models of hypertension
32.	MP	Tsweleng	University of Western Cape	The caregiving relationships of AIDS-orphaned adolescents and primary caregivers: A Systematic Review
33.	B	Tyabashe-Phume	University of Cape Town	Development of a Conceptual Framework for Self-Advocacy of Adults with Intellectual Disability
34.	A	Van der Watt	Stellenbosch University	Factors associated with distress following a romantic relationship dissolution: The moderating role of attachment style
35.	L	Zondagh	University of Western Cape	Design, synthesis, and biological evaluation of edaravone derivatives bearing the N-benzyl pyridinium moiety as multifunctional anti-Alzheimer's agents
36.	E	Mabotha	University of Cape Town	Can biomarkers in scalp hair help predict patients at risk of a heart attack?

SAMRC RESEARCH CAPACITY DEVELOPMENT INITIATIVE (RCDI): POST-GRADUATE PROGRAMME

No.	Initials	Surname	University/ Research Unit	Abstract Title
1.	NT	Banda	University of Venda	Whole genome sequencing of *Mycobacterium tuberculosis* and assessment of treatment outcome.

2.	MD	Kgakishe	University of Limpopo	Cisplatin supplementation with *Momordica balsamina* extracts to mitigate cisplatin-induced nephrotoxicity
3.	MS	Mashilo	University of Venda	The pharmacogenetics of ADME polymorphisms in tuberculosis patients from rural healthcare facilities in the Vhembe District of Limpopo
4.	T	Madzaga	University of Venda	The prevalence of hypertension among pregnant women in Sekhukhune District, Limpopo province
5.	N	Mkhize	Mangosuthu University of Technology	Investigating the efficacy of two South African medicinal plants in the treatment of lung cancer using experimental and computational methods.
6.	NP	Ndlovu		Synergistic activity of Sutherlandia frutescence and Vancomycin on Staphylococcus aureus and Enterococcus faecalis.
7.	R	Pillay	Mangosuthu University of Technology	Soil-transmitted helminthiasis and human papillomavirus co-infections: Influence of microRNA expression on female genital tract immunity and cervical carcinogenesis
8.	KG	Rakau	Sefako Makgatho Health Sciences University	Investigation of ligand compounds that can block rotavirus VP8* from binding to the host's histo-blood group antigens
9.	PY	Sikosana	Mangosuthu University of Technology	Investigating the efficacy of three South African medicinal plants in the treatment of lung cancer using experimental and computational methods.

SAMRC RESEARCHER DEVELOPMENT GRANT (RDG)

No.	Initials	Surname	University/ Research Unit	Abstract Title
1.	DEK	McPherson	University of Cape Town	Enhanced Recovery After Trauma Surgery (ERATS) : A randomized controlled trial

SAMRC CLINICIAN RESEARCHER (MD.PHD) DEVELOPMENT PROGRAMME

1. Ameliorating the foreign body response to polymeric implants using helminth-derived extracellular vesicles

T.O Amoa[1], N. Davies[1], W. Horsnell[1]

[1]University of Cape Town

BACKGROUND

Once introduced into the body, all biomaterial implants become targets of the host immune system triggering a vigorous cascade of immune events that can lead to fibrous encapsulation of the implant, limited tissue integration, neovascularization and ultimately implant failure. Even with the less sophisticated implants, it is conservatively estimated that at least 10% fail due to this foreign body immune response (FBR). To our knowledge the potential use of excretory secretory products (ESP) from helminths that have co-evolved with the host to achieve immunoregulation, creating a tolerogenic environment despite their large sizes has not been investigated. And so, we hypothesize that a sustained delivery of helminth-derived extracellular vesicles (EV), a more defined component of the ESP (excretory-secretory product) containing proteins and miRNA, localized to a polymeric biomaterial implant will dampen the FBR that leads to fibrous encapsulation of the implant and limited host-biomaterial interaction.

METHODS AND UPDATES

FACS analysis of preliminary in vivo animal studies in mice with the isolated extracellular vesicles show a downregulation of the Naïve T cell population and total CD4+ T cell population after 7 days following a single dose of Ascaris lumbricoides intraperitoneal injection. Repeat studies are underway this month. An incidental finding of the presence of human IgG4 antibody binding to an antigen in the isolated Ascaris lumbricoides extracellular vesicles points to another novel factor of these extracellular vesicles to further investigate. Thus far, Nippostrongylus brasiliensis and Ascaris lumbricoides EVs have been successfully isolated, characterized and demonstrated uptake into human dermal fibroblasts and human umbilical vein endothelial cells. Outstanding work includes: 1. Macrophage phenotype differentiation analysis. 2. Proteomic assays 3. Establishment of sustained release of helminth EVs from hydrogels and influence on the biomaterial immune environment and FBR in a rodent model.

RESEARCH AND CONCLUSION

Delivery of nematode extracellular vesicles has the potential to regulate the various host immune responses such that an implanted biomaterial is no longer considered foreign. At a minimum it should allow for enriched delineation of the roles of the diverse players in the FBR. Lastly, there are potential applications of the findings from this research in other inflammatory disorders- of particular interest to me are cardiovascular pathologies.

2. Post-trial oral pre-exposure prophylaxis access among women from Durban, South Africa

I Beesham[1], M Beksinska[1], C Milford[1], J Smit[1], L Mansoor[2]

[1]MatCH Research Unit (MRU), Department of Obstetrics and Gynaecology, Faculty of Health Sciences, University of the Witwatersrand, Durban, South Africa; [2]Centre for Aids Programme of Research in South Africa (CAPRISA), Durban, South Africa

BACKGROUND

Oral pre-exposure prophylaxis (PrEP) is increasingly being provided as human immunodeficiency virus (HIV) prevention standard of care in HIV endpoint-driven clinical trials; however, little is known about oral PrEP access and continuation among participants post-trial exit, which we explore in this abstract.

METHODS

We conducted semi-structured, in-person interviews, from November to December 2021, with 13 women from Durban, South Africa who initiated oral PrEP as part of the HIV prevention package during the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial. These women elected to continue using PrEP at the trial exit in 2018 and were referred for PrEP refills. The interview guide probed for barriers and enablers to post-trial PrEP access, and current and future PrEP use. Interviews were audio-recorded and transcribed. Thematic analysis was facilitated using NVivo. We present preliminary findings from the analysis of 10 interviews.

RESULTS

Of the 10 women, five had accessed PrEP post-study exit, four did not access PrEP, and one discontinued due to side effects. Only one woman was still using PrEP at the time of the interview. Enablers to post-trial PrEP access included facilities located close to participant's homes, short waiting queues at PrEP facilities, PrEP introduction and promotion and facilities, a referral letter from the research site, friendly and helpful providers, and transport provided from the research site to PrEP facility. Barriers to post-trial PrEP access included PrEP facilities having long waiting queues and/or being located far from women's homes, being unable to afford transport fares to access PrEP, attitudes of PrEP providers, and non-availability of PrEP at some facilities. Most women who were not on PrEP reported wanting to use it again, particularly if barriers to access could be removed and PrEP was easily available at facilities.

CONCLUSION

Our study identifies several barriers to accessing oral PrEP post study exit. Strategies to enhance post-trial oral PrEP access and continued use are needed. These include increasing PrEP availability and removing barriers to access.

3. Integrating palliative care into primary care for patients with chronic lung disease

L Farrant[1], R Harding[2], R van Zyl-Smit[3], L Gwyther[1]

[1]Dept Family, Community and Emergency Care, Faculty of Health Sciences, University of Cape Town;
[2]Cicely Saunders Institute of Palliative Care Policy and Rehabilitation, King's College London, London, UK;
[3]Division of Pulmonology and Department of Medicine University of Cape Town & Groote Schuur Hospital.

BACKGROUND

People living with chronic lung diseases (CLD) that progress over time experience burdensome physical and psychological symptoms and progressive decrease in quality of life. A palliative approach to care alongside disease-directed care is advised. Universal Health Coverage (UHC) makes provision for such palliative care at point of primary care. However, access to such care is currently limited for patients with CLD in primary care in South Africa.

METHODS

The aim of the PhD is to determine the feasibility of integrating palliative care into primary health care for patients with CLD, with the objectives relating to the three components of this multistage mixed methods study, including: i) cluster stepped wedge hybrid type two design Randomised Control Trial (RCT) with nested in-depth qualitative interviews, to explore the feasibility and acceptability of integration of palliative care into standard care for patients with CLD in primary care settings in Cape Town; ii) survey and in-depth interviews exploring barriers to diagnosis and staging in primary care; iii) systematic review of the literature on models of integration in LMICs to refine Theory of Change-designed RCT intervention with recommendations for integration of palliative care into primary care.

RESULTS

Quantitative analysis of the RCT is underway. Interim thematic analysis of professional focus group discussions suggests health system barriers, the need for clinical mentoring for extended periods of time, with clear channels for ongoing expert palliative care engagement and clinical support for professionals in primary care.

CONCLUSION

There is need for a co-ordinated approach to the integration of palliative care into the health system, spanning all levels of care, supporting quality continuity of care, with specific emphasis on systems for primary and community care. Ongoing data collection and analysis aims to explore key care pathway considerations and indicate potentially feasible models of integration of palliative care into primary care for patients with CLD.

4. Surgical health service capacity and utilisation in Gauteng and Mpumalanga

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BACKGROUND

The burden of unmet surgical need is significant. Consensus surrounding the critical indicators for the quantification of, and capacity to meet, this need is lacking. This study aims to develop the appropriate instruments and methodologies needed to conduct a comprehensive and pragmatic situational analysis of the capacity to deliver quality surgical, anaesthetic and obstetric (SAO) care in the South African public sector.

METHODS

This is a multi-method study with ethics clearance for Phase 1 (HREC number: M210912). Phase 1 comprises a scoping review on SAO outcomes data sources and semi-structured expert interviews to map SAO outcomes reporting practices; a cross-sectional study of functional operating theatre capacity, utilisation and productivity in Southern Gauteng; a cross-sectional study of surgical service utilisation and novel metric validation; a Delphi method validation of a facility SAO care capacity tool; and a surgical case volume audit. All Phase 1 studies are underway. Phase 2 will follow with retrospective audit of peri-operative mortality rate (POMR); a cross-sectional study comprising administration and validation of the adapted facility readiness tool. Phase 3 will assess the feasibility of a surveillance and response system for routinely measuring system-level risk-adjusted POMR. Interview data is recorded and transcribed using Otter-AI. Data is captured using the secure, online data collection tool REDCap.

RESULTS

Complex barriers to health system data collection exist in the public health sector including weak primary data quality and accessibility and low availability of facility managers to participate in the various studies. Challenges in obtaining study site and NHRD approval continue to delay data collection. However, data collection is satisfactory for all Phase 1 studies.

CONCLUSION

This study will provide the crucial research infrastructure and health systems strengthening needed for the sustainable monitoring and evaluation of appropriate indicators of the capacity to deliver SAO care in the South African public sector.

5. Clinical Factors, Environmental Risk factors and Microbiome signatures of Helicobacter Pylori in a South African cohort

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BACKGROUND

According to the Global Cancer Observatory (GLOBOCAN) 2018, gastric cancer (GCA) remains the 5th most common cancer and 3rd most common cause of cancer death. Environmental factors associated with GCA are *Helicobacter. pylori* (*H. pylori*) infection, diet, and smoking. We aimed at understanding the risk factors associated with GCA in South Africa (SA).

METHODS

We conducted a retrospective cohort study to determine the epidemiology of GCA among patients who are 18 years and above. Their demographic data, clinical risk factors, endoscopic and histologic pathology was collated from folders and electronic data for patients with biopsy-proven GCA.

RESULTS

Ninety patients were included with a mean age of 61 ± 11.7; 63.3% were males. At least 39% had hypertension, while 13% had diabetes. 61% were smokers, with at least 14.4% reporting alcohol use. Furthermore, at least 21% and 26.7% were non-steroidal anti-inflammatory drugs (NSAID) and proton pump inhibitor (PPI) users respectively. The commonest presenting symptoms and indications for gastroscopy were weight loss (71%) and epigastric pain (66.7%). Anaemia was common; 61% had a Hb<12g/dL on presentation, with mean haemoglobin of 10.6 ± 3.4. 70% of the cohort had associated gastritis, gastric ulcers or duodenitis at endoscopy; the commonest site

of gastric pathology was in the corpus (40%). The commonest location of reported GCA was in the lesser curvature (27%), whilst only 6.7% of tumours were in the cardia and fundus. On histology, chronic atrophic gastritis with inflammation was noted in at least 32% of samples. The overall rate of *H. pylori* on the biopsy specimen was 19% while 54% were *H. pylori* negative.

CONCLUSION

The risk of GCA is higher in adult males above 50 years and smokers. Weight loss, epigastric pain and anaemia are common features. Chronic atrophic inflammation in a third of patients was the likely precursor lesion, highlighting the contributions of *H. pylori* in the aetiopathogenesis of GCA. The limitations were those of missing data, but notwithstanding, this study gives insights into the profile of GCA in SA. Prospective cohort studies are necessary.

6. ESKAPE plus Candida Colonisation among Neonates in a Regional South African Hospital

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BACKGROUND

Neonatal *colonisation* with multidrug resistant (MDR) ESKAPE (*Enterobacter spp.*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterococcus faecium*) pathogens and *Candida spp.* is an established precursors to invasive neonatal hospital-acquired infections, which cause most neonatal deaths in low- and lower-middle income countries. Current local data on neonatal colonisation and antimicrobial susceptibility is necessary to guide prevention and treatment strategies for invasive neonatal infections.

METHODS

A prospective, observational, longitudinal surveillance for ESKAPE pathogens and *Candida* spp colonisation of neonates at Thelle Mogoerane Regional Hospital (TMRH) in Johannesburg South Africa from the 25 October 2021 to 30 April 2022. Neonates recruited at birth, had four samples (nasal, 2x skin and rectal) collected within 24hrs of birth and again at subsequent visits after 48 – 96 hours, for the duration of their admission. Demographic data obtained from the neonates' files. Samples reached the laboratories within 6 hours and had microbiological and antimicrobial susceptibility testing (nasal, skin, and rectal) as well as fungal culture procedures (skin) done.

RESULTS

102 neonates recruited. We found 79% neonates colonised with ESKAPE pathogens, 44% of these colonised within 24 hours of birth, and 45% colonised with *Candida* spp. The three most prevalent ESKAPE pathogens were *Klebsiella pneumonia* (51%), *Enterobacter* spp (18%) and *Enterococcus faecium* (11%). The three most isolated *Candida* spp were *Candida parapsilosis* (70%), *Candida auris* (19%) and *Candida albicans* (10%). Ten (12%) of the colonised neonates demised. The gram-negative ESKAPE isolates showed decreased susceptibility to

cephalosporins and carbapenems whilst the gram-positive isolates showed varying susceptibility to vancomycin and linezolid.

CONCLUSION

We found a high prevalence of MDR ESKAPE and *Candida spp* neonatal colonisation. *K. pneumoniae* shown to be a dominant, early, and long-term in hospital coloniser of admitted neonates. Sequencing of the isolates from this cohort will help with both local prevention strategies as well as future maternal vaccine interventions.

7. The clinical and biochemical effects of atrial fibrillation on HFrEF; a Sub-Saharan African perspective

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BACKGROUND

Sub-Saharan Africa (SSA) has seen a sharp increase in cardiovascular disease-related mortality. Part of this increase is evidenced by a growing burden of heart failure and atrial fibrillation (AF) risk factors. Atrial fibrillation is a common comorbidity of heart failure with reduced ejection fraction (HFrEF) which predisposes to an increased risk of morbidity and mortality. Studies that were done in high-income countries (HIC) suggest that there may be an essential role for ethnic differences. However, in the absence of accurate epidemiological data in Sub-Saharan Africa, this cannot be proven. To date, there has never been a prospective systematic description of patients with HFrEF/AF and HFrEF/sinus rhythm (SR). Our study aimed to describe the clinical and biochemical profile of patients with HFrEF/AF and HFrEF/SR in a Sub-Saharan African cohort

METHODS

The study was conducted in the Division of Cardiology at Charlotte Maxeke Academic Hospital in Johannesburg, South Africa. We consecutively enrolled 141 patients with HFrEF. Baseline clinical characteristics and exploratory biomarkers were recorded. All participants underwent comprehensive echocardiography. The novel's left atrial strain was measured using 2D-speckle tracking echocardiography. These values were compared between patients in SR and in AF.

RESULTS

The prevalence of AF was 21.38 %. Hypertensive heart disease was the leading cause of HFrEF (36%). HFrEF/AF patients were significantly older (66.7 ± 11.9) than those in SR (53.7 ± 14.4) (p=0.000) with significantly different racial proportions (p=0.001). Coronary artery disease was prevalent in patients with HFrEF/AF. Patients with HFrEF/AF had significantly lower Kansas City Cardiomyopathy Questionnaire scores (29.83 ± 15.27) compared to those in SR (44.26 ± 16.30) (p=0.000) as well as worsening functional class (NYHA III-IV; 64.3% vs 22.7%, p=0.000). Measured levels of sST2 were greater in HFrEF/AF patients 40.45ng/mL (17.6-68.6) vs 20.8 ng/mL (7.9-44.0) in HFrEF/SR (p=0.031). Similarly, that of GDF-15 (457.85 ng/mL [263.4 – 754.3] vs 699.30 ng/mL [485.8-1007.4]; p=0.014). Levels of galectin 3 showed no difference across groups. Patients with HFrEF/AF had a significantly greater left atrial volume (ml) (83.9 [64-99.9]) than those with HFrEF/SR (61.53 ± 25.46) (p=0.038). Left atrial strain reservoir function (%) was significantly lower in patients with HFrEF/AF (29.00 ± 13.60) compared to those with HFrEF/SR (41.56 ± 15.46) (p=0.0004).

CONCLUSION

Our findings demonstrate that patients with HFrEF/AF are older than those in SR, but much younger compared to patients in HICs. Hypertensive heart disease is a major cause of HFrEF in South Africa. We demonstrate that patients with HFrEF/AF are clinically worse off than those with HFrEF/SR. Atrial fibrillation is a marker of fibrosis and disease severity in HFrEF. Patients with HFrEF/AF had elevated sST2 levels, a more deformed left atrium morphologically, and poor tissue doppler function. On strain imaging, HFrEF/AF patients had poor left atrial reservoir function.

8. Profiling molecular pathways and therapeutic targets in endometrial cancers occurring in Black South African women

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BACKGROUND

Endometrial cancer (EC), which is classified as type 1 and type 2, is the most common gynaecological malignancy in developed countries and has a higher incidence in white women. Despite EC's lower incidence in Black women, this population's mortality is up to 80% greater than that of white women. The less common, more aggressive type 2 EC subtypes have the worst prognosis and predominantly occur in African-Americans. Despite this disproportionate aggressive behaviour, the genomics of EC in black South African women is largely unexplored.

METHODS

Retrospective epidemiological, clinical and outcomes data, from 2012 to 2016, will be analysed from the files of patients seen in the Department of Medical Oncology, at the Steve Biko Academic Hospital. This data will be used to describe the predominant EC histotype and the patients' 5 year survival rates in our cohort. Using the histology reports from files of patient's seen, purposive selection of 96 type 2 EC archived FFPE (formalin-fixed paraffin-embedded) tissue blocks from black females will be done, followed by RNA (ribonucleic acid) extraction and library preparation for RNA sequencing (RNA-seq). Digital droplet polymerase chain reaction (ddPCR) will be used for RNA-seq validation and mutational analysis. Once bioinformatic analysis of the molecular signatures from our cohort is carried out, the results will be compared to USA (United States of America) genomic information from the Genomic Data Commons.

RESULTS

South African data on EC is lacking and, in a country, predominated by black Africans, this disease and its racial disparities warrants further study. We hope to gain important insights into the pathogenesis of EC in Black South African women and ascertain if Type 2 EC is the predominant subtype in this cohort.

CONCLUSION

The molecular information gathered from this study will improve our understanding of the aggressiveness of endometrial cancers in Black patients. The exploration of the aberrant molecular pathways in Black Africans will assist in identifying future drug targets and help address EC's racial disparities.

Unfortunately, in 2021 I experienced delays from the Faculty of Health Sciences, School of Medicine PhD committee. I obtained approval to submit my proposal to the Research Ethics

Committee in February of 2022 from an alternate PhD committee and I am currently awaiting approval.

9. TB genomes, disease and transmission in an HIV-endemic rural South African district

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BACKGROUND

We characterized prevalent tuberculosis (TB) in an HIV-TB-endemic rural South African population with wide-scale ART uptake.

METHODS

Between 2018-2020, adolescent and adult residents of a rural demographic surveillance area in KwaZulu-Natal, South Africa were offered multi-disease screening, including TB symptom screening and digital chest x-ray. People with symptoms or radiological abnormality (CAD4TBv5 score ≥25) had sputum collected for GeneXpert Ultra and MGIT liquid culture. Cultured isolates underwent phenotypic drug sensitivity testing and whole genome sequencing. Those not on TB treatment with evidence of *Mycobacterium tuberculosis* in the sputum were considered to have undiagnosed TB. We compared people with undiagnosed TB to those without TB and to those on TB treatment, and asymptomatic undiagnosed TB to symptomatic.

RESULTS

0.4% of enrolled participants (41/18041) were on TB treatment. 1.0% (174/18041) had undiagnosed TB. Compared to people without TB, people with undiagnosed TB were more likely to be male (OR 1.8, p<0.001), smokers (OR 2.7, p<0.001) and HIV-positive (OR 2.3, p=0.004). Compared to those on treatment, the undiagnosed were more likely to be HIV-negative (OR 2.3, p=0.003). 82.2% (143/174) of people with undiagnosed TB reported no symptoms, and their self-reported health score (median 98 [IQR 80-100]) was similar to those without TB (90 [80-100]). Compared to symptomatic people, the asymptomatic were similar in age, sex and HIV status, and less likely to be underweight (BMI<18.5; OR 0.29, p=0.038) or smoke tobacco (OR 0.32, p=0.012). 10.9% (19/174) of sputum samples from people with undiagnosed TB showed phenotypic evidence of resistance to at least one anti-TB drug. Of these, 47.4% (9/19) met criteria for MDR, 10.5% (2/19) for pre-XDR, and 26.3% (5/19) were INH-mono-resistant. 89.4% (17/19) of individuals with phenotypic drug resistant TB were asymptomatic, and 84.2% (16/19) reported no previous TB treatment. In total, GeneXpert Ultra, the first line for identifying drug-resistant TB in

South Africa's national TB strategy, identified only 15.7% (3/19) cases of phenotypic drug resistance.

CONCLUSION

There is a high prevalence of undiagnosed TB in rural KwaZulu-Natal and over 80% of these individuals report no TB symptoms. More than half of undiagnosed TB is among the HIV-negative (in contrast to less than 30% of clinically diagnosed), suggesting enhanced screening in the HIV-negative population is needed. Phenotypic drug resistance testing demonstrated high levels of drug resistance, the majority of which were identified in asymptomatic individuals. Further research is needed to understand the progression and transmission of asymptomatic TB, which dominates active disease in the region.

10. Investigation of novel strategies for treatment of patients with HIV-associated disseminated TB

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BACKGROUND

Tuberculosis (TB) is the leading cause of death and hospitalisation among HIV-positive patients world-wide. Our research group reported that 12-week mortality was 21.5% in an observation cohort of 576 hospitalised HIV-positive patients, 65% of whom had disseminated TB. The burden of disseminated TB among HIV patients is high and leads to a high mortality.

METHODS

The main trial is a Phase III, 2x2 factorial, randomised controlled superiority trial (RCT) of high dose rifampicin (35mg/kg) plus levofloxacin versus rifampicin at 10mg/kg as part of standard antituberculosis therapy and prednisone (1.5 mg/kg) versus placebo for the first 2 weeks. Patients will then continue standard TB therapy for 24 weeks. We will enroll 732 patients and the overall aim is to assess safety and efficacy of the interventions. The main objective is to assess 12-week mortality without increased hepatic toxicity. My PhD is nested within this trial including pharmacokinetic and a biomarker sub study.

RESULTS

To date we have recruited 150 patients. I have written up the protocol for the PK sub study with the objective of defining pharmacokinetics of high dose rifampicin and standard rifampicin in a subset of patients. I am also collecting samples for a biomarker sub study with the objective of describing and comparing the change in mycobacterial load in a subset of patients in the 2 rifampicin arms. The biomarkers that are proxy for mycobacterial load that we are evaluating are urine LAM, urine Xpert ultra, blood Xpert ultra and TB blood culture.

CONCLUSION

We are testing interventions using drugs that exist in our setting and are accessible. If the interventions lead to a reduction in mortality, these drugs will avert a substantial number of deaths. The results will provide evidence for change in management of these patients.

