

# **ANNUAL REPORT** 2021/2022



# CONTENTS

List of Abbreviations	2
Acting Executive Director's Overview	10
Deputy Director's Overview	16
Centre for Emerging Zoonotic and Parasitic Diseases	20
Centre for Enteric Diseases	32
Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses	38
Centre for HIV and Sexually Transmitted Infections	42
Centre for Respiratory Diseases and Meningitis	55
Centre for Tuberculosis	61
Centre for Vaccines and Immunology	71
Division of Public Health Surveillance and Response	75
National Cancer Registry	87

1 **İ** 

# LIST OF ABBREVIATIONS

ACV	Acyclovir
AFCRN	African Cancer Registry Network
AFDUC	Acute febrile disease of unknown cause
AFENET	African Field Epidemiology Network
AFP	Acute flaccid paralysis
AGYW	Adolescent girls and young women
AMP	Antibody-mediated prevention
AMR	Antimicrobial resistance
AMRRL	Antimicrobial Resistance Reference Laboratory
AOR	Adjusted odds ratio
AORTIC	African Organisation for Research and Training in Cancer
ANDEMIA	African Network for Improved Diagnostics, Epidemiology and Management of Common Infectious Agents
ARMMOR	Antimalarial Resistance Monitoring and Malaria Operational Research
AR	Attack rate
ART	Antiretroviral therapy
ASSAf	Academy of Science of South Africa
ASIR	Age standardised incidence rates
ATCC	American Type Culture Collection
BC	Breast cancer
BCAH	Burden of cancers attributable to HIV
BDQ	Bedaquiline
BEEZ	Bio-Surveillance and Ecology of Emerging Zoonoses
BSL 3	Biosafety level 3
BSL 4	Biosafety level 4
BMD	Broth microdilution
BSAC	British Society for Antimicrobial Chemotherapy
BSc	Bachelor of Science
BSI	Bloodstream infection
BTech	Bachelor of Technology
BV	Bacterial vaginosis
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CAST-NET	Cryptococcal Antigen Screen-and-Treat National Evaluation Team
СС	Collaborating Centre
CCHF	Crimean-Congo haemorrhagic fever
CCRN	Cervix Cancer Research Network
CDC	Centers for Disease Control and Prevention
CDW	Corporate Data Warehouse
CED	Centre for Enteric Diseases
CESAR	Centre for Epidemiology and Statistical Analysis Research
CEZPD	Centre for Emerging Zoonotic and Parasitic Diseases
CFZ	Clofazimine
cgMLST	Core-genome multi-locus sequence typing
CHAMPS	Child Health and Mortality Prevention Surveillance Programme
CHARM	Centre for Healthcare-Associated Infections and Antimicrobial Resistance
CHC	Community Health Centre
CHIVSTI	Centre for HIV and Sexually Transmitted Infections
CHRU	Clinical HIV Research Unit

CI	Confidence interval
СМЈАН	Charlotte Maxeke Johannesburg Academic Hospital
CPGR	Centre for Proteomic and Genomic Research
CrAg	Cryptococcal antigen
CRC	Colorectal cancer
CRDF	Civilian Research and Development Foundation
CRDM	Centre for Respiratory Diseases and Meningitis
CRE	Carbapenem-resistant Enterobacteriaceae
CROI	Conference on Retroviruses and Opportunistic Infections
CRS	Congenital rubella syndrome
CRyPTIC	Comprehensive Resistance Prediction for Tuberculosis: An International Consortium
CS	Congenital syphilis
CSF	Cerebrospinal fluid
СТВ	Centre for Tuberculosis
CVI	Centre for Vaccines and Immunology
DAFF	Department of Agriculture, Forestry and Fisheries
DBS	Dried blood spot
DCAP	Delamanid Controlled Access Programme
DDT	Dichlorodiphenyltrichloroethane
DEA	Department of Environmental Affairs
DHIS	District Health Information System
DLM	Delamanid
DNA	Deoxyribonucleic acid
DOH	Department of Health
DOL	Department of Labour
DPHSR	Division of Public Health Surveillance and Response
DRC	Democratic Republic of Congo
DREAMS	Determined, Resilient, Empowered, AIDS-Free, Mentored, and Safe Women
DRS	Drug resistance survey
DST	Department of Science and Technology
DTM&H	Diploma in Tropical Medicine and Hygiene
EBK	Empirical bayesian kriging
ECP	Eastern Cape Province
ECMM	European Confederation of Medical Mycology
ECV	Epidemiological cut-off value
EIA	Enzyme immunoassay
EID	Early infant diagnosis
ELISA	Enzyme-linked immunosorbent assay
EML	Electron Microscope Laboratory
ENDTB	Expand New Drugs Market for TB
EOC	Emergency Operations Centre
EPBCR	Ekurhuleni Population-based Cancer Registry
EPI	Expanded Programme on Immunisation
ERICA-SA	Evolving Risk Factors for Cancer in African Populations
ERP	Emergency response plan
ESBL	Extended-spectrum beta-lactamase
ESC	Extended-spectrum cephalosporins

ESKAPE	Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species
ESRU	Empilweni Services and Research Unit
ETL	Extract, transform and load
EVD	Ebola virus disease
FBI	Foodborne illness
FDA	Food and Drug Administration (US)
HPV	
HR	High-risk
HR	Human Resources
	Human Sciences Persoarch Council
	HIV VACCINE ITIAIS NELWORK
IAEA	International Atomic Energy Agency
IANPHI	International Association of National Public Health Institutes
IARC	International Agency for Research on Cancer
IBBS	Integrated HIV Bio-Behavioral Surveillance
IFI	Invasive fungal infection
lgG	Immunoglobin G
IHR	International Health Regulations
ILFU	Initial loss to follow-up
ILC	Inter-laboratory comparison
ILI	Influenza-like Illness
IMD	Invasive meningococcal disease
IMGT	Immunogenetics
FELTP	Field Epidemiology and Laboratory Training Programme
FETP	Field Epidemiology Training Programme
FIC	Fractional inhibitory concentration
FIDSSA	Federation of Infectious Diseases Societies of Southern Africa
FPD	Foundation for Professional Development
FSP	Free State Province
GAM	Global AIDS Monitoring
GASP	Gonococcal Antimicrobial Surveillance Programme
GCIG	Gynaecological Cancer Intergroup
GDOH	Gauteng Department of Health
GIS	Geographic information system
GLASS	Global Antimicrobial Resistance Surveillance System
GLI-AFRO	Global Laboratory Initiative – Africa
GOARN	Global Outbreak Alert and Response Network
GP	Gauteng Province
GPEI	Global Polio Eradication Initiative
GTI	Gastrointestinal tract infections
GUS	Genital ulcer syndrome
GWAS	Genome-wide association study
HAI	Healthcare-associated infection
HASA	Hospital Association of South Africa
HAstV	Human astrovirus

HBV	Hepatitis B virus
hc2	Hybrid capture
НСС	Hepatocellular carcinoma
HCW	Healthcare worker
HEU- HIV	HIV exposed uninfected
Hib	Haemophilus influenzae type B
HIPSS- HIV	Incidence Provincial Surveillance System
HIV	Human immunodeficiency virus
HIVDR	HIV drug resistance
HPCSA	Health Professions Council of South Africa
IMS	Incident management system
iNTS	Invasive nontyphoidal salmonellae
IPC	Infection prevention and control
IPD	Invasive pneumococcal disease
IQC	Internal quality control
IQR	Interquartile range
IRS	Residual insecticides
ISHS	Institute for Social and Health Sciences
ITNs	Insecticide treated bed nets
ITS	Internal transcribed spacer
iVDPV	Immune-deficiency associated vaccine derived poliovirus
IVIG	Intravenous immunoglobulin
IWHOD	International Workshop on HIV and Hepatitis Observational Databases
JCS	Johannesburg Cancer Case-control
JEE	Joint External Evaluation
KCL	Kings College London
KPIS	Key population implementation science
KS	Kaposi sarcoma
KZN	KwaZulu-Natal
LARS	Laboratory-based antimicrobial resistance surveillance
LC	Liver cancer
LDA	Linear discriminant analysis
LFA	Lateral flow assay
LIS	Laboratory information system
LMIC	Low- and middle-income countries
LP	Limpopo Province
LPA	Line probe assay
LR	Liferisk
LRTI	Lower respiratory tract infection
LTBI	Latent TB infection
LZD	Linezolid
MADCaP	Men of African Descent Cancer of the Prostate
MARV	Marburg virus
MBRT	Molecular Biosciences Research Thrust
MDR	Multidrug-resistant
M&E	Monitoring and evaluation
MGIT	Mycobacteria growth indicator tube
MHCU	Mental healthcare users

mHealth	Mobile Health Application
MIC	
MIR	Mortality incidence ratios
MIST	Multi-locus sequence typing
MIVA	Multiple-locus variable number tandem repeat analysis
MMed	Martiple focus variable number tandern repeat analysis
MNORT	Multisectoral National Outbreak Response Team
MoA	Memorandum of agreement
MP	Mpumalanga Province
MPAC	Malaria Policy Advisory Committee
MPH	Master of Public Health
МРТВ	Microbiologically confirmed pulmonary tuberculosis
MRC	Medical Research Council
MRSA	Methicillin-Resistant Staphylococcus aureus
MSc	Master of Science
MSM	Men-who-have-sex-with-men
MTA	Material transfer agreement
MUS	Male urethritis syndrome
MVD	Marburg viral disease
NAAT	Nucleic acid amplification test
NADC	Non-AIDS defining cancer
NAGI	National Advisory Group on Immunisation
NAPHS	National Action Plan for Public Health Security
NAPHISA	National Public Health Institute of South Africa
NATJoints	National Joint Operations Committee
NCI	National Cancer Institute
NCNGU	Non-chlamydial non-gonococcal urethritis
NCP	Northern Cape Province
NCR	National Cancer Registry
NDOH	National Department of Health
NDMC	National Disaster Management Centre
NECSA	South African Nuclear Energy Corporation
NHLS	National Health Laboratory Service
NIAID	National Institute of Allergy and Infectious Diseases
NICD	National Institute for Communicable Diseases
NICU	Neonatal intensive care unit
NIH	National Institutes of Health
NIOH	National Institute for Occupational Health
NISEC	National Immunisation Safety Committee
NITAG	National Technical Advisory Group on Immunization
NMC	Notifiable Medical Conditions
NMCSU	Notifiable Medical Conditions Surveillance Unit
NMMU	Nelson Mandela Metropolitan University
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NP	Nucleocapsid protein
NPSP	National Pneumonia Surveillance Programme
NRF	National Research Foundation
NRTI	Nucleoside reverse transcriptase inhibitors
NSP	National Strategic Plan

j 6

NTBRL	National TB Reference Laboratory
NTCP	National Tuberculosis Control and Management Programme
NTP	National TB Programme
NTPn	Non-typeable pneumococci
NWP	North West Province
OR	Odds ratio
ORU	Outbreak Response Unit
OSCC	Oesophageal squamous cell carcinoma
PathRED	Pathology Research and Development
РСР	Pneumocystis jirovecii pneumonia
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PEF	Polio Essential Facility
PEPFAR	The United States President's Emergency Plan for AIDS Relief
PET	Provincial Epidemiology Team
PFGE	Pulsed field gel electrophoresis
PHASA	Public Health Association of South Africa
PHC	Primary healthcare centre
PhD	Doctor of Philosophy
PHE	Public Health England
PHEOC	Public Health Emergency Operations Centre
PHIRST-SA	Prospective Household Observational Cohort Study of Influenza, Respiratory Syncytial Virus and other
	Respiratory Pathogens Community Burden and Transmission Dynamics in South Africa
PHRU	Perinatal HIV Research Unit
PI	Protease inhibitors
PLHIV	People living with HIV
PMS	Post-marketing surveillance
PMTCT	Prevention of mother-to-child transmission
POC	Point-of-care
POPs	Persistent organic pollutants
PRF	Poliomyelitis Research Foundation
PRL	Probabilistic record linkage
PRL	Parasitology Reference Laboratory
PS-MTM	Prime Store Molecular Transport Medium
РТ	Proficiency testing
PTS	Proficiency testing scheme
РТВ	Pulmonary tuberculosis
PWID	People who inject drugs
PZA	Pyrazinamide
QALY	Quality-adjusted life-year
QFT-Plus	QuantiFERON-TB Gold Plus
QIV	Quadrivalent influenza vaccine
RAPIDD	Research and Policy for Infectious Disease Dynamics
RAST	Rapid Annotation using Subsystems Technology
RAV	Resistance-associated variant
RCV	Rubella-containing vaccines
REC	Human Research Ethics Committee
REDCAP	Research Electronic Data Capture
Rfa	Reports for action

RMMCH	Rahima Moosa Mother and Child Hospital
RMPRU	Respiratory and Meningeal Pathogens Research Unit
RMR	Rifampicin mono-resistance
ROC	Receiver operating curves
RPR	Rapid plasma reagin
RR	Rifampicin-resistant
RSV	Respiratory syncytial virus
RTI	Respiratory tract infections
RT	Reverse transcriptase
RT-PCR	Reverse transcription polymerase chain reaction
RTQII	Rapid Test Quality Improvement Initiative
RV	Rhinovirus
RVF	Rift Valley fever
SABSMM V	South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (Fifth Wave)
SACIDS	Southern African Centre for Infectious Disease Surveillance
SACEMA	South African Centre of Excellence in Epidemiological Modelling and Analyses
SADC	Southern African Development Community
SAFETP	South African Field Epidemiology Training Programme
SAHPRA	South African Health Products Regulatory Authority
SAM	South African HIV Cancer Match Study
SAMA	South African Medical Association
SAMEC	South African Malaria Elimination Committee
SAMHMS	South African Men's Health Monitoring Survey
SAMRC	South African Medical Research Council
SANAS	South African National Accreditation Systems
SANC	South African Nursing Council
SaNTHNet	South African National Travel Health Network
SAPHRA	South African Health Products Regulatory Authority
SARGDDC	South African Regional Global Disease Detection Centre
SARI	Severe acute respiratory infection
SASMO	South African Society of Medical Oncology
SASTM	South African Society of Travel Medicine
SBIMB	Sydney Brenner Institute for Molecular Bioscience
SC	Steering Committee
SCC	Sputum culture conversion
SCCmec	Staphylococcal cassette chromosome mec
SCRI	Severe chronic respiratory illness
SDW	Surveillance Data Warehouse
SG	Serogroup
SHEA	Society for Healthcare Epidemiology of America
SI	Serial interval
SIMU	Surveillance Intelligence Management Unit
SIR	Secondary infection rate
SIT	Sterile insect technique
SMS	Short message service
SNP	Single nucleotide polymorphism
SNSF	Swiss National Science Foundation
SOP	Standard operating procedure

SPH	School of Public Health
SPI-RT	Stepwise Process for Improving the Quality of HIV Rapid Testing
SRI	Severe respiratory illness
SRL	Survival Research Laboratory
SSA	Sub-Saharan Africa
ST	Sequence type
Stats SA	Statistics South Africa
STI	Sexually transmitted infection
TAC	TaqMan Array Card
ТВ	Tuberculosis
TBF	Tick bite fever
TBSAP	Tuberculosis South Africa Project
TEPHINET	Training Programme in Epidemiology and Public Health Interventions Network
TIV	Trivalent influenza vaccine
ТК	Thymidine kinase
TNM	Tumour, node, metastasis
ТР	Treponema pallidum
TWAS	The World Academy of Sciences
TWG	Technical Working Group
UICC	Union for International Cancer Control
UCSF	University of California, San Francisco
UCT	University of Cape Town
UJ	University of Johannesburg
UNEP	United Nations Environment Programme
UNICEF	United Nations Children's Emergency Fund
UNISA	University of South Africa
UP	University of Pretoria
US	United States of America
USAID	United States Agency for International Development
USAMRIID	US Army Medical Research Institute of Infectious Diseases
VE	Vaccine effectiveness
VCRL	Vector Control Reference Laboratory
VDPV	Vaccine-derived poliovirus
VDPV2	Vaccine-derived poliovirus type 2
VDS	Vaginal discharge syndrome
VHF	Viral haemorrhagic fever
VISP	Vaccine-induced seropositivity
VL	Viral load
VPIBD	Vaccine preventable and invasive bacterial disease
VTS-A	Vaccine-induced seropositivity Testing Service-Africa
WCP	Western Cape Province
WDGMC	Wits Donald Gordon Medical Centre
WGS	Whole genome sequencing
Wits	University of the Witwatersrand
WHO	World Health Organization
XDR	Extensively drug-resistant



**Prof Adrian Puren** Acting Executive Director

# **INTRODUCTION**

The COVID-19 pandemic has repositioned the strategic importance of the NICD in detecting, containing and responding to infectious disease threats in South Africa, the Southern African Development Community (SADC) region and Africa. As a credible health partner to the National Department of Health, the WHO and the Africa CDC, the institution provides technical support and expertise through the continual surveillance of communicable diseases, outbreak response, specialised diagnostic services, research and training, capacity building and provincial epidemiology services. It furthermore provides the global health community with valuable information on communicable diseases.