11. Facial Imaging in FASD screening by Oral Health practitioners in South Africa

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BACKGROUND

South Africa carries the highest prevalence of Foetal Alcohol Spectrum Disorder (FASD) globally. Even so, the condition remains underdiagnosed and misdiagnosed. Facial imaging tools have shown potential for use in FASD screening and diagnosis. Oral health practitioners (OHPs) are well positioned to screen for medical conditions at a community level. This study aims to assess the suitability of OHPs in South Africa to screen for FASD using facial imaging tools.

METHODS

This study consists of several phases: (1) A questionnaire of OHPs knowledge, beliefs, practices and willingness to screen for FASD; (2) A scoping review evaluating the state of evidence of facial imaging technologies in screening for FASD; (3) An assessment of the accuracy of the Face2Gene app in screening for FASD in a South African cohort; (4) The development of guidelines and recommendations for the use of facial imaging technology to screen for FASD by South Africans OHPs.

RESULTS

Results from the published scoping review indicate insufficient evidence to support the use of the available imaging tools for screening for FASD at a community level. The Face2Gene application most closely conforms to the ideal properties of a screening tool identified in the review; however, accuracy on a large South African cohort has not been tested. Results from the pilot questionnaire indicate that OHPs currently have limited knowledge of FASD but are willing to undergo training in this regard.

CONCLUSION

FASD has a considerable societal and economic burden in South Africa and is a neglected area of research and policy. This study has significant potential to impact the curriculum of under- and postgraduate OHPs, thus, expanding their role to include screening for FASD and influencing health policy.

12. Penile Barrier Integrity; a mechanistic search for the effectiveness of Medical Male Circumcision in HIV prevention

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BACKGROUND

The biological mechanisms underlying Human immunodeficiency virus (HIV) risk reduction following medical circumcision remain ill-defined. We sought to understand two aspects of whether circumcision can improve skin barrier integrity of the penis: in the absence and presence of an asymptomatic sexually transmitted infection (aSTI); the rationale being that changes in skin barrier integrity led to a lower risk of HIV susceptibility.

OBJECTIVES

We used hand-held meter devices to measure changes to skin barrier integrity in various sites on

the penis of adults assigned male sex at birth. In vivo measurements of transepithelial water loss (TEWL) and skin hydration (proxies for barrier integrity) were taken directly on penile skin before and after MMC and in the absence/presence of an aSTI, the most common being Chlamydia trachomatis (approx. 11%).

METHODS

Vapometers and moisture meters SC, D, and EpiD were used to measure TEWL (n=155) and dermal surface hydration (n=170) of the glans, inner foreskin, and penile shaft before circumcision. Follow-up measurements were made at 2, 12, and 24 weeks after circumcision in the glans and shaft (n=16). Urines were collected for aSTI screening.

RESULTS

Compared to the shaft (16 g/hr/m2 &), there was higher TEWL in the inner foreskin and glans in the absence of an aSTI (Medians of 27.6 and 22.3 g/hr/m2; both p<0,0001 respectively). Furthermore, the inner foreskin hydration (Median 86,46 au) had increased hydration compared to the shaft (Median 54,61 au) p value<0,0001. Follow-up at six months after circumcision showed a significant decrease in TEWL in the glans (p=0.011) from the baseline, matching that of the shaft. Finally, prior to circumcision, the glans of participants with aSTI showed higher hydration compared to STI-negative participants (97.4 vs 52.3 au; p= 0.0380).

CONCLUSION

Reduced TEWL after MMC in the glans without an aSTI suggests that skin barrier integrity increases after medical circumcision and may partly contribute to lower HIV-1 susceptibility. The higher glans skin moisture content in the presence of an aSTI before circumcision could create an infection-friendly niche and potentially lead to higher HIV-1 susceptibility.

13. Decreased hepatic steatosis in adolescents with perinatal HIV switching to dolutegravir-containing regimens

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BACKGROUND

Although dolutegravir (DTG) has a favourable metabolic profile, it has been linked to excess weight gain. We evaluated changes in hepatic steatosis in adolescents with perinatally acquired HIV switching to a DTG-containing regimen.

METHODS

Adolescents on antiretroviral therapy (ART) were assessed annually in a prospective cohort study with anthropometry, transient elastography with controlled attenuation parameter (CAP) and fasting metabolic profiles. ART regimens were determined independently of the study. Virologically suppressed adolescents both remaining on unchanged ART (84% protease inhibitor) or switched to dolutegravir for a minimum of four months were studied.

RESULTS

68 adolescents (baseline median age 13.5 years [IQR 12.5-14.4 years]; 42 [62%] female) were followed for a median of 56 weeks (IQR 49 – 105 weeks), 30 switched to DTG. There was no baseline difference in CAP between groups. There was no significant change in body mass index z-score in either group, but median CAP in the DTG group decreased by -40dB/m (IQR -51 to -31dB/m) after a median of 44 weeks (IQR 28 – 50 weeks) on DTG, compared to +1dB/m (IQR -29 to +14dB/m) in adolescents not switched ($p<0.01$). Total cholesterol and triglycerides were lower in those switched. Whereas hepatic steatosis prevalence decreased from 17% to 3% in lean adolescents switched to dolutegravir, its prevalence doubled from 8% to 16% in those not switched.

CONCLUSION

Adolescents switched to a DTG-containing regimen had reduced hepatic steatosis, total cholesterol and triglycerides with no excess weight gain compared to those on unchanged ART.

14. Strengthening Child & Adolescent Mental Health Systems and Services in the Western Cape of South Africa.

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BACKGROUND

Mental health disorders represent the greatest burden of disease in children and adolescents. Most young people live in low- and middle-income countries (LMICs) like South Africa. Previous research has shown that child and adolescent mental health systems and services (CAMHSS) in South Africa remain neglected across all the World Health Organization health system building blocks. This project aims to strengthen CAMHSS in South Africa.

METHODS

1) A targeted review to identify CAMHSS strengthening innovations across LMICs in different WHO regions was conducted.

2) A cross-sectional, nationwide electronic survey was conducted to determine CAMH service provider perspectives on the state of CAMHSS in South Africa and areas to be prioritised for strengthening.

3) A series of theory of change (Toc) workshops will be conducted with stakeholders to develop a programme theory for a CAMHSS strengthening initiative in the Western Cape

4) The implementation of an evidence-based practice in the primary care setting using the exploration, preparation, implementation, and sustainment framework

RESULTS

The targeted review identified twelve CAMHSS-specific strengthening projects in LMICs geared towards strengthening primary care services, capacity-building, and task-sharing, intersectoral collaboration, public mental health literacy, improving research, and using digital technologies. Preliminary analysis of the survey results suggests that deficits in CAMHSS identified in the Western Cape are similar in other South African provinces. The ToC workshop identified the following long-term outcomes as necessary for strengthening CAMHSS 1) the development of tertiary “centres of expertise”, 2) well-functioning, integrated clinical systems, 3) adequate, child-friendly infrastructure 4) integrated governance structures and established links with other sectors

and 5) prioritisation on the public agenda. Results for implementation to follow.

CONCLUSION

South Africa CAMHSS has deficits across the health system building blocks. Implementation strategies that have been used in other LMICs and may be used to addressing this problem. This will require the development of stakeholder informed health system strengthening initiatives.

15. Symptom number and reduced pre-infection training predict prolonged return to training after SARS-CoV-2 in athletes: AWARE IV

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PURPOSE

To determine factors predictive of prolonged return to training (RTT) in athletes with recent SARS-CoV-2 infection

METHODS

Cross-sectional descriptive study. Athletes (n=207) with confirmed SARS-CoV-2 infection completed an online survey detailing the following factors: demographics (age, sex), level of sport participation, history of co-morbidities and pre-infection training (training hours and competition 7 days before infection), SARS-CoV-2 symptoms (26 in 3 categories; “nose and throat”, “chest and neck”, and “whole body”) and days to RTT. The main outcome was the hazard ratios (HR; 95%CI) for athletes with vs. without a factor, explored in univariate and multiple models. A HR<1 was predictive of prolonged RTT (reduced % chance of RTT in the 42 days after symptom onset). Significance was $p<0.05$.

RESULTS

Age, level of sport participation and history of co-morbidities were not predictors of prolonged RTT. Significant predictors of prolonged RTT (univariate model) were (HR;95%CI): female (0.6;0.4-0.9; p=0.01), reduced training (1.03;1.01-1.06; p=0.003), and not competing in the 7 days pre-infection (0.54;0.37-0.78; p=0.001), presence of symptoms by anatomical region [any “chest and neck” (0.6; 0.4-0.8; p=0.004) and any “whole body” (0.6; 0.4-0.9; p=0.025)], and several specific symptoms. Multiple models show that the greater number of symptoms in each anatomical region (adjusted for training hours in the 7 days (pre-infection) was associated with prolonged RTT ($p<0.05$).

CONCLUSION

Reduced pre-infection training hours and the number of acute infection symptoms may predict prolonged RTT in athletes with recent SARS-CoV-2 infection. These data can assist physicians as well as athletes or coaches in planning and guiding RTT in athletes after SARS-CoV-2 infection. Future studies can explore whether these variables can be used to classify severity of acute respiratory infection in athletes

SAMRC INTERNSHIP SCHOLARSHIP PROGRAMME (ISP)

1. Host genetic variant analysis for COVID-19 outcomes in the African population

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BACKGROUND

COVID-19 is highly variable in its clinical presentation with host genetic variation being implicated in the heterogeneous outcomes found. Several studies have identified variants in genes significantly associated with susceptibility or severity outcomes. These studies have been largely restricted to the European and Asian population groups with no genetic data to currently represent the associated outcomes of African COVID-19 patients.

METHODS

An in-house bioinformatic pipeline is currently being used to analyse secondary African genomic data from the publicly available 1000 genomes project. A further 1189 whole genome sequences and 267 whole exome sequences obtained with permission from various consortiums will also be analysed. A public resource database has been created which consists of all published COVID-19-associated gene regions.

RESULTS

A list of gene regions associated with COVID-19 outcomes has been compiled and is being used to analyse variants, both known and novel, in the African population data obtained. Currently, the pipeline is being modified and tested on a small number of genomes and outputs are being analysed to ensure accuracy for larger datasets. The web-based database, the Coronavirus host genetics South African (COHG-SA) database (http://covgene.bi.up.ac.za) has been made publicly available online and is updated regularly with newly published COVID-19 host genetic content.

CONCLUSION

The lack of data from African individuals regarding genetic variation in COVID-19-associated genes is concerning since many of these genes are potential targets for drug repurposing, discovery, and subsequent treatment. The COHG-SA database we have created houses genes associated with COVID-19 outcomes under a single resource and will aid in facilitating researchers and or clinicians in understanding how genetics may predispose individuals or population groups to the various COVID-19 outcomes. The results from this study together with the COHG-SA database will therefore be clinically significant for COVID-19 treatment in ethnolinguistic groups from Africa.

2. The Economic Burden, Well-Being, And Social Determinants Of Diabetes In South Africa

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BACKGROUND

South Africa is currently facing a diabetes epidemic. The incidence rate increased in both urban and rural settings, equally affecting both genders. Diabetes decreases the quality of life (QoL) while increasing the risk of premature death and reducing work productivity. QoL and productivity losses due to diabetes are not well understood, particularly within the African context. In addition, social determinants of health (SDoH) regarding diabetes care utilisation are equally not understood, and to our knowledge, no such study exists. This study aims to examine and analyse the economic burden, well-being and productivity loss among diabetics in South Africa as well as assess the SDoH effect on diabetes care utilisation.

METHODS

This study is a sub-study of Project Mind. The baseline and follow-up data from Project Mind will be used for this PhD. The descriptive and logistic regressions will be performed to identify the effect of SDoH on diabetes care. While EQ-5D-3L will be used to assess the QoL in diabetes. A life table modelling, and decision analysis will be utilised with simulated follow-up of the participants to quantify PALYs using Stats SA data. In addition, the cost will be estimated from the patient perspective, to establish the cost of diabetes care drivers.

PROGRESS TO DATE

Proposal submitted to the internal reviewers and awaiting presentation date and an outcome. However, considerable progress has been made in the systematic literature review.

CONCLUSION

The study hopes to provide further insight into the economic burden, well-being, and social determinants of diabetes in South Africa. This information may assist the government to formulate adequate policies to attend to the growing problem of the diabetes epidemic in South Africa. In addition, it will provide crucial scientific evidence for understanding the resource implications of the diabetes burden in the context of proposals for National Health Insurance.

3. The *in vitro* approach to identify CatS-inhibitor compound(s) from *Hypericum perforatum* plant

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BACKGROUND

Cathepsin S (CatS) activity is implicated in several pathological processes leading to the development of cardiovascular diseases (CVDs). In normal physiology, the inhibition of CatS is highlighted as a promising intervention in reducing plaque development and diminishing the effect of CVDs. Therefore, this study aims to identify the inhibitory effect of procyanidin, chlorogenic acid, and quercetin compounds against CatS activity.

METHODS

The molecular operating environment (MOE) approach was utilized for evaluating potential inhibitors of CatS protein (PDB ID: 4P6G) and the ligand. The inhibitory effects of the compounds isolated from *Hypericum perforatum* (procyanidin, chlorogenic acid, and quercetin) were investigated by preparing their essay according to the Cathepsin S inhibitor screening kit (ab 185437) and were quantified using a fluorimeter microplate reader.

RESULTS

Procyanidin formed covalent interactions with the active site Cys25 and had the best s-score of -7.352 Kcal/mol. Noncovalent CatS inhibitors including quercetin and chlorogenic acid occupied the S2 and S3 pockets of the CatS enzyme with an s-score of -5.220 Kcal/mol and -5.586 Kcal/mol, respectively. These results indicated a good interaction for the inhibition of CatS and allowed us to further evaluate the suitability of these inhibitors as potential drugs for CVDs. The ability to inhibit the CatS enzyme activity for procyanidin and quercetin showed a dose-dependent manner. These two compounds proved to be strong inhibitors of CatS at a higher concentration of 65% - 100% and 16% - 76% at ten-fold concentration, respectively. This demonstrated the great inhibition of CatS which can be beneficial in treating CVDs, including atherosclerosis.

CONCLUSION

The *in vitro* study demonstrated a strong CatS inhibitory effect by the selected compounds. Thus, it can be hypothesized that *Hypericum perforatum* may be considered for the treatment of CVDs and this is based on their ability to inhibit CatS.

4. Effect of endo/exogenous female sex hormones on HIV-1C latent reservoir reactivation

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BACKGROUND

The persistent latent reservoir is the major drawback to developing an HIV cure. Latent reservoir is comprised of replication competent but transcriptionally silent viruses. While the mechanisms that govern HIV latency are not fully elucidated, a previous study demonstrated that estrogen receptor-1 (ESR-1) was a key factor regulating HIV-1 subtype B (HIV-1B) latency. Inter-subtype genetic variation has been mapped to the viral promoter, 5' long terminal repeat (LTR) that drives viral gene transcription. However, the effects of ESR-1 on other subtypes such as HIV-1 subtype C predominantly found in Sub Saharan Africa are unknown. Therefore, the major aim of this study is to investigate the effect of endogenous and exogenous female sex hormone levels on the reservoir size and reactivation potential in women living with HIV (WLHIV) who are on suppressive cART in South Africa. To this effect we undertook to determine the ESR-1 expression profile, its association with the reservoir size and reactivation potential in young WLHIV in Durban, South Africa.

METHODS

Total RNA was extracted from pure CD4+ T cells at different time points (transmission, 1 year post infection prior to combination antiretroviral therapy (cART) initiation and 2 years post successful cART), cDNA was synthesized, ESR1 mRNA expression levels quantified by qPCR and reactivation potential determined by TILDA.

RESULTS

My preliminary data show a trend towards higher ESR-1 mRNA levels in CD4+ T cells obtained WLHIV at 1 year post infection compared to at transmission and 2 years post successful cART from young WLHIV. Currently (June-September 2022) I am at Erasmus MC in Rotterdam, The Netherlands receiving training on reactivation using TILDA.

CONCLUSION

While samples at 1 year post infection showed a pattern towards higher expression, more samples need to be processed. TILDA will be performed on the samples of interest.

5. Association between PBD adherence and cardiometabolic risk profile in commercial taxi drivers

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BACKGROUND

Consumption of unhealthy foods and having a sedentary lifestyle predisposes individuals to non-communicable diseases (NCDs). This study investigated the association between plant-based diet (PBD) adherence and cardiometabolic risk in high-risk commercial taxi drivers in the Cape Metropole.

METHODS

Secondary cross-sectional analysis was conducted among commercial taxi drivers who consumed street foods sold by vendors. Two hundred and thirty-seven commercial taxi drivers were conveniently sampled from Bellville and Cape Town taxi ranks. A validated questionnaire was administered to obtain quantified dietary data using a 24-hour recall and fasting blood samples were collected for biochemical analysis. Statistical analyses were performed by study area to determine the association between PBD adherence and cardiometabolic risk, while adjusting for energy intake and age in the regression models.

RESULTS

The analytic sample consisted of 189 males with a mean age of 40 ± 10.6 years. Taxi drivers operating in Cape Town had significantly greater PBD adherence than those in Bellville: 45% vs 22% for the overall PBD index (PDI), p=0.003; 26% vs 25% for the healthful PBD index (hPDI), p=0.004; and 33% vs 23% for the unhealthful PBD index (uPDI), p=0.320. hPDI was positively associated with fasting high-density lipoprotein cholesterol (HDL-C) and negatively associated with triglyceride levels; standardised beta co-efficient (β) = 0.148, p=0.043 and β = -0.145, p=0.046, respectively. Logistic regression analysis revealed a sustained positive association between hPDI and fasting HDL-C; adjusted odds ratio (AOR) = 1.82, 95% confidence intervals (95% CI): 1.15-2.88, p=0.011. Moreover, hPDI had a positive association with hs-CRP >3 mg/L; AOR=1.54, 95%CI:1.00-2.38, p=0.051.

CONCLUSION

Greater adherence to the hPDI was positively associated with HDL-C and sub-clinical inflammation in commercial taxi drivers. These preliminary findings need confirmation and larger

and more elaborated studies, to be explored for prevention and control interventions.

6. Nutrient density relative to cost of commonly consumed foods

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BACKGROUND

Cost of food is one of the key drivers of food choices, and poor dietary intake is often attributed to unaffordability of nutritious food. The present study aimed to determine the nutrient density of foods relative to cost with the aim to identify foods within food groups with the best nutritional value per cost.

METHODS

A checklist was developed for recording type, unit, and cost of 116 food items. Food prices were obtained from the websites of three national supermarkets and were used to calculate cost per 418kJ for each food item. Nutrition composition data was obtained from the South African Food Composition Tables. The Nutrient Rich Food (NFR9.3) score was calculated based on nine nutrients to encourage (protein, fibre, vitamin A, vitamin C, vitamin D, vitamin B12, calcium, magnesium, and iron) and three nutrients to limit (saturated fat, added sugar and sodium). Nutrient density relative to cost was calculated as NFR9.3/cost per 418kJ.

RESULTS

Vitamin A-rich vegetables and fruits had the highest NRF9.3 score (109) and sugary foods had the lowest NRF9.3 score (-34). Overall, vegetables and fruits had the highest cost per 418kJ. Foods with the lowest cost per 418kJ were predominately starchy foods, oils and fats and high fat foods and sugary foods. Fortified starchy foods such as maizemeal and bread had the best nutritional value per cost. Vegetables with the best nutritional value per cost were carrots, butternut, and orange-fleshed sweet potato. Oranges and bananas were the fruits with the best nutritional value per cost. Sources of protein with the best nutritional value per cost were beans, lentils, chicken giblets, eggs, soya mince and pilchards.

CONCLUSION

This study has identified foods with the best nutritional value per cost. Findings from this research can be used to assist South African consumers in identifying nutrient dense and affordable foods when shopping.

7. Tuberculosis (TB) infectiousness and transmission (TITAN)

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BACKGROUND

Tuberculosis (TB) is a respiratory disease caused by *Mycobacterium tuberculosis* (*Mtb*) infection

indirectly transmitted from one person to another via aerosols that remain airborne. Tuberculosis is one of the leading causes of death globally and the second most infectious disease. In 2021, the World Health Organization (WHO) reported 1.5 million deaths from TB-infected persons. Most studies have used animal infection models to understand airborne survival and infectiousness of mycobacteria. Critical to aerosolisation of any pathogenic microorganism, is the ability to survive stresses experienced during aerosolisation. The probability of *Mtb* successfully infecting a host during airborne transmission is dependent on various factors in addition to its airborne survival characteristics, which may also vary between strains.

METHODS

We determined the effectiveness of the anti-TB drug after two weeks of effective treatment. Patients' respiratory aerosols were quantified and measured culturability.

We also used a Sampler for *In Vitro* Aerosols (SIVA) to optimise and measure mycobacterial viability from recoverable aerosolised bacilli. Non-pathogenic *M. Bovis - Bacille Calmette-Guérin (*BCG) Pasteur strain was used to assess recovery over time by quantifying culturability from solid and liquid culture, and *Mtb* DNA (7H11, MGIT, and Gene Xpert MTB/RIF Ultra).

RESULTS

Anti-TB drug treatment reduced the infectiousness of respiratory aerosols from TB patients captured from normal breathing and cough using a Human Aerosol Chamber (HAC).

SIVA has shown the ability to study mycobacterial aerosols. The culturability of aerosols is reduced as a result of aerosolisation. However, we do not have enough data to conclude the effect of aerosolisation from different *Mtb* strains.

CONCLUSION

This data will inform us whether 2 weeks of effective anti-TB treatment is enough to consider a TB patient non-infectious. Furthermore, this will influence when patients can be considered "safe" to be discharged from the hospital and could lead to a decline in infectiousness as a potential endpoint for TB infection and more effective treatment trials.

Differences in epidemiological success and virulence of *Mtb* strains is not clear whether they are associated with airborne survival. SIVA will be used to further understand this phenomenon.

8. Association between microRNAs, glucose control and outcomes in diabetic pregnancies

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BACKGROUND

In 2021, 16.7% of pregnancies were complicated by type1 (T1D), type 2 (T2D) or gestational diabetes (GDM). Maternal diabetes is associated with adverse outcomes for mothers and their children, with the frequency of the adverse outcomes related to the type of diabetes. Although conflicting results are reported, adverse outcomes are more common in pregnancies complicated by pregestational diabetes than GDM. The aim of the study is investigating the effect of different types of diabetes in pregnancy on adverse outcomes.

METHODS

Objective 1: A scoping review on literature on the association between maternal diabetes and adverse outcomes. **Objective 2:** Investigating the association between maternal diabetes and adverse outcomes in a smaller cohort (n= 183) at Biko Academic Hospital (SBAH). **Objective 3:** A large audit investigating adverse outcomes in pregnancies complicated by T1D, T2D and GDM (n= 688) at SBAH and Kalafong Provincial Tertiary hospital (KPTH) between 2008 and 2019. **Objective 4:** Correlate pregnancy miRNA patterns with six weeks and six months post pregnancy miRNA patterns, and perinatal outcomes and glycemic control.

RESULTS

Objective 1: *A systematic review to explore the association between maternal diabetes and adverse pregnancy outcomes* submitted for publication. **Objective 2:** Article investigating the association between maternal diabetes and adverse outcomes at SBAH is outlined and preliminary results are underway. **Objective 3:** Maternal and perinatal outcomes database at SBAH is 65% complete and at KPTH is 30% complete. **Objective 4:** MiRNA validation for collected samples is underway. The 6 weeks follow-up enrolment is underway. Selected outcomes include gestational age at delivery, mode and route of delivery, fetal growth, birth weight, Apgar score and fetal outcome. All participant data has been captured on excel and transfer to RedCap is also underway.

CONCLUSION

This study will advance our knowledge and understanding of how maternal diabetes and glucose control affect perinatal outcomes. Clinically, these miRNAs may facilitate stricter glucose control during pregnancy and help decrease adverse maternal and fetal pregnancy outcomes.

9. Prevalence of Norovirus and Rotavirus in wastewater in the City of Cape Town metropolitan

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BACKGROUND

Norovirus (NoV) and Rotavirus (RV) are the most common enteric viruses causing acute gastroenteritis (AGE) amongst all ages globally. NoV is the leading cause of non-bacterial sporadic cases and outbreaks of AGE, as well as the major source of foodborne gastroenteritis worldwide. While RV mostly affects neonates and children under the age of five, with long-term environmental stability, resulting in infection lasting longer than two months. AGE outbreaks in children, have a significant impact on public health, making surveillance for NoV and RV imperative. However, it's unclear how testing wastewater for the presence of AGE can affect the prevalence of human infection. Thus far, no research in South Africa has shown a link between wastewater viral loads and clinically reported cases. As a result, this retrospective study aims to screen NoV and RV in wastewater from the City of Cape Town to assess their prevalence and correlation with clinical outcomes.