National Treasury funds core surveillance activities through the provision of a conditional grant, while select research projects are grant-funded from external agencies and donor funds. The NICD comprises seven disease-focused centres, including a transversal Division of Public Health Surveillance and Response (DPHSR). The 500-strong staff complement includes pathologists, scientists, epidemiologists, medical technologists and technicians, and surveillance officers.

# Highlights

10

The transversal support services that were pivotal in supporting the NICD COVID-19 response include Information Technology, Communications, Biosafety and Biosecurity, and Occupational Health. The Information Technology team created the platforms for the integration of private-sector laboratory SARS-CoV-2 test data and developed the Outbreak Response System for COVID-19, while rapidly enabling electronic systems for the new way of work.

The Division of Biosafety and Biosecurity was instrumental in initiatives that included training of laboratory staff in preparation of SARS-CoV-2 virus isolation and proliferation. System upgrades, commissioning and the recertification of the Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD)'s BSL4 and BSL3 facilities were completed with continued biocontainment engineering support for the NDoH.

The staff, residents and graduates of the South African Field Epidemiology Training Programme (FETP) responded to demand for epidemiological capacity for COVID-19 and 15 other outbreaks throughout all the provinces. The FETP continued its training by developing a Google online classroom platform, an innovation mirrored by other programmes. The team developed a regional strategic plan to facilitate the training of 200 field epidemiologists in southern Africa and secured funding from the US and Africa CDC to realise this need. The University of Pretoria awarded Master of Public Health degrees to two MSc residents and the University of the Witwatersrand awarded degrees to five FETP residents. The South African FETP offered applied epidemiology training to 35 district and provincial frontline health professionals in the Eastern Cape, while data management training was provided to 115 staff in seven districts in the Northern Cape and the Free State.

The Occupational Health Clinic attended to 1 070 visits throughout the year. Some 741 employees from both the NHLS and the NICD were tested for COVID-19, with 132 testing positive. In addition, risk assessments, counselling and occupational health support was provided to those who were exposed to COVID-19.

The Communications Unit was a hive of activity, delivering impressive results. Media coverage increased by 38%, social media platforms grew by 9% on Twitter, 51% on Facebook and 558% on LinkedIn, while 47 videos were produced.

# **Centre for Emerging and Parasitic Diseases**

The Centre for Emerging and Parasitic Diseases (CEZPD) continued to support the malaria control and elimination agenda of the provincial, national and regional programmes. In collaboration with the University of California-San Francisco, it is establishing a targeted amplicon-sequencing platform to advance malaria elimination by providing more accurate information on parasite relatedness and movement in South Africa.

In response to the potential threat that malaria parasites with deletions in the HRP2 gene pose to the effectiveness of HRP2- based malaria rapid diagnostic tests, the CEZPD implemented a surveillance programme for the detection of parasites carrying these deletions. The morphological keys to the *Anopheles* mosquitoes of sub-Saharan Africa were revised and updated from the 1987 version, providing an important resource for general vector biology and control. To support malaria elimination in South Africa and the greater southern African region, the CEZPD established a regional malaria slide bank. To date, 154 batches, comprising 26 623 slides, six proficiency testing surveys, as well as microscopy training slide sets, have been produced and shared with other southern African countries.

As a part of a bio-surveillance programme for arboviruses, the CEZPD investigated the possibility of undetected Rift Valley fever virus (RVFV) infections in patients visiting healthcare facilities in the northern parts of KwaZulu-Natal between April 2018 and August 2019. The detection of IgM and IgG antibodies to RVFV in human serum samples confirms the recent circulation of the virus in the tropical coastal plain region of South Africa in the absence of reported clinical disease and indicates that RVFV infections are misdiagnosed or underreported. This situation highlights an urgent need for the improvement of diagnosis and awareness of RVFV and other arbovirus diseases in this part of South Africa in order to reduce the disease burden and the potential misuse of anti-malaria treatment.

# **Centre for Enteric Diseases**

The Centre for Enteric Diseases (CED) provides the South African community with epidemiological and laboratory support in response to food- and water-borne outbreaks. The centre provided epidemiological and laboratory testing support for 18 outbreaks and documented a further 45 outbreaks in which further investigation was hampered by either insufficient epidemiological or sample testing data.

In outbreaks associated with bacterial pathogens, whole-genome sequencing of isolates was conducted to assist with investigations and outbreak source attribution. All listeriosis cases reported to the Notifiable Medical Conditions (NMC) system were actively followed up, and the WGS of isolates was performed to ensure the early detection of any potential clusters or outbreaks.

Typhoid fever surveillance was enhanced through the routine WGS of typhoid fever isolates, which assisted in the investigation of an ongoing outbreak and monitoring of antimicrobial resistance trends.

Routine diarrhoeal disease sentinel surveillance in selected sites continued, with plans to expand surveillance to additional sites that had been temporarily halted because of the COVID-19 pandemic. A remarkable decline in the prevalence of rotavirus was noted in 2020, coupled with the absence of a seasonal increase in cases typical of the annual rotavirus season. *Shigella* spp. continued to be the leading cause of diarrhoeal hospitalisations in children under five years of age.

Other areas of research in the centre include increasing the capacity for the WGS of enteric bacteria to improve outbreak detection and investigation, improved diagnosis of common enteric infections in Africa, and the use of metagenomics on sewage samples to explore antimicrobial resistance.

# Centre for Healthcare-associated Infections, Antimicrobial Resistance and Mycoses

The Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses (CHARM), incorporates two national reference laboratories for antimicrobial resistance (AMR) and mycoses and houses the National Biological Sample Collection of pathogenic bacteria and fungi. The centre serves as a WHO collaborating Centre for AMR. It is the national focal point for the WHO's Global Antimicrobial Resistance Surveillance System (GLASS) and supports national and regional PTSs. In 2020/21, the centre collated electronic laboratory data on AMR pathogens causing bloodstream infections from the public and private sector, and reported this data through an AMR dashboard.

The centre completed surveillance of *Acinetobacter baumannii* bacteraemia, continued surveillance for carbapenem-resistant Enterobacterales bacteraemia, *Candida auris* infections and cryptococcal meningitis, and started new surveillance for *Enterococcus* bacteraemia. In addition, the centre supported data collection for sites participating in the NDoH/Clinton Health Access Initiative (CHAI)/Unitaid flucytosine access programme for cryptococcal meningitis. The centre set up national surveillance for neonatal infections (Baby GERMS) and completed retrospective data collection for six years (2014 to 2019) and the enrolment of neonates into an enhanced surveillance project at six regional hospitals' neonatal units. Work continued on a multi-year laboratory project to support and improve the national NHLS Cryptococcal antigen (CrAg) screening programme through laboratory training, a PTS, results for action, sample re-testing and new assay evaluations.

The mycology team continued to evaluate the effectiveness of this CrAg screening programme using a retrospective cohort study design. The mycology reference laboratory completed work on a case series describing blastomycosis in South Africa, including a newly discovered human pathogen called *Blastomyces emzantsi*.

# Centre for HIV and STIs

The Centre for HIV and STIs (CHIVSTI) has a strong track record in the research disciplines of HIV virology, HIV immunology, HIV/ STI epidemiology, HIV/STI diagnostics and HIV-STI interactions. It addresses the challenges of HIV and STI diseases through various programmes, including but not limited to surveillance of disease burden and antimicrobial resistance, the measurement of endpoint infections and detection, broadly neutralising antibodies as part of prophylactic HIV vaccine and antibody-mediated protection clinical trials and exploring an HIV 'cure' strategy.

SARS-CoV-2 has been a significant focus of the HIV Virology Section in the past year. The centre responded to the COVID-19 outbreak by seconding staff to the Emergency Operations Centre from March 2020. Several existing assays were adapted for COVID-19 research, including serological assays using spike and receptor domain ELISAs, neutralisation assays and Fc effector assays. These assays supported an array of projects, including the investigation of convalescent plasma for the treatment of severe disease and the measurement of immune correlates in SARS-CoV-2 infected longitudinal cohorts and vaccine trials, including the South African Ox1Cov-19 Vaccine VIDA-Trial trial.

During the period under review, the centre continued to implement enhanced congenital syphilis surveillance with support from the WHO. The enhanced surveillance involved the introduction of a case investigation form (CIF) to accompany the standard NMC case notification form (CNF). The NICD, in collaboration with the NDOH and its partners, has scaled up training of the congenital syphilis notification process to raise awareness of the condition and improve the quality of surveillance data. It is expected that the centre's congenital surveillance will provide data for evaluating the impact of the dual HIV/syphilis test to be introduced in the 2021/22 fiscal year.

#### Centre for Respiratory Diseases and Meningitis

The Centre for Respiratory Diseases and Meningitis (CRDM) continued to play a leading role in the response to the COVID-19 pandemic in South Africa. It supported the National COVID-19 Incident Management Team, playing a leading role in the epidemiology and laboratory streams. The centre produced regular COVID-19 surveillance reports, including, but not limited to the Weekly Epidemiological Brief, the Weekly Testing Summary and the COVID-19 reproductive number.

A number of detailed epidemiologic reports were also published in the Communicable Diseases Surveillance Bulletin. The CRDM laboratory set up a SARS-CoV-2 diagnostic polymerase chain reaction (PCR) test to detect the first cases of COVID-19 in the country, and then supported roll-out to public and private-sector laboratories throughout the country, as well as supporting African laboratories as needed.

The CRDM laboratory is a WHO COVID-19 regional reference laboratory and has provided support to many African countries in this capacity. Initially, this was done through testing, training and support to establish in-country testing, coupled with ongoing support for quality assurance and interlaboratory comparisons. More recently, this has expanded to include assisting with the sequencing of SARS-CoV-2-positive specimens and supporting in-country sequencing efforts.

The CRDM performed systematic sero-surveys of SARS-CoV-2 antibodies in three provinces from November 2020 to April 2021, and implemented studies of COVID-19 shedding, disease progression, burden, household transmission and molecular epidemiology.

The centre continued with the core function of surveillance. Syndromic surveillance programmes included the pneumonia and influenza-like illness surveillance systems in public hospitals and health clinics, as well as the private general practitioner network (Viral Watch). These programmes aim to describe the burden, seasonality and characteristics of influenza, respiratory syncytial virus (RSV) and *Bordetella pertussis*, and were expanded to include systematic surveillance for COVID-19. Laboratory-based surveillance programmes including pneumococcus, meningococcus, *Haemophilus influenzae*, and group A and group B streptococcus with a focus on outbreak detection and the impact of interventions. These programmes documented marked reductions in the burden of all other respiratory pathogens under surveillance in 2020.

In 2020, four additional postgraduate students joined the CRDM as part of the NIH-funded South Africa-Pittsburgh Public Health Genomic Epidemiology Research Training Programme (SAPPHGenE), which aims to develop research in public health genomics in South Africa.

# Centre for Tuberculosis

The Centre largely focused on the COVID-19 response, with senior staff providing critical support to the COVID-19 pandemic response. Prof Nazir Ismail served as the NICD lead on the Incident Management Team, Dr Harry Moultrie served on the COVID-19 Ministerial Advisory Committee and coordinated the South African COVID-19 Modelling Consortium (SACMC), which provided modelling support for multiple structures, including the NDoH, the National COVID-19 Command Council (NCCC), the MAC, National Treasury and the public.

The impact of the COVID-19 epidemic and public health restrictions on laboratory investigations and the diagnosis of TB in South Africa was investigated. The centre provided the National TB Programme and National TB Think Tank with a bi-weekly analysis of Xpert TB testing volumes, Xpert positive tests, positivity rate and rifampicin-resistant tests to support the TB COVID-19 recovery plan.

As part of the advancing diagnostics, epidemiology and treatment function of the centre, several new cutting-edge diagnostic technologies were evaluated during this period, which include the Xpert MTB/XDR, GeneXpert OMNI, Hain Fluorotype and BDMAX platforms for the rapid molecular detection of *M. tuberculosis* and accompanying drug resistance. Data generated were submitted to the WHO for review and was used for the recent recommendations of these molecular assays. The centre also initiated assessments of next-generation sequencing technologies (whole-genome sequencing) for diagnostic utility in predicting drug resistance and the molecular epidemiological surveillance of transmission networks and an early warning system for outbreak detection in two high-burden districts in South Africa.

The Comprehensive Resistance Prediction for Tuberculosis, an international consortium of which the centre is a full member, established to delineate genetic drug resistance prediction using WGS, has completed its five-year programme. Preliminary data generated from this activity has been shared with the WHO to develop the first mutation catalogue associating mutations across the genome with drug resistance. The WHO has also appointed the centre to Technical Expert Groups for the development of and guidance on policies and recommendations related to these new technologies.

# Centre for Vaccines and Immunology

As the regional reference laboratory for polio surveillance, the Centre for Vaccines and Immunology (CVI) identified vaccine-derived poliovirus type 1 (VDPV1) from Madagascar, and VDPV2 from Angola, Burkina Faso, Congo, Cote d'Ivoire, the Democratic Republic of Congo, Ethiopia, Guinea, Liberia, Mali, Niger, the Republic of South Sudan and Sierra Leone from acute flaccid paralysis cases. Type 2 Sabin polioviruses were detected from countries using monovalent oral polio vaccine type 2 to halt VDPV2 transmission in Angola, Burkina Faso, Cote d'Ivoire, the Democratic Republic of Congo, Ethiopia, Guinea, Mali, Niger, the Democratic Republic of Congo, Ethiopia, Guinea, Mali, Niger, the Republic of South Sudan, Sierra Leone and Zambia. From environmental sewage samples, VDPV2 was confirmed from Angola, Congo, Cote d'Ivoire, the Democratic Republic of South Sudan.