METHODS

RNA extracted from wastewater collected as part of the SARS-CoV-2 surveillance from January 2021 to November 2021 will be used, with a focus on the metro's three major WWTPs: Athlone,

Cape Flats, and Zandvliet. For NoV and RV surveillance, RNA will be amplified using RT-PCR with primers targeting the NSP3 region of Rotavirus A and the ORF1/2 junction of Norovirus (GI and GII). Following that, the experimental results will be compared to retrospective clinical data obtained from local health authorities to determine the virus's prevalence in different communities. Ethical clearance to access clinical data will be obtained before the commencement of the study.

EXPECTED RESULTS

We hypothesize that an increase in NoV and RV in wastewater will be correlated with an increase in clinical cases. As a result, this study will demonstrate the use of WBE in tracking the development of NoV and RV outbreaks within communities.

10. Child and adolescent sexual abuse interventions in developing countries: A scoping review protocol

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BACKGROUND

There is a concern about the high prevalence of child and adolescent sexual abuse (CASA) in developing countries due to the adverse consequences posed by CASA on victims. The CASA victims are exposed to physical, psychological, sexual, and reproductive health consequences to mention a few. Despite this knowledge, there islimited research that focuses on the available CASA interventions in developing countries. This scoping review aims to comprehensively explore available CASA interventions for children and adolescents in developing countries to identify gaps and inform future intervention development.

METHODS AND ANALYSIS

Four databases (PsychAricles, SocINDEX, Google scholar, and Jstor) will be used to obtain peer-reviewed and grey literature published up to 2022. The study will include qualitative, quantitative, and mixed methods studies that examine prevention and support intervention focusing on children and adolescents in developing countries. Interventions that are prevention-based and those that are meant for post-sexual abuse will be included in this study. Search output will be exported to Endnote. Screening and data abstraction will be conducted by two or more reviewers independently. The narrative analysis will be used to analyse the data and PRISMA guidelines will be followed for reporting the findings.

ETHICS AND DISSEMINATION

This is a scoping review and therefore does not require ethics approval. The dissemination strategy for this review includes peer review publication and presentation at conferences.

CONCLUSION

Interventions in developing countries predominantly focus on prevention strategies for this population with few focusing on post CASA. Even when these interventions are available, they implemented at school which excludes out of school adolescents. While prevention interventions are important, there is also serious need for interventions for those with a history of CASA to address implications such as SRH consequences posed by CASA. Therefore, research also

needs to focus on interventions for victims post CASA. The efficacy of currently available interventions also needs to be investigated.

11. Novel and rapid tests for diagnosis of tuberculosis using non-sputum specimens

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BACKGROUND

When *Mycobacterium tuberculosis* (*Mtb*) can infect the lungs (pulmonary TB; PTB), but when it affects other sites of the body, it is called extrapulmonary TB (EPTB). Tuberculosis culture offers low sensitivity while Xpert MTB/RIF Ultra (Ultra) offers improved sensitivity due to the inclusion of two insertion elements (*IS*6110 and *IS*1081), which could result in greater TB detection in non-sputum specimens, but the diagnostic accuracy of Ultra in non-sputum specimens remains unevaluated. Our overarching aim is to evaluate the diagnostic accuracy of Ultra on pericardial fluid, pleural fluid, cerebrospinal fluid, bronchoalveolar lavages and bronchial washes and fine needle aspirates (FNAs) from lymph nodes in adults in patients with presumptive EPTB or PTB respectively, undergoing routine clinical investigation. Ultra will be compared to Xpert on site-of-disease fluid in a head-to-head analysis; as well to paired non-site-of-disease fluid such as urine when available.

METHODS

Pericardial, pleural, FNAs, bronchial and cerebrospinal fluid (CSF) will be collected from different consenting patients with suspected EPTB and PTB undergoing routine testing. Once collected, Xpert and Ultra will be prepared by adding sample reagent buffer to samples in a 2:1 ratio, vortexing, and incubating for a total of 15 minutes. Thereafter, the sample is placed into the Xpert or Ultra cartridge in a biosafety level 3 laboratory and run in the Xpert instrument for a minimum of 1.5 hours. Study results, patient demographics, and 12-week follow-up information are stored on the REDCap database and used for diagnostic accuracy analyses per cohort.

RESULTS

The fine needle aspirate cohort has completed recruitment and data was published in 2021. Data for the pericardial (n=155) and bronchial cohorts (n=350) are mature and two manuscripts are currently in preparation for publication in 2022. Patient recruitment and specimen testing for the CSF (n=178) and pleural (n=120) cohorts are still ongoing.

CONCLUSION

We showed that Ultra on FNAs is highly sensitive and detects more TBL than Xpert. Preliminary analyses show that Ultra on pericardial fluid (PF) is more sensitive than Xpert, and similar to Ultra on concentrated PF. Whether this is the same for the remaining non-sputum cohorts remains to be evaluated. Similar analyses will thus be done for the other cohorts in the study. Recruitment for pleural fluid (120/250), CSF (178/250) and bronchial fluids (350/500) are currently ongoing within the study until sufficient patients are recruited for each fluid type for PhD and publication purposes.

12. Discriminatory Gleason grade group signatures of prostate cancer: An application of machine learning methods

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BACKGROUND & AIM

One of the most precise methods to detect prostate cancer is by evaluation of a stained biopsy by a pathologist under a microscope. However, this is not only laborious, but also relies on the experience of the pathologist and tends to suffer from the lack of reproducibility of biopsy outcomes across pathologists. As a result, computational approaches are being sought and machine learning has been gaining momentum in the prediction of the Gleason grade group. In this work, using whole genome sequence data from South African prostate cancer patients, an application of machine learning and biological experiments were combined to understand the challenges that are associated with the prediction of the Gleason grade group.

METHODS

A series of machine learning binary classifiers (XGBoost, long short-term memory (LSTM), gated recurrent unit (GRU), Logistic regression (LR), and Random Forest (RF) were created only relying on DNA sequences input features where the target class was the prediction of the Gleason grade group.

RESULTS

All the models were not able to adequately discriminate between the DNA sequences of the studied Gleason grade groups (Gleason grade group 1 and 5). However, the models were further evaluated in the prediction of tumor DNA sequences from matched-normal DNA sequences, given DNA sequences as the only input source. In this new problem, the models performed acceptably better than before with the XGBoost model achieving the highest accuracy of 74 ± 01, F1 score of 79 ± 01, recall of 99 ± 0.0, and precision of 66±0.1

CONCLUSION

While the prediction of the Gleason grade group has typically been studied from the output of a biopsy, this work presented a novel approach of attempting to predict the Gleason grade group from raw DNA sequences using machine learning. While this prediction task did not work out satisfactorily mostly due to a small sample size and having many sequences that shared a substantial amount of sequence homology, the prediction task was then changed to a tumor vs. normal classification task where the models were given raw DNA sequences as input and asked to classify the sequences into either tumor or normal. In this new problem, the models performed satisfactorily with the XGBoost model achieving the highest accuracy.

13. Knowledge and attitudes regarding feedback of individual genetic results findings in Genomics research: A baseline assessment survey

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BACKGROUND

Knowledge and attitudes towards genetic conditions and genomics research plays a critical role to inform context specific ethical conduct in genomics research. Effective engagement of individuals from underrepresented groups is regarded as a critical milestone towards ethical frameworks to guide informed consent and the return of individual genetic research results where culturally sensitive engagement strategies are explored. This survey aims to establish baseline knowledge and attitudes that could potentially inform context specific return of individual results in genomics research.

METHODS

A cross-sectional descriptive survey was conducted among 138 parents and caregivers of children living with Neurodevelopmental conditions recruited for Neurodev study at Red Cross children's hospital. A questionnaire was administered to gather demographic data on age, gender, marital status, level of education as well as baseline knowledge and attitudes towards genetics, genomics research, informed consent and feedback of individual findings.

RESULTS

The average age of our participants was 42 years old, with the majority (90%) of our participants being women. Of these 48% were single mothers compared to 40% who were married or in some form of partnership. Twelve percent of our participants where either divorced or widowed. With regards to education status 65% had secondary education, followed by 19% with tertiary education level and 13% with primary school education. About 2% had special needs education and only 1.4% had no formal education at all. The mean total score for knowledge about genetics was 65% with 75% knowledge that genes play a role in health. With regards to feedback of findings, our study 81,6% only wanted feedback of genetic testing results if it could explain the medical conditions in the family and if that result could improve the quality of their life.

CONCLUSION

These research findings offer insights for contextualised framework that could potentially inform ethically framed communication strategies for feedback of findings in genomics research

14. Genetic and epigenetic associations with child development and mental health

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BACKGROUND

Childhood developmental and mental health disorders encompassing neurodevelopmental, behavioural and emotional disorders are an emerging global concern, with adverse effects on children's physical, psychological and social well-being. Childhood behavioural disorders account for approximately 3.4% of the global burden of disease and in South Africa 1 in 20 children are

affected (i.e., Attention-deficit /Hyperactivity disorder). While there is growing interest in delineating the biological underpinnings of child development and mental health outcomes, there remains a paucity of data emerging from LMICs, in which the majority of the global childhood population resides. This project aims to address this gap by exploring potential genetic and epigenetic associations with development and mental health in childhood in a South African setting.

METHOD

This work leverages data from the Drakenstein Child Health Study, an ongoing South African birth cohort study. Two systematic reviews (S.R) (according to PRISMA guidelines) are undertaken, on polygenic risk (objective 1) and epigenetic age (EA) deviation (objective 2), respectively; in relation to development and mental health in childhood and adolescence. Potential genetic contributions will then be empirically explored by generating polygenic risk scores (PRS i.e. the weighted sum of risk alleles) in the target dataset (DCHS) using appropriate discovery genome-wide association study summary statistics (objective 3). Epigenetic associations with the outcomes of interest will be explored via epigenetic age deviation at birth (relative to chronological gestational age) (objective 4) and DNA methylation risk scores (i.e. the weighted sum of select methylation markers' beta values) (objective 5).

RESULTS

The first S.R (objective 1) found high ADHD PRS was associated with adverse developmental and mental health outcomes in children and adolescents. Further, other studies in the S.R described associations between PRS for bipolar and schizophrenia with mental disorders in childhood. No associations between ADHD PRS and adverse developmental and mental health outcomes in the DCHS offspring were identified (objective 3). A write-up of these findings is currently underway as well as submission of the second S.R (objective 2) protocol, and PROSPERO registration.

CONCLUSION

The findings of the PRS S.R suggest that PRS for neurodevelopmental and mental health disorders may associate with adverse neurodevelopmental and mental health outcomes, from early childhood to adolescence. In addition, these associations seemed not to be phenotype-specific, suggesting potential shared genetic variation across the phenotypes of interest. However, empirical findings suggest that there is no association between genetic risk for ADHD (as indexed by PRS) and development and mental health in the DCHS childhood cohort. Further work is warranted to verify the empirical findings using ancestry-specific summary statistics.

15. Transcriptomic approach to the early development of severe asthma

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BACKGROUND

Corticosteroids (CSS) are the mainstay therapy for asthma, however, there has been a growing trend of patients for whom these therapies are ineffective. Research of underlying mechanisms may give insight into the etiologies of CS resistance and identify future therapeutic targets. And because asthma has proved to be a disease of complex nature presenting with multiple endotypes and some of these endotypes with poorly understood manifestation is poorly, it is critical to understand, through research, the early events that determine the development of asthma severity that ultimately result in poor lung growth and function in adults.

METHODS

To study whether childhood exposure to environmental allergens determines asthma severity development, we have simulated these events in a mouse model of severe asthma. We assessed inflammatory responses and pathology through flow cytometry, ELISA assay, and histology following exposure of young mice to either house dust mite (HDM) alone or a combination of HDM and lipopolysaccharide (LPS) or ß-glucans. RNA sequencing will be applied to identify new genes associated with severe asthma.

RESULTS

Allergen exposure of young mice at an early lung developmental stage promotes poor lung function and the manifestation of steroid-resistant asthma driven by an exaggerated Th1 and Th17 response.

CONCLUSION

An uncontrollable Th1 and Th17 play a significant role in the early development of steroid-resistant asthma. The identification of key biomarkers and genes that contribute to the manifestation of CS asthma will provide insight into improved diagnostic tools or treatment strategies that will eminently effect change on existing policies related to the management of severe asthma in clinics.

16. Role of dyslipidemia in modulating coenzyme-Q10 and mitochondrial function in cardiac muscle

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BACKGROUND

Palmitic acid (PA) is an essential component of the cellular membrane and plays a crucial role in cell signaling. It is synthesized endogenously and can be found in the diet. However, its excessive availability, due to overnutrition, may lead to the development of oxidative stress, cardiac toxicity, and metabolic dysregulation, such as dyslipidemia which is implicated in the generation of oxidative stress. Therefore, it has become important to understand how excessive PA affects the endogenous levels of coenzyme Q_{10} (CoQ) within the myocardium and its association with mitochondrial dysfunction.

METHODS

Cultured cardiac (H9c2) cells were exposed to different concentrations of PA (0.06, 0.125, 0.25, 0.5, 0.75 and 1 mM) over time (4,8,16 and 24 hrs). The assays performed included ATP assay for metabolic activity and cell viability and seahorse for mitochondrial respiration. Oxidative stress was measured by assessing the production of reactive oxygen species (ROS) using a fluorescent dye and detecting intracellular antioxidants like superoxide dismutase (SOD) using commercial kits.

RESULTS

Lower doses of PA (≤0.125 mM) improved the cellular metabolic activity and mitochondrial

respiration (p≤0.01), while ameliorating oxidative stress at all time points. Interestingly, these effects were consistent with the maintenance of CoQ levels. The dose of PA (≥ 0.5 mM) did not affect the metabolic activity but suppressed mitochondrial respiration and promoted oxidative stress in a time-dependent manner at both 16 and 24 hrs as shown by reduced maximal respiration (p<0.001) and increased ROS production (p≤0.01). Moreover, the results showed that PA doses >0.5 significantly decreased the activity of SOD (p<0.001) from 16 hrs in a dose-dependent manner.

SUMMARY AND CONCLUSION

Targeting the regulation of PA under pathophysiological conditions is instrumental for paving the path leading to worsening of metabolic complications**.** These findings can also be used for potential therapeutic interventions to combat the risk of diabetic cardiomyopathy. However, more experiments are yet to be conducted to understand the underlying mechanisms further.

17. A pilot study to document *Schistosoma mansoni* infection in Chinese rhesus macaque

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BACKGROUND

Rhesus macaques (RM) are permissive hosts for *Schistosoma* infections. Mature worm populations initiate egg production, but after variable periods, the host can naturally clear the infection. This study aims to investigate and document *Schistosoma mansoni (Sm)* infection in the Chinese rhesus macaque model to on the efficacy of candidate HIV vaccines in subsequent studies.

METHODS

Four RM previously challenged with simian-human immunodeficiency virus (SHIV) were percutaneously exposed to 500 cercariae of NMRI strain of *Sm*. To confirm infection, fresh stool samples were collected at weeks 12, 13, and 14 post *Sm* exposure and assessed by Sterlight Kato-Katz kit according to the manufacturer's instructions. The thick smears of the fecal samples were microscopically examined for enumeration of *Sm* eggs. Virological analysis was conducted at 4-week intervals using real-time reverse transcriptase-PCR (RT-PCR) to measure the viral loads in peripheral blood.

RESULTS

The Sterlight Kato-Katz performed at week 12 post-*Sm* exposure confirmed *Sm* infection in one of the four animals (64 eggs/gram). No *Sm* eggs were observed for the other 3 animals or in subsequent time points. The viral loads of all animals remained at low levels and below 5 SIVgag copies per ml at all timepoints (m= 0.276 SIVgag SIVgag copies/ml; SD= 0.76 SIVgag copies/ml; range= 1.8 SIVgag copies/ml) indicating that there were no viral spikes. We could confirm infection in one of the four animals by Sterlight Kato-Katz assay. Egg output is reported to start declining after week 8 due to the immunological clearance of the infection and this could be the reason that no eggs were observed by weeks 13 and 14.

CONCLUSION

The low levels of viral loads could indicate low-intensity infections with *Sm*. We seek to further employ other methods including the anti-*Sm* IgM/IgG ELISA and circulating anodic antigen ELISA as supplementary tools to confirm infection in these animals.

18. Novel sputum and non-sputum-based TB diagnostics in unselected ART-naïve HIV-positive outpatients

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BACKGROUND

Sputum expectoration is often challenging in HIV-positive people, especially among those initiating antiretroviral therapy (ART) who often have early TB disease and minimal symptoms. Symptom screening is the triage tool for TB diagnosis despite its poor implementation and suboptimal specificity. Recently, the World Health Organization (WHO) suggested C-reactive protein (CRP) be used in addition to symptom screening among HIV-positive adults. This study aims to show the diagnostic accuracy of current and novel TB tests in ART-initiators, who are typically missed due to their asymptomatic status and inability to produce sputum. We tested ART initiators, irrespective of symptom status, using a battery of diagnostic tests. We evaluated the diagnostic accuracy of point-of-care (POC) CRP, symptom screening, sputum-Xpert MTB/RIF Ultra (Ultra), concentrated urine-Ultra, prospective next generation urine Fujifilm SILVAMP TB-LAM (FujiLAM), and the Alere urine-lateral flow lipoarabinomannan assay (LF-LAM).

METHODS

20-40µl fingerprick blood was collected for POC-CRP testing. 25-100ml urine (20ml for concentrated urine-Ultra, 60µL for LF-LAM and FujiLAM each), and three 1-4ml induced sputa were collected [two for MGIT960 culture (reference standard), one for Ultra].

RESULTS

12% (122/1053) study participants had TB. CRP (>10mg/L) had similar sensitivity to symptoms [79% (94/119) vs 76% (91/119); p=0.640] and increased specificity [63% (530/837) vs 49% (412/837); p<0.001]. Sputum-Ultra sensitivity was 71% (74/104), and 47% (12/26) in asymptomatic patients. POC-FujiLAM had improved sensitivity than urine-Ultra [56% (38/68) vs 24% (25/103); p<0.001], and LF-LAM [15% (15/103); p=0.001], and similar specificity to both tests.

CONCLUSION

POC-CRP could reduce unnecessary confirmatory testing by 14% than symptom screening. Sputum-Ultra detected ~50% asymptomatic cases that would ordinarily not be tested using symptoms triage. TB detection can be improved when urine POC-FujiLAM is implemented. This work formed part of an individual participant data meta- analysis that was used by the WHO to recommend the use of CRP (>5mg/L) in HIV-positive adults and adolescents.

19. Investigation of Cancer Risk and Survival for Lynch Syndrome Patients Carrying the Same Pathogenic Variant *MLH1* c.1528T>C

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BACKGROUND

Lynch syndrome (LS) accounts for about 2-5% of all colorectal cancers (CRC). Also, LS patients carrying different pathogenic variants (PV) develop other cancers including endometrial, ovarian, breast (female) and prostate at a younger age and at a higher rate than the general population. We sought to investigate the cancer risk and survival for LS patients carrying the same PV in a South African population.

METHODS

We conducted a retrospective study of our unique cohort of 364 LS patients diagnosed with the same c.1528T>C PV in the *MLH1* gene, between 1997 and 2021. Data on surveillance, cancers, and outcomes were collected and analysed by age, gender, and colonoscopy screening. We compared cancer-affected patients and determined differences in their overall survival. Statistical analysis was performed using SPSS version 27. We used chi-square test, and the survival analyses were performed using Kaplan–Meier method with Cox proportional hazard.

RESULTS

Forty percent (147/364) of LS PV carriers were affected with cancer. The mean age of cancer diagnosis was 41 years (range 5-72, SD; ±11.52). Approximately 48% (70/147) of patients were diagnosed with cancers below the age of 40 years. Most of the younger patients were significantly more likely to be males than females (OR=2.1, 95% CI [1.8-8.1]; p= 0.009). The overall survival was significantly affected by gender, with male patients having poor survival (HR=2.3, 95% CI [1.1-7.2]; p=0.039). Having less than three colonoscopies also significantly contributed to poor survival (HR =4.5, 95% CI [2.1-11.0]; p<0.001). Patients who were diagnosed with cancer at age below 40 years had significantly poor survival compared to patients who were diagnosed at age greater than 40 years (HR= 3.0, 95% CI [1.8-9.1]; p<0.001).

CONCLUSION

In our LS cohort (i.e. carrying a PV in the *hMLH1* gene), cancers presented in male patients at a younger age compared to female patients. A lack of adherence to the recommended surveillance guidelines is an important contributor to morbidity and mortality. In addition to improving communication with the cohort, our ongoing work seeks to investigate alternative means of clinical surveillance that are less intrusive than the current international standard i.e. regular colonoscopies.

20. Utilization of CRISPR-interference to elucidate hierarchies of DNA repair mechanisms in *Mycobacterium tuberculosis*

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BACKGROUND

Mycobacterium tuberculosis (*Mtb*), the causative agent of tuberculosis (TB), is the leading cause of death due to a single infectious bacterial agent. Mechanisms involved in DNA damage repair are associated with the evolution and development of drug-resistant *Mtb* infections during treatment. The DnaE2-dependent DNA damage tolerance and UvrB-containing nucleotide excision repair (NER) pathways have consistently been identified in studies investigating intrinsic and acquired resistance to anti-TB chemotherapy. Previous work in our lab focused on elucidating additional uncharacterized mechanisms that may mitigate the absence of both pathways under conditions of DNA damage. Using whole-genome random transposon (Tn) mutagenesis in *M. smegmatis (Msm)*, putative “compensatory” genes were identified in single deletion mutants lacking either *uvrB* or *dnaE2*. The current research aims to extend these previous findings by validating the identified gene interactions in *Mtb*.

METHODS

Mtb dnaE2 and *uvrB* deletion mutants will be created by allelic exchange. From the 1073 genes identified in the *Msm* Tn libraries, we specifically selected 59 high-confidence genes with the potential to mitigate the absence of both pathways under conditions of DNA damage. The inducible CRISPR-interference (iCRISPRi) system will be used to assess the impact of silencing these selected candidate genes in the respective *Mtb* gene-deletion backgrounds.

RESULTS

To date, *Mtb* homologs of the 59 genes identified from the *Msm* screen have been silenced using the iCRISPRi approach in both *Mtb* wild-type and Δ*dnaE2* background strains, resulting in the generation of 118 *Mtb* hypomorphs. Additionally, a *Mtb uvrB* knockout mutant is under construction, into which a separate panel of iCRISPRi constructs will be introduced.

CONCLUSION

The hypomorphs generated in the two DNA repair-deficient backgrounds will enable direct assessment of the capacity for genome-wide screens to uncover genes critical for DNA damage tolerance. These findings will allow further exploration of ancillary targets designed to cripple mechanisms involved in intrinsic and adaptive resistance to antimycobacterial drugs.

21. Anxiety and depression in new-onset atrial fibrillation among men and women.

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BACKGROUND

Atrial fibrillation (AF) is the most common cardiac rhythm disorder in clinical practice with its patients five times more likely to suffer from stroke and have a higher mortality-risk. Sparsely conducted studies highlight a possible association of anxiety and depression with new-onset AF. Physiological mechanisms underlying this have not been investigated, although, it has been highlighted that anxiety and depression may trigger the autonomic nervous system (ANS) which could be a crucial factor in the etiology of AF. Thus, we aimed to investigate the association between anxiety and depression with new-onset AF and how the ANS function affect this association in men and women.

METHODS

Incident AF was assessed in 8813 men and women from the Rotterdam prospective-cohort study, with mean ages 65 and 66 respectively, from 2006 until 2014. Participants were categorised according to anxiety and depression diagnoses. Cox proportional-hazards model were utilised to adjust for traditional AF risk factors and assess the association of anxiety and depression with AF.

RESULTS

During follow-up, 652 (7.3%) participants developed AF, of these participants, 7,2% had anxiety, and 6,1% had depression. The hazard ratios (HRs) were 1.38 (95% CI: 0.81-2.35) for men with anxiety, while women had HRs of 0.90 (95% CI: 0.63-1.30). For depression, the HRs were 0.97 (95% CI: 0.51-1.88) for men while HRs were 1.07 (95% CI: 0.73-1.59) for women. Thus far diagnosed anxiety and depression shows no associated of onset AF in both men and women. Interestingly, phobia a subtype of anxiety presented higher HRs; 3.05 (95% CI: 1.35-6.88) in men compared to HRs of 1.17 (95% CI: 0.58-2.37) in women. Further analysis will be conducted.