Sabin poliovirus type 2 was confirmed in environmental samples from Angola, Burkina Faso, Cote d'Ivoire, the Democratic Republic of Congo, Ethiopia, Niger, the Republic of South Sudan and Zambia. From South African environmental surveillance, the sequencing of a Sabin poliovirus type 3 suggested that polio vaccine coverage in the district and/or province may be suboptimal and heightened surveillance was recommended. The NICD is one of few sites globally that plan to host a Polio Essential Facility for work with polioviruses under high containment.

Building on its expertise in environmental surveillance from sewage, the centre is leading the South African Collaborative COVID-19 Environmental Surveillance (SACCESS) network to identify and map SARS-CoV-2 distribution in sewage. From 1 April 2020 to 31 March 2021, 205 wastewater samples were processed for SARS-CoV-2 from nine sites in Gauteng, two sites in the Western Cape, two sites in the Free State, four sites in the Eastern Cape, two sites in KwaZulu-Natal and one site in Limpopo.

SARS-CoV-2 was identified in 169 samples (82%). Using next-generation sequencing, the 501Y.V2 variant was successfully detected in a sewage sample from the Eastern Cape in November 2020. SARS-CoV-2 is considered non-infectious from sewage samples, but the viral RNA remains detectable. Sewage monitoring may provide accessory information to the NDoH for planning geographically localised interventions. Sewage surveillance infrastructure holds promise for monitoring other pathogens.

# Division of Public Health Surveillance and Response

The division of Public Health Surveillance and Response (DPHSR) played a pivotal role in the national COVID-19 pandemic response through the activities of the Emergency Operations Centre, the Outbreak Response Unit and the Provincial Epidemiology Team.

This included daily epidemiological updates to the NDoH at all levels and an interactive dashboard to assist provinces in their response. The DATCOV hospital surveillance platform provided valuable data on hospitalisations and deaths related to COVID-19. It also provided information on the long-term effects of COVID-19 and the impact of co-morbidities on COVID-19 mortality.

The division participated in the National Incident Management Team, providing epidemiological expertise and guidance.

Support was provided to the pathogen-specific centres within the NICD, and to the NDoH for other infectious disease outbreaks. The NICD clinicians' call service provided valuable support to clinicians facing challenging infectious disease case diagnosis and management. The provincial epidemiology team provided operational support to the provinces, including outbreak and surveillance activities, data analysis and daily situation reports. The provincial epidemiologists provided an important link between the NICD and the provincial health departments in responding to COVID-19, as well as to HIV and TB.

The GERMS-SA surveillance platform supported surveillance within the pathogen-specific NICD centres. These nationwide activities covered a broad range of pathogens and included laboratory surveillance, syndromic surveillance for pneumonia and influenza-like illness, acute febrile illness, neonatal sepsis and diarrhoea at sentinel hospitals and clinic sites. The platform was also used for COVID-19 specific studies.

The NMC Surveillance System fulfilled its mandate to receive notifications on diseases and conditions of public health importance. COVID-19 was included in the list of notifiable diseases, and additional modules are being added, including the long-term sequelae of COVID-19 infection. The NMC Surveillance System is in the process of being migrated to a new platform that will optimise and enhance use by its many stakeholders.

# National Cancer Registry

The National Cancer Registry is the main source of cancer incidence data for the country used for cancer resource allocation and programme implementation. It provides both pathology- and population-based cancer registration data for South Africa through its varied cancer surveillance programmes. The NCR produced the 2016 and 2017 cancer incidence reports for South Africa, highlighting the leading cancers in the country, but also demonstrating age-standardised, age-specific incidence rates and lifetime risks for all cancer types. The pattern of cancers reported was consistent with previous years, with breast and cervical cancer being the most common cancers in women, and prostate and colorectal cancers being the leading cancers in men.

The NCR also published the 2019 population-based cancer registry results from the Ekurhuleni District of Gauteng. With hospital wards being closed, outpatient services being suspended and restrictions on surveillance officer movement due to COVID-19, overall case finding was limited. Despite these challenges, 2 541 new cancer cases were registered for the year under surveillance. The NCR will continue to monitor the incidence of cancer cases reported from the Ekurhuleni District to provide a comprehensive picture of cancer incidence in the country.

An exciting new initiative at the NCR is the establishment of a Childhood Cancer Registry for the country. Childhood cancers are classified and reported in a unique manner that is different to adult cancers. Therefore, the registration of childhood cancers requires a dedicated and uniquely skilled expert. The NCR is pleased to announce that Natasha Abraham was nominated and appointed as the regional expert for childhood cancers by the International Agency for Research on Cancer (IARC) Global Initiative for Cancer Registry Development. The NCR plans to publish its first Childhood Cancer Incidence Report in the new financial year.

# Appreciation

The NICD would like to thank the NHLS for its innovative leadership and key laboratory support during the COVID-19 pandemic. It also acknowledges the technical and financial support from the NDoH, National Treasury, as well as development and technical partners. The Institute remains resolute and unswerving in its efforts to manage communicable diseases and inform public health policies. It believes that improving regional and global collaborative efforts will contribute to the betterment of all, and that its successes will ultimately benefit society as a whole.



Dr Natalie Mayet Deputy Director

# DEPUTY DIRECTOR'S OVERVIEW

The extraordinary circumstances presented by the COVID-19 pandemic, highlighted the significant role of the transversal departments that included the Division of Biosafety and Biosecurity, Communications, Information Technology, South African Field Epidemiology Training and Occupational Health. The pandemic demonstrated the importance of leveraging existing networks and international partnerships to increase understanding of COVID-19 and to facilitate a global response to the health crisis.

# **DIVISION OF BIOSAFETY AND BIOSECURITY**

The Division of Biosafety and Biosecurity (DBB) was instrumental in various COVID-19 response initiatives that included the following:

- Provision of training for laboratory staff in preparation for SARS-CoV-2 virus isolation and proliferation
- Construction of the Regional Diagnostic Demonstration Centre
- System upgrades, commissioning and recertification of the CEZPD BSL4 and BSL3 facility
- Continued biocontainment engineering support for the National Department of Health (NDoH)
- Facilitation of the use of the Diagnostic and Research Import/Export Blanket Permits
- Assistance to the NDoH in collating a list of minimum requirements for laboratory compliance with SARS-CoV-2 diagnostic and research testing

The division is also a member of the Southern Africa Regional Collaborating Centre Biosafety and Biosecurity Technical Working Group, and contributed to the formulation of the Regional Biosafety and Biosecurity Legal Framework for African Union Member States.

In addition, Zibusiso Masuku, Biosafety Technical Manager at the NICD, is a member of the SARS-CoV-2 Airborne Transmission Technical Working Group of the Ministerial Advisory Committee (MAC) that informed the MAC Advisory on Airborne vs Aerosol transmission of SARS-COV-2, and a member of the South African Bureau of Standards-Technical Committee that informed the SANS1050-4 Standard for B1/B2 (Hard Ducted) Exhausted (Micro-) Biological Safety Cabinets and adopted ISO/IEC Guide 98-1:2009 Uncertainty of Measurement.

# Teaching and training

The DBB conducted 16 continuing professional development (CPD)-accredited training activities with highly specialised experts, and has various collaborative activities with international leaders in biorisk management training, such as Sandia National Laboratories.

# Communications

In fulfilment of its vision, the Communications Unit remained unwavering in providing factual, timeous and reliable communicable disease information to all members of the public.

For the period under review, the Unit managed to increase website page views by more than 200% and media coverage by 38%. A noteworthy highlight for social media is the volume of growth enjoyed across all platforms, including a staggering 558% growth on LinkedIn, 51% on Facebook and 9% on Twitter.

The team had to expand its capacity by incorporating the services of a Stakeholder Relations Specialist, Client Liaison and Marketing Officer and Graphic Designer, in order to keep abreast of public health developments, advance COVID-19 content and maintain health awareness campaigns of tuberculosis, malaria and other infectious diseases. The production of relevant communication material, publications, reports, multimedia and campaigns continued to provide the platforms for sharing science in support of the national COVID-19 response.

# Information Technology

The Information Technology team spearheaded the platforms for the on-boarding of private sector laboratory SARS-CoV-2 test data, and developed the Outbreak Response System for COVID-19. The team continued with the development of the Notifiable Disease Surveillance System, whilst rapidly enabling electronic systems for the new way of work. Throughout the period under review, the team maintained service levels above 98%, despite changes in the staffing structure with the departure of the Head of IT at the end of November 2020.

# **Occupational Health**

The Occupational Health Clinic attended to 1 070 visits throughout the period under review. A total of 741 employees were tested for SARS-CoV-2, with 132 testing positive. In addition, risk assessments, counselling and support was provided by the occupational health team for those who were exposed to COVID-19. Most employees contracted the virus outside the workplace. None of the 18 surveillance officers who tested positive for COVID-19 could recall an event where there was failure of personal protective equipment (PPE) while taking swabs on patients. However, these incidents were reported to Department of Labour due to the inherent exposure risk of the tasks in the hospital environment.

A total of 42 incidents and accidents was recorded, with an upward trend in incidents in comparison to the last two financial years – 38, 37 and 42 incidents respectively. The majority of these incidents were first-aid cases, with a biological exposure in the Centre for Tuberculosis that resulted in an occupational disease.

# **Partnership/Networks Global Health**

The Deputy Director was involved in the Incident Management Team for the COVID-19 response, and was appointed on the Africa Task Forum for Novel Coronavirus (AFTCOR), which rapidly pulled together experts from African Members States to share ideas and explore common solutions. The AFTCOR Case Management Technical Working Group is a subgroup formed with NICD representation. The NICD collaborated extensively with various local and international networks and remains an active member of the International Association of National Public Health Institutes, as we share valuable lessons during the COVID-19 outbreak.

# South African Field Epidemiology Training (SAFETP)

SAFETP is a two-year competency-based training programme. It was initiated in 2006, and has since trained 90 graduates, presented 300 abstracts at major scientific conferences and investigated more than 250 outbreaks. The programme uses an established applied epidemiology curriculum, providing an accredited Master of Science (MSc) degree from either the University of Pretoria or the University of the Witwatersrand. Currently, the programme has the largest cohort of 26 residents, six professional nurses, one physician, five veterinarians, three clinical associates, three laboratorians and other allied health professionals with a primary degree in the health sciences.

The significant impact of SAFETP was the involvement of residents, alumni and staff to support the provinces in the national COVID-19 response. More than 70% of the provincial epidemiologists are SAFETP graduates, with SAFETP staff and residents being deployed to different districts in KwaZulu-Natal, Free State, Limpopo and Northern Cape to strengthen data management workflow processes, data quality checks, analysis and interpretation of data, reporting or dissemination of findings, and capacity building for district epidemiology and surveillance teams.

In addition to the two-year Advanced FETP tier, SAFETP offers the three-month Frontline FETP course to equip frontline healthcare practitioners with the fundamental skills used in frontline surveillance and response.

# **Outbreaks**

Residents of the 2020 SAFETP cohort have been integrally involved in COVID-19 response support activities, such as the analysis and interpretation of COVID-19 data. Residents were involved in five COVID-19 cluster investigations and six outbreaks investigations. These included multidrug-resistant *Acinetobacter baumannii* in the neonatal ward at a provincial tertiary hospital in Gauteng, a cluster of COVID-19 infections among healthcare workers in KwaZulu-Natal, the KwaZulu-Natal Rage outbreak in matriculants and a COVID-19 outbreak in a mental healthcare facility in North West, which highlighted the need to increase awareness of the unique challenges faced by mental healthcare settings.

Other investigations included a case of human rabies, a case of suspected human anthrax and the rapid increase in COVID-19 deaths at a mental healthcare facility. The outbreak of African swine flu among pigs in a communal farm in Gauteng was investigated, with key recommendations made to the Gauteng Department of Agriculture and Rural Development. Suspected rabies exposure at the Lion and Cheetah Sanctuary on the border of the Dinokeng Game Reserve was also investigated. In addition, a typhoid outbreak in Malawi is being investigated with water samples testing positive for *Salmonella* Typhi.

# Policy contributions

SAFETP is working with the NDoH to have epidemiologists listed as a formal cadre of staff in the health service, and have developed the curriculum for joint integrated disease surveillance and response (IDSR) training with the NDoH.

# Teaching and training

With universities suspending all in-person teaching classes, SAFETP rapidly modified all teaching materials to adapt to online teaching and transitioned all teaching sessions into virtual classes using the Google Classroom platform. The transition greatly assisted the programme to continue with teaching programs despite COVID-19 restrictions and ensured that all residents completed their training. The platform is used to provide remote mentorship to residents that are in the field for experiential learning, and to provide training and epidemiological support to NDoH stakeholders.

In the period under review, five residents from the 2018 cohort graduated with a Master of Public Health (MPH), conferred by the University of Pretoria, and two graduated with an MSc in Epidemiology, conferred by the University of Witwatersrand. In January 2021 SAFETP enrolled its largest cohort of 16 residents. The programme enrolled two residents from Lesotho and three residents from Eswatini as part of its commitment to the World Health Organization (WHO) to build the regional epidemiology capacity of 200 epidemiologists. Seven dissertations were produced as part of core learning activities.

In October 2020, SAFETP staff, in collaboration with the NDoH, facilitated four training workshops on COVID-19 preparedness and response for health workers in the Northern Cape. In total, 96 health workers from five districts, namely Francis Baard, ZF Mgcawu, Pixley ka Seme, John Taolo Gaetsewe and Namakwa, were trained.

Two districts in the Free State were trained on data management and analysis, with the training of 41 people, including data clerks, surveillance officers, data capturers, data analysts and data managers.

Between February and March 2021, the SAFETP team conducted the first week-long virtual FETP Frontline training for district and provincial health professionals from the Eastern Cape.

A virtual Supervisors' Training Workshop, aimed to build capacity for identified field site supervisors was held, highlighting the role of the field site supervisor linked to FETP core learning activities.

Dr Lazarus Kuonza, Head of the South African Field Epidemiology Training Program, continues to serve on the Quality Assurance and the Policy Advocacy subcommittees of the African Field Epidemiology Network Board of Directors.