CONCLUSION

Our findings will add to the scarce literature of the association of psychological factors and their contribution to onset and progression of cardiovascular diseases (CVD) and would possibly highlight the need for mental health to be included in primordial prevention framework of CVDs.

22. Cluster randomized controlled trial of Stepping Stones and Creating Futures to reduce mental health challenges among young men in informal settlement in KwaZulu-Natal Province, South Africa

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BACKGROUND

Informal settlements are high density areas in and around cities, characterized by a lack of formal

planning and basic amenities, being known in South Africa for high levels of mental disorder driven by violence, and complex social and economic challenges. In particular, young men's poor mental health goes untreated, with relatively few evidenced-based interventions available in this setting.

METHODS

This cluster randomized controlled trial investigated the effectiveness of Stepping Stones and Creating Futures (SS/CF), a participatory gender transformative and economic empowerment intervention, on the mental health of young men living in South African informal settlement. 674 young men ages 18–30 years were recruited in 34 clusters in Durban's urban informal settlements. Clusters were randomly allocated (1:1) to either the experimental SS/CF or control arm and participants were followed-up over 24-months. Intention-to-treat analysis based on generalized estimating equations (GEE) were fitted to quantify the impact of SS/CF on the men's anxiety and post-traumatic stress (PTS) symptomatology.

RESULTS

This randomized study demonstrated a significant reduction in poor mental health among young men in particularly challenging circumstances. At end of the 24 months follow-period, anxiety (adjusted odds ratio [aOR]: 0.64, p=0.04, 95% CI=0.42, 0.97) and PTS (aOR=0.56, p=0.03, 95% CI=0.34, 0.94) were significantly lower for group assigned to the SS/CF compared to the control group.

CONCLUSION

SS/CF, livelihoods strengthening intervention designed to address poverty and other socio-economic challenges in informal settlements reduced anxiety and PTS among men with chronic mental health challenges living in informal settlements. The effective reduction of mental disorder by Stepping Stones and Creating Futures may improve the quality of life of young men as they grow into adulthood. The intervention's economic empowerment component will also give them skills to work with and equip them for their futures, which may continue to be challenging.

23. Role of CysLTR1 during *Mycobacterium tuberculosis* and *Listeria monocytogenes* infection in mice

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BACKGROUND

Cytokines and eicosanoids (epoxyeicosatreinoic acids, prostanoids and leukotrienes) are secreted by antigen presenting cells to activate the adaptive immunity. Leukotrienes (LTs) are a subfamily of eicosanoids generated from 5-lipoxygenase-metabolism of arachidonic acid to LTB_4 and cysteinyl LTs (cysLTs). CysLTs are pro-inflammatory lipids that have pathobiological functions in asthma. CysLTs function through three G-protein coupled receptors (CysLTR1, CysLTR2 and GPR99). The CysLTR1 and its ligand function has been well elucidated in asthmatic and allergic responses, however, its role in bacterial infections is unknown. *Mycobacterium tuberculosis* (*Mtb*) and *Listeria monocytogenes* (*LM*) are both bacteria that can cause serious human infections. *Mtb* continues to be the lead cause of death from infectious diseases worldwide, with South Africa

being one of the countries with the highest tuberculosis (TB) burden, while *LM* causes severe infection in immunocompromised individuals, neonates, and pregnant women. Therefore, the aim of this study is to elucidate the role of CysLTR1 on disease progression in C57BL/6 and Balb/c mice during *LM* and *Mtb* infection.

METHODS

C57BL/6 and Balb/c CysLTR1 knockout mice were used to investigate the role of this gene during *Mtb* and *LM* infections. Mortality and time course experiments were performed on both backgrounds.

RESULTS

Our results so far demonstrated that C57BL/6 CysLTR1 knockout mice are more susceptible to *Mtb* infection when compared to wildtype mice. The susceptibility to infection was accompanied by increased neutrophils and lung inflammation at 3-, 6-, and 12-weeks post infection. On the other hand, C57BL/6 knockout mice had comparable survival as the littermate controls but, had increased neutrophil recruitment to site of infection during *LM* infection at 3- and 7-days post infection. Balb/c knockout mice are susceptible to *LM* infection but, mechanism of susceptibility must still be investigated.

CONCLUSION

The results obtained from this study will give us a better understanding of the role of CysLTR1 in bacterial infection and whether it can be used as a therapeutic target for adjunctive TB treatment.

24. Investigating the impact of mycobacterial cell-cell heterogeneity on susceptibility to anti- tuberculosis (TB) chemotherapy.

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BACKGROUND

As agent of tuberculosis (TB), Mycobacterium tuberculosis is a leading infectious cause of death globally. The success of M. tuberculosis as human pathogen derives in part from its ability to survive host-mediated antibacterial defenses, as well as clinical interventions including extended duration combination chemotherapy. Understanding the molecular mechanisms underpinning these characteristics is essential to the development of improved anti-TB interventions. The mycobacterial mutasome is a DNA damage-inducible complex that has been implicated in SOS-induced mutagenesis and the emergence of drug-resistance during antibiotic therapy. In prior work, we observed that mutasome induction is not uniform in a population of clonal bacilli exposed to the same exogenous genotoxic stress. By elucidating a mechanism for generating heterogeneity under applied stress, our goal is to identify targets for novel interventions aimed at curbing the evolution of drug resistance.

METHODS

By applying a panel of transcriptional reporter mutants in combination with single-cell time-lapse fluorescence microscopy, fluorescence-activated cell sorting (FACS), transcriptomics and proteomics, this study is investigating the possibility that a sub-population of “SOS-active” cells might be primarily responsible for stress induced drug resistance.

RESULTS

Flow cytometric data and microscopic analyses of antibiotic exposed transcriptional reporter mutants revealed that mutasome induction is heterogenous, such that four distinct sub-populations were detected: SOS-positive, unresponsive, *recA*-positive and *dnaE2*-positive. Single cells were obtained by FACS for downstream assessment of fitness and mutagenic advantage. Time-kill curves with ciprofloxacin and moxifloxacin for the four sub-populations were similar to that of the wild type. The four sub-populations displayed ≤4-fold increase in MIC for linezolid and vancomycin. High rifampicin mutation frequencies were recorded for the *recA*-positive (8.25239 x $^{-07}$) and *dnaE2*-positive (8.11607 x $^{-07}$) subpopulations.

CONCLUSION

Collectively, these data point to the importance of the reported heterogenous mycobacterial mutasome induction in mutagenesis and a possible role in the emergence of drug resistance.

25. Morphological phenoprinting of essential genes in mycobacteria using inducible CRISPR interference.

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BACKGROUND

The development of novel, shorter tuberculosis (TB) drug therapies remain an urgent priority. However, new TB drug development is complicated and undermined by a poor understanding of mycobacterial metabolism. This work aims to study the impact of essential gene transcriptional silencing on cell morphology, utilizing a chemical-genetic approach that links morphological phenotypes to on-target gene silencing via inducible Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-interference. In previous work we demonstrated the utility of this “phenoprinting” approach for gene function and drug mechanism-of-action (MOA) predictions. Here, we aim to develop the methodology further for rapid triaging of whole-cell active small molecules and pre-clinical anti-TB drug candidates of unknown MOA by expanding the existing database of *Mycobacterium smegmatis* (*Msm*) phenoprints as well as extending the approach to *Mtb* via selective targeting of a subset of representative, high-priority drug target genes.

METHODS

A total of 9 new anhydrotetracycline (ATC)-inducible CRISPRi knockdowns were designed for the ParB-mCherry *Msm* bioreporter background, with 61 constructs generated to target *Mtb* genes of interest. In addition, three new bioreporter backgrounds were constructed comprising transcriptional fusions to sentinel genes involved in mycobacterial DNA damage, cell wall maintenance, and respiration, respectively.

RESULTS

Consistent with prior observations, genes within the same biosynthetic pathway produced similar phenoprints. Notably, our preliminary results indicate the conditional essentiality of *Msm nadD*, contrary to database predictions. The newly generated fluorescent bioreporter constructs did not incur a fitness cost on *Msm* and expression was specifically induced relative to expected on-target controls.

CONCLUSION

Phenoprinting offers a reproducible and adaptable method for development as a key tool in rapid MOA elucidation of novel antimycobacterial agents.

26. Novel methods for the oral-based diagnosis of tuberculosis in an HIV-endemic setting

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BACKGROUND

Tuberculosis (TB) diagnosis depends on sputum-based detection of *Mycobacterium tuberculosis* (*Mtb*). People self-reporting to the clinic with symptoms require a rapid diagnostic investigation. In addition, people living with HIV (PLHIV) who have a high risk of TB as well as those who have asymptomatic early-stage disease, often cannot produce sputum meaning that they have very low concentrations of bacilli in their secretions. Identifying accessible non-invasive sample types such as oral washes and testing these with highly sensitive rapid diagnostic tools, such as Xpert MTB/RIF Ultra (Ultra), create new opportunities for non-sputum-based diagnosis, especially amongst those with paucibacillary disease.

METHODS

Oral washes (20ml) were collected from microbiologically culture confirmed TB-positive and confirmed TB-negative patients. The oral washes were decontaminated before archiving at -20˚C until further processing. Sputum induction was done for the participants who struggled to provide adequate sputum sample for microbiological testing using culture. Sputum culture served as the microbiological reference standard (MRS). Oral washes were tested retrospectively using the Ultra assay.

RESULTS

Of the 40 (20 TB and 20 TB-negative) patients tested in this study, twenty (50%) tested positive for Ultra on oral washes, with 80% (16/20) correctly identified when compared to the MRS. Twenty patients tested negative of which 80% (16/20) were correctly identified as non-TB cases using the MRS. Sensitivity and specificity were both 80% (95% confidence interval: 56, 94). When the diagnostic accuracy was stratified by HIV status, HIV-negative patients had improved sensitivity compared to HIV-positive patients [94% (70, 100) vs. 25% (1, 81); p=0.002].

CONCLUSION

Ultra on oral washes yielded promising results with a sensitivity of 80%, indicating that *Mtb* DNA can be detected in oral washes and could potentially replace sputum. This has implications for TB detection in patients who struggle to produce sputum. However, this analysis needs to be extended to include a larger sample size and a wider representation of the TB disease spectrum.

27. One in five South Africans are multimorbid

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BACKGROUND

Multimorbidity is defined as having two or more long-term disease conditions in an individual. It is a global research priority, yet relatively little is known about it in low and middle income countries. Information about the prevalence of multimorbidity and factors associated with it can assist in healthcare planning and targeting groups of people for interventions. This study aimed to determine the prevalence of multimorbidity by age and sex, as well as factors associated with multimorbidity.

METHODS

This study analyses the nationally representative 2016 South African Demographic Health Survey. The sample included 10 336 youth and adults who completed the Adult Health questionnaire and approximately 7 961 people who provided biomarkers. Youth aged 15-17 years were included as this age group is commonly considered adults in population-based national surveys. Multivariate logistic regression was used to measure the association of multimorbidity with age, sex, living in an urban or rural area, education level, wealth level, employment status, body mass index, current alcohol or tobacco use.

RESULTS

Multimorbidity was present in 20.7% (95% CI: 19.5% – 21.9%) of participants; in 14.8% (95% CI: 13.4% - 16.3%) of males and 26.2% (95% CI: 24.7 – 27.7%) of females. Multimorbidity increased with age; with the highest odds in the 55 - 64 years old age group (OR: 24.910, 95% CI: 14.901 - 41.641, $p < 0.001$) compared to those aged 15 – 24 years. The odds of multimorbidity was also higher in young females compared to young males (OR: 2.734, 95% CI: 1.50 – 4.99, p= 0.001). Possessing tertiary education (OR: 0.722, 95% CI: 0.537 - 0.97, p=0.031), being employed (OR: 0.813, 95% CI: 0.675 - 0.979, p=0.029) or currently using alcohol (OR: 0.815, 95% CI: 0.686 – 0.968, p=0.02) was protective against multimorbidity.

CONCLUSION

Multimorbidity is prevalent within the South African population, with females and older adults being most affected. However, multimorbidity is also observed in younger adults and most likely driven by the high prevalence of HIV and hypertension.

28. Genomic characterization of *Acinetobacter baumannii* associated with neonatal sepsis and stillbirths in a South African population

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BACKGROUND

Multi-drug resistant hospital-acquired invasive *Acinetobacter baumannii* (*A. baumannii*)

overwhelmingly contributes to neonatal deaths, particularly in low-middle income countries (LMIC) where the burden of sepsis in neonates is higher. Strategies for preventing *A. baumannii-associated* neonatal deaths and stillbirths are thus needed to optimize the health of the mother-baby dyad. While the antigenic structure of *A. baumannii* organisms is diverse and complex, studies investigating virulence factors and clonal groups associated with pathogenicity are scarce, especially in LMIC settings where molecular epidemiology is poorly characterized. Thus, the study undertakes whole-genome sequencing (WGS) of *A. baumannii* isolates which are associated with neonatal invasive disease and stillbirths.

METHODS

The study uses WGS to genetically characterize *A. baumannii* isolates that have been collected as part of the Child Health and Mortality Prevention Study (CHAMPS) Network platform, Minimally Invasive Tissue Sampling (MITS) study, and Group B *Streptococcus*-Cohort study in infants less than 90 days of age. The archived isolates are cultured on CHROMagar plates, followed by genomic DNA extraction done on BioMérieux NucliSens® easyMAG®, and sequencing performed on Illumina Miseq Platform. Data analysis is processed through trimmomatric SPAdes, Kraken and Quast, Prokka, and PubMLST.

RESULTS

Antimicrobial resistance phenotypes resulted in a high antibiotic resistance rate greater than 90%, with isolates exhibiting resistance to more than seven classes of antibiotics and most susceptible to ceftazidime and colistin. Data generated from this study will enable an understanding of the link between *A. baumannii* phylogenic and extra-intestinal virulence. Also, defining the population structure of its antibiotic resistance gene repertoire, the size, and content of its pan-genome, and the phylogenetic relationships amongst strains associated with neonatal invasive disease.

CONCLUSION

Genomic characterization studies are needed to develop prevention approaches (vaccine, monoclonal antibodies, innovative infection prevention, and control tools) to reduce antimicrobial resistance to sepsis in neonates.

29. Effect of age on brown adipose tissue and batokines gene expression in type 2 diabetic (db/db) mice

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BACKGROUND

Brown adipose tissue (BAT), a thermoregulatory organ known to promote energy expenditure, has been extensively studied as a potential avenue to combat obesity and type 2 diabetes. BAT secretes specialized signalling molecules called batokines, to regulate various metabolic processes. Although it has such astonishing capacity, BAT content declines with age, and this has been poorly investigated especially in the context of diabetes. Thus, current study aimed to elucidate the impact of age on BAT morphology and batokines gene expression in db/db mice.

METHODS

Type 2 diabetic “db/db” mice and control littermates db/+ mice were monitored from the age of 8-, 12-, and 18-weeks. Body weights, fasting blood glucose levels, and insulin levels were monitored weekly. Subsequently, insulin resistance was determined using Homeostasis Model of

Assessment for Insulin Resistance. At pre-determined experiment time points, animals were sacrificed and the interscapular BAT was collected for histological analysis using haematoxylin and eosin staining. Real-time quantitative PCR was performed to determine the expression of batokines, including fibroblast growth factor 21 (FGF21), bone morphogenic protein 8b (Bmp8b), vascular endothelial growth factor-A (VEGF-A), and growth differentiation factor (GDF)-15 which regulate glucose metabolism, sympathetic neurite outgrowth, vascularization, and immune cells recruitment, respectively.

RESULTS

In comparison to age-matched db/+ mice, db/db mice displayed significant age-dependent increase in body weights (38.20 ± 0.44 g; 44.60 ± 0.89 g; 58.20 ± 0.83 g, $p<0.001$), fasting blood glucose (11.38 ± 1.70 mmol/L; 16.42 ± 1.21 mmol/L; 21.08 ± 1.95 mmol/L, $p<0.001$) and insulin levels (8.71 ± 0.70 mIU/L; 5.63 ± 0.61 mIU/L; 5.60 ± 0.45 mIU/L, $p<0.001$), and insulin resistance (3.36 ± 0.77; 2.97 ± 0.66; 5.24 ± 0.53, $p<0.001$) at 8-, 12-, and 18-weeks respectively. Consistently, BAT displayed whitening marked by significant increase in adipocytes area at 8-weeks ($p<0.05$),12-weeks ($p<0.05$), and 18-weeks ($p<0.001$). This was accompanied by decreased batokines gene expression of FGF21 (0.15 folds, $p<0.05$), Bmp8b (0.52 folds, $p<0.05$), VEGF-A (0.17 folds, $p<0.05$), and GDF-15 (0.73, $p<0.001$), which was more prominent at 18-weeks.

CONCLUSION

This data provides a better understanding of age-related brown adipocyte whitening (or dysfunction), and it brings new targets to further studies that aim to treat obesity and type 2 diabetes.

30. Novel biomarkers, including computer-aided radiological screening, for the community-based detection of tuberculosis

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BACKGROUND

Tuberculosis (TB) is a leading cause of death from a single infectious agent. Globally, ~35% (almost 1 in 3) of TB cases are 'missed' and 40-50% of the TB case burden in sub-Saharan Africa remains undiagnosed within the community. Therefore, it is crucial to evaluate novel biomarkers, including artificial intelligence (AI)-based computer-aided detection (CAD), to detect TB during community-based active case finding (ACF) in order to improve TB control.

METHODS

Utilising clinical, radiological, and microbiological data from prospective, community-based, ACF studies conducted in South Africa and other sub-Saharan African countries, this study will (i) determine a population-specific CAD threshold for detecting TB during community-based ACF by analysing digital x-rays with multiple CAD software and comparing ACF with passive case finding (n=1 500), (ii) investigate CAD and other novel biomarkers of TB infectiousness by comparing infectious and non-infectious TB cases (n=100), and (iii) bio-phenotype community based individuals with sub-clinical TB by evaluating clinical, radiological, microbiological, and host characteristics, and comparing these characteristics between sub-clinical and symptomatic TB cases (n=1 500).

RESULTS

Recruitment is ongoing for the prospective, community-based, ACF studies where data is being collected for this study. Samples are being collected for all participants and analysis of biomarker accuracy is ongoing.

CONCLUSION

The results of this study may have substantial implications for public health policy and practice, and has the potential to improve our knowledge of TB detection, infectiousness, and transmission.

31. COVID-19 impact on provision of pre-exposure prophylaxis among key populations: a review

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BACKGROUND

The nature of the impact of the COVID-19 pandemic on the provision of HIV prevention services such as pre-exposure prophylaxis (PrEP) in Sub Saharan African needs to be studied in-depthly. The region bears a disproportionate burden of HIV infections globally. This is important to understand the impacts of COVID-19 on the provision of PrEP, to those likely to be most impacted by COVID-19, particularly the key populations, to sustain gains made to address infectious diseases, and maintain people's access to life-saving health services. The objective of this study was to characterize the nature and extent of the impact of COVID-19 on the provision and uptake of PrEP services among key populations in Sub-Saharan Africa.

METHODS

A review of the literature was conducted on provision of PrEP services during COVID-19 (2020-to current). This review was designed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A protocol outlining the review methods was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022342841).

RESULTS

Changes in the provision and uptake of PrEP services were observed during COVID-19 period. A range of barriers to uptake and provision of PrEP services during the COVID-19 for key populations were identified, e.g. logistics around PrEP collection, mental health and stock outs. Adverse impacts were experienced by both PrEP service providers and PrEP users. Some facilities changed PrEP services from being facility based to enhanced delivery platforms for example by providing telemedicine, multi-month dispensing, peer demand creation, virtual post PrEP initiation support.

CONCLUSION

The COVID-19 interrupted PrEP services and disrupted the traditional ways of delivering PrEP to key populations but paved the way for innovative strategies in PrEP service delivery. Innovative approaches to PrEP services delivery are required and they need to be scaled up to reduce HIV new infections.

32. The effect of HAART on renal function in HIV-infected patients

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BACKGROUND

The proximal renal tubules are constantly exposed to highly active antiretroviral therapy (HAART) among human immunodeficiency virus (HIV)-infected patients, which can induce a decline in renal function. Beyond using the common assessing tools which include serum markers like creatinine and estimated glomerular filtration rate (eGFR), assessing the markers of oxidative stress, inflammation and tubular damage has become important to identify proximal renal tubular dysfunction as an early or primary abnormality of HAART nephrotoxicity in patients with HIV.

METHODS

The cross-sectional study enrols both HIV-negative and infected patients on HAART and HAART-naïve living in Limpopo Province between June 2022 and December 2024. Basic measurements of renal function will include serum F_2-isoprostanes, malonaldehyde (MAD), advanced glycation products (AGEs), C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor (TNF-α), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM-1), beta-2 microglobulin (β2M), osteopontin, alpha-1-microglobulin, cystatin and eGFR whilst other anthropometric measurements and cardiometabolic profiles collected will be body mass index (BMI), waist circumference, serum glucose and lipids.

RESULTS

Renal dysfunction is strong risk factor for cardiovascular disease. The results of the current study will significantly impact the management of renal dysfunction and the prevention of cardiovascular disease among patients with HIV on HAART

CONCLUSION

This study may assist relevant stakeholders to make informed decisions in the implementation of interventions aimed at reducing the burden of renal dysfunction. The study will provide important information on the effect of HAART on biomarkers of oxidative stress, inflammation and renal tubular function which may be helpful in the diagnosis of renal dysfunction in clinical practice.

33. Exploring the potential of DNA methylation as biomarkers for screening gestational diabetes mellitus

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BACKGROUND

Gestational diabetes mellitus (GDM) is associated with an increased risk of pregnancy complications and adverse health outcomes in mothers and their offspring. DNA methylation has been identified as a key regulator of metabolic adaptation during pregnancy and may offer

potential as biomarkers for screening women at risk of developing GDM. The primary aim is to characterise DNA methylation signatures in whole blood and examine associations with metabolic risk in women with/without GDM. The secondary aims are to investigate the association between single nucleotide variations (SNVs) and DNA methylation and conduct functional studies in a cell model of GDM.

METHODS

Determine methylation status of three genes, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1A), protein tyrosine phosphatase receptor type N2 (PTPRN2) and Insulin gene enhancer protein (ISL1), identified from a previous genome-wide study, in larger sample of women with/without GDM, using bisulfite pyrosequencing. Bioinformatics and statistical analysis will be performed to identify transcription factors that bind to differentially methylated CpG sites and correlate the differentially methylated genes and GDM risk factors. Screen for the presence of SNVs in the promoters of differentially methylated genes and conduct gain-of-function and loss-of-function to overexpress or silence differentially methylated genes associated with GDM.

RESULTS

Thus far, differentially methylated CpG sites located within the three genes of interest were identified using UCSC and Ensembl genome browsers, and pyrosequencing primers were designed using, PyroMark Assay. Orders have been processed and pyrosequencing optimisation will be underway shortly. Furthermore, a scoping review focusing on experimental models for GDM is currently in the developmental stages, to be submitted to an ISI peer reviewed open access Journal.

CONCLUSION

We anticipate identifying novel DNA methylation signatures associated with GDM, to serve as biomarkers to screen GDM. The scoping review will help us identify *in vitro* model studies that are best possible experimental model for GDM.

34. The impact of COVID-19 on HIV treatment services among key populations: a review

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BACKGROUND

Key populations remain under-researched, under-served, and marginalized in HIV studies and in the HIV response, due to stigma, discrimination, and criminalization despite their significant contribution to the HIV burden. In addition to these long standing and historical barriers, the emergence of the COVID-19 pandemic has hampered the HIV response. For instance, the interruption of HIV treatment services may have more severe effects among key populations due to their increased risk of HIV acquisition and transmission. This study aimed to assess the changes in HIV treatment indicators, barriers, and facilitators to delivery and access to HIV treatment pre- and post-COVID-19 among key populations.

METHODS

The systematic review included full text and accessible publications of original studies conducted in Sub-Saharan African countries on HIV treatment indicators and services among key populations from pre-COVID-19 (2018-2019) to peri-COVID-19 (2020-2021). This review study was carried

out using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and is registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42022341813).

RESULTS

The preliminary results showed that different countries in Sub Saharan Africa experienced varying impacts of COVID-19 in the access and utilization of HIV treatment services during COVID-19 pandemic, with studies in South Africa and Zimbabwe reporting a decrease during the initial stages of lockdown which later picked up, while Nigeria was able to ensure continuity of HIV treatment services during COVID-19. Factors such as stigma and discrimination consistently remained barriers for key populations before and during COVID-19. The review of the interventions implemented is still being conducted.

CONCLUSION

The review is still underway. The findings have the potential to guide the tailoring of HIV services and in the implementation of targeted approaches for key populations to adequately access HIV treatment services ahead of the 2030 goal of achieving epidemic control.

35. Common risk for epilepsy identified by GWAS: A systematic review

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BACKGROUND

Epilepsy is one of the most diagnosed neurobiological disorders, affecting 50 million individuals worldwide, with approximately 80% of epilepsy cases occurring in low and middle-income countries (LMICs). The aetiology of epilepsy is known to have genetic contributions, yet despite the numerous genome-wide association studies (GWAS) conducted for epilepsy, robust genetic variants have largely not been identified. The aim was to identify common genetic variants for epilepsy by systematically reviewing common genetic risk variants that have been identified from epilepsy GWASs.

METHODS

The systematic review was conducted using the updated PRIMSA protocol. EbscoHost, PubMed, Scopus, Web of Science and UCT's Primo were selected as the relevant databases for searching. Medical subject heading (MeSh) terms were used in the search string, which included the terms "GWAS", "genome wide association stud*", genome wide association analys*", "genome wide stud*", "epileps*" and "seizure disorders". A total of 400 studies met the inclusion criteria, from which ten were extracted. The quality of each of the studies were evaluated using the Q-Genie tool. The screening, extraction and quality assessment was completed independently by a second reviewer. Endnote was used for exporting all studies selected from databases and exported to Covidence for title, abstract and full text screening, and extraction.

RESULTS

From the ten studies reviewed, a total of 38 significant single nucleotide polymorphisms (SNPs) were observed, of which only one variant was shown to be associated in more than one study, rs11890028, however, this could be due to an overlap in samples in the respective studies. This SNP is located intron 7 of the sodium voltage-gated channel alpha subunit 1 (*SCN1A*) (2q24.3), a gene commonly mutated in epilepsy patients. Several other studies reported epilepsy risk variants located in *SCN1A*; namely rs6732655, rs6432877, rs12987787, rs4667876 and rs7587026.

CONCLUSION

The results of this study highlight the importance of systematically reviewing GWAS findings for risk variants reported to be associated to epilepsy disorders. Despite a total of 38 significant variants found to be associated to epilepsy across several studies of mixed ancestral samples, only one SNP (rs118900280) was identified in two of the GWAS. As a number of studies found associations between *SCN1A* variants and epilepsy, future research in this disorder should perhaps focus on genetic variants located in sodium channel genes.

36. Assessing the effect of imbalance correction through oversampling in the prediction of injury prevalence in distance runners

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BACKGROUND

It has been found that injury prevalence, e.g. overall injury, medial tibial stress syndrome, hamstring injury, calf injury, etc., in distance runners in the Two Oceans Marathon races (21.1km and 56km), is very low compared to the distance runners that do not experience injury. Due to this imbalance in injury prevalence data, most classifiers will train to be biased towards the majority class, i.e. distance runners that reported no injury. The aim of this research project is to assess the effect of predicting injury prevalence without addressing the target imbalance compared to correcting the imbalance before prevalence prediction.

METHODS

Data collected by the South African Medical Research Council on Two Oceans Marathon runners will be used. The data will be partitioned into a training and test set using a 80:20 split. Firstly, a logistic regression will be applied to the original unchanged/imbalanced training dataset to create a benchmark model for comparison. Next, separate sampling, a well-known under-sampling method, will be used to create a balanced training dataset on which the same logistic regression will be modelled. In addition to this, an ensemble model (e.g. random forest) will be applied to the original/imbalanced training data for a further level of comparison as these models are known to handle imbalanced targets better than traditional binary classifiers. The three models will be assessed using measures such as misclassification rate, ROC and other measures of model accuracy. Each model will then be used to score the test dataset to determine which model is the champion.

RESULTS

The project is still in the data preparation phase and as such not results are at this stage available for reporting.

CONCLUSION

It is envisioned that the research project results could possibly provide guidelines for modelling imbalanced data that could better identify distance entrants susceptible to injuries. This knowledge, which would include injury risk factors, could assist healthcare professionals in their prevention and rehabilitation efforts.

37. Identification of *Mycobacterium tuberculosis* essential genes that potentiate the efficacy of anti-TB drugs

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

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BACKGROUND

High annual mortality rate renders tuberculosis (TB) a great global health threat. The emergence of drug-resistance further poses a significant challenge towards successful treatment of the disease. Therefore, there is an urgent need for the development of new antitubercular drugs. In this study, we propose utilization of CRISPR interference (CRISPRi) technology to conduct gene-gene and chemical-gene interaction to predict gene-gene combinations (synthetic lethality) whose transcriptional knockdown result in rapid bacterial death. Inhibitors of the products (enzymes) encoded by the genes identified here will instantly become attractive drug candidates in TB combination therapy.

Aim:

Identify gene products (enzymes or receptors) whose inhibitors will form strong combination therapies with existing TB antibiotics to achieve highly effective and shortened TB treatment.

Objectives:

1. Selection of 50 target essential genes. (completed)
2. Generation of CRISPRi single- and double-gene knockdown strains of *Mycobacterium tuberculosis (Mtb)* and *Mycobacterium smegmatis (Msm)*. (On going)
3. Optimization of screening methods to determine possible gene-gene combination (gene pair). (Not started)
4. Selection of gene-gene combination that display strong synergy or lethal interaction in *Msm* hypomorphs by reduction factor. (Not started)
5. Confirmation of the selected strong gene-gene combination (from 4) in *Mtb* by deep sequencing or phenotype assays. (Not started)
6. Infection of macrophage-like cells (THP-1 macrophages) with *Mtb* hypomorphs. (Not started)
7. Investigating *in vitro* and *in vivo* chemical-genetic and chemical-chemical interaction on *Mtb* hypomorphs. (Not started)

METHODS

Using multiple available databases, we selected 50 genes in *Mtb* and *Msm* according to the following criteria: Essentiality in *Mtb* (identified by Minato Y et al., 2019; DeJusus et al., 2017; Griffin et al., 2011); non-human homologs (selected using KEGG database); not involved in DNA replication, RNA transcription and protein translation (KEGG database and BioCyc database); non-target of existing anti-TB drugs; high vulnerability index (selected using pebble rockefeller database); only one gene selection in multistep metabolic pathways (selected using KEGG database). CRISPRi strains will be generated in *Mtb* and *Msm* using a PLJR965 and PLJR962 plasmids respectively. Knockdown strains will be confirmed by deep sequencing, RT-qPCR, and phenotype assays. To determine gene-gene interaction, CRISPRi multiplex will be utilized to simultaneously knockdown one of the 10 gene target of anti-TB drug and one of the 50 selected essential genes. Synthetic lethality will be established by comparing the rate of bacterial death and growth inhibition of the double gene knockdown strain through measurement of colony forming unit (CFU). Additionally, chemical-genetic interaction will be determined by treating

CRISPRi strains with either first- or second-line anti-TB drug while chemical-chemical interaction will be determined by treating CRISPRi strains with a combination of two drugs, an anti-TB drug and inhibitors of essential targets. Ability of the mutants to survive macrophages will be determined using THP-1 macrophages.

RESULTS

Objective 1: 50 essential genes were successfully selected.

BONGANI MAYOSI NATIONAL HEALTH SCHOLARSHIPS PROGRAMME (BM-NHSP)

1. Proteomic profiling and biomarker discovery in acral lentiginous melanoma using FFPE tissue

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BACKGROUND

Acral lentiginous melanoma (ALM) is a histological subtype of cutaneous melanoma (CM), most commonly found in people of colour. Although unrelated to ultraviolet radiation, it has a dismal prognosis, and its aggressive phenotype remains poorly understood. Proteomics is a novel technique that can used to identify and characterize disease-associated biomarkers. We have employed proteomics to compare profiles of ALM to other subtypes of melanoma and skin cancers; with the aim of identifying potential proteomic biomarkers of ALM theragnosis.

METHODS

43 formalin-fixed-paraffin-embedded (FFPE) tissue samples representing six lesional groups were retrieved from the surgical pathology archives of the National Health Laboratory Services at the University of Cape Town and the University of Witwatersrand. The groups included 4 subtypes of melanoma, basal cell carcinoma and squamous cell carcinoma. Proteins from these samples were extracted, digested, desalted, and subjected to label-free shotgun proteomics. Data generated was pre-processed and bioinformatically analysed using a relative quantitative algorithm. Intensity-based absolute quantification values from Maxquant were then used for statistical analysis in the Perseus software.

RESULTS

Overall, a total of 419 protein groups were identified. Of these, 406 proteins were found in the melanoma tissue samples, with 167 proteins unique to ALM. Proteins related to pigmentation such as MLANA was found to be upregulated in ALM. This protein is involved in melanoma biogenesis and plays a vital role in the expression, stability, tracking and processing of melanocyte protein PMEL critical to the formation of stage II melanosomes. Top biological processes that were enriched included immune response, cellular component assembly, neutrophil degranulation, regulated exocytosis, and cell activation.

CONCLUSION

These preliminary findings from our search for potential biomarkers among South African ALM patients, serves as a foundation for further statistical analysis and identification of precision biomarkers of ALM, as well as identification of proteins related to pigmentary perturbations.

2. Behavioural and social drivers of human papillomavirus vaccination in eThekwini District (KwaZulu-Natal)

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Background

Cervical cancer is the second most common cancer in women in South Africa. Infection with human papillomavirus (HPV) is the cause of cervical cancer, which can be prevented by HPV vaccination.

There is wide variation in HPV vaccination coverage among districts in SA; with the lowest coverage being 40% in eThekwini a sub-district in KwaZulu-Natal. There could be many barriers which affect HPV vaccine uptake in KwaZulu-Natal. There is thus a need to understand the reason for sub- optimal district HPV vaccination coverage in the Province. The aim of this research is to investigate HPV vaccination barriers in eThekwini District of KwaZulu-Natal.

Methods

The study will consist of three main phases. We will apply a mixed methods approach, including a quantitative survey (phase 1) and in-depth interviews (phase 2) among caregivers and frontline healthcare workers to determine the drivers of HPV vaccination uptake. In addition we will conduct an overview of systematic reviews of interventions for improving HPV vaccination coverage (phase 3)

Results

The research is still ongoing.

Conclusion

The study will provide knowledge on the main barriers facing HPV vaccination and provide contextually-tailored solutions for how these barriers might be addressed. Policy briefs will be formulated from this study aimed at government policymakers and others who formulate or influence policy.

3. Preliminary findings for a PTSD Coach intervention in a resource constrained setting

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BACKGROUND

Posttraumatic stress disorder is a prevalent and impairing mental health condition in the general population with data suggesting individuals in resource constrained settings have limited access to essential treatments. Freely available internet-based interventions, such as PTSD Coach (mobile application), can help address this gap and improve access to and efficiency of care. The primary aim of this study is to evaluate the feasibility and effectiveness of an internet- based counsellor supported PTSD Coach (PTSD Coach-CS) intervention for adults with PTSD.

METHODS

This single blind, two parallel arm randomised controlled trial randomised participants to a PTSD Coach-CS or enhanced Treatment as Usual (e-TAU). PTSD Coach-CS participants attended four weekly sessions of 30-40min in duration each. E-TAU participants receive a detailed referral letter that include a request for psychological assistance at primary health care level. A clinical psychologist blinded to intervention allocation monitors all participants from (T1) pre- to (T2) post-intervention, to (T3) one-month and to (T4) three-month follow-up. The primary outcome is PTSD symptom severity changes from pre-intervention to follow-up between the two treatment arms. Secondary outcomes are related to: (i) depression and anxiety symptom changes, and (ii) neurocognitive functioning changes. PTSD intervention effectiveness will be determined using both intent-to-treat and completer analyses using Repeated Measures Analysis of Variance. To examine treatment differences on both primary and secondary outcomes, incorporating confounder variables, generalised estimating equations and a linear mixed-effects model approach was employed.

RESULTS

Data collection is currently underway. We aim to present the findings available at the time of presentation.

CONCLUSION

To our knowledge this is the first time PTSD Coach is evaluated in a resource constrained setting such as South Africa. A low-cost, volunteer-based intervention may aid to alleviate some of the burden on health care resources through upskilling and task-shifting of mental health care services in South Africa.

4. The perceptions of older people living with HIV/AIDS towards physical activity and exercise

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BACKGROUND

Older people living with HIV (OPLWH) require significant levels of support, including healthcare and rehabilitation interventions. People that are HIV positive are living longer with HIV, but still experience health-related impairments that affect functional activity, participation in day-to-day interactions, livelihoods, and overall quality of life. Physical activity should be included as part of the comprehensive medical management for OPLWH but often a gap exists in understanding and prescription. Our study aimed to explore the perceptions of OPLWH about physical activity and exercise.

METHODS

The study adopted a phenomenological, qualitative design, using in-depth interviews, to understand OPLWH perceptions of physical activity and exercise, and their need for, and access to, physical activity and exercise programmes in their communities in South Africa. Sixteen individuals voluntarily participated in face-to-face, semi-structured interviews which took place in a healthcare facility where they received regular treatment. All participants were 50 years and older.

RESULTS

The interview data revealed three overarching themes, namely: motivation for physical activity and exercise; barriers to physical activity and exercise; and proposed structure of physical activity and exercise.

CONCLUSION

The qualitative nature of our study provided an in-depth understanding of the perceptions of OPLWH about physical activity and exercise. Our study highlighted the interplay between motivating factors and barriers, and the structural components of physical activity and exercise, which can possibly influence the design and implementation of a physical activity intervention programme for OPLWH.

Keywords: HIV/AIDS, Physical activity, Rehabilitation, Ageing

5. Testing WhatsApp-based microlearning for South African primary care healthcare workers, to fill knowledge gaps and to extend the reach of the National HIV and TB Healthcare

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BACKGROUND

The National HIV and TB Healthcare Worker (HCW) Hotline, based in the Division of Clinical Pharmacology at the University of Cape Town, provides clinical support to HCWs across South Africa. The hotline pharmacists frequently note significant drug-drug interactions during consultations, about which many of the HCWs are unaware. We did an online survey of HCW knowledge of the interactions and found gaps in both awareness of the interactions and how to adjust dosing. HIV is dynamic and guidelines are regularly updated. Ongoing training and mentorship of healthcare workers is vital for optimal patient care. This has traditionally been done face-to-face, at centralised points, but distance, cost and lack of human resources hamper it. WhatsApp-based learning has shown benefit in teaching elsewhere and SA has 93% WhatsApp penetration.

METHODS

A pragmatic, mixed-methods, cluster-randomised study will test the efficacy, acceptability, and feasibility of WhatsApp-based training on national ART guidelines in under-resourced districts in the Eastern Cape: interactive 10-minute case-based “micro’ lessons or control. Its effect on knowledge, and use, of the hotline for clinical mentorship will also be measured. All nurses and community health workers in included clinics will be invited to participate and cluster randomised. Outcomes will be measured using pre-and post-knowledge questionnaires; WhatsApp interaction analysis; focus groups; folder reviews to establish effect on patient care, and analysis of queries received by the hotline before, during, and after the intervention.

RESULTS

The proposal has been approved by the UCT Human Research Ethics Committee and permission to run the project has been obtained from the Eastern Cape Department of Health. Measurement tools are being tested for reliability and validity and a pilot study has been done. As of mid-October, we are currently recruiting healthcare workers in the 48 study clinics in the Joe Gqabi, Chris Hani and Amathole districts.

CONCLUSION

The findings of this study have the potential to provide a simple, adaptable, and scalable training alternative, a concept which can be used across medical modalities in South Africa and further afield. If it proves effective, it may contribute to healthcare systems strengthening through improving HCW knowledge and support.

6. Physical activity in community dwelling persons with traumatic spinal cord injuries

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BACKGROUND

Physical activity is an important factor needed to combat the morbidity and mortality associated with a spinal cord injury. We should therefore promote physical activity throughout the chain of care. Subjective measurements of physical activity often present inconsistencies, hence the use of an objective measurement such as an accelerometer is recommended. The purpose of this study is to investigate the feasibility of accelerometers to measure physical activity in an acute setting in a traumatic spinal cord injury sample.

METHODS

A cross sectional design was employed. Process feasibility was assessed and proxies for feasibility were recruitment rate and protocol adherence. Participants were recruited consecutively from a specialized spinal cord injury unit providing acute care. Each participant was fitted with one accelerometer on their non-dominant wrist, to be worn for a minimum of eight hours per day, for five consecutive days.

RESULTS

A total of 15 participants with paraplegia were recruited over three months, thus recruitment rate was an average of five participants per month. An average wear time of 15.7 hours/day (SD:2.2) was documented. Participants spent 87% of their time engaging in sedentary physical activity (13.7 hours/day, SD:2.2), followed by 12.7% of light intensity physical activity (2 hours/day, SD:1.1) and lastly, 0.3% of their time engaging in moderate to vigorous intensity physical activity (3mins/day, SD:7).

CONCLUSION

Participant recruitment in the study was low, hence the expansion of the research setting is recommended. The majority of participants adhered to the protocol as outlined, and were able to wear the device comfortably for longer than the prescribed time per day. Sufficient quality physical activity data was obtained from this feasibility study.

7. Developing practice guideline for enhancing communication in hearing families with deaf children

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BACKGROUND

According to the World Health Organisation (WHO), deafness is one of the most neglected disabilities and one which is worse in developing countries. In South Africa, auditory disability prevalence is estimated to be between 5.2% and 6.4% in children below the age of nine years. Problem statement: What is the scope of a practice guideline to ensure that intervention meets the needs and priorities of hearing families and their deaf school children living in rural areas in order to improve communication outcomes and relationships in their households? The aim of the study was to develop a practice guideline to enhance relationships and communication between deaf school children and their hearing families within a rural home context.

METHODS

The study used systematic and interpretive approaches using both quantitative and qualitative approaches. The mixed methodology was conducted in two phases. Phase one was a descriptive survey design using a quantitative method in the form of a questionnaire. 100 parents,100 learners and 12 educational professionals participated in phase one giving information that will assist in the development of the tool in phase three. In phase two, 10 parents and 10 learners were selected from phase one to participate in the interviews. Phase three is for the development of the tool based on the information from phase one and two.

RESULTS

An expected outcome for this study is the development of recommendations and a practice guideline for deaf children diagnosed late from under resourced environments. A clinical protocol is being developed to enhance communication in families.

CONCLUSION

The developed guideline is expected to have an impact on the Basic Department of Education policies both regionally and nationally, providing recommendations for a strategic management plan and practice guidelines for this vulnerable and marginalized population.

8. Descriptive Review of Online Information Resources for Stroke: A Scoping Review.

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BACKGROUND

People with stroke and their caregivers experience numerous information needs; internet-based resources may offer cost-effective ways to improve access to information about this condition and its management, including the availability of resources and support. The quality of online health information is, therefore, an important consideration for both developers and consumers of these online resources.

METHODS

This study aimed to map and evaluate the content, readability, understandability, design, and quality characteristics of freely available online information resources (ie, websites) that provide information and self-help strategies post-stroke. This descriptive review followed the five systematic and rigorous methodological steps that are recommended for scoping reviews, which include the following: (1) identifying the research question, (2) identifying relevant studies, (3) selecting the studies, (4) charting the data, and (5) collating, summarizing, and reporting the results. Data is being synthesized and analysed thematically.

RESULTS

As of June 2022, the findings of the scoping review are being drafted as a manuscript for submission to JMIR, an open-access peer-reviewed journal. Ethical approval was not required for this review, as it included publicly available information.

CONCLUSION

This study is novel and evaluated the typology, content, and design-related criteria of online information resources for stroke. Comprehensively mapping existing resources will assist developers with gaining insight into gaps across a range of quality criteria. The results of this review identified exemplar online health information resources of good quality and where improvements are needed. An evaluation of these resources by target users will be incorporated in a follow-up study to validate the results of the review from the user's perspective. The exemplar resources, identified during the review, will inform the design of a South African–specific stroke-related digital health intervention.

(WC = 280)

9. An exploration of emerging collaboration models between Traditional Health Practitioners and Mental Health Practitioners in South Africa

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BACKGROUND

In South African (SA) communities some people presenting with symptoms of a mental health disorder seek care from both Traditional Health Practitioners (THPs) and Mental Health Practitioners (MHPs). For this reason, practitioners, patients, and policy makers globally have been advocating for collaboration between the two systems of healing. This study will explore collaboration practices between THPs and MPHs treating mental health disorders in SA.

METHODS

This is a multi-phased, mixed study, comprised of computer-based research and primary qualitative studies. In the first study, a scoping review was carried out. In the second phase, we adopted a qualitative multi-case study design to examine the nature and process of collaborations between THPs and BHPs. Data was collected using in-depth video and telephone interviews and document analysis from purposely sampled cases of THP and MHP, between August 2021-June 2022. Interviews were transcribed verbatim and coded on Nvivo. This data is currently being analysed through the collaborative governance regime conceptual framework lens, using a narrative case study analysis approach. Phase 3 will engage approximately ten THPs and MHP on phase 1 and 2 study findings.

RESULTS

Results for phase one were reported in the previous report. Out of the nine cases we planned to include in this study, we could only collect data from eight cases. Six of the cases had 2-3 participants each, while two cases had 1 participant each. Collectively, these cases yielded 16 interviews. Further, we conducted document reviews for one of the cases. Data was coded under 5 headings: collaboration description; collaboration drivers, collaboration processes, collaboration impact and collaboration recommendations. Preliminary findings indicate that the nature of collaboration between THPs and BHPs are informal and deficient. This is similar across 7 cases, with 1 case more formalised collaboration.

CONCLUSION

Practitioners in this study illustrated that in SA current collaborations for mental health are rare and informal. Although this might be the case, our study showed that it is possible for THPs and MHPs to work together in delivering mental health services.

10. Investigating the gut microbiome in Foetal Alcohol Spectrum Disorders

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BACKGROUND

The prevalence of Foetal Alcohol Spectrum Disorders (FASD) in the Western Cape is up to 31%, significantly higher than the global prevalence of 0.77%. Alcohol consumption alters gut microbial composition and compromises the integrity of the intestinal barrier thereby allowing bacteria to enter the bloodstream, and in doing so, be transported to the foetus. Altered foetal bacterial colonisation may subsequently alter infant gut microbiota functioning resulting in increased risk of developing a neurodevelopmental disorder. This study therefore aimed to (1) compare the gut microbial composition of women who birthed infants diagnosed with and without FASD and (2) compare the gut microbial composition of infants diagnosed with and without FASD.

METHODS

16S ribosomal RNA V1-V2 region sequencing was performed on microbial DNA extracted from 207 maternal stool samples and 211 infant stool samples. The *dada2* pipeline, *PhyloSeq* and *vegan* were used to process the data, calculate diversity measures and compute the statistical analyses of microbial composition.

RESULTS

Ruminococcus was lower (q = 0.02978) in women with infants with FASD, while *Alloprevotella* was higher (q = 0.04262) in these women. In the maternal cohort, 62 women birthed infants diagnosed with FASD, 39 women birthed infants with a deferred diagnosis, and 106 women birthed infants without FASD. In the infant cohort, 61 infants were diagnosed with FASD, 43 infants had a deferred diagnosis, and 107 infants did not have FASD. *Megasphaera* (q = 0.02598), *Prevotella* (q = 0.02688), and *Bifidobacteria* (q = 0.03159) were found to be higher in infants diagnosed with FASD.

CONCLUSION

A lower abundance of *Bifidobacteria* has been observed in children with Autism Spectrum Disorder (ASD), therefore the higher *Bifidobacteria* abundance observed in infants diagnosed with FASD was unexpected. Similar to findings in individuals diagnosed with ASD in other low- and middle-income countries, *Prevotella* was found to be higher in infants diagnosed with FASD. Although further investigation is required, the microbial differences observed in this study may contribute to the neurocognitive deficits' characteristic of FASD. These findings are promising for microbe-based therapeutic interventions to reduce the extent of neurocognitive deficits and the debilitating symptoms associated with FASD.

11. Molecular & histological effects of a novel aptamer on diet-induced obesity and steatohepatitis.

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BACKGROUND

The development of non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH) is strongly associated with obesity. Characterized by hepatocellular damage, NASH is further aggravated by chronic low-grade systemic inflammation due to abnormalities in lipid metabolism. Current therapeutic interventions have limitations in that they possess harmful side effects or otherwise prove ineffective. Therefore, this study aims to suppress adipocyte inflammation and correct steatohepatitis by developing an aptamer-mediated drug delivery system against disease-specific biomarkers.

METHODS

In silico approaches were utilized for the screening and selection of aptamers. Recombinant protein expression was conducted by transforming *E. coli* BL21 Star™ (DE3) One Shot® competent cells with a plasmid containing the gene of interest. Positive transformants were analyzed using colony polymerase chain reaction (PCR), then cultured and induced at an OD_{550} of 0.7 with 0.4 mM IPTG for optimized protein production. The establishment of *in vitro* models of obesity and hepatic steatosis were investigated by differentiating 3T3-L1 pre-adipocytes and inducing HepG2/C3A hepatocytes with oleic acid, respectively. Total protein was extracted from the respective *in vitro* models, and the expression of disease-specific biomarkers was screened

using western blotting.