# **Research output**

# Journal articles

- [1] Gavhi F, Kuonza L, Musekiwa A, et al. Factors associated with mortality in children under five years old hospitalized for severe acute malnutrition in Limpopo province, South Africa, 2014–2018: a cross-sectional analytic study. PLoS One. 2020;15(5): e0232838. Available from: <u>https://doi.org/10.1371/journal.pone.0232838</u>
- [2] Sikhosana ML, Kuonza L, Motaze NV. Epidemiology of laboratory-confirmed mumps infections in South Africa, 2012–2017: a cross-sectional study. BMC Public Health. 2020;20:668. Available from <u>https://doi.org/10.1186/s12889-020-08835-x</u>
- [3] Mathebula R, Kuonza L, Musekiwa A, et al. Trends in RPR seropositivity among children younger than two years in South Africa, 2010–2019. J. Trop. Pediatr. 2021 Feb;67(1). <u>https://doi.org/10.1093/tropej/fmab017</u>

# Conferences

- [1] International conferences: 4
- [2] Local conferences: 6



# CENTRE FOR EMERGING ZOONOTIC AND PARASITIC DISEASES (CEZPD)





Prof Janusz Paweska Centre Head

# BACKGROUND

The Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD) serves as both the national and regional hub for diagnosis, surveillance, outbreak response, research, teaching and training related to zoonotic viral, bacterial and parasitic diseases, particularly those associated with risk group 3 and 4 pathogens. These include the following:

- Viral haemorrhagic fevers (VHFs) such as Ebola and Marburg viral diseases, Lassa fever and Lujo haemorrhagic fever (LHF)
- Arthropod-borne diseases such as Rift Valley fever (RVF), Crimean-Congo haemorrhagic fever (CCHF), yellow fever, dengue fever, chikungunya fever, Sindbis fever, West Nile fever, Zika fever, malaria, plague and rickettsioses
- Rabies and rabies-related infections
- Bacterial diseases such as anthrax, botulism, brucellosis and leptospirosis
- Parasitic opportunistic infections
- Diarrhoeal disease in children under five years of age
- Schistosomiasis
- Soil-transmitted helminthic diseases

CEZPD plays an important part in supporting the provincial, national and regional malaria control and elimination programmes. It contributes to policy advice and technical support, as well as the training of scientists, medical technologists and epidemiologists in emerging and re-emerging zoonotic and parasitic diseases. It is an internationally recognised resource of expertise for referral diagnostic services, outbreak response and consultations under the mandate of the WHO regional reference laboratory for plague and the WHO Global Outbreak Alert and Response Network (GOARN). The centre operates highly specialised laboratory facilities, including the positive-pressure suit biosafety level (BSL) 4, BSL-3 laboratories, a transmission electron microscope and insectaries for housing the vectors of malaria and arboviruses for insecticide resistance and vector competence studies. These facilities represent both national and regional strategic resource capacity for diagnosis, surveillance, outbreak response and research of priority zoonotic viral, bacterial and parasitic diseases in Africa. CEZPD operates the most advanced high- and maximum-biocontainment medical laboratory infrastructure in the country and in Africa. This allows for the conducting of diagnostic services and operational research on dangerous and newly emerging zoonotic pathogens with epidemic-prone potential (including the recently emerged SARS-CoV-2 responsible for the COVID-19 pandemic), and in particular to support the NICD/NHLS COVID-19 capacity for SARS-CoV-2 isolation in cell culture systems, shedding and transmissibility studies, as well as the development and validation of COVID-19 diagnostic assays.



**Figure 1:** Staff of CEZPD's Special Viral Pathogens Laboratory, dressed in BSL3 protective equipment, examining cultures of monkey kidney cells (Vero E6) under a light microscope in the CEZPD BSL-3 laboratory for cytopathic effect (pathological structural changes in host cells caused by viral replication), following inoculation of Vero E6 cells with clinical material (nasopharyngeal and oropharyngeal swabs) collected from a suspected local case of COVID-19.

National Institute For Communicable Diseases | Annual Overview | 2020/21



Figure 2: (Left) Cytopathic effect caused by the replication of SARS-CoV-2 in a monolayer of Vero E6 cells.

**Figure 3:** (Right) An electron microscope image of SARS-CoV-2 virion from a clinical isolate with a crown (*'corona'*) of spathulate peplomers – a characteristic of members of the Coronaviridae – negatively stained with 2% phosphotungstic acid, imaged at 120 000 times magnification with an Olympus Quemesa camera at 120 kV on an FEI BioTwin transmission electron microscope.

# Surveillance

In response to increased reports of malaria parasites with HRP2/3 deletions, which allow them to evade detection by HRP2-based malaria rapid diagnostic tests, the CEZPD Laboratory for Antimalarial Resistance Monitoring and Malaria Operational Research expanded its surveillance programme to include surveillance for parasites with HRP2 deletions. To date, the HRP2/3 deletion has not been detected in any of the samples analysed by the laboratory. However, all 1 132 malaria-positive samples assessed carried the mutations associated with increased tolerance to lumefantrine, one of the components in the drug combination recommended for the treatment of uncomplicated malaria in South Africa. While no mutations associated with artemisinin-resistance were detected, the confirmation of artemisinin-resistant parasites in Rwanda highlights the need for sustained routine drug efficacy monitoring in South Africa.

A total of 9 943 *Anopheles* mosquitoes was referred to the CEZPD Vector Control Laboratory from sentinel sites in KwaZulu-Natal, Mpumalanga and Limpopo provinces. The presence of five malaria vector species (*Anopheles arabiensis*, *An. merus*, *An. vaneedeni*, *An. funestus* and *An. parensis*), which contribute to ongoing residual malaria transmission in South Africa, were identified among these collections. These data provide part of the evidence base for adopting additional malaria vector control/elimination methods that are designed to target outdoor-resting mosquitoes.



**Figure 4:** Mass rearing of larvae of the major malaria vector (*Anopheles arabiensis*) as part of a project to assess the feasibility of using the sterile insect technique for the control of malaria vectors in South Africa.

Geographic expansion and re-emergence of RVF virus (RVFV) in the last four decades, which is associated with high health and socioeconomic losses, along with the potential for its further international spread, are of great concern for veterinary and public health worldwide. As a part of arbovirus biosurveillance, the CEZPD Special Viral Pathogens Laboratory (SVPL) investigated the possibility of undetected RVFV infections in patients visiting healthcare facilities in the northern tropical part of KwaZulu-Natal for the period April 2018 to August 2019. This study detected IgM and IgG antibodies to RVFV in human serum samples, confirming the recent circulation of RVFV in the tropical coastal plain region of South Africa, despite the absence of reported clinical disease. The study indicates that RVFV infections in northern KwaZulu-Natal are misdiagnosed or underreported. This situation highlights an urgent need for improvement of diagnosis and awareness of RVF and other arbovirus diseases in this part of South Africa in order to reduce disease burden and potential misuse of anti-malaria treatment.

In order to alert public health authorities to the possibility of increased human plague risk, the CEZPD Special Bacterial Pathogens Laboratory (SBPL) continued surveillance for plague in susceptible rodent populations in Nelson Mandela Bay Municipality (Coega area) and eThekwini Municipality. Due to the COVID-19 pandemic and various levels of lockdown, sample collection was hindered and only a limited number of rodents were tested, of which all were found to be negative for plague anti-F1 antibodies.

# **Outbreaks**

The CEZPD Parasitology and Vector Control Laboratories investigated four outbreaks of odyssean malaria. This form of malaria is acquired in non-endemic areas by persons with no travel history, transmitted by infected mosquitoes that are likely imported in road vehicles such as minibus taxis. These outbreaks affected nine individuals, several of whom required intensive care, with one death. The outbreaks highlight the large flow of traffic into Gauteng from surrounding malaria-endemic provinces and neighbouring countries.

# **Policy contributions**

The centre made numerous contributions to the review and development of policies, guidelines, operating procedures and strategies. These include the following:

- Contribution to the malaria vector control policies of South Africa's national and provincial malaria control programmes. This was done by collating and interpreting malaria vector surveillance and insecticide susceptibility data. Analysis of these data provides information on malaria receptivity and risk, and enables judicious choices of insecticide for annual control operations
- Contribution to the 2020/21 report on the assessment of the production and use of dichlorodiphenyltrichloroethane (DDT) and its alternatives for disease vector control in its capacity as a WHO-nominated member of the DDT Expert Group of the United Nations Environment Programme (UNEP)
- Development of national guidelines for rabies post-exposure prophylaxis in humans in South Africa
- Contribution to the drafting and review of the laboratory diagnostic section of the WHO plague operational guideline
- Contribution to the development of a community-based malaria screen, test and treat strategy, which aims to expand malaria case management services to vulnerable, hard-to-reach populations/communities

#### **Diagnostic services**

Ten cases of human rabies were confirmed by the SVPL in 2020. These cases were reported from KwaZulu-Natal (n=4), Eastern Cape (n=4) and Limpopo (n=2) (Figure 4). Rabies is a fatal Category I notifiable medical condition in South Africa.



2 1 0

24

2011

2012



2014

2013

KwaZulu-Natal Eastern Cape

From a total of 11 suspected viral haemorrhagic cases during the period under review, two cases of CCHF were laboratory diagnosed by SVPL in 2020. The cases were reported from North West and Free State, and tick exposure was reported prior to developing illness.

2015

Limpopo

2016

Free State

2017

Mpumalanga

2018

North West

2019

2020



# Figure 6: Laboratory-confirmed CCHF cases by province, South Africa, 2011-2020.

The Arbovirus Reference Laboratory investigated suspected endemic and exotic arboviral disease cases, including chikungunya, Rift Valley fever, dengue, Zika fever, Ross River and Japanese encephalitis. The laboratory experienced a reduction of close to 80% in diagnostic submissions, most likely due to the effects of COVID-19 on the healthcare system (from 390 submissions in the previous year, to 71 during the period under review) and the reduction of risk of arboviral infections in travellers (for example dengue, Zika and other non-endemic arboviral infections).

The CEZPD SBPL continued to provide diagnostic services for zoonotic bacterial pathogens causing diseases such as anthrax, plaque, leptospirosis, botulism and brucellosis.

The Parasitology Reference Laboratory provides a specialised parasitic pathogen diagnostic service for the public-sector laboratories, both by conventional methods and, increasingly, polymerase chain reaction (PCR) assays; for example for toxoplasmosis, amoebiasis and pneumocystosis. The Parasitology Reference Laboratory, with financial support from the Global Fund and the Eliminating Eight (E8) countries, established the Regional Malaria Slide Bank for supporting malaria laboratory diagnosis in southern African countries. In 2020/21, some 6 357 slides in 40 batches were manufactured for microscopist training and external quality assessment by participating regional laboratories. A malaria slide cross-checking service was implemented for the Mpumalanga Malaria Control Programme laboratories in Tonga and Bushbuckridge.



The Vector Control Reference Laboratory (VCRL) was awarded a 17025 SANAS accreditation.

**Figure 7:** Staff of the CEZPD Parasitology Reference Laboratory preparing mass blood films for the NICD/E8 Regional Malaria Slide Bank. The Bank was established to support malaria elimination programmes in South Africa and the greater southern African region. To date, 154 batches comprising 26 623 slides, six proficiency testing panels, as well as microscopy training slide sets, have been produced and shared with other southern African countries.

# **Research Activities**

#### Epidemiology of human rabies in South Africa: 2008-2018

NICD investigators: J Weyer, V Dermaux-Msimang, A Grobbelaar, C le Roux, N Moolla, JT Paweska, LH Blumberg

Rabies is a fatal zoonosis of warm-blooded animals. Despite being preventable and controllable, rabies continues to scourge human populations in developing countries. This is primarily due to the inability to control domestic dog-transmitted rabies cycles in these settings. Human rabies cases continue to be reported annually in South Africa. Previous investigations have shown the association between the occurrence of human rabies cases and dog rabies cases in the country. A study was conducted to describe the epidemiology of laboratory-confirmed human rabies cases in South Africa for the period 2008-2018. The study was a retrospective document review using the case register and data collected for cases during routine diagnostic investigations. The latter was available at the reference laboratory. A total of 105 human cases was reported during this period, with cases reported from all provinces in South Africa, except for Western Cape. Children and young adults remain the most affected, as reported for periods preceding the study period. Domestic dogs also remained the most important vector of rabies to the human population in South Africa. Nearly half of the cases did not seek any medical intervention following the exposure event.

# Development of a recombinant antigen-based indirect immunofluorescence assay for rapid and safe detection of Lassa fever antibodies

NICD investigators: N Moolla, J Weyer

**Collaborators:** J Bell, W Markotter (University of Pretoria)

Viral VHFs are associated with high mortality rates. A need therefore exists for rapid detection and identification of their causative agents. Most VHFs are classified as BSL-4 pathogens and pose a risk of laboratory-acquired infections. Recombinant proteinbased diagnostic tools would mitigate these risks. Lassa fever virus (LFV) affects over 500 000 Africans annually, yet there are no commercially available serological tests for detection of anti-LFV antibodies. This project aims to develop an indirect immunofluorescence antibody assay (IFA) for serodiagnosis of Lassa fever without the need to handle infectious LFV in BSL4. The primary advantages of an IFA are the convenience and speed with which results can be obtained. Traditionally, IFAs utilise virus-infected cells. In the case of LFV and other VHFs agents, this requires the use of BSL-4 facility. In this study, we develop a recombinant protein based IFA for the detection of antibodies to nucleocapsid and glycoproteins of LFV. The assays show good specificity, and further work aimed at clinical validation is underway. This work has also contributed to the completion of an MSc-level postgraduate qualification.



Figure 8A: Detection of LFV NP expression by IFA.

Figure 8B: Detection of LFV NP by Western blot.

# Identifying the entomological drivers of malaria transmission in South Africa

NICD investigators: B Brooke, G Munhenga, S Oliver, Y Dahan-Moss, M Kaiser, E Jamesboy, L Koekemoer, M Coetzee Collaborators: LEO Braack, M Riddin (University of Pretoria), S Irish (Centres for Disease Control and Prevention)

Accurate identification to species level of malaria vector mosquitoes is critical to understanding their biological characteristics, such as susceptibility to insecticides, leading to the design of control methods. To this end, the morphological keys to the *Anopheles* mosquitoes of sub-Saharan Africa were revised and updated from the 1987 version, and the molecular methods for species identification were re-assessed and improved. These developments will continue to be used to strengthen vector surveillance activities in South Africa by enabling a deeper assessment of *Anopheles* species assemblages in endemic districts.

#### Molecular identification and phylogenetic characterisation of unusual zoonotic parasites in southern Africa

NICD investigators: J Frean, D du Plessis, B Moodley, LM Sun

Collaborators: D Stead (Walter Sisulu University)

Precise identification and phylogenetic relationships are able to be provided for unusual pathogens, including parasites. We have described a new piroplasm parasite of humans, *Anthemosoma garnhami*, that is closely related to *Babesia* species, and previously only found in rodents. The exact taxonomic position of a *Gnathostoma* species, a zoonotic nematode acquired by eating raw fish and isolated from a human patient in Botswana, is likewise being determined.

# Teaching and training

CEZPD staff provided and contributed to the following teaching and training activities during the period under review – mostly delivered via virtual platforms in order to observe COVID-19 public health requirements and regulations:

- NICD Short Course for Registrars
- NICD Virology and Parasitology Intensive Courses for Registrars
- NICD Medical Scientist Intern Rotation for Virology, Microbiology and Parasitology
- Medical parasitology training for intern scientists, pathology registrars, undergraduate medical and veterinary students, students
  of the Collaborative MSc Tropical Animal Health (Faculty of Veterinary Science, University of Pretoria, and Institute of Tropical
  Medicine, Antwerp, Belgium) and doctors enrolled in the Postgraduate Diploma in Tropical Medicine and Hygiene at the
  University of the Witwatersrand
- Lectures for the MSc in Epidemiology and MSc in Vaccinology degree programmes at the University of the Witwatersrand
- Training of laboratory personnel of the Agricultural Research Council Onderstepoort Veterinary Research (ARC-OVR) in Rift Valley fever inhibition ELISA (16-18 November 2020)
- Enhancing Research for African Network (ERFAN) and University of Pretoria virtual Rift Valley fever course (23-27 November 2020)
- Training in *Anopheles* morphology, mosquito colony maintenance and basic entomological surveillance for eight participants of the KwaZulu-Natal malaria control programme (9-13 November 2020)
- Training in the use of PCR for vector surveillance for one participant each from the KwaZulu-Natal and Mpumalanga malaria control programmes (8–19 March 2021)
- Training in malaria vector surveillance, WHO wall cone bioassay and basic mosquito morphology to participants in Rustenburg (23-27 November 2020)
- Contribution to Malaria Case Management Workshops for Gauteng healthcare workers (11 March 2021) and for Mpumalanga
  malaria programme staff (16-17 March 2021)
- Contribution to the MSc in Medical Entomology by coursework programme at the University of the Witwatersrand, VIRL 7013
   (22–26 March 2021)



**Figure 9:** Prof JT Pawęska and Dr O Hellferscee providing training to the staff of the ARC-OVR in serological diagnosis of RVF using an inhibition ELISA developed by CEZPD NICD/NHLS. This training is a part of a technology transfer collaboration agreement between NICD/NHLS and ARC-OVR to strengthen the One Health programme in South Africa, and was supported by Ecohealth Alliance.