RESULTS

Five aptamers that bind to the biomarker with high affinity were identified. Molecular dynamic simulations showed the aptamers to be stable in the presence of the protein. Recombinant expression and purification of the target protein were successfully achieved. *In vitro* models were established, although lipotoxicity was observed in the hepatocytes at high concentrations of oleic acid. This will be repeated to ensure the reduction of lipotoxicity. The screening of disease-specific biomarkers using western blotting is currently underway.

CONCLUSION

The *in silico* approach has provided aptamer sequences, which are currently being synthesized. Further studies to validate their binding specificity against the protein and in cell culture models will be investigated soon.

12. Identification of *Mycobacterium tuberculosis* immunogenic adhesin proteins as diagnostic and vaccine candidate

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BACKGROUND

Mycobacterium tuberculosis (Mtb) remains a global public health epidemic and has the highest cause of mortality of any infectious disease. Mycobacterial adherence plays a major role in the establishment of an infection within the host. Adhesin molecules produced on the bacterial cell surface facilitate attachment to host receptors and cell-surface components. These proteins are uniquely expressed in bacterial cells and may pose a viable source for exploitation in serological applications. The purpose of this study is to explore alternative and novel TB-related adhesin proteins. These may be used as biomarkers for potential TB diagnostic applications and candidate vaccine development

METHODS

Computational analysis of the *Mtb H37Rv* whole genome was used to predict potential novel adhesin proteins. Conserved hypothetical genes (n=10) were selected for the laboratory-based experimental study to determine adhesin potential by cloning into the PGEX-6P-1 plasmid vector. Confirmed recombinant plasmids were then subjected to protein expression by induction using Isopropyl ß-D-1-thiogalactopyranoside (IPTG) to determine optimal protein expression conditions.

RESULTS

In Silico analysis generated 776 potential adhesins among conserved hypothetical proteins. The experimental study included selected genes with the potential immunogenic stimulus (Rv1200, Rv2598, Rv3238c, Rv2272, Rv3209, Rv3067, Rv3491, and Rv0679c) and controls (Rv0475 and Rv3717). These genes were cloned into a PGEX-6P-1 expression vector and transformed into *E.coli* (Dh5a) cells. Current laboratory work includes the optimization of protein expression. Evaluating optimal parameters with temperature (25ºC, 30ºC, and 37ºC), time interval of induction (T_0-T_5) and IPTG concentrations (0.25mM-1.25mM). Subsequently, optimally expressed proteins will be confirmed by Western blotting and purified using Glutathione affinity chromatography. Identification of the extracellular matrix binding adhesin potential will be performed by Far-Western blotting analysis using Laminin, Fibronectin, and Collagen.

CONCLUSION

Selective parameters for optimal expression of these novel proteins are required for upscaling protein production for downstream applications. This is particularly important in the purification process.

13. A communal Holistic Therapeutic Approach for Psychosocial Health Management Among Southern African Indigenous Communities

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BACKGROUND

It is reported that mental health remains in the backseat of the global health care system, although the World Health Organization (WHO) illuminated the importance of mental health since at least 2001. However, the scourge of mental health continues unabatedly particularly in the low-income countries. There is an estimate of more than 1 billion people affected by mental health worldwide. Where 1 in 3 South African suffers from mental health whereas, only 1 in 10 have access to mental health. Evidently, the current mental health approach is seeing fewer positive outcomes.

The aim of this study is to develop, confirm, and validate a communal holistic therapeutic approach for psychosocial health management in Southern African indigenous communities (South Africa and Malawi). This will be achieved through the following objectives;

1. Conceptualization of a typology (***phase I***)
2. Conducting an integrative literature review to compare and contrast the constructs emerged from the typology (***phase II***)
3. Developing a preliminary approach
4. Confirming and validating the approach through expert validation (***phase III***)

METHODS

A multiphase sequential qualitative method is being used to conceptualize a typology from an existing conceptual framework through Grounded Theory (**phase one**). Followed by critical, integrative literature review where the development of hypothetical models to inform phase three of the research (**phase two**). Lastly, content validity index (CVI), content validity ratio (CVR) and Kappa statistic will be used for confirming and validating hypothetical models (**phase three**).

RESULTS

N/A

CONCLUSION

The anticipated outcome will contribute to the renaissance of indigenous health practices. Furthermore, the outcome will inform health policies to foster needs aligned health care practices. Teaching and learning curriculums will be inclined to the context of Africa. Lastly, further research will be informed.

14. Socioeconomic Status And Related Sociodemography Of Unpaid Family Caregivers For The Visually Impaired Patients: A Systematic Review

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BACKGROUND

Socioeconomic status (SES) is an intricate and multidimensional concept incorporating employment status, education, and income, which interact with sociodemographic factors (e.g. age and gender) to serve as barriers to providing care to visually impaired persons. The above is mainly because the visually impaired rely on family members for financial and physical support. Also, female adults have tended to provide such care owing to societal and cultural norms, thus exerting pressure on those who are expected to provide care. Therefore, this review study intends to highlight prior investigations by comparing SES and Sociodemography of caregivers in developed and developing countries and how they interact in caregiving.

METHODS

The study applied seven evidence-based practice steps found in nursing to search literature using a PICO system. The Boolean strategy used articles to search related articles by combining keywords such as caregivers, sociodemography and socioeconomic status from 2009 to 2022. The studies were registered using the Prisma flow chart diagram to exclude and categorically include those relevant to the study question. The word search found seven studies, two and five done in developing and developed countries, respectively.

RESULTS

Overall, the study found that males in developing countries (Nigeria and India) were more likely to provide care than in developed countries (USA and Mexico). However, Canada showed to have more males providing care than Nigeria. Also, most females provided care, and most caregivers had higher education in both developed and developing countries. However, the majority were unemployed in developing countries. In developed countries, most studies did not report caregivers' income and employment status.

CONCLUSION

SES of caregivers should include all variables of social classification and sociodemographic information to understand the interaction of the above determinants of health in providing care to the visually impaired.

15. Detection of drug resistance in *Mycobacterium tuberculosis using next generation* sequencing

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BACKGROUND

Next generation sequencing (NGS) technology is currently a comprehensive alternative to existing conventional drug susceptibility testing (DST) methods used for detection of *Mycobacterium tuberculosis* (*Mtb*) drug resistance. However, the complexity of sequencing platforms and skill requirements for implementing the technologies as well as interpretation of data has limited their uptake in low-income settings. Our study aims to determine mutations that will be used to develop a free online Bioinformatics analysis tool that detects *Mtb* drug resistance and lineages from raw NGS data.

METHODS

One-hundred *Mtb* isolates were sub-cultured in BACTEC MGIT 960 system. Prior DST, the *M. tuberculosis* isolates were confirmed for pure culture and non-contaminated by Zhiel-Neelsen staining and blood agar respectively. The phenotypic DST was determined for the first-line drugs using MGIT- antimicrobial susceptibility test -streptomycin (STR), isoniazid (INH), rifampin (RIF) and ethambutol (EMB), and -Pyrazinamide (PZA) systems. The NGS TB-profiler tool will be used to determine the *Mtb* mutations.

RESULTS

Of the 100 isolates evaluated, 37 were susceptible to STR, INH, RIF, EMB and PZA. The 33 drug resistant isolates are consisted of MDR-TB (19 isolates) and mono resistant cases (INH=7, STR=3, PZA =3, RIF =1). Thirty were excluded due to presence of contamination on MIGIT tubes, blood agar or microscopic evaluation.

CONCLUSION

Our complete genome sequences will be analysed to determine mutations that will be used for bioinformatics tool development. The developed bioinformatics tool will have an impact in TB treatment and vaccine development by rapidly detecting drug resistant strains and associated mutations.

16. SARS-CoV-2 antibody kinetics in adults and pregnant women after natural infection

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BACKGROUND

The continuous increase of coronavirus disease 2019 (COVID-19) cases caused by severe acute

respiratory syndrome coronavirus-2 (SARS-CoV-2) infection remains of significant concern globally. The presence of antibodies following natural infection with many viruses including Hepatitis A, Hepatitis B, and influenza suggests a protective immune response including in people living with HIV (Human Immunodeficiency Virus) (PLWH). Few data are, however, available on antibody kinetics to SARS-CoV-2 in PLWH. This study aims to determine the levels and duration of SARS-CoV-2 IgG, IgA, and IgM against full-length spike, full-length nucleocapsid, and Receptor Binding Domain (RBD)-specific antibodies among adults and pregnant women who were infected with SARS-CoV-2 during the 1st and 2nd, waves stratified by HIV status.

METHODS

This is a retrospective longitudinal study nested within an active, prospective, hospital-based COVID-19 surveillance study that was initiated in early March 2020, at Chris Hani Baragwanath Academic Hospital, in Soweto. Patients with SARS-CoV-2 infection confirmed by PCR (Polymerase Chain Reaction), who were enrolled in the COVID-19 surveillance study were followed up for 1 year with systematic blood collection. The serum or plasma is being used in the current study to determine the SARS-CoV-2 antibody response using an in-house standardized high-throughput multiplex Luminex immunoassay and Microarray. All statistical analyses will be done using Stata version 13, and the results will be considered significant if the p-value is ≤0.05.

RESULTS

Training for Luminex immunoassay has been completed. Overall, 2280 samples from 457 participants stratified as adults (general population) and pregnant women are eligible for the current study; these include 180 PLWH and 277 without HIV. Of the 2280 samples, 460 samples have been tested for SARS-CoV-2 IgG using Luminex immunoassay.

CONCLUSION

The results from this study will inform the vaccine producers on the possible impact that HIV status has on the immunological response to the SARS-CoV-2 infection, most especially now with the rapid emergence of new SARS-CoV-2 variants.

17. Trends and determinants of late antenatal care initiation in three East African countries. A population based cross-sectional analysis

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BACKGROUND

Early antenatal care is critical for the mother and new-borns' health. Antenatal care is often delayed in Sub-Saharan Africa. The trends of late antenatal care initiation have not been thoroughly investigated in the region. Thus, the aims to examine the trends and determinants of late antenatal care initiation in the Democratic Republic of Congo, Kenya, and Tanzania from 2007-2016.

METHODS

The study employed Demographic Health Surveys data of reproductive-age women seeking antenatal care in the Democratic Republic of Congo (2007-2013/14), Kenya (2008-2014), and Tanzania (2010-2015/16). Bivariate and multivariate analysis was conducted per survey, taking sampling weights into account. The determinants of late antenatal care initiation were measured using multivariate logistic regression models and the trends were assessed using prediction

scores.

RESULTS

Late antenatal care initiation declined in Tanzania (60.9%-49.8%) and Kenya (67.8%-60.5%) but increased in the Democratic Republic of Congo (56.8%-61.0%) between surveys. In the Democratic Republic of Congo, higher birth order was associated with antenatal care initiation delays from 2007-2014, whilst rural residency (AOR:1.28;95%CI:1.09-1.52), lower maternal education (AOR:1.29;95%CI:1.13-1.47) and lower-income households (AOR:1.30;95%CI:1.08-1.55) were linked to antenatal care initiation delays in 2014. In Kenya, lower maternal education and lower-income households were associated with antenatal care initiation delays from 2008-2014, whilst rural residency (AOR:1.24;95%CI:1.11-1.38) and increased birth order (AOR:1.12; 95%CI:1.01-1.28) were linked to antenatal care initiation delays in 2014. In Tanzania, higher birth order and larger households were linked to antenatal care initiation delays from 2010-2016, whilst antenatal care initiation delays were associated with lower maternal education (OR:1.51;95%CI:1.16-1.97) in 2010 and lower-income households (OR:1.45;95%CI:1.20-1.72) in 2016.

CONCLUSION

The improvement in use of antenatal care is not uniform across countries in the region and sociodemographic subpopulations within countries. These findings warrant the development of appropriate interventions targeting the disadvantaged populations to achieve universal access to care.

18. Investigating the potential of traditional medicine in reactivation of latent HIV-1

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BACKGROUND

Combination antiretroviral therapy does not cure HIV-1 and the principal barrier to cure is a remarkably stable reservoir of latent HIV-1 in resting CD4+ T cells. New and improved latency reversing agents are necessary to target viral reservoirs (such as CD4+ T cells) and facilitate their eradication, and possible HIV-1 cure. Here, we seek to investigate a plant-based traditional medicine product as a potential agent to reactivate resting CD4+ T cells and induce transcription of latently infected CD4+ T cells.

METHODS

To evaluate the *in vitro* antiviral activity of the Mixture (4 plants combined) and SDK-2 (a single plant extract), HIV-1C (CM070P.1 and CM019P.1.2) and HIV-1B (NL4.3 and YU2) viral stocks were generated by co-transfection of HEK-293T cells using polyethylenimine transfection reagent. TZM-bl cells were treated with the Mixture and SDK-2 separately and luciferase activity was quantified. To evaluate the HIV (Human Immunodeficiency Virus) latency reversal activity using an established *in vitro* HIV-1 latent J-Lat model, the reactivation potential of the Mixture and SDK-2 were investigated by stimulating J-Lat cells at different concentrations.

RESULTS

SDK-2 extract inhibited NL4.3, CM070P.1 and CM019P.1.2 replication in a dose dependent manner (5µg/ml – 300µg/ml). However, the YU2 virus was more resistant to SDK-2 treatment. SDK-2 was more potent in inhibiting subtype C viruses (CM070P.1 and CM019P.1.2) when compared to subtype B viruses (NL4.3 and YU2). The Mixture extract did show dose dependent inhibition of the NL4.3, CM070P.1, CM019P.1.2 viruses but had reduced activity against the YU2 virus.

A comparison of the doses used to measure the potency of the Mixture extract and SDK-2 in reversing latent HIV-1 from J-Lat cells showed that these extracts showed reactivation potential of latent HIV-1. In these studies, treatment of J-Lat C cells with 106ng/ml phorbol myristate acetate (PMA-positive control) induced 90.2% GFP positive cells, while treatment of J-Lat C cells with 100µg/ml, 106µg/ml and 200µg/ml of SDK-2 extract induced 70.1%, 70.7% and 90.9% GFP-positive cells, respectively. Furthermore, treatment of J-Lat C cells with 325µg/ml of Mixture extract induced 4.32% GFP positive cells.

CONCLUSION

Thus, this current data suggests that the Mixture and SDK-2 possesses both anti-HIV and HIV-1 latency reversal activities. Mechanisms of latency reversal studies of both the Mixture and SDK-2 are ongoing.

Keywords**:** HIV-1**,** African traditional medicine, latency reversal, latent reservoir

19. Development of aptamer-based drug delivery systems for the treatment of obesity.

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BACKGROUND

The efficacy of current anti-obesity drugs is limited by adverse toxic side effects, reduced solubility, reduced bioavailability, and lack of specificity. As a result, the drugs are used for a limited period to avoid side effects. Due to these limitations and the unabated rise in obesity, novel, and improved approaches for treatment of obesity are urgently needed. The dysfunction of the white adipose tissues (WATs), as endocrine organs, has been found to be responsible for obesity and its associated disorders, hence the WATs have become prime candidates for therapeutic intervention. Targeted-drug delivery systems holds the promise for the treatment of obesity because of their improved drug efficacy and safety. Therefore, the aim of this study is to develop aptamer-based drug delivery systems for obesity treatment.

METHODS

Nanoparticles were synthesized using a single-step sonication method to encapsulate quantum dots. They were then functionalized with an aptamer and characterized using a zetasizer. To evaluate the feasibility of the aptamer to target the WATs, the aptamer-functionalized quantum dots-loaded nanoparticles were intravenously injected into obese and lean mice. The bio-distribution of the quantum dots was assessed by fluorescence emission using the IVIS Lumina II animal imaging system.

RESULTS

The functionalized nanoparticles had a size of 216.8 ± 3.53 nm and poly-dispersity index of 0,088 ± 0.006. The bio-distribution of functionalized nanoparticles showed significantly higher fluorescence intensities in the subcutaneous, epididymal, and omental adipose tissues, in both obese and lean mice. In contrast, low fluorescence intensities were observed in the retroperitoneal adipose tissues. Livers of lean mice showed higher fluorescence intensities than those of obese mice. No fluorescence was observed in the kidneys and spleens of lean or obese mice.

CONCLUSION

The current work has demonstrated the feasibility of targeting aptamer-functionalized nanoparticles to the WATs. Further studies are currently underway to investigate the therapeutic effect of the drug-loaded aptamer-functionalized nanoparticles *in vitro* and *in vivo*.

20. Allergic Rhinitis, Rhinoconjunctivitis and Hay fever symptoms among preschoolers are associated with school transport mode

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BACKGROUND

Allergic rhinitis (AR) is a common condition affecting many people in the world and this include children.

Mpumalanga province is associated with poor air quality and elevated concentrations of criteria pollutants, with transport being identified as one of the major contributors. Environmental air pollution is considered a risk factor for Allergic rhinitis. However, the study findings are mostly inconsistent and key contributing determinants in the development of allergic rhinitis are still unclear. Therefore, the aim of the study was to investigate the association between the school transport mode and allergic rhinitis symptoms, rhinoconjunctivitis and hay fever among pre-schoolers in Mpumalanga Province, South Africa.

METHODS

An analytical cross-sectional study consisting of 3145 participants was conducted in Mpumalanga South Africa. The pre-schoolers' mean age was 4. 05 (SD=1.22) years. Most pre-schoolers were within the age range of 3 to 5 years, which fell within the 50th percentile. A modified international study of asthma and allergies in childhood (ISAAC) questionnaire was used to collect data from the caregivers of pre-schoolers. The school transport modes that the child used to get to school; Walking, Taxi/Bus, Motor car, combination and other. Bivariate analysis was performed between potential risk factors and dependent variables. Risk factors that showed association in the bivariate analysis were included in the multiple logistic regression to develop a final model.

RESULTS

The prevalence of self-reported rhinitis ever, current rhinitis rhinoconjunctivitis and hay fever was 21,17, 8 and 4 % respectively. The percentage usage of transport modes or how the pre-schoolers get to school were as follows: Walking (52.9%), Taxi/Bus (26.9%), Motor car (16.6%), Combination (1.8%) and other (0.7%). Rhinitis ever, current rhinitis, current rhinoconjunctivitis and hay fever were significantly associated with the frequent use of motorcar to school, (OR 1.45 95 % CI: 1.15 − 1.83), (OR 1.62 95 % CI: 1.27–2.08), (OR 1.64 95 % CI: 1.17–2.29) and (OR 3.36 95 % CI: 2.16–5.21) respectively. No associations were observed between trucks/buses/taxis traffic in resident area and allergic rhinitis symptoms in the multiple analyses.

CONCLUSION

The study shows a high prevalence of allergic rhinitis symptoms amongst Pre-schoolers. The results have shown that frequent use of motorcar was significantly associated with the prevalence of allergic rhinitis symptoms in preschool children. This study findings will provide future researchers with baseline data when monitoring new allergic rhinitis symptoms trends in Mpumalanga.

21. Pharmacogenomics of warfarin: unique profiles important for an African-specific dosing algorithm

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BACKGROUND

Warfarin remains the highly prescribed anticoagulant, particularly in poorly resourced settings such as Africa. However, its narrow therapeutic range and difficulty in prescribing an accurate starting dose makes it one of the most challenging therapeutics to manage. Pharmacogenetics has become more applicable in guiding the prescription of warfarin therapy with better safety profiles. Pharmacogenetics of warfarin has swiftly advanced in other world populations such as Europeans, however, among Africans, the field is slowly paced with limited studies and no pharmacogenetic dosing algorithm developed to date. Thus, the study aimed to describe the African pharmacogenetic variation and profile genetic markers that could serve as predictors for an African-specific warfarin dosing algorithm.

METHODS

A total of 75 candidate variants were profiled among 503 recruited participants comprised of black Africans (BA, i.e., South Africans and Zimbabweans) and South Africans of mixed ancestry (MA) using various molecular techniques which included iPLEX PGx74 Mass array system, TaqMan genotyping assay and Sanger sequencing. Subsequently, whole exome sequencing was conducted on selected BA to screen for unknown and known African specific genetic variants that could have been missed through the candidate variants approach. Bioinformatics and statistical tools were employed to determine identified variants' allele frequencies, compare with world populations, associate with warfarin dose, and develop a warfarin dosing regression model.

RESULTS

Results revealed qualitative and quantitative differences in the variants' allele frequency distribution and linkage disequilibrium mapping among BA and MA. Furthermore, over 60% of pharmacogenetic variants' allele frequencies varied when comparing BA to Europeans and

Asians. Genetic markers *MTHFR c.788C>T, EPHX1 g.26978G>C, PROC c.G423T, CYP2C8 c.805A>T (*2)* and *CYP3A5 c.624G>A (*6)* were significantly associated with warfarin dose requirements and contributed to the BA warfarin dosing regression model, in addition to the African specific *CYP2C9* variants and *CYP2C rs12777823G>A*. Conversely, *VKORC1* SNPs (i.e., *VKORC1 g.-1639G>A, c.1173C>T*, and *9041G>A)* had a significant effect on warfarin dose requirement among MA, thus a haplotype comprised of the *VKORC1* markers was the main genetic contributor to the MA regression model, similarly to the dosing models reported among Europeans.

CONCLUSION

Black Africans portray unique and diverse genetic markers important for an African specific warfarin pharmacogenetics-dosing algorithm. Further buttressing the importance of including African populations in pharmacogenomics studies to ensure health equity.

22. Association of maternal vaginal microbiome and adverse foetal birth outcomes

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BACKGROUND

The complex and dynamic microbial community in the vaginal tract is an important factor in a woman's vaginal health. Imbalances of the vaginal microbiome may predispose women to ascending colonisation of the genital tract and increased risk of adverse birth outcome. Despite the increasing number of studies using the 16S rRNA sequencing to investigate the vaginal microbiota during pregnancy, there are no unique microbial characteristics associated with poor birth outcomes. Shotgun metagenomics sequencing provides a tool to reveal the community structure and function of genes.

METHODS

The vaginal microbiome (VMB) study is nested into a cohort study (Bukhali) which is currently been undertaken at the Developmental Pathways Health Research Unit (DPHRU), Chris Hani Baragwanath Academic Hospital (CHBAH). Briefly, enrolled women were trained to self-collect vaginal swabs at each of the study visits (i.e. 10-16, 24-28 and 32-36 weeks for pregnant women), baseline and exit at 18 months for non-pregnant women. The VMB study has enrolled 423 pregnant women, which are currently being followed up from first trimester to delivery and 1696 non-pregnant women. The study enrolment will continue until December 2022.

RESULTS

The vaginal swabs are currently being tested by qPCR to validate the integrity of the samples and ensure samples were collected correctly. From 423 pregnant samples collected, 288 have been tested by qPCR. Further, the Open array panel was designed based on the most abundant species in the vagina from 46 vaginal swabs collected from different women. Among some species that were detected were *L. iners* (n=24/46; 52.17%), *L. amnionii* (n=18/46; 39.13%), *G. vaginalis* (n=17/46; 36.96%), *A. vaginae* and *BVAB2* (n=16/46; 34.78%).

CONCLUSION

Further testing of the self-collected samples is currently being undertaken at VIDA and more samples will be tested on the open array panel. The findings of this research will enable us to understand the specific microbes that may be influencing poor birth outcomes, beyond the presence or absence of microbial taxa.

23. Traditional And Modern Intercept Of Smokeless Tobacco Use In South Africa

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BACKGROUND

Tobacco is globally responsible for about 8 million annual deaths. There is smoked and smokeless tobacco (eg. snuff). In South Africa (SA) snuff is used as a remedy to treat headaches, toothaches and nosebleeds and traditional healers (TH) use it in their practice. However, people, specifically women, also use snuff as a sexual stimulant which is risky as it can cause several types of cancerous or potentially malignant lesions. This study aims to explore the use (prevalence, quitting behaviour and perceptions of harm) of SLT in SA using the Global Adult Tobacco Survey SA. It will also determine traditional healers' ways and reasons for using SLT and explore the ways and reasons that patrons of traditional healers use SLT

METHODS

This study will use a mixed method approach. It will conduct a scoping review on the published knowledge of STL use in SA. Then use data from the first Global Adult Tobacco Survey South Africa (GATS-SA) for the quantitative phase of the study. For the qualitative phase it will interview TH's and patrons of TH. Descriptive statistics and logistic regression will be used to analyse the quantitative data on SPSS, while reflexive thematic analysis with the aid of NVivo will be used to analyse the qualitative data.

RESULTS

Analysis of quantitative data and fieldwork of qualitative phase will begin soon after ethics approval is received for this study.

CONCLUSION

This study will provide information that can be used to encourage more SLT users to quit, discourage young people from initiating SLT use and advocate for more effective measures to control tobacco use in SA. Such measures can be used to design a culturally sensitive intervention to assist with SLT addiction.

24. Unfavourable outcomes and transmission dynamics in patients with drug-resistant tuberculosis receiving bedaquiline

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BACKGROUND

Drug-resistant tuberculosis (DR-TB) remains out of control in many parts of Sub-Saharan Africa and has the potential to destabilise National TB programs in these countries. Our understanding of the epidemiology of patients who fail treatment, using new and repurposed drugs (WHO defined group-A drugs), is grossly limited. In this trial, we aim to describe participants who fail a bedaquiline-containing drug-resistant TB regimen and identify potential biomarkers to prognosticate failure in those with DR-TB and to use sequencing to describe transmission dynamics of treatment failure and relate these to clinical and prognostic characteristics.

METHODS

We will recruit patients from facilities across Cape Town to describe the epidemiology, resistance profile, toxicity-related linezolid interruption, and outcomes in patients with DR-TB. We will also collect de-identified retrospective patient data from patient folders and databases to create an electronic registry. We will evaluate the predictors of outcome, infectiousness (through cough aerosol sampling, radiological characteristics, measures of bacterial load, and contact tracing), and the utility of biomarkers (including urine proteomic signatures and imaging).

RESULTS

Data collection instruments have been finalised and the database setup has been completed on the secure RedCap platform. A site initiation visit was held on 14 May 2022 and staff has been delegated. De-identified data have been received from the electronic drug resistant web database and analysis has been initiated. Prospective participant recruitment will be initiated in June 2022.

CONCLUSION

To date, we have obtained University of Cape Town Ethics Committee approval for the project protocol. We have also obtained city, government, and institutional approvals to initiate recruitment. The project has progressed well. We obtained all required regulatory approvals and initiated data collection. We aim to prepare a manuscript for publication in the coming months. Findings from this project could have a meaningful impact on DR-TB management guidelines.

25. Associating gut-microbiota profiles with HbA1C and immunity in type-2 diabetics/non-diabetics, with/without COVID-19.

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BACKGROUND

The gut-microbiota has attracted much research over the past years and is believed to be involved in the pathogenesis and progression of type-2 diabetes mellitus (T2DM). However, there is an underrepresentation of correlation studies demonstrating the role the gut-microbiota plays T2DM in different African populations. Literature has highlighted the importance of studying the microbiome in different populations because there are variable factors affecting microbial diversity and composition in both health and disease. These factors include cultural habits, diet, ethnicity, and geographical location. The present study will profile the gut-microbiota of study participants and determine the relationship between dysbiosis and glycated haemoglobin (HbA1C) levels in a South African population. In addition, the proposed study will also investigate the relationship between dysbiosis and antibody-mediated immunity, especially in T2DM patients, as they are commonly known to have a weak immune-system, which makes them prone to developing

infectious diseases such as COVID-19.

METHODS

This observational study that consists of T2DM patients and a non-diabetic comparison group. Diabetic patients will be recruited from the Diabetes Clinic based at Dr. George Mukhari Academic Hospital, while non-diabetics will be recruited through posters, which will be displayed at both the hospital and university. A questionnaire to collect information about patient demographics and other important information will be conducted. Once samples are collected, genetic analysis and clinical measurements will also be conducted. Results of the study will be analysed using the Stata software.

RESULTS

The study is on-going, and results have not yet been analysed. However, the results of this study will form a solid basis for potential future studies that will employ more sophisticated study designs such as clinical trials.

CONCLUSION

The study will create awareness about the possibility of additional and novel strategies (taking the gut-microbiota into consideration) on how T2DM can be controlled, such as supporting the clinical use of certain microbes from the gut-microbiota as potential therapy in the form of faecal microbiota transplantation, or by promoting the implementation of less expensive and simpler solutions such as promoting healthy eating i.e., food stimulating the presence of good gut microbes.

26. Anti-Cancer Effects Of Dodonaea Viscosa, A Herbal Medicine Used By Traditional Healers

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BACKGROUND

Cancer is a leading problem worldwide. In South Africa, high HIV prevalence is a compounding factor, with the incidence of certain cancers being high among HIV-positive individuals. One such cancer is Burkitt lymphoma (BL). Increasingly, cancer patients, are using traditional medicines (TM), as they fear the side effects associated with conventional treatments. While conventional treatments are researched and tested, TM are not. Therefore, there is a need to assess the clinical benefits of TM when used alone or in conjunction with chemotherapy, so that they can be administered safely and effectively. This study investigates the anti-cancer effects of extracts from the plant *Dodonaea viscosa* (DVE), prescribed by a group of traditional healers in the Western Cape.

METHODS

BL cell lines were exposed to DVE, and specific cellular effects (cell viability, proliferation, apoptosis, and morphology) were measured. A xenograft model was used to assess the effect of DVE on tumour formation *in vivo.*

RESULTS

We previously demonstrated potent anti-cancer properties of DVE in the BL cell line, Ramos. These findings have now been confirmed in a second BL cell line, BL41. Our results show that DVE inhibits the viability of BL41 cells, demonstrated using the WST-1 assay. Using a caspase3/7

activity assay, DVE was shown to enhance apoptosis, which was corroborated using Annexin V assays and cell cycle profiling. Additionally, DVE-treated cancer cells displayed morphological characteristics typical of those undergoing apoptosis, as shown by microscopy. The next phase of the project, which determines the effect of DVE on tumour formation is currently being investigated.

CONCLUSION

Extracts from the *Dodonaea viscosa* plant have potent anticancer properties, as shown in *in vitro* assays. We are thus following the pathway towards the development of a novel therapeutic agent which could be used in combination with existing therapy to improve the outcome of BL patients. Future work will involve analysing the mechanism of action of DVE.

27. Maternal depression and infant nutritional status in rural areas of Thulamela local municipality in Limpopo province

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BACKGROUND

Depression during pregnancy and after pregnancy is a global concern. Pregnant woman and woman with newborns who have depression tend to be less responsive towards their babies and they are less likely to bond with their babies which may contribute to neglect nurturing roles. The mental outcomes of untreated depression during and after pregnancy are associated with adverse public health and social consequences for both mother and baby. The purpose of the study is to explore the association between maternal depression (both pre and postnatal depression), and child nutritional status. The objectives of the study are to determine the prevalence of prenatal and postnatal depression, to determine whether prenatal depression is a risk factor for postnatal depression. To determine whether maternal depression is a risk factor for child and infant malnutrition and factors associated with maternal depression (prenatal and postnatal depression) and child nutritional status.

METHODS

The study will use prospective cohort and quantitative design. All 20 health facilities will have equal chance to be selected, and a sample size of 200 pregnant women on their third trimester will be selected. The researcher will administer the questionnaire to the participants to obtain information on socio-demographic data, clinical information, partner related information, baby related information to women who have given birth and social support. Depressive symptoms will be assessed using Edinburg for both pre- and postnatal depression. The data for children from 12 months will be assessed using World Health Organization classification of nutritional status of infants and children.

RESULTS

The results are not yet available

CONCLUSION

There are a limited studies reported on the prevalence of prenatal and post-natal depression and how it affects the child growth. There is no cohort study from pre to postnatal depression that also links its results to nutritional status of the children.

28. The Role Of The Tumour Microenvironment Components In Cancer Cell Behaviour And Drug Response

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BACKGROUND

Chemoresistance is one of the leading causes of cancer-associated deaths and is a challenge during cancer treatment. Most studies focus on tumour cell-associated chemoresistance mechanisms, but recent reports suggest the tumour microenvironment (TME) plays a key role in the development of chemoresistance and malignancy progression. The TME is composed of cells including fibroblasts, mesenchymal stem cells (MSCs), cancer stem cells (CSCs) and the extracellular matrix (ECM). The aim of this study was to investigate cancer cell-stromal interactions within the TME focusing on fibroblasts, MSCs, CSCs and the ECM as well as the development of a model that mimic solid tumours in cellular characteristics and drug response.

METHODS

Using transwell-plates, MSCs were investigated as potential sources of cancer-associated fibroblasts (CAFs) in solid tumours. To assess the prognostic value of CSCs, the expression and malignant behaviour of CSC markers were also examined in clinicopathologically-confirmed oesophageal cancer biopsies and in vitro. The role of the extracellular matrix in the development of chemoresistance was also evaluated, using 3D cell-derived ECM models. A tumour spheroid model was used to mimic in vivo solid tumours and responses to drugs.

RESULTS

The expression of CAF markers, α-SMA and vimentin, increased significantly in MSCs co-cultured with cancer cells indicating conversion of mesenchymal stem cells into CAFs-like cells. Clinical oesophageal cancer biopsies stained strongly for the CSC markers, CD44 and ALDH1A1, demonstrating the presence of CSCs in tumours. FACS-isolated CSCS exhibited high levels of CSC markers, self-renewal markers and drug resistance proteins, and thus linked to increased drug resistance versus cancer cells. Culture of cancer cells on decellularized extracellular matrices abrogated the effect of drugs on cancer cells demonstrating that the ECM play a key role in drug resistance. Lastly, tumour spheroids displayed increased resistance to cisplatin and thus suggest that 3D co-culture system can significantly be used to study cancer cell-stromal/microenvironmental interactions and drug responses.

CONCLUSION

Overall, this study demonstrates the critical role played by the tumour microenvironment in tumour growth and metastasis and provides new insights into cancer treatment.

29. Interactions between Covid-19 and Tuberculosis

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BACKGROUND

South Africa has a high prevalence of active Tuberculosis (TB) and widespread exposure to *Mycobacterium tuberculosis* (Mtb) without active disease. Recent data suggests that 98% of the population has been exposed to severe acute respiratory syndrome virus-2 (SARS-CoV-2) since the beginning of the coronavirus disease-2019 (Covid-19) pandemic. Little is known about the effect of previous SARS-CoV-2 on the immune responses to Mtb exposure. The aim of this PhD project is to explore the interactions between these two infections in the local Cape Town population through an epidemiological study and a series of investigations into the peripheral blood and lung immune milieu in participants with Mtb exposure and recent Covid-19.

METHODS

The first study in this project was a targeted seroprevalence study conducted shortly after the first wave of Covid-19 in Cape Town. Thereafter, the impact of recent SARS-CoV-2 infection and other clinical and technical factors on bronchoalveolar lavage (BAL) fluid characteristics (cell yield, differential count, viability, and volume yield) was investigated in 337 participants with active TB, exposure to Mtb, and healthy community controls. Next, a panel of 50 soluble biomarkers (on the Luminex platform) was performed on serum collected from 87 critically ill Covid-19 patients, looking for signals associated with outcomes of both Covid-19 and TB. Lastly, the results of flow cytometry, multiplex soluble biomarker assays and Mtb killing assays in peripheral blood mononuclear cells from people with recent Covid-19 with active TB, or recent Mtb exposure, or healthy community controls (n=20 for each group), will be compared to the same groups with no evidence of previous Covid-19.

RESULTS

The seroprevalence survey validated the use of the Abbott SARS-CoV-2 IgG in the local community and found that low-income communities with high prevalence of TB were also those most affected by Covid-19 after the first wave. These results have been published and informed the design of the following immunology studies. Investigation of the BAL fluid characteristics found that recent SARS-CoV-2 was associated with significantly lower proportions of neutrophils and higher proportions of lymphocytes but did not affect other BAL characteristics in participants with varying Mtb exposure and TB disease. Analysis and manuscript drafting are ongoing. The Luminex assays have been performed on serum from 87 critically ill Covid-19 patients, and cleaning of the clinical data is ongoing. Full analysis and manuscript preparation will begin shortly. The candidate is currently training in the basic laboratory protocols and techniques required to perform the flow cytometry, Luminex and Mtb killing assays on the 149 processed samples are earmarked for the last study in this project.

CONCLUSION

These data will provide some answer to whether previous SARS-CoV-2 infection is a risk factor for poor outcome to Mtb exposure in our local population, which we have shown has a high exposure to both infectious agents.

30. Nano-embedded 3D-bioplatforms for Ocular Tissue Regeneration

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BACKGROUND

Posterior Segment Eye Diseases (PSEDs) such as age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy, affect tissues of the eye; vitreous humor, retina, optic nerve, and choroid, resulting in visual impairment and blindness. The complex anatomy and physiology of the eye poses significant barriers in efficient therapeutic delivery, necessitating intravitreal administration. However, current intravitreally delivered therapies have major drawbacks and low patient compliance. Efficient treatment of PSEDs remains a challenge and requires the development of more effective therapeutics capable of eliminating the need for repeat intraocular injections, achieving sustained and controlled therapeutic release, and promoting tissue regeneration via the body's healing mechanisms.

METHODS

Gene delivery nanocarriers targeting cluster of differentiation 44 (CD44) in retinal pigment epithelium cells (RPE) have been constructed for the treatment of retinal diseases. Nanocarriers based on hyaluronic acid (HA)-2 aminothiazole (HA_2AT) and HA- 2-aminobenzimidazole (HA_2AB) copolymers were developed. The copolymers were quaternized using iodoethane to enable the entrapment of genetic material. For preliminary studies, miR-128 was encapsulated into the nanoparticles. The copolymers and nanosystems were characterised using DLS, FTIR, NMR and SEM.

RESULTS

Following synthesis, nanoparticles were formulated, the charge, size and morphology of the nanosystems carrying miR-128 was determined. HA was used as a control and showed a charge of -12, HA_2AT_miR-128 charge was 5.54 and size was ~89 nm whilst HA_2Benzo_miR-128 NP charge was 6.27 and size was ~78 nm. SEM micrographs depicted all nanoparticles to be spherical.

CONCLUSION

Current therapies for retinal diseases cannot achieve sustained and targeted therapeutic delivery. The designed nanosystem uses HA to target the retina via CD44 receptors and utilises the positive charge on the nanosystem to promote gene encapsulation. The slightly positive charge, size and properties of the nanosystem are hypothesized to promote targeted and sustained gene delivery and expression, which are currently under investigation.

31. Differences in the gut microbiome in rat models of hypertension

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BACKGROUND

Hypertension is a significant risk factor for cardiovascular disease, including stroke, ischemic heart disease, heart failure, kidney failure, and atherosclerosis. The prevalence of hypertension is increasing rapidly in sub-Saharan and particularly in South Africa. Although the cause of essential hypertension remains unknown, recent studies suggest dysbiosis in gut micro-organisms may be an underlying cause. Studies have shown an association between infection and the human ulcer-causing bacterium Helicobacter pylori and hypertension, increased blood pressure (BP), and decreased BP following successful eradication. This study aimed to determine the impact of *Helicobacter spp*, rat models of hypertension.

METHODS

Microbiome species were determined from 16S rRNA and ITS sequencing using an Illumina sequencer on DNA extracted from faecal samples of spontaneously hypertensive rats (SHR) and the SHR ancestral Wistar Kyoto rats. Beta and alpha diversity indices provided the difference in diversity and abundance of the gut microbiome. Differences in the microbiota and tail-cuff BPs were determined (SHR; n=22) and the ancestral (WKY; n=22) after treatment with antibiotics to eradicate *Helicobacter spp*. and following subsequent re-infection with the human pathogen *H. pylori* live cultures (Ethical clearance 2019/04/31/c).

RESULTS

Preliminary data showed the number and abundance of *Helicobacter spp* were 25% more prevalent in SHRs than in WKY. BP decreased significantly after antibiotic treatment from 175±6mmHg to 120±5mmHg (p=0.0039) and 139±3mm Hg to 113±6mm Hg (p=0.0065), in SHR and WKY rats, respectively. Modest BP increases by re-infection with the human *H. pylori* in both WKY and SHR rats. The analysis of the microbiome data is in progress.

CONCLUSION

This study demonstrated a differential abundance of *Helicobacter spp*. in rat models of hypertension. A BP decrease in SHR and WKY rats after treatment to eradicate these bacteria was observed, showing that there is an association between gut microbiome and hypertension.

32. The caregiving relationships of AIDS-orphaned adolescents and primary caregivers: A Systematic Review

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BACKGROUND

Children and adolescents orphaned by Acquired Immune Deficiency Syndrome (AIDS) are vulnerable given their exposure to the negative effects of AIDS, and orphanhood, with risk for poor

developmental outcomes. The review aims to provide insight into the qualities of AIDS-orphaned adolescents' and caregivers' relationships.

METHODS

We conducted the literature search through nine electronic databases. The combination of key words used for the search were: (caregiving relationships); (orphans OR AIDS orphaned children OR AIDS orphaned adolescents); (primary caregivers); and (quality caregiving); (orphans); (HIV and AIDS). The search took place between 24 January and 28 February 2022. The review included both peer- and non-peer-reviewed literature published in 2010 – 2020. We assessed studies identified for full-text review for quality based on the orphan and/or caregiver reports, and the suitability of research questions and methods. We used the following three stages of meta-synthesis analysis from the selected studies: *refutational syntheses*, *reciprocal syntheses*, and *line of argument*.

RESULTS

The search yielded 2,090 titles. Twelve articles representing 11 studies fulfilled the inclusion criteria. These studies reported similar forms of economic, psychosocial and health-related hardships experienced by caregivers. However, the studies also showed that - despite the hardships - the majority of caregivers, particularly grandmother carers, found contentment in orphan care, and were able to provide needed care and support. This resulted in positive caregiving relationships, with the orphans faring well emotionally. Some relationships, however, were experienced negatively due to unresolved grief / familial issues for both caregivers and orphans, and the caregivers' overall lack of interest in providing care.

CONCLUSION

Findings suggest that intervention efforts need to be intensified to: (a) alleviate poverty in households affected by the HIV and AIDS pandemic; (b) strengthen the community psychosocial support programmes for orphans and their caregivers; and (c) integrate clinical services with community programmes for emotional healing.

33. Development of a Conceptual Framework for Self-Advocacy of Adults with Intellectual Disability

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BACKGROUND

People with intellectual disability have limited opportunities to participate in self-advocacy and policy making processes. They face various individual and structural barriers that hinder them from becoming self-advocates. In high-income countries, self-advocacy movements are thriving and people with intellectual disability are involved in policy making processes and other self-advocacy initiatives. However, in South Africa there are very few self-advocacy movements and involvement of people with intellectual disability is still lacking.

METHODS

Data from qualitative methods (a scoping literature review, semi-structured interviews, and focus group discussions) were analysed thematically using Atlas.ti, then triangulated to develop a conceptual framework for empowering persons with intellectual disability to self-advocate for their social and health policy priorities, through the lens of empowerment theory and the concept of Ubuntu.

RESULTS

From the scoping review four main themes emerged: self- advocacy, conceptual/theoretical frameworks used for self-advocacy by people with disabilities, inclusive citizenship and experiences of self-advocates involved in advisory bodies. Twenty-five semi-structured interviews were conducted, and they yielded four main themes: (a) understanding self- advocacy for people with intellectual disability in South Africa, (b) barriers to full participation in society, (c) inclusion of people with intellectual disability in society, and (d) importance of Ubuntu in self-advocacy for people with intellectual disability. From these results a conceptual framework for self-advocacy for people with intellectual disability was developed and translated into an easy-to-read format.

CONCLUSION

Stakeholder, policy, and legislative support for people with intellectual disability's inclusion in policy development and implementation processes are necessary but not sufficient for such participation to occur. Tangible strategies are needed to move support to action, to strengthen participation through self-advocacy skills and practical exposure to the policy and service development environment.

34. Factors associated with distress following a romantic relationship dissolution: The moderating role of attachment style

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BACKGROUND

Romantic relationship dissolutions (RRDs) during emerging adulthood may lead to severe psychological distress. Attachment style influences emotion regulation and how people cope with stressful events. Attachment style as a moderator of breakup distress has not been explored. First, the association of breakup distress with (i) the number of prior traumatic RRDs; (ii) relationship characteristics prior to the breakup; and (iii) breakup characteristics were investigated. Secondly, we investigated the moderating role of attachment style in these associations.

METHODS

Participants (*n*=886; female=70.1%; mean age=20.52 years) completed a demographic and relationship questionnaire, an attachment style measure, and the Breakup Distress Scale (BDS). Univariate tests were used to assess sociodemographic, relationships, and breakup variables associated with total BDS scores. Separate Structural Equation Models, with total BDS scores as the endogenous variable, were run for each attachment style (i.e., secure, anxious-ambivalent, avoidant) to assess for moderating effects.

RESULTS

Participants reported relatively high BDS scores (mean=33.73, mode=32) compared to previous studies. Factors significantly associated with BDS scores included the number of prior traumatic RRDs, relationship characteristics prior to the breakup (e.g., perceived closeness), and breakup characteristics (e.g., initiator status and reason for the breakup). Secure, avoidant, and anxious-ambivalent attachment styles moderated the relationship between these factors.

CONCLUSION

Non-marital RRDs are associated with significant distress in emerging adults. Interventions, such

as support groups where students can talk about their feelings without judgment, should consider breakup characteristics, reasons for the breakup, and attachment style.

Keywords: attachment style, breakup distress, moderation analysis, romantic relationship breakups, SEM, students

35. Synthesis and biological evaluation of edaravone derivatives bearing the *N*-benzyl pyridinium moiety as multifunctional anti-Alzheimer's agents

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BACKGROUND

Dementia is estimated to affect 50 million people worldwide with Alzheimer's Disease (AD) contributing to an estimated 60-70% of these cases. One of the pathological hallmarks of AD is the formation and aggregation of amyloid-beta (Aβ) peptide fragments. One of the upstream events of Aβ formation is the cleaving of the amyloid precursor protein by β-secretase 1(BACE-1) resulting in the formation of neurotoxic $A\beta_{1-42}$ fragments. The edaravone based pyridinium derivatives (EBPD's) were previously synthesized and exhibited multi-target activity against various AD targets. Therefore, in this study we propose to further investigate the EBPD's anti-AD potential.

METHODS

The EBPD's will be assessed for their abilities to attenuate $A\beta_{1-42}$ self-aggregation, acetylcholinesterase (AChE)-induced $A\beta_{1-42}$ aggregation and $A\beta_{1-42}$ fibril disaggregation using *in vitro* fluorometric assays. The BACE-1 inhibitory, kinetic and selectivity over BACE-2 activity of the compounds will be assessed via *in vitro* protein-based fluorometric assays. The compounds *in vitro* drug-blood plasma stability will be determined. The structural activity relationships (SARs) between the EBPD's and previously mentioned targets will be assessed using various *in-silico* methods. The synthesis of the EBPD's was upscaled to increase the compound's yield.

RESULTS

The upscale of the EBPD's synthesis and the purchasing of the required consumables and reagents for the *in vitro* assays was conducted. The standard operating procedures of the *in vitro* assays were developed and scrutinised to ensure reproducible and accurate results. The *in-silico* protein-protein docking of AChE and $A\beta_{1-42}$ peptide fragment was conducted and the docked poses exhibited correlation to previous experiments.

CONCLUSION

We will obtain further understanding of the EBPD's activity to various anti-AD targets and the mechanism of action to attenuate or inhibit these targets. The *in-silico* studies will assess the SARs between the compounds and targets to assist future structural optimization of the EBPD's. The blood-plasma stability is crucial in the development of potential pharmaceuticals.

36. Can biomarkers in scalp hair help predict patients at risk of a heart attack?

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BACKGROUND

Cardiovascular disease (CVD) is the leading cause of death amongst non-communicable diseases (NCD), of which are higher than those of HIV/AIDS and tuberculosis combined. Despite the implementation of strategies to reduce premature mortality rates from NCDs, there is a need for diagnostic tools for early disease detection and control of CVD risk factors. Hair testing could help identify at-risk people and potentially offer opportunities for long-term biomarker detection to reduce CVDs.

METHODS

This is a pilot study designed to compare levels of biomarkers in 3cm scalp hair from 30 acute myocardial infarction (MI) patients and 30 age-matched healthy controls. Cases are patients admitted for myocardial infarction (MI), and controls are dermatology clinic patients with no history of heart disease. Dietary lipids were extracted from hair using different extraction methods.

RESULTS

Four methods for extracting lipids from serum and one from hair were identified and compared. The butanol/methanol (BUME) is both non-toxic and performed the best in identifying myristic, pentadecanoic, palmitelaidic, palmitic, oleic, and stearic acids as well as cholesterol.

CONCLUSION

Even though we were unable to identify triglycerides, this study provides evidence that simultaneous detection of dietary lipids associated with the risk of MI can be extracted from hair. In the next phase of this project, this method will be used to compare lipids between MI patients and healthy controls. Validation of this approach could improve screening and early disease detection because of the longer window of exposure (weeks-to-years, depending on length) that hair has over serum; the current testing substrate.