# Postgraduate students:

During the period under review, CEZPD staff was involved in the supervision or co-supervision of 26 postgraduate students, comprising the following:

- BSc Hons: 5
- MSc: 9
- MPH (Field Epidemiology): 1
- PhD: 11

Six students, supervised by CEZPD staff, graduated in the period under review. These comprised the following:

- BSc Hons: 3
- MSc: 1
- PhD: 2

# Professional development, awards and honours

- MSc student, Alexander Jeanrenaud, was awarded the most prestigious MSc by 100% research degree by the Faculty of Health Sciences of the University of Witwatersrand. This candidate was also awarded the Junior WO Neitz medal for most outstanding MSc degree by the Parasitology Society of South Africa
- Dr M Kaiser and Dr J Weyer attended three training courses by American Biosafety Association between 15 and 30 October
   2020: basic risk assessment, basic threat assessment for laboratory biosecurity programmes and managing potential for human failure through biosafety critical task analysis
- Dr J Weyer and Dr O Hellferscee were appointed as joint lecturers in the Department of Microbiology and Infectious Diseases in the University of the Witwatersrand's School of Pathology (Faculty of Health Sciences)
- Dr J Weyer was appointed as associated editor to Frontiers in Virology, whilst Dr O Hellferscee was appointed as review editor to the same journal
- Dr J Coertse was appointed as Extraordinary Lecturer in the Department of Medical Virology in the University of Pretoria's School of Medicine (Faculty of Health Sciences)
- Dr Jaishree Raman received a C2 rating from the National Research Foundation (NRF)
- Prof J Pawęska was nominated as a member of the African Union Scientific, Research and Innovation Council Advisory Board on Science, Technology and Innovation Strategy Intervention for COVID-19. In addition, he was invited by Frontiers in Microbiology as editor on the research topic 'Host and pathogen mechanisms underpinning viral ecology and emerging infections', re-appointed as Extraordinary Professor in the Department of Medical Virology, University of Pretoria School of Medicine, Faculty of Health Sciences, from 1 October 2020 to 30 September 2023, and received the Gold Medal Award from the South African Medical Research Council in recognition of outstanding lifelong scientific contributions to health research in developing countries



**Figure 10:** Prof J Pawęska, accompanied by his wife, Małgorzata, receiving the Gold Medal Award from the South African Medical Research Council in recognition of his outstanding lifelong scientific contributions to health research in developing countries.

# **Research output**

# Journal articles

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# Books

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# Conferences

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# CENTRE FOR ENTERIC DISEASES (CED)





Dr Juno Thomas Centre Head

# BACKGROUND

The goal of the Centre for Enteric Diseases (CED) is to facilitate the understanding, management and prevention of enteric diseases by providing up-to-date and locally relevant information. There are currently four areas of focus, namely:

- Foodborne diseases, which are globally recognised as a threat to food safety and security
- Waterborne diseases, which can affect public health in instances where unsafe water is utilised, and are often associated with large outbreaks
- Priority enteric diseases under routine surveillance, which comprise epidemicprone conditions such as typhoid, cholera and listeriosis
- Rotavirus, which is a vaccine-preventable disease in South Africa

The centre comprises a small team of specialists with extensive experience in enteric diseases. Activities include surveillance, public health-orientated research, outbreak investigation and response, reference laboratory services, regional technical and laboratory testing assistance, as well as international collaborations.

The COVID-19 pandemic rendered the period under review particularly challenging for many reasons, including the following:

- Several senior staff members were seconded to support COVID-19-related activities
- Hospital-based research surveillance studies were interrupted
- The syndromic surveillance programme, nested in GERMS-SA and which was planned to start during 2020, was postponed
- Whole-genome sequencing of enteric bacteria for active surveillance and outbreak investigations was severely impacted, due to prioritisation of testing SARS CoV-2 samples

Staff from the centre continued to network with both the global and local scientific communities. Local communities were supported through education and information on hand hygiene and SARS-CoV-2, which was distributed via the media.

Internal teaching and training remained a priority, and six postgraduate candidates graduated during the period under review. One of the centre's medical scientists was registered with the Health Professionals Council of South Africa (HPCSA) in independent practice.

# Surveillance

# Acute diarrhoeal disease surveillance

The centre monitors diarrhoeal disease in all ages in selected sentinel sites to define the major aetiological agents and environmental factors associated with disease, and estimate the associated hospitalisations and deaths. Diarrhoeal disease surveillance activities (routine surveillance and research studies) were severely impacted by the COVID-19 pandemic during 2020, with fewer patients seeking healthcare and restricted admission to hospital for life-threatening conditions only.

During the period under review, 192 samples were submitted for routine surveillance testing, and rotavirus was detected in 6% (11/192). The 'normal' rotavirus season in South Africa was affected in 2020, with most cases detected in September and October rather than July or August. The number of cases was also lower than would be expected in a typical rotavirus season. A similar trend was noted for the detection of other enteric pathogens (including viruses, bacteria and parasites), in that case numbers were low in the first half of the year then increased once lockdown restrictions were eased. These unusual patterns likely reflect the effect of non-pharmaceutical COVID-19 interventions (in particular social distancing and hand hygiene), as well as government restrictions (including the closure of schools and nursery schools) on the transmission of enteric pathogens.

An interim analysis of patients with diarrhoeal disease in a three-year surveillance study (2018–2020) found that fewer common enteric pathogens were detected in HIV-positive adults (52%) compared with HIV-positive and HIV-negative children (81% and 85% respectively). This suggests a potential limitation of routine diagnostic tests in identifying infectious causes of diarrhoeal disease in

HIV-positive adults. Further investigation is warranted, especially as most patients older than five years of age enrolled in the study were HIV-positive.

## National listeriosis surveillance

All cases of listeriosis, alerted through the notifiable medical conditions (NMC) system and corporate data warehouse (CDW), were followed up by the centre's staff to ensure the collection of additional testing data, comprehensive food history and isolate referral. All *Listeria* isolates routinely underwent whole-genome sequence (WGS) testing. Between 1 April 2020 and 31 March 2021, 84 cases of listeriosis were reported from eight provinces. This amounts to two cases fewer than what was reported for the previous financial year. Gauteng had the majority of reported cases (44%, 37/84) followed by Western Cape (32%, 27/84) and KwaZulu-Natal (11%, 9/84). No cases were reported from Mpumalanga during the period under review. An average of two cases per week (range: 0-4 cases per week) was recorded. The majority of the cases were neonates  $\leq 28$  days (39%, 33/84), followed by persons in the following age groups: 15-49 years (25%, 21/84), 50-64 years (17%, 14/84),  $\geq 65$  years (17%, 14/84), and children between 30 days and 14 years (2%, 2/84).

# Outbreaks

The centre continues to play a leading role in the investigation and response to outbreaks of food- and water-borne disease, and clusters or suspected outbreaks of epidemic-prone enteric pathogens. The centre's staff routinely follow up on alerts of suspected enteric disease outbreaks reported through the NMC system, and provide both epidemiological and laboratory support. During the 2020/21 period, the centre responded to 18 outbreaks. Selected outbreaks are described below.

#### Foodborne disease outbreaks

Outbreaks were recorded at the following institutions:

- A correctional facility in Nelson Mandela Bay Metropolitan in the Eastern Cape (May 2020): The outbreak was caused by *Shigella flexneri* type 2a and affected ten inmates in two holding cells
- A correctional facility in Sarah Baartman District in the Eastern Cape (December 2020): The outbreak was caused by *Salmonella* Typhimurium and affected 16 inmates
- A year-end function at a primary school in uThukela District in KwaZulu-Natal (December 2020): Six cases were reported, including one fatality. Food served at the function was sampled and tested positive for *Bacillus cereus* and *Staphylococcus* species. Three stool specimens were screened, with one positive for norovirus GII (which was likely an incidental finding and not associated with consumption of the incriminated food items). The cause of the outbreak was not identified
- A secondary school in Tshwane Metropolitan in Gauteng (March 2021): The outbreak affected 109 learners. The most likely cause of the outbreak was foodborne intoxication resulting from contamination of food with toxin-producing bacteria

Outbreaks were recorded at the following events:

- A traditional ceremony hosted at a household in eThekwini Metropolitan in KwaZulu-Natal (September 2020): The outbreak affected 21 people who consumed goat meat, and was caused by *Salmonella* Vejle
- A tombstone unveiling ceremony in eThekwini Metropolitan in KwaZulu-Natal (November 2020): The outbreak affected 46 people, and was caused by *Salmonella* Typhimurium. Contaminated beef was the most likely vehicle of infection
- A birthday celebration hosted at a household in Nelson Mandela Bay Metropolitan in the Eastern Cape (March 2021): A total of 18 cases was reported, following consumption of a cake bought from a local supplier. *Salmonella* species was identified as the likely cause of infection, and the cake filling was the most likely vehicle of infection

Outbreaks were reported in the following household or localised community settings:

- A cluster in uMzinyathi District in KwaZulu-Natal (June 2020): A goat that died of unknown causes was slaughtered at a household, and the meat shared with extended family, neighbours and friends. The outbreak affected 25 people, and was caused by *Salmonella* Berth.
- A celebration in Alfred Nzo District in the Eastern Cape (December 2020): A cow that died after calving was slaughtered at a household, and the meat shared with extended family, neighbours and friends. The outbreak affected 57 people, one of whom died. *Salmonella* Typhimurium was identified as the cause of the outbreak

- A household in Ekurhuleni Metropolitan in Gauteng (April 2020): The outbreak was caused by *Shigella* species and affected two people
- A household in uThukela District in KwaZulu-Natal (April 2020): Three people were affected by the outbreak. They had consumed homemade beer, which was made using a sanitiser, among other ingredients. The illness was likely due to chemical intoxication
- A household in Tshwane Metropolitan in Gauteng (May 2020): The outbreak was caused by *Salmonella* Typhi and affected three household members

Outbreaks affecting larger communities were reported in the following health districts:

- Lejweleputswa District in the Free State (September 2020 to November 2020): A total of 67 cases of norovirus infection in children was reported from a private hospital, and a contemporaneous increase in cases of diarrhoeal disease was reported by public healthcare facilities in the area. Ninety-four stool specimens collected from children with diarrhoea at several healthcare facilities in the area were submitted to the centre for testing. Norovirus genogroup II was detected in 67% (63/94) of the samples. Norovirus GII.P31/GII.4 Sydney strain was identified as the cause of the outbreak, and contaminated municipal drinking water was the likely vehicle of infection
- Cape Winelands District in the Western Cape (October 2020 to March 2021): Through the use of whole-genome sequencing, ten enteric fever cases caused by genetically-linked *Salmonella* Typhi were identified. The source of the outbreak is still under investigation

A further 45 enteric outbreaks were reported, but further investigation was precluded by insufficient epidemiological data and lack of clinical, food or environmental specimen collection and testing.

# **Diagnostic services**

The virology and bacteriology reference laboratories provide a range of specialised tests to support diagnostic laboratories in public and private health sectors, and also to provide rapid diagnostic and confirmatory testing for epidemic-prone pathogens. These include the following:

- Specialised rotavirus testing and rotavirus typing
- Specialised testing for other enteric viruses, including astrovirus, adenovirus, norovirus and bocavirus
- Specialised molecular screening for enteric pathogens
- Specialised testing for Vibrio cholerae
- Specialised testing for diarrhoeagenic E. coli, including Shiga toxin-producing E. coli
- Specialised testing for Salmonella species, including serotyping and molecular testing
- Specialised testing for *Listeria* species
- Experimental metagenomics for investigation of patients with pathogen-negative diarrhoeal disease

# **Research activities**

#### Community survey for diarrhoeal diseases in Soweto, 2020

NICD investigators: SL Johnstone, NA Page, J Thomas

**Collaborators:** SA Madhi, P Mutevedzi, N Myburgh, C Herrera, MJ Groome (South African Medical Research Council: Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand)

In South Africa, there are limited data on the burden of diarrhoea at a community level, specifically in older children and adults. Randomly sampled households were enrolled from an existing urban health and demographic surveillance site. A household representative was interviewed to determine associated risk factors and occurrence of diarrhoea for all household members in the past two weeks, including symptoms and health-seeking behaviour. The diarrhoeal rate was high across all age groups in this community. However, older children and adults were less likely to present to healthcare, and are underrepresented through facility-based clinical surveillance. Current diarrhoeal surveillance represents a fraction of the overall cases occurring in the community.
#### Handwashing practices in Soweto, South Africa, in February 2020

NICD investigators: SL Johnstone, NA Page, J Thomas

**Collaborators:** SA Madhi, P Mutevedzi, N Myburgh, C Herrera, MJ Groome (South African Medical Research Council: Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand)

Addressing poor handwashing practices, a known risk factor for infectious diseases, requires an understanding of current behaviour in the community. We undertook a cross-sectional community survey in Soweto, South Africa, to determine handwashing practices and factors affecting these practices. Households with inadequate handwashing practices were significantly more likely to have experienced a diarrhoeal episode in the past two weeks than those with adequate handwashing practices. Older respondents and those with a basin in the same room as the toilet were more likely to have adequate handwashing practices, specifically associated with better use of soap for handwashing. Educational messaging to improve handwashing should be targeted at young adults and the importance of using soap should be highlighted.

#### **Teaching and training**

CED staff provided and contributed to the following teaching and training activities during the period under review:

- SEQAFRICA virtual training course on WGS (February to May 2021): This course aims to build capacity for WGS in African countries, with a focus on its application in surveillance for antimicrobial resistance. Anthony Smith contributed to organising the training, and served as facilitator, lecturer and trainer
- SAFETP, hosted by the NICD at the University of the Witwatersrand
- MSc Epidemiology and Biostatistics, MSc Vaccinology and Diploma in Tropical Medicine and Hygiene (DTM&H) courses,
   presented by the University of the Witwatersrand

#### Postgraduate students

Staff from the centre participated in the following specialised NICD training courses:

- NICD registrar training course: 11 pathology registrars (microbiology and virology)
- NICD training course rotations in enteric bacteriology and virology laboratories:
   6 medical intern scientists (microbiology, molecular biology and virology)
- Virology registrars attended the intensive virology training course

#### Professional development

- Anthony Smith was appointed as an Extraordinary Professor in the Department of Medical Microbiology in the University of Pretoria's School of Medicine (Faculty of Health Sciences)
- One intern medical scientist was registered with the HPCSA for independent practice
- Three intern medical scientists are currently training at the CED

#### **Research output**

#### Journal articles

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CENTRE FOR HEALTHCARE-ASSOCIATED INFECTIONS, ANTIMICROBIAL RESISTANCE AND MYCOSES (CHARM)





Prof Nelesh Govender Centre Head

#### BACKGROUND

The centre incorporates two national reference laboratories for antimicrobial resistance and mycoses, both of which are accredited to ISO 15189: 2012 requirements, and houses the National Stock Culture Collection of pathogenic bacteria and fungi. The centre is a WHO Collaborating Centre for antimicrobial resistance (AMR) and serves as the national focal point for WHO's Global Antimicrobial Resistance Surveillance System (GLASS). Furthermore the centre acts as an expert site for provision of external quality assessment programmes for AMR. The epidemiology team supports priority surveillance projects, conducts outbreak investigations and is involved in the set-up and evaluation of national public health programmes for people living with advanced HIV disease.

#### Surveillance

Healthcare-associated infections (HAI) surveillance

NICD investigators: NP Govender, L Shuping, E Chikwuma

**Collaborators:** T Avenant, N du Plessis, K Masemola, D Pillay, M Ngobese, C Mackay, S Mahmud Yakoob, S Abrahams, J Black, N Ramncwana, F Naby, S Haffejee, H Dawood, J Green, T Martin, A Abrahams, E Mosenye, M Maila

The centre implemented a real-time alert system to detect outbreaks of healthcare-associated bloodstream infections among neonates at Kalafong (Gauteng), Grey's (KwaZulu-Natal), Dora Nginza (Eastern Cape) and Thelle Mogoerane (Gauteng) hospitals. We conducted training of hospital personnel to use the outbreak alert mobile software application. The pilot project commenced on 1 February 2019, but was halted in 2020 after technical issues with the mobile application. A contractor was appointed in 2021 to improve the functioning of this application.

#### Antimicrobial resistance surveillance

NICD investigators: O Perovic, NP Govender, L Shuping, H Ismail, M Smith, R Mpembe, S Jallow

Collaborators: GERMS-SA network, SA Society for Clinical Microbiology

Senior members of the centre represented NICD on a newly-constituted Ministerial Advisory Committee for AMR, WHO AMR Surveillance and Quality Assessment Collaborating Centres Network and the WHO Strategic and Technical Advisory Group for AMR. Several approaches are currently used by the centre for AMR surveillance. These include the following:

- National or sentinel isolate-based surveys: Bacterial and fungal isolates, cultured from patients who meet the surveillance case definitions, were submitted to the centre's reference laboratories for identification, antimicrobial susceptibility testing and genotyping. During the period under review, the centre conducted surveillance for bacteraemia caused by carbapenem-resistant Enterobacterales (2015-2021) and all infections caused by *Candida auris* (2018-2021)
- Enhanced laboratory surveillance: Detailed clinical information was collected from patients admitted to sentinel hospitals who met the surveillance case definitions. During the period under review, the centre conducted enhanced surveillance for bloodstream infections caused by carbapenem-resistant Enterobacterales (until the end of 2020)
- Electronic laboratory surveillance: Annual data were compiled on bloodstream infections caused by the ESKAPE bacterial
  pathogens. Line list data from public- and private-sector pathology laboratory information systems were merged by NICD's
  SIMU, cleaned and made available through the AMR dashboard on the NICD website. The dashboard displays interactive and
  exportable AMR maps by geographic location, pathogen, antimicrobial agent and health sector. AMR data for the public sector
  are available to facility level. A combined public/private AMR report on key organisms-antimicrobial agents is available from the
  NDOH (http://www.health.gov.za/index.php/antimicrobial-resistance)

39

#### Surveillance for mycoses

NICD investigators: N Govender, R Mpembe, T Maphanga, S Naicker, L Shuping, H Ismail, R Mashau, J Paxton Collaborators: GERMS-SA network, Clinton Health Access Initiative (CHAI)

WHO recommends a combination of amphotericin B and flucytosine (5-FC) as first-line treatment for patients with cryptococcal meningitis. 5-FC is still not registered in South Africa. A 5-FC access programme, coordinated by CHAI, was expanded in 2020. The centre continued enhanced surveillance for cryptococcal disease to assess the impact of national reflex cryptococcal antigen screening (from 2016 onwards) and 5-FC use (from 2018 onwards). The GERMS case report form was expanded to collect information on 5-FC/amphotericin B toxicity and 10-week outcomes. These data were used to motivate for expansion of the pilot project to additional hospitals in 2020 and early 2021. As of March 2021, 59 hospitals received 5-FC, and the centre has assisted with coordination of data collection and analysis. Passive laboratory-based surveillance for rarer invasive mycoses continued.

#### **Outbreaks**

The centre led or participated in the investigations of several healthcare-associated outbreaks during the period under review, including an outbreak of *Serratia marcescens* infections in several dialysis units in Gauteng Province. Since the latter outbreak involved a potentially-contaminated product, a report was also issued to the South African Health Products Regulatory Authority (SAHPRA).

#### WHO Collaborating Centre for AMR

As a WHO Collaborating Centre for AMR, the centre participated in the WHO AMR Surveillance and Quality Assessment Collaborating Centres Network, which was formed to support the implementation of GLASS (https://www.who.int/glass/reports/en/). The NICD collaborated on activities to strengthen countries' capacity for developing and implementing AMR surveillance, and provided an external quality assessment programme (https://ptschemes.nicd.ac.za/Home/Bacteriology).

#### **Research activities**

#### FLEMING FUND REGIONAL GRANT FOR EXTERNAL QUALITY ASSESSMENT IN AMR

#### NICD investigators: O Perovic, M Smith, R Badat

The centre was selected as one of three sites for an external quality assessment programme on AMR in the African region. This programme aims to improve the capacity of microbiology laboratories to perform pathogen identification and antimicrobial susceptibility testing and in turn, to improve AMR surveillance reporting. During the reporting period, preparations were conducted to initiate this programme.

#### CAST-NET

NICD investigators: NP Govender, G Greene, D Desanto, J Paxton, R Mashau, A Shilubane, N Valashiya, L Steynfaardt, S Kutta Collaborators: University of Minnesota, US CDC, Epicentre

The CAST-NET project aims to evaluate the effectiveness of the national reflex cryptococcal antigen screen and treat intervention and pilot programmatic approaches to optimising it. This project is supported by an NIH R01 grant (2016-2022). With the assistance of a field data collection partner, Epicentre, the centre completed retrospective collection of clinical information on a cohort of nearly 3 000 CrAg+ persons screened between February 2017 and January 2019 in 27 sub-districts (in all nine provinces). A clinical team at CHARM is currently abstracting data from patient records for data analysis. In February 2021, the CAST-NET team began Part 2 of the study aimed at addressing operational gaps identified in the cascade of care for CrAg+ persons.

#### Baby GERMS-SA: Neonatal sepsis surveillance in South Africa

NICD investigators: NP Govender, S Meiring, R Mathebula, O Perovic, M Smith, R Mpembe, V Quan, A von Gottberg, L de Gouveia, S Walaza, C Cohen

Collaborators: A Dramowski, C Mackay, R Phayane, T Mailula, O Mekgoe, C Kapongo, Dr Maphosa

Worldwide, neonatal mortality remains high, accounting for 46% of childhood deaths in 2015, with infectious diseases responsible for approximately 600 000 neonatal deaths. In sub-Saharan Africa, which carries a high burden of global childhood deaths, the aetiology

of these neonatal infections and their resulting burden are not well understood. We aimed to gain a deeper understanding of the burden and aetiological factors of neonatal infections in urban and rural sub-Saharan Africa through the development of a two-tiered surveillance programme. Through Tier 1, we conducted national surveillance of invasive culture-confirmed neonatal infections at all public-sector hospitals in South Africa. Tier 2 was nested within Tier 1, and focused on a detailed characterisation of neonatal infections occurring at six secondary-level institutions (provincial/regional neonatal units). Data from the surveillance programme are being used to describe the pathogen-specific aetiology, antimicrobial susceptibility and clinical profile of neonatal infections at different levels of health-care in South Africa. We characterised selected multi-drug resistant bacterial and fungal pathogens in detail by whole genome sequencing. As of 31 March 2021, national surveillance data from 2014-2019 for approximately 40 000 culture-confirmed neonatal infection cases have been collated and analysed. Clinical data collection on 935 laboratory-confirmed neonatal infection episodes occurring between October 2019 and September 2020 at six provincial/regional hospitals was completed and data are being analysed.

#### Prevalence of AMR genes in animals and humans

NICD investigators: O Perovic, W Strasheim, A Singh-Moodley, M Lowe Collaborators: Prof EMC Etter, Dr JM Mokoele, A Jonker (University of Pretoria)

The routine use of antibiotics for therapeutic, prophylactic and growth promotion in food animals is linked to increase AMR in human medicine. This ongoing project aims to describe antibiotic resistance genes present in food animals and livestock workers, reservoirs from which spill-over may occur into the community and/or hospital environments. A commercial pig farm was visited in December 2019. Twenty-three production houses were sampled. In total, 113 pig faecal droppings were collected. A total of 64 human participants was enrolled in the study after obtaining informed consent. A rectal swab was self-collected and each participant completed a questionnaire. Quantification of antimicrobial usage, antimicrobial susceptibility testing and further molecular testing are at different stage of processing and some are finalised for submission for publication.

#### Characterisation of strains from public- and private-sector ICUs in Gauteng province

NICD investigators: M Lowe, O Perovic

**Collaborators:** Dr Teena Thomas (NHLS), Dr Warren Lowman (Wits Donald Gordon Medical Centre), Dr Trusha Nana (NHLS), Dr Vindana Chibabhai (NHLS)

In this study, we aimed to estimate the prevalence of resistance to antimicrobial agents including colistin in *A. baumannii* isolated from patients in intensive care units (ICUs) in public and private hospitals in Gauteng. In addition, we obtained clinical, demographic and patient outcome information to assess significance of *A. baumannii* bacteraemia.

#### ATLAS - Surveillance and Epidemiology of Antimicrobial Resistance Programme (Pilot)

Investigators: O Perovic, M Smith, R Kganakga, N Bulbulia, A Sesoko

Collaborators: NICD Sequencing Core Facility, Pfizer, conducted by Micron Group

This is a multi-year initiative to develop a scalable surveillance platform using the Antimicrobial Leadership Testing and Surveillance (ATLAS) core methodology, supported by a robust public-private partnership that expands surveillance capacity in low- and middleincome countries. This ATLAS satellite programme will enable additional studies to be undertaken, all based around the core of the ATLAS methodology. It will begin with a pilot phase to demonstrate success of the methodologies, prior to wider engagement with other regions.

The ATLAS Satellite Program Pilot will have the following three elements or work streams:

- 1. Microbiological (AMR) study
- 2. Epidemiological data collection
- 3. Local microbiology database

This AMR Satellite Program Pilot is being conducted in Ghana, Kenya, Malawi and Uganda. Each country will have one or two laboratory sites in hospitals where existing laboratory infrastructure can be utilised. CHARM will serve as a Central Reference Laboratory, and will perform all phenotypic and genotypic work.

#### Whole genome sequencing of Candida auris

NICD investigators: S Naicker, T Maphanga, R Mpembe, M Ali, A Ismail, NP Govender Collaborators: US CDC

WGS has been applied to determine the molecular epidemiology and track outbreaks caused by this near-clonal pathogen. Approximately 249 South African *C. auris* strains have been sequenced by NICD to date. Whole genome phylogenetic analysis characterised most South African *C. auris* strains as clade III (African clade), the clade first reported from South Africa, but a small number of clades I (South Asian clade) and IV (South American) strains suggest early introductions from other regions.

#### Antifungal resistance of Candida auris

NICD investigators: T Maphanga, S Naicker, R Mpembe, NP Govender, M Ali, A Ismail Collaborators: Broad Institute of MIT and Harvard, USA

We tested the resistance profile of bloodstream *C. auris* isolates collected between the 2016 and 2017 surveillance period. We found that majority of isolates were resistant to at least one antifungal agent. Only 6% of the isolates were multidrug resistant and 1% were pan-drug-resistant. Sequenced isolates belonged to clade I, III and IV. Clade I isolates were more likely to be multidrug resistant than those belonging to the other two clades. We also identified common mutations across the different clades. Most South African *C. auris* isolates were resistant to azoles, though resistance to polyenes and echinocandins was less common. We observed mutations in resistance genes even in phenotypically-susceptible isolates.

#### In vitro antifungal activity of manogepix

NICD investigators: T Maphanga, R Mpembe, S Naicker, NP Govender Collaborators: Amplyx Pharmaceuticals, USA

Manogepix is an active moiety of fosmanogepix, a novel antifungal agent currently in Phase 2 clinical trial for treatment of invasive fungal infections including those caused by *C. auris*. We tested the *in vitro* activity of manogepix and other currently used antifungal agents against South African bloodstream *C. auris* isolates. Manogepix exhibited potent activity against all isolates tested, including multidrug and pan-drug-resistant isolates. These *in vitro* data support manogepix as a promising candidate for treatment of *C. auris* infections.

#### Molecular epidemiology of Cryptococcus in South Africa

#### NICD investigators: S Naicker, T Maphanga, E van Schalkwyk, NP Govender

**Collaborators:** Translational Genomics Research Institute, Westmead Institute for Medical Research (University of Sydney), Universidad del Rosario (Bogota, Colombia)

We found high genetic diversity in clinical *Cryptococcus* strains from South Africa. We performed WGS on *Cryptococcus* molecular types endemic to Southern Africa. Whole genome phylogenetic analysis showed certain cryptococcal isolates in closely-related clusters suggesting that people in South Africa may acquire infection caused by these organisms from a common environmental source. South African cryptococcal isolates were also related by whole genome phylogenetic analysis to isolates from geographically distinct regions such as Brazil and Colombia, suggesting a genetic link between African and South American strains. We still need to analyse antifungal resistance and virulence patterns.

#### Teaching and training

CHARM staff provided and contributed to the following teaching and training activities during the period under review:

- NICD online short course for registrars and ID fellows
- Mycology online workshop for registrars and ID fellows
- MMed (Pathology) Molecular Course (University of the Witwatersrand)
- BHSc Molecular Medicine III (Innate and Adaptive Immunology) (University of the Witwatersrand)
- BHSc Biochemistry (Vaccines) (University of Johannesburg)
- MSc Epidemiology and Biostatistics (University of the Witwatersrand)
- MPH (University of Pretoria)

- MSc Vaccinology (University of the Witwatersrand)
- DTM&H (University of the Witwatersrand)
- PhD, MSc, MTech, MPH (SAFETP) and MMed supervision

#### Postgraduate students

Eleven students were enrolled for postgraduate studies as follows:

- MPH: 2
- MTech: 1
- MSc: 2
- PhD:6

Three students graduated in the period under review. These comprised the following:

- MPH: 1
- MSc: 1
- PhD: 1

#### **Research output**

#### Journal articles

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- [2] Bowell M, Robinson L, Govender NP. Skin and mucosal manifestations of a systemic mycosis in AIDS. S. Afr. J. HIV Med. 2020. In press
- [3] Maphanga TG, Naicker SD, Gómez BL, et al. Cross-reactivity of a *Histoplasma capsulatum* antigen enzyme immunoassay in urine specimens from persons with emergomycosis in South Africa. Med. Mycol. 2020 Dec 16:myaa100. Online ahead of print. DOI: 10.1093/mmy/myaa100.
- [4] Schwartz IS, Muñoz JF, Kenyon CR, et al. Blastomycosis in Africa and the Middle East: A comprehensive review of reported cases and reanalysis of historical isolates based on molecular data. Clin. Infect. Dis. 2020;ciaa1100. Online ahead of print. DOI: 10.1093/cid/ ciaa1100.
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- [12] Shroufi A, Govender NP, Meintjes G, et al. Time to embrace access programmes for medicines: lessons from the South African flucytosine access programme. Int. J. Infect. Dis. 2020;95:459-61.
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- [14] Essel V, Tshabalala K, Ntshoe G, et al. A multisectoral investigation of a neonatal unit outbreak of *Klebsiella pneumoniae* bacteraemia at a regional hospital in Gauteng province, South Africa. S. Afr. Med. J. 2020;110(8):783-90.
- [15] Dramowski A, Velaphi S, Reubenson G, et al. National Neonatal Sepsis Task Force launch: supporting infection prevention and surveillance, outbreak investigation and antimicrobial stewardship in neonatal units in South Africa. S. Afr. Med. J. 2020;110(5):360-3.
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#### Technical reports/guidelines

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- GLASS Early Implementation Report. 2020. ISBN: 978-92-4-000558-7. Available from: <u>https://apps.who.int/iris/bitstream/hand</u> <u>le/10665/332081/9789240005587-eng.pdf?ua=1</u>

#### Conferences

- [1] International conferences: 2
- [2] National conferences: 3



# CENTRE FOR HIV AND STIs (CHIVSTI)





Prof Adrian Puren Centre Head

#### BACKGROUND

Sexually transmitted infections (STIs), including those caused by HIV types 1 and 2, remain a major public health problem in Africa. Published estimates of the Joint United Nations Programme on HIV/AIDS for 2020 show that South Africa has the highest burden of HIV infections, with recent estimates of 7.8 million people living with HIV.