SAMRC RESEARCH CAPACITY DEVELOPMENT INITIATIVE (RCDI) POST-GRADUATE PROGRAMME

1. Whole genome sequencing of *Mycobacterium tuberculosis* and assessment of treatment outcome

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BACKGROUND

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis (M. tb)* that belong to the family *Mycobacteriaceae*. TB has been reported to be one of the leading cause of deaths with statistics that indicated over 2 million deaths a year and over a billion people infected. Tuberculosis is curable; however, the emergence of drug resistance has made it difficult to control TB infections. The Sustainable Development Goal (SDG) for 2030 is to end TB. This means an effective, early, and rapid detection method is needed to ensure proper treatment for patients. Therefore, whole genome sequencing (WGS) method may come as solution due to its capability of high-resolution genotyping and identification. This method has been reported to cover more comprehensive information of microorganisms and known to simultaneously predict the drug resistance. Thus, this study focusses on sequencing the whole genome of *M. tb* directly from sputum samples of TB active patients to help identify genes associated with treatment as well as drug resistance genes. This will help to evaluate the treatment outcomes of the current regimens and monitor transmission.

METHODS

The study is being conducted in healthcare facilities of Vhembe district. Ethical clearance from the University of Venda (SMNS/20/MBY/13/2104); Department of Health Provincial (REF: LP 2021-11-001) as well as from district offices have been obtained. Sputum samples will be collected from the participating patients and stored for analysis. DNA extracted direct from sputum samples will be extracted in a BSL 3 laboratory at the University of Venda under Prof Bessong's laboratory. Anyplex II assay will be performed following the manufacturer's instructions to determine whether the patients are suffering from MDR/XDR TB. Results will be interpreted using an automated Segene Reader software. Whole genome sequencing will be done following the manufacturer's instruction (Genomics labs at SUN-MRC). Results will be interpreted to determine and know the potential mutations and the effect that they have on treatment outcomes. Phylogenic trees will be constructed using the obtained genome wide single-nucleotide polymorphism (SNP) to determine the origins.

RESULTS

A total of 34 healthcare facilities in the Vhembe district have been approached to form part of the study as sample collection sites. At time of visits, some of the healthcare facilities have indicated that they do not have any active TB patients; some have indicated to have patients with MDR and XDR TB and lastly, some had those who have experienced treatment failure. Two healthcare facilities require presentation to be done with their research board; appointments dates have been set and presentation will be done in the next coming week.

EXPECTED RESULTS

The prevalence of MTB and MDR/XDR TB stains in Vhembe district will be determined. The

uncovered mutations in genes that predict phenotypic resistance to antidrug TB drugs will be determined by WGS and signifies its importance for making an informed decision to the type of treatment therapy that should be administered to the patient. The phylogenetic tree will help assess the success of the treatment being administered in the healthcare facilities of Vhembe district.

CONCLUSION

This study will highlight on the importance of implementing WGS in healthcare facilities to implement individualised medication; to reduce tuberculosis burden.

KEYWORDS: *Mycobacterium tuberculosis*, Multidrug Resistance TB, Treatment outcome; Whole genome sequencing

2. Cisplatin supplementation with *Momordica balsamina* extracts to mitigate cisplatin-induced nephrotoxicity

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BACKGROUND

Despite being a highly effective anticancer drug, cisplatin`s long-term use and high dosage lead to organ toxicities in particular nephrotoxicity. This is an adverse effect caused by the accumulation of cisplatin in the kidneys and is experienced by 20–35% of patients undergoing cisplatin treatment. This presents a great hurdle that limits the clinical efficacy and curative potential of cisplatin. Thus, there is a need for novel strategies, such as adjuvant therapies, that minimise or potentially reverse cisplatin-induced nephrotoxicity without affecting its therapeutic efficacy. This study aims to assess the potential of *M. balsamina leaf* extracts to mitigate cisplatin-induced nephrotoxicity in HEK-293 and MDA-MB-231 cells and its efficacy.

METHODS

The effects of co-treating HEK-293 or MDA-MB-231 cells with *M. balsamina* extracts and cisplatin will be assessed using the CCK-8 assay and the mode of cell death assessed using the Annexin V and Dead Cell assay. The potential on mitochondrial membrane, DNA damage and reactive oxygen species generation will be assessed using the muse mitopotential, multi-color DNA damage and oxidative stress assays. Further evaluation of malondialdehyde, catalase and glutathione levels will be done using lipid peroxidation, catalase activity and intracellular glutathione detection assays, respectively. Western blot analysis will be used to assess the expression profiles of proteins involved in the nuclear erythroid-2-related factor 2 pathway.

RESULTS

This proposed study has been approved by the School Research and Ethics Committee (ScREC-SMLS) at the University of Limpopo. Progress has been made in acquisition of *M. balsamina* leaves and the extraction process is underway with the Agrifood Technology Station at the institution.

CONCLUSION

The effect of *M. balsamina* on the efficacy of cisplatin may potentially lead to its establishment as supplements for cancer patients undergoing cisplatin treatment or other drugs that cause nephrotoxicity.

3. The pharmacogenetics of ADME polymorphisms in tuberculosis patients from rural healthcare facilities in the Vhembe District of Limpopo

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BACKGROUND

According to World Health Organization (WHO) tuberculosis (TB) is the second leading cause of death after the coronavirus disease (COVID-19) among infectious diseases globally. Although TB is curable, resistance to anti-TB drugs poses challenges to eradicating this disease. The rate of TB mortality remains alarmingly high due to the emergence as well as the spread of drug-resistant TB (DR-TB). In addition, the side effect associated with the use of anti-TB drugs is hepatotoxicity. This observation has been associated with host genetic variation in the genes involved in drug absorption, distribution, metabolism, and excretion (ADME). The African population has a high genetic diversity yet their genomic information on the genetic contribution and treatment of TB is understudied. Hence, the current study seeks to investigate the pharmacogenetic analysis of ADME polymorphisms in TB patients from rural healthcare facilities in the Vhembe District, Limpopo province.

METHODS

Twenty-five blood samples of TB patients and 13 controls will be recruited from Vhembe Health Care facilities. Samples will be collected from August 2022 to December 2022. Polymerase chain reaction (PCR) and next-generation sequencing (NGS) will be used to identify the genes associated with the patient's treatment outcome. Targeted SNPs will be genotyped for ABCB1 (C3435T, G2677T, C1236T, and rs3842), SLCO1B1 (T521C, C463A [rs11045819], and rs4149032), PXR (C63396T and T44477C), and CAR (rs2307424).

RESULTS

The permission to conduct the current study was granted by the University of Venda Research Ethics Committee (SMNS/20/MBY/13/2104) followed by the Limpopo Department of Health (LP_2021-11-001) and the Vhembe District office (s5/6). Currently, busy with sample collection and deoxyribonucleic (DNA) extraction in preparation for sequencing. The findings will contribute to genetic data on TB treatment in Limpopo, South Africa known, and be added to the scientific database.

CONCLUSION

This will help patients, clinicians, and policy makers to effectively manage treatment of DR-TB in the Vhembe District.

4. The prevalence of hypertension among pregnant women in Sekhukhune District, Limpopo province.

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BACKGROUND

Hypertension is a major risk factor of maternal and perinatal morbidity and mortality. Hypertension complicates about 10% of all pregnancies. South Africa has not yet reached Millennium Development Goal 4a and Millennium Development Goal 5a goals. However, it is making progress towards achieving sustainable development goal 3, which emphasizes good health and wellbeing by reducing neonatal mortality to below 12/100. Hypertension (22.8%) is the second major cause of maternal mortality in the Sekhukhune District. Preterm birth complication (6.6%) is the third major cause of mortality among children less than 5 years.

PURPOSE

The aim of this study is to determine the prevalence of hypertension and its associated risk factors among pregnant women in Sekhukhune District.

METHODS

A cross-sectional study will be collected among pregnant women attending their antenatal services at the selected healthcare services in Sekhukhune District, South Africa. Their ages will range from 18 years and above. Hypertension will be defined by self-report to be on hypertension medication or systolic blood pressure equal or greater than 140mmHg or/and diastolic blood pressure equals or greater than 90mmHg. Questionnaire will be used to obtain information on the risk factors of hypertension. Ethical clearance will be obtained from the University of Venda Ethics Committee. The researcher will seek permission to collect data from the Limpopo Department of Health. All ethical procedures will be followed to ensure the safety of the participants. The SPSS version 27.0 will be used to analyse data. Descriptive statistics will be used to present hypertension results. Pearson's Chi-square test will be used to determine the association between hypertension and its associated risk factors. The level of significance will be set at ≤0.05.

RESULTS/PROGRESS

The proposal had been approved by the Department and faculty board, and now it is progressing to the executive University higher degree committee.

5. Investigating the efficacy of two South African medicinal plants in the treatment of lung cancer using experimental and computational methods.

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BACKGROUND

Globally cancer is one of the leading causes of death in public health. In South Africa, lung cancer ranks as the number one cause of cancer deaths. The lung cancer incident rate is expected to double by the year 2030 in Africa. This has resulted in the exploration of African traditional

methods to curtail the spreading of the disease. Medicinal plants play a major role in primary health care in many developing countries and the usage of African traditional medicine is the oldest and most diverse of all therapeutic systems. Medicinal plants such as *Curcuma longa* L. and *Tulbaghia violacea*, have been identified as potential deterrents or inhibitors of many types of cancers including lung cancer. In this study we will explore the areas of computational modelling and natural products chemistry, which have contributed much to design, discovery, and development of new and/or improved drugs that can be used in the treatment of lung cancer.

METHODS

Experimental:

Plants will be identified and collected by botanist from various locations in Durban, KZN and confirmed by the South African Biodiversity Institute. All plants will be dried in an oven (30 - 60°C) and grounded to small size using a miller. Plant material will be extracted using CP grade solvents and concentrated using a Rotavap, to yield extracts which will be stored at 4°C. High-performance liquid chromatography (HPLC), Nuclear magnetic resonance (NMR) spectroscopy, thin layer chromatography (TLC) will be used to separate, isolate, purify and elucidate the structure of compounds. The anti-inflammatory, antioxidant and anti-toxicity *in vitro* activity of the extracts and isolated compounds will be determined.

Computational modelling:

Computational molecular modelling that will be performed is as follows: Autodock will be utilized for the virtual screening of compounds from the Zinc Database, the Drug Bank, and the South African Natural Compounds Database (SANCDB). The virtual screening workflow panel includes Input, Filtering, Preparation, Receptors and Docking tabs. MD simulations will be run in the AMBER 18 software package with an integrated graphics processing unit (GPU) for the periodic boundary conditions necessary for long-range electrostatic interactions (cut off =12). The CPPTRAJ module would be used to do the MD post-analysis (RMSD, RMSF, Rog, PCA, and the binding free energy calculation).

RESULTS

It is expected that the invitro anti-inflammatory, antioxidant, and anti-toxicity effects of the plants will be determined together with the likely mechanisms involved.

CONCLUSION

Both the experimental and computational modelling results will assist in understanding the drug-cancer protein interactions and mechanisms involved.

6. Synergistic activity of Sutherlandia frutescence and Vancomycin on Staphylococcus aureus and Enterococcus faecalis.

NP Ndlovu,R Molathlegi, NW Nsele

BACKGROUND

The growing number of infections caused by species that have developed resistance towards available antibiotic regimens has shown the need to explore other treatment options. Currently, there is a worldwide problem in communities and hospitals dues to infections caused by Methicillin Resistance Staphylococcus Aureus (MRSA) and Vancomycin Resistance Enterococcus (VRE)superbugs. As a result, this study aims to assess the combined effect of *Sutherlandia frutescence* and vancomycin on *Staphylococcus aureus* and *Enterococcus faecalis* by mixing the antibiotic with a plant extract.

METHODS

For this Project, Sutherlandia frutescence (S. frutescens) will be used. S. frutescens will be harvested from Silverglen Nature Reserve early in the morning. The German Homeopathic Pharmacopoea extraction method will be used for both water-based and ethanol extraction. The extracts will then be used to assess the antibacterial activity against MRSA, Methicillin Sensitive Staphylococcus Aureus (MSSA) and Enterococcus faecalis. The minimum inhibitory concentration of the antibiotic will be assessed, followed by disc and well diffusion to assess if S. frutescens is able to reduce the growth of isolates alone and/or in combination with vancomycin. Cytotoxicity assays will be conducted to assess the cytotoxicity effect of S. frutescens on cell lines.

RESULTS

For this experiment, it was hypothesized that Sutherlandia frutescence will enhance vancomycin's antibacterial effect against Staphylococcus aureus and Enterococcus faecalis. Vancomycin will be tested against Staphylococcus aureus and Enterococcus faecalis for zone of inhibition. Sutherlandia frutescence will be tested against S. aureus and E. faecalis for zone of inhibition. To prove the hypothesis, the combination of Vancomycin and Sutherlandia frutescence will be tested against S. aureus and E. faecalis. Zone of inhibition will be compared. Expectations would be that zone of inhibition of Vancomycin alone and plant alone will be smaller compared to the combination of vancomycin and Sutherlandia frutescence which will be larger.

CONCLUSION

Since it has become difficult for doctor to treat patients since Vancomycin antibiotics can no longer inhibit the second stage of cell wall synthesis in *MRSA* and VRE isolates, unless it is administered in combination with other antibiotics. This research will inform us if there is hope of whether combination therapy with medicinal plants particularly *S. frutescens* and Vancomycin can be used in the treatment of Staphylococcus aureus and Enterococcus faecalis. This will inform future studies which might lead to work that may be translated into policy or practice.

7. Soil-transmitted helminthiasis and human papillomavirus co-infections: Influence of microRNA expression on female genital tract immunity and cervical carcinogenesis

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BACKGROUND

Soil-transmitted helminths (STH) are endemic to resource-poor tropical and sub-tropical regions, where the risk of co-infection with bacterial and viral pathogens is common. Complex STH-host interactions result in systemic immune regulation. Typically, STH induce a type 2 immune phenotype with bystander effects on unrelated conditions including viral co-infections. The influence of STH on female reproductive health and immunity is underexplored, particularly in South Africa where STH and sexually transmitted infections such as human papillomavirus (HPV)

are prevalent. Furthermore, the role of microRNAs (miRNAs), a class of small non-coding RNAs, in STH-host interactions is poorly understood. miRNAs are known to regulate various essential biological processes during normal development, while dysregulated miRNAs are implicated in disease processes. Although this field of research is rapidly growing, little is known about how STH influence miRNA expression profiles and host immunity to HPV in the female genital tract (FGT). This study aims to determine how *Nippostrongylus brasiliensis* (Nb) infection alters the miRNA profile of the FGT, and the effects thereof on immunity to HPV and susceptibility to cervical carcinogenesis.

METHODS

An *in vivo* murine model, either singly or co-infected with Nb, a murine hookworm, and/or HPV will be used. Next-generation sequencing (NGS) will be used to identify differential expression of key parasite and/or host-specific miRNAs. Based on the findings from NGS, an *in vitro* model will be used to examine the effects of key miRNAs on target genes associated with host immunity and cervical carcinogenesis.

RESULTS

The results of this study will elucidate whether differential expression of miRNAs is associated with altered immunity in the FGT of models singly and co-infected with Nb and/or HPV.

CONCLUSION

Findings from this study will be pivotal to linking helminthiasis and HPV co-infection with cervical carcinogenesis.

8. Investigation of ligand compounds that can block rotavirus VP8* from binding to the host's histo-blood group

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BACKGROUND

Rotaviruses are recognised globally as the leading cause of acute gastroenteritis in children under 5 years of age. The virus gains entry into the human cell by attaching to receptors such as histo-blood group antigens (HBGAs) available on the host gut epithelia through its viral protein 8* (VP8*). Currently, there are no approved antiviral drugs that can be given to children having acute rotavirus gastroenteritis. This study aimed to discover potential inhibitors to rotavirus VP8*, which can block the HBGAs binding site.

METHODS

A total of 6837 3D structures of ligands compounds were retrieved from ZINC15 database and prepared by minimizing their energy using Pyrx-virtual screening software. And 3D structures of rotavirus P[6] and P[8] VP8* were retrieved from the Protein Data Bank. The HBGA binding sites on VP8* were identified as reported in literature and used as targets for docking. Molecular docking of the ligand compounds to the HBGA binding site on VP8* was carried out using the VINA algorithm within the Pyrx-virtual screening software. The docking scores generated and bonds formed between the rotavirus VP8* and ligands were analysed.

RESULTS

Molecular docking revealed that 11 ligands and a single ligand showed the best docking scores (<-8 kcal/mol) towards VP8* of rotavirus P[6] and P[8], respectively. The graphical visualisation of the VP8*-ligand docking interactions showed that, most of these ligands bound with VP8* using ionic bonds and hydrogen bonding. Of all the identified ligands, Emend (Zinc ID 27428713) displayed potential therapeutic properties against VP8* of rotavirus P[6], as it bound to the HBGA site on VP8* using hydrogen bonding.

CONCLUSION

Emend, an aprepitant used to treat nausea and vomiting, could be used in rotavirus infected patients who are vomiting. This may reduce the severity of infection and the risk of dehydration. This drug should be investigated in *in-vitro* and *in-vivo* studies for effectiveness against rotavirus.

9. Investigating the efficacy of three South African medicinal plants in the treatment of lung cancer using experimental and computational methods.

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BACKGROUND

Traditional medicinal plants are vital in the African traditional healthcare system which is the oldest form of treatment for various chronic diseases including cancer. Africa has a rich biodiversity of traditional medicinal plants used by traditional health practitioners in the treatment of many ailments, at low cost. These medicinal plants have shown many biological properties including anti-inflammatory, antioxidant, and antibacterial activities. Phytochemicals with anti-cancer properties have also been isolated. Lung cancer is a malignancy with the highest mortality rate because it is often undetected until the later stages of the disease when it affects the patient's quality of life. Natural product chemistry, and computational modelling play significant roles in the design, discovery, and development of new and/or improved drugs that can be used in the treatment of lung cancer.

METHODS

Plants will be collected and identified by a botanist and confirmed by the South African National Biodiversity Institute. Samples will be dried in an oven, ground and extracted using various organic solvents. Extracts will be concentrated to yield crude extracts which will be stored in a fridge. Extracts will be fractionated using gravity column chromatography and monitored using thin-layer chromatography. High-performance liquid chromatography will be used to profile extracts and to isolate and purify compounds. Nuclear magnetic resonance spectroscopy will be used to elucidate the structure of compounds. Anti-cancer activity of extracts will be determined through antioxidant, cytotoxicity and cell proliferation inhibition assays. Computational methods, namely, structure-based drug design, ligand-based drug design, and virtual screening will be explored in this study. Molecular modelling will be performed for this study. Therefore, Autodock will be utilized for the virtual screening of compounds from the Zinc Database, the Drug Bank, and the South African Natural Compounds Database (SANCDB). The virtual screening workflow panel includes Input, Filtering, Preparation, Receptors and Docking tabs. MD simulations will be run in the AMBER 18 software package with an integrated graphics processing unit (GPU) for the periodic boundary conditions necessary for long-range electrostatic interactions (cut off =12). The CPPTRAJ module would be used to do the MD post-analysis (RMSD, RMSF, Rog, PCA, and the binding free energy calculation).

1. Enhanced Recovery After Trauma Surgery (ERATS) : A randomized controlled trial

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BACKGROUND

Enhanced recovery after surgery (ERAS) employs a multimodal perioperative care pathway designed to attenuate the surgical stress response and accelerate postoperative recovery. Implementation thereof has led to reductions in postoperative complications and hospital length of stay. These benefits should be easily transferrable to the trauma patient population, since they are generally younger, fitter and metabolically stable.

Penetrating abdominal trauma remains a substantial burden of disease in the Western Cape and this has led to severe constraints on the available resources, with delayed discharges due to poor ambulation, post operative complications, and delayed enteral feeding.

A pilot study by Moydien et al. in 2015 from the centre showed that enhanced recovery protocols can be successfully implemented with significant shorter hospital stays without any increase in postoperative complications in patients with penetrating abdominal trauma.

The purpose of the study is to evaluate an ERAS protocol in a randomized controlled study.

METHODS

This is a single-centre, randomized control study. The intention is to treat all stable patients with penetrating abdominal trauma undergoing exploratory laparotomy, and to investigate whether there is a difference in outcome when allocated either to perioperative care according to ERAS protocol or to a control group which will receive standard post operative care.

RESULTS

The study has recruited 104 patients. Twenty patients have been excluded according to study criteria. Eighty-four patients were needed for an 80 % power and have been included in the study. The data is currently being collated and will then undergo statistical analysis.

CONCLUSION

We hypothesize that implementing an “ERATS” protocol, will lead to a reduction in morbidity, and hospital stay , with a subsequent decrease in costs. Following this study we aim to introduce this as a new standard protocol , and thus change the current practice in stable penetrating trauma patients undergoing explorative laparotomy.

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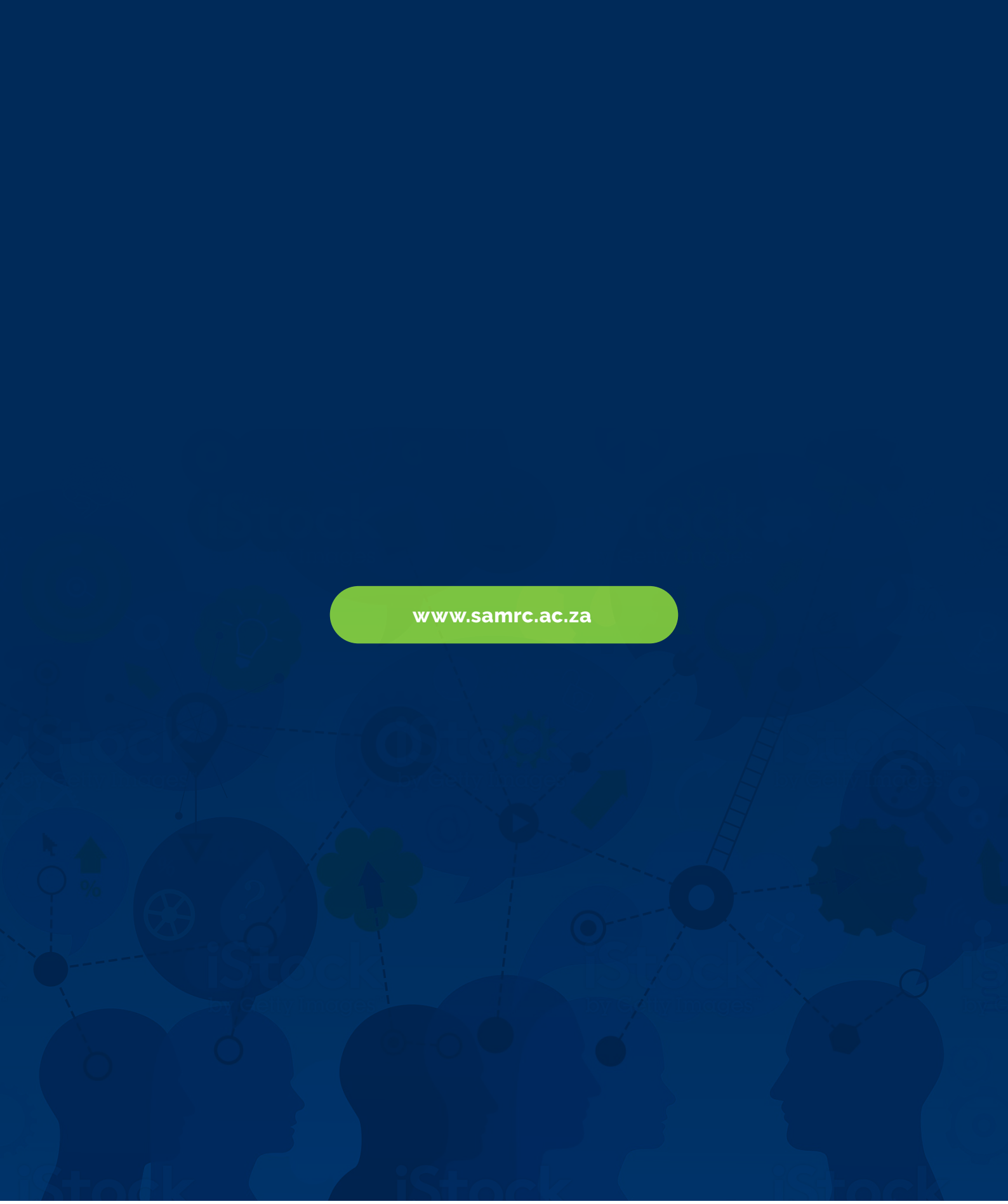

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