CHIVSTI has a strong track record in the research disciplines of HIV virology, HIV immunology, HIV/STI epidemiology, HIV/STI diagnostics and HIV-STI interactions. It addresses the challenges of HIV and STI diseases through various programmes, including the following:

- Surveillance of disease burden and antimicrobial resistance
- Measurement of endpoint infections and detection
- Broadly neutralising antibodies as part of prophylactic HIV vaccine and antibody-mediated protection clinical trials
- Exploring an HIV 'cure' strategy
- Development and implementation of reference diagnostics and implementation science

CHIVSTI consists of the following four sections:

- HIV Virology
- Cell Biology
- HIV Molecular and Serology
- Sexually Transmitted Infections

The centre also provides a suitable academic environment for successful supervision of undergraduate and postgraduate students and postdoctoral fellows. The centre has well-established links and collaborations with various key national and international organisations in the field of HIV and STIs.

#### Surveillance

#### Congenital syphilis

During the period under review, the centre continued to implement enhanced congenital syphilis surveillance with support from the WHO. The enhanced surveillance involved the introduction of a case investigation form (CIF) to accompany the standard NMC case notification form (CNF). Both CNFs and CIFs were meant to be submitted by healthcare providers within seven days of making a diagnosis. Analysis of the surveillance data during Quarter 4 of the period under review found that, from January to December 2020, there were 373 clinical notifications of congenital syphilis notified to the NICD from all provinces in the country. The majority of notifications were from Gauteng (23.9%), KwaZulu-Natal (49.3%) and Western Cape (16.4%), together accounting for 89.3% of notifications. During all four quarters of 2020, there was a general trend towards an increase in cases. Among congenital syphilis cases with a CIF submitted (n=303), analysis for the prevention of congenital syphilis cascade was done. The cascade showed 88% of infants notified as cases had maternal evidence of a syphilis test before delivery, with 98% of them having a documented syphilis result, 90% being rapid plasma regain (RPR) positive, and 83.3% treated with at least one dose of benzathine penicillin.

However, there was some evidence of late screening and treatment, with the duration from testing to treatment being 37 days (interquartile range 2-129 days) and 43% delivered less than 28 days after the test. Since the release of the report, the NICD, in collaboration with the NDoH and its partners, has scaled up training of the congenital syphilis notification process to raise awareness of the condition and improve the quality of surveillance data. This training has been included in the sexual and reproductive health services package of training being rolled out by the NDoH. It is expected that the centre's congenital surveillance will provide data for evaluating the impact of the dual HIV/syphilis to be introduced in the 2021/22 fiscal year.

Aetiological surveillance of STI syndromes is essential for validating and updating the existing national STI syndromic management guidelines used at primary healthcare centres throughout the country. A critical component of the surveillance programme is monitoring antimicrobial susceptibility profiles for the emergence of extensively drug-resistant (XDR) *Neisseria gonorrhoeae*, resistant to extended-spectrum cephalosporins. Ceftriaxone-resistant gonorrhoeae is a Notifiable Medical Condition (Category 3). South Africa is one of few African countries to submit *Neisseria gonorrhoeae* antimicrobial resistance data annually to the WHO GLASS. In 2020, fixed sentinel sites for ongoing annual STI surveillance were established at high-volume primary healthcare centres in three key provinces (Gauteng, KwaZulu-Natal and Western Cape).

#### Paediatric HIV monitoring and evaluation

The centre supported the NDoH by analysing and reporting HIV-related data from the NHLS Data Warehouse. Reporting included secure online distribution, via the NICD's self-service portal, of results for action (RfA) reports as per the 2019 National HIV Guidelines, monthly reports on early infant diagnosis, paediatric and adolescent HIV viral load monitoring, and maternal prevention of mother-to-child transmission HIV viral load monitoring, and validation of UNAIDS 90-90-90 target achievement at the district level.

#### The 2019 Antenatal HIV Serosurvey results

The national antenatal HIV prevalence was estimated at 30.0% (95% CI: 29.4%–30.6%). This figure was 0.7% points lower than the prevalence reported in 2017 (30.7%, 95% CI: 30.1%–31.3%). The highest HIV prevalence was in KwaZulu-Natal (40.9%, 95% CI: 39.6%–42.3%) followed by Eastern Cape (36.5%, 95% CI: 35.2%–37.9%). The lowest overall HIV prevalence was in Western Cape at 17.9% (95% CI: 16.2%–19.7%).

HIV prevalence among the 15–24 year age group continued to show a steady decline – with prevalence declining from 11.2% to 10.3% (P value=0.07), and from 21.8% to 19.4% (P value <0.01) among the 15–19 year and 20–24 year age groups respectively between 2017 and 2019. Of the 11 321 HIV-positive pregnant women in the survey, 97.6% (11 046) already knew they were HIV-positive at the time of the survey, and of these, 96.0% (10 271) were already on antiretroviral therapy (ART) at the time of the survey.

The coverage of ART in the prevention of mother-to-child transmission (PMTCT) programme was high in all age groups. HIV prevalence among pregnant women has remained largely unchanged at around 30% since 2004. The consistent decline in HIV prevalence among young women (15–24 years) is encouraging, as this age group experiences a high rate of HIV incidence (1.5%) compared to their male counterparts (0.5%). The high PMTCT ART coverage, regardless of age group, shows the success of the PMTCT programme. Promising progress has been observed in the number of HIV-positive women initiating ART before pregnancy, although young women (15–24 years) were still less likely to know their HIV-positive status before pregnancy, compared to older women (>35 years).

#### **Outbreaks**

The centre responded to the COVID-19 outbreak. Staff were seconded to the Emergency Operations Centre from March 2020. The support to the COVID-19 response continued throughout the period under review.

#### **COVID-19** response

SARS-CoV-2 has been a significant focus of the HIV Virology Section in the past year. We adapted several existing assays for COVID-19 research, including serological assays using spike and receptor domain ELISAs, neutralisation assays and Fc effector assays. These assays supported an array of projects, including the investigation of convalescent plasma for treatment of severe disease and the measurement of immune correlates in SARS-CoV-2 infected longitudinal cohorts and vaccine trials, including the South African Ox1Cov-19 Vaccine VIDA-Trial trial.

The section contributed to the national response to COVID-19, performing South African Medical Research Council (SAMRC)-funded research to assess the durability and kinetics of neutralising responses to SARS-CoV-2. The Section also actively contributed to the research to address 501Y.V2, by addressing the potential reduced sensitivity of new variants to infection and vaccine-induced antibodies to inform the possibility of increased reinfection and reduced vaccine efficacy.

#### Core activities as an endpoint laboratory for the HIV Vaccine Trials Network (HVTN)

CHIVSTI conducts validated endpoint antibody and molecular diagnostic assays for the HVTN. The HIV Virology Section played a key role in generating the data for the antibody-mediated prevention (AMP) trial conducted in southern Africa (HVTN 703), which ended in August 2020. The data were critical for assessments of neutralisation sieving effects as a measure of protective efficacy and assisted in estimating protective neutralisation titres against HIV infection. The laboratory has also contributed to the assessments of antibody levels in the CAPRISA 012 trial that is testing CAP256-VRC26.25 for HIV prevention, led by Prof Salim Abdool Karim.

#### **Policy contributions**

During the period under review, CHIVSTI made the following contributions:

- Standard Treatment Guidelines and Essential Medicines List for Primary Healthcare (Chapter 12 Sexually Transmitted Infections)
- Standard Treatment Guidelines and Essential Medicines List for Adult Hospital Level of Care (Chapter 25 Sexually Transmitted Infections managed at Secondary Level of Care)
- World Health Organization 2021 Guidelines for the Management of Symptomatic Sexually Transmitted Infections

#### **Diagnostic services**

During the period under review, CHIVSTI made the following contributions:

- Specialised reference testing (in-house and commercial PCR assays) for persistent (non-resolving) STI syndromes, child sexual abuse and other complicated STI cases
- · Verification of Neisseria gonorrhoeae culture identification and antimicrobial susceptibility testing in selected cases
- Genotypic and phenotypic acyclovir-resistance testing in herpes simplex virus 2
- Treponema pallidum molecular testing of vitreous fluid for the diagnosis of syphilitic uveitis
- Molecular testing for *Klebsiella granulomatis* (granuloma inguinale)
- Mycoplasma genitalium macrolide and fluoroquinolone resistance testing

#### **Research activities**

48

#### Antibody isotype switching as a mechanism to counter HIV neutralization escape

NICD investigators: C Scheepers, V Bekker, SI Richardson, B Oosthuysen, T Moyo, P Kgagudi, D Kitchin, M Nonyane, B Mabvakure, BE Lambson, A Ismail, L Morris, PL Moore

**Collaborators:** C Anthony, T York, D Mielke, C Williamson (University of Cape Town), NJ Garrett, SS Abdool Karim (CAPRISA), Z Sheng, L Shapiro (Columbia University)

Neutralising antibodies (nAbs) to highly variable viral pathogens show remarkable diversification during infection, resulting in an 'arms race' between virus and host. Studies of nAb lineages have shown how somatic hypermutation (SHM) in immunoglobulin (Ig)variable regions enables maturing antibodies to neutralise emerging viral escape variants. However, the Ig-constant region (which determines isotype) can also influence epitope recognition. Here, we use longitudinal deep sequencing of an HIV-directed nAb lineage, CAP88-CH06, and identify several co-circulating isotypes (IgG3, IgG1, IgA1, IgG2, and IgA2), some of which share identical variable regions. First, we show that IgG3 and IgA1 isotypes are better able to neutralise longitudinal autologous viruses and epitope mutants than can IgG1. Second, detrimental class-switch recombination (CSR) events that resulted in reduced neutralisation can be rescued by further CSR, which we term 'switch redemption'. CSR thus represents an additional immunological mechanism to counter viral escape from HIV-specific antibody responses.

#### SARS-CoV-2 501Y.V2 escapes neutralisation by South African COVID-19 donor plasma

NICD investigators: CK Wibmer, F Ayres, T Hermanus, M Madzivhandila, P Kgagudi, BE Lambson, S Meiring, A von Gottberg, C Cohen, L Morris, JL Bhiman, PL Moore

**Collaborators:** M Vermeulen, K van den Berg (South African National Blood Service), T Rossouw, M Boswell, V Ueckermann (University of Pretoria)

SARS-CoV-2 501Y.V2 (B.1.351), a novel lineage of coronavirus causing COVID-19, contains substitutions in two immunodominant domains of the spike protein. Here, we show that pseudovirus expressing 501Y.V2 spike protein escaped three classes of

therapeutically relevant antibodies. This pseudovirus also exhibits substantial to complete escape from neutralisation, but not binding, by convalescent plasma. These data highlight the prospect of reinfection with antigenically distinct variants and foreshadows reduced efficacy of spike-based vaccines.

#### Two randomised trials of neutralising antibodies to prevent HIV-1 acquisition

#### NICD investigators: L Morris, S Takuva

**Collaborators:** L Corey, PB Gilbert, M Juraska, ST Karuna, S Edupuganti, NM Mgodi, J Hural, MJ McElrath, DJ Donell, N Kochar, AK Randhawa, AC deCamp, E Rudnicki, C Bentley (Fred Hutchinson Cancer Research centre), DC Montefiori (Duke University), Y Huang (Xiamen University), P Gonzales (Hospital Nacional Dos de Mayo), R Cabello (Asociacion Civil Via Libre), C Orrell (Desmond Tutu HIV Foundation), JR Lama (Asociación Civil Impacta Salud y Educación), F Laher, EM Lazarus (Perinatal HIV Research Unit), J Sanchez (Universidad Nacional Mayor de San Marcos), I Frank (University of Pennsylvania), J Hinojosa (Hospital de Manises), ME Sobieszczyk (Columbia University), KE Marshall (University of Sussex), PG Mukwekwerere (University of Zimbabwe), J Makhema (Botswana-Harvard AIDS Institute Partnership), LR Baden, N Espy (Harvard Medical School), JI Mullins, JG Kublin (University of Washington), C Williamson (University of Cape Town), MMG Lorenzo, DN Burns (National Institute of Allergy and Infectious Diseases), E Piwowar-Manning (Johns Hopkins University), N Sista, P Andrew (FHI 360), G Gray (South African Medical Research Council), JE Ledgerwood, JR Mascola (Vaccine Research centre), MS Cohen (University of North Carolina)

Whether a broadly neutralising antibody (bnAb) can be used to prevent human immunodeficiency virus type 1 (HIV-1) acquisition is unclear. We enrolled at-risk cisgender men and transgender persons in the Americas and Europe in the HVTN 704/HPTN 085 trial and at-risk women in sub-Saharan Africa in the HVTN 703/HPTN 081 trial. Participants were randomly assigned to receive infusions of a bnAb (VRC01) at a dose of either 10 or 30 mg per kilogram (low-dose group and high-dose group, respectively) or placebo, for ten infusions in total every eight weeks. HIV-1 testing was performed every four weeks. The VRC01 80% inhibitory concentration (IC80) of acquired isolates was measured with the TZM-bl assay. VRC01 did not prevent overall HIV-1 acquisition more effectively than placebo, but analyses of VRC01-sensitive HIV-1 isolates provided proof-of-concept that bnAb prophylaxis can be effective.

#### Efficacy of the ChAdOx1 nCoV-19 COVID-19 vaccine against the B.1.351 variant

#### NICD investigators: JN Bhiman, A Ismail, CK Wibmer, PL Moore

**Collaborators:** SA Madhi, V Baillie, CL Cutland, C Briner, G Kwatra, M Malahleha, A Moultie, C Taoushanis, A Thombrayil, A Izu (University of the Witwatersrand), M Voysey, P Aley, T Lambe, S Rhead, AJ Pollard (University of Oxford), AL Koen, S McKenzie (South African Medical Research Council), L Fairlie, E Horne, M Masenya, F Patel, S van Eck (Wits Reproductive Health and HIV Institute), SD Padayhachee, M Masilela, K Molapo (Setshaba Research centre), K Dheda, SL Barnabas (University of Cape Town), QE Bhorat, AE Bhorat (Soweto Clinical Trials centre), K Ahmed (King's College London), S Bhika (University of Otago), J du Plessis (North-West University), A Jose (Manipal College of Pharmaceutical Sciences), M Laubscher, S Oelofse (University of Cape Town), S Pillay, H Tegally, T de Oliveira (KRISP), M Groenewald, L Rossouw (Stellenbosch University), NM Durham, EJ Kelly, TL Villafana (AstraZeneca Biopharmaceuticals), S Gilbert (Jenner Institute), H Rodel, SH Hwa, A Sigal (Africa Health Research Institute)

Assessment of the safety and efficacy of vaccines against SARS-CoV-2 in different populations is essential, as is investigation of the efficacy of the vaccines against emerging SARS-CoV-2 variants of concern, including the B.1.351 (501Y.V2) variant first identified in South Africa. We conducted a multicentre, double-blind, randomised controlled trial to assess the safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) in people not infected with HIV in South Africa. Participants 18 to less than 65 years of age were assigned in a 1:1 ratio to receive two doses of vaccine containing 5×1010 viral particles or placebo (0.9% sodium chloride solution) 21 to 35 days apart. Serum samples obtained from 25 participants after the second dose were tested by pseudovirus and live-virus neutralisation assays against the original D614G virus and the B.1.351 variant. The primary endpoints were safety and efficacy of the vaccine against laboratory-confirmed symptomatic coronavirus 2019 illness (COVID-19) more than 14 days after the second dose. Between 24 June and 9 November 2020, we enrolled 2026 HIV-negative adults (median age, 30 years). A total of 1 010 and 1 011 participants received at least one dose of placebo or vaccine, respectively. Both the pseudovirus and the live-virus neutralisation assays showed greater resistance to the B.1.351 variant in serum samples obtained from vaccine recipients than in samples from placebo recipients. In the primary endpoint analysis, mild-to-moderate COVID-19 developed in 23 of 717 placebo recipients (3.2%) and in 19 of 750 vaccine recipients (2.5%), for efficacy of 21.9% (95% confidence interval [CI], –49.9 to 59.8). Among the 42 participants with

COVID-19, 39 cases (92.9%) were caused by the B.1.351 variant. Vaccine efficacy against this variant analysed as a secondary endpoint was 10.4% (95% Cl, –76.8 to 54.8). The incidence of serious adverse events was balanced between the vaccine and placebo groups. A two-dose regimen of the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate COVID-19 due to the B.1.351 variant.

#### Paediatric HIV functional cure and early ART

NICD investigators: CTTiemessen, M Paximadis, D Schramm, S Shalekoff, GG Sherman

**Collaborators:** L Kuhn, E Abrams, S Morris, AJ Yates, L Dziobek-Garrett, AJN Anelone, Y Shen, S Shiau (Columbia University), A Coovadia (ESRU, RMMCH), K Technau (ESRU), R Strehlau, M Burke, A Coovadia (ESRU), F Patel (WHRI), J Schroter, RJ de Boer (Utrecht University) on behalf of the LEOPARD study team and the EPIICAL Consortium

The NIH-funded LEOPARD clinical trial of very early ART of in utero-infected infants completed enrolment and follow up of patients at the end of March 2019. This trial was designed to better understand viral latency in early treated HIV-infected children in order to lead to more effective treatment strategies for children with the ultimate goal of achieving functional cure or viral remission (funded as a NIH U01 grant: PI Louise Kuhn, RSA PIs CT Tiemessen, R Strehlau).

One study found that pre-ART viral loads and CD4 parameters in utero-infected infants associated with these same parameters in their mothers. In our current setting of high maternal ART coverage, pre-ART infant viral loads are low, and disease severity in infected infants may be masked by maternal ART taken during pregnancy. Another study utilised mathematical modelling to describe viral dynamics in very early treated infants in the first year of life (among 43 who had consistent viral load decline to <20 RNA copies/ ml). This study concluded that HIV dynamics was similar to that found in adults and other infant groups, although the lifespans of short-lived cells appeared longer. The latter finding requires further verification, as might be explained by poor drug efficacy and/ or less effective immune responses in neonates, or insufficient sampling during the rapid viral load decline phase. Furthermore, neonates with higher pretreatment CD4% or lower pretreatment viral load trended towards achieving viral suppression more rapidly. Collectively, findings from the LEOPARD study have thus far demonstrated the feasibility and the importance of providing very early ART in newborns, and have raised the need to consider additional interventions to achieve virological control on ART and towards the future goal of achieving post-treatment functional cure or remission in children.

# Demographic and behavioural risk factors associated with reduced susceptibility of *Neisseria gonorrhoeae* to first-line antimicrobials in South African men with gonococcal urethral discharge

#### NICD investigators: R Kularatne, T Kufa, L Gumede, V Maseko

Among 685 men with gonococcal urethral discharge, almost 30% practiced oral sex and were at risk for pharyngeal gonococcal infection. In univariate analysis, male circumcision (OR 0.69; 95%CI 0.49-0.99), and recent sex outside the country (OR 1.83; 95%CI 1.21-2.76) were significantly associated with having a Category 1 *N. gonorrhoeae* isolate. In a multivariable model, only sex outside the country increased the odds of being infected with a decreased susceptible/resistant *N. gonorrhoeae* isolate (OR 1.64; 95%CI 1.05-2.55). These findings warrant the intensification of *N. gonorrhoeae* AMR surveillance among recently-arrived migrant and overseas traveller populations, as well as the inclusion of extragenital specimens for *N. gonorrhoeae* AMR surveillance purposes.

#### Treponema pallidum macrolide resistance and molecular epidemiology in southern Africa, 2008-2018

#### NICD investigators: I Venter, E Muller, R Kularatne

We determined the prevalence of 23S rRNA macrolide resistance-associated point mutations in 135 *Treponema pallidum*-positive surveillance specimens from Botswana, Zimbabwe and South Africa between 2008 and 2018. A significant increase in the prevalence of A2058G macrolide resistance-associated point mutations was observed in specimens collected after 2015. There was a high level of molecular heterogeneity among *T. pallidum* strains with strain type 14d/f being predominant. There was a significant association between macrolide resistance and strain types 14d/f and 14d/g, but no association between macrolide-resistant *T. pallidum* and HIV co-infection. The majority of South African *T. pallidum* strains, as well as strains containing the A2058G mutation, belonged to the SS14-like clade.

#### Phenotypic and genotypic acyclovir (ACV) resistance surveillance of genital herpes simplex virus-2 (HSV-2) in South Africa NICD investigators: E Muller, V Maseko, R Kularatne

Phenotypic and genotypic ACV antiviral susceptibility profiles were compared, for 67 HSV-2 positive surveillance specimens collected from a Johannesburg sentinel surveillance facility between 2018 and 2020. No thymidine kinase (TK) resistance-associated mutations were detected, and all 52 cultivable HSV-2 isolates were susceptible to ACV with IC50 <2 mg/L. Five TK amino acid changes of unknown significance were therefore grouped as natural polymorphisms. Our data will contribute to the establishment of a comprehensive database of HSV acyclovir resistance-associated mutations and polymorphisms.

# Molecular characterisation and detection of fluoroquinolone and macrolide resistance determinants in *Mycoplasma genitalium*, South Africa (2015-2018).

#### NICD investigators: P Mahlangu, E Muller, R Kularatne

Between 2015 and 2018, 196 *M. genitalium* positive genital discharge specimens were collected from males and females presenting to sentinel surveillance sites across all nine provinces of the country. Of these, 1.7% (3/180) specimens had detectable macrolide resistance-associated mutations. There were no detectable fluoroquinolone resistance-associated mutations. Ongoing *M. genitalium* macrolide resistance surveillance is essential, as an increasing prevalence of macrolide resistance will prompt a revision of STI management guidelines.

#### Teaching and training

CHIVSTI staff provided and contributed to the following teaching and training activities during the period under review:

- Teaching in the School of Public Health at the University of the Witwatersrand and South African Field Epidemiology Programme continued. Lectures in HIV surveillance were delivered to the MSc and MPH students
- The centre contributed to the three-week course for NICD-specific training of pathology registrars. Areas covered included both HIV and STIs, with a focus on areas that registrars would not usually encounter in routine settings

#### Postgraduate students

A total of 25 students was enrolled for postgraduate studies as follows:

- MPH: 1
- BSc Hons: 1
- MSc: 13
- PhD: 10

Four students graduated in the period under review. These comprised the following:

- MMed: 1
- BSc Hons: 1
- PhD: 2

#### Professional development, awards and honours

- Prof Penny Moore was awarded an B1 rating from the NRF
- Prof Penny Moore was appointed as a member of the South African Ministerial Advisory Committee on Vaccines, and served on both the Technical Working Group on Variants and Workstream One for the V-MAC
- Dr Simone Richardson was awarded the Norman Letvin Early Career Investigator Award from the Collaboration for AIDS Vaccine
  Discovery (CAVD)
- Dr Simone Richardson was awarded the L'Oreal/UNESCO Women in Science Young Talents Fellowship in December 2020. This
   was for her work on Fc Effector Function in SARS-CoV-2 vaccination and infection
- MSc student, Itai Ncube, won the prize for best student poster in Molecular and Comparative Biosciences during the Wits Faculty of Health Sciences Research Day held on 15 October 2020

#### **Research output**

#### **Journal articles**

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#### Conferences

- [1] International conferences: 25
- [2] National conferences: 11
- [3] Local conferences: 7

#### **Grant funding**

Funding to support the centre's work was obtained from the following organisations:

- South Africa Medical Research Council (SAMRC)
- National Health Laboratory Service Research Trust (NHLS RT)
- National Research Foundation Incentive Funding for Rated Researchers (NRF)
- National Research Foundation Professional Development Programme (NRF)
- Department of Science and Innovation (DSI)/National Research Foundation (NRF) Chair of HIV Vaccine Translational Research
- Poliomyelitis Research Foundation (PRF)
- National Institutes of Health (NIH)
- European and Development Countries Clinical Trials Partnership (EDCTP)
- President's Emergency Plan for AIDS Relief (PEPFAR)



CENTRE FOR RESPIRATORY DISEASES AND MENINGITIS (CRDM)





#### BACKGROUND

The Centre for Respiratory Diseases and Meningitis (CRDM) is a resource of surveillance, diagnostics, expertise and research in the field of communicable respiratory diseases and meningitis for South Africa and the African continent. The centre generates data and provides expertise related to respiratory diseases and meningitis of public health importance to the NDoH and healthcare providers, as well as regional and international collaborators, to assist with the planning of public health policies and programmes, and response to respiratory and meningitis disease outbreaks. CRDM is also a source of capacity building and formal training within South Africa and the African region.

CRDM continued with response activities to the COVID-19 pandemic, as well as its core function of surveillance through syndromic and laboratory-based surveillance programmes. Syndromic surveillance programmes included the pneumonia and influenza-like illness (ILI) surveillance systems in public hospitals and primary healthcare clinics, as well as the private, general practitioner network (Viral Watch).

The focus of these programmes is to describe the burden, seasonality and characteristics of disease caused by influenza virus, respiratory syncytial virus (RSV) and *Bordetella pertussis*. Laboratory-based surveillance programmes include invasive pneumococcal and meningococcal disease, with a focus on outbreak detection and the impact of interventions.

The centre is responsible for six Category 1 notifiable medical conditions (NMCs): acute rheumatic fever, COVID-19, diphtheria, meningococcal disease, pertussis and respiratory disease caused by a novel respiratory pathogen, as well as two Category 2 NMCs: *Haemophilus influenzae* type b (Hib) disease and legionellosis. Throughout the period under review, the centre provided ongoing laboratory and epidemiology support to the NDoH for suspected cases of diphtheria, pertussis, legionella and meningococcal disease.

#### Surveillance

#### Group for Enteric Respiratory and Meningitis Surveillance – South Africa (GERMS-SA)

This programme conducts national, laboratory- and population-based active surveillance for invasive pneumococcal and Hib disease to evaluate the ongoing impact of the pneumococcal conjugate vaccine (PCV) and the Hib conjugate vaccine.

The centre also contributed data on numbers and serogroups of *Neisseria meningitidis* and supported diagnostic testing and outbreak response for suspected cases of meningococcal disease. GERMS-SA surveillance data contributed to a global study describing the sustained reduction in invasive *N. meningitidis*, *H. influenzae* and *Streptococcus pneumoniae* disease, which coincided with country-specific containment measures implemented in response to the COVID-19 pandemic. Surveillance for group A and group B streptococci was enhanced from April 2020, where clinical data at selected sites were collected to complement the phenotypic and genotypic investigation performed on the isolates. CRDM furthermore participated in the Baby GERMS-SA Neonatal Surveillance at six enhanced surveillance sites to understand the burden and aetiological factors of neonatal sepsis occuring at secondary level institutions.

#### Syndromic surveillance for respiratory illness

The National Pneumonia Surveillance Programme (NPSP) continued to operate in five provinces. Surveillance is conducted for severe respiratory illness (SRI) to determine pathogens of public health importance. Another site, Tintswalo Hospital in Mpumalanga, was added in February 2021. Systematic surveillance for outpatient influenza-like illness (ILI) and suspected pertussis is ongoing at outpatient public sector clinics in four provinces. An ILI site was re-established in November 2020 in Agincourt, Mpumalanga. The Viral Watch ILI surveillance network of general practitioners continues to operate in eight provinces, providing data on influenza virus circulation and strains for vaccine input, timing of the influenza season and annual estimates of influenza vaccine effectiveness.

The NPSP and ILI programmes incorporate testing for additional emerging pathogens when required. These programmes aim to describe the burden, risk groups, seasonality and characteristics of influenza, RSV and *Bordetella pertussis*, and were expanded in April 2020 to include systematic surveillance for COVID-19 in South Africa. Additional studies allow the investigation of factors associated with severity of illness and effectiveness of vaccine programmes. Similar to data from other southern hemisphere countries, surveillance data from these programmes showed an unprecedented decline in influenza circulation during the 2020 winter season, and a decrease in circulation of RSV and *B. pertussis* partly due to widespread implementation of measures to mitigate transmission of SARS-CoV-2. The programmes were able to describe community transmission of SARS-CoV-2 in South Africa.

#### Outbreaks

#### COVID-19

CRDM played a leading role in the response to the COVID-19 pandemic in South Africa. CRDM supported the National COVID-19 Incident Management Team, particularly in the Epidemiology and Laboratory streams. The centre produced regular COVID-19 surveillance reports, including but not limited to the Weekly Epidemiological Brief, the Weekly Testing Summary and the COVID-19 reproductive number. A number of detailed epidemiologic reports were also published in the Communicable Diseases Surveillance Bulletin. The CRDM laboratory set up a SARS-CoV-2 diagnostic PCR test to detect the first cases of COVID-19 in the country. Together with the NDOH and other partners, the centre has contributed to ongoing review of COVID-19 guidelines for case finding, diagnosis, management and public health response in South Africa. Additional guidelines were also developed for different sectors, such as education.

From 26 January 2020 to mid-March 2020, CRDM was the only SARS-CoV-2 testing laboratory nationally and regionally, while laboratories in the public and the private sector prepared to rapidly expand laboratory testing capacity in both sectors. The CRDM laboratory was appointed as a WHO COVID-19 international regional reference laboratory and provided technical support and training to many African countries. During 2020, CRDM, in collaboration with other centres within the NICD, expanded SARS-CoV-2 testing capacity to include serology (with in-house and commercial assays) and SARS-CoV-2 viral culture. In addition, CRDM staff consulted on numerous expert committees and working groups for WHO, Africa Centres for Disease Control (Africa CDC) and WHO African Region (AFRO). CRDM was also a founding member of the Network for Genomic Surveillance in South Africa (NGS-SA), using routine surveillance sequencing of SARS-CoV-2 to assist in the detection of new SARS-CoV-2 variants as the pandemic progressed in South Africa and regionally.

Additionally, the centre obtained funding to conduct a range of COVID-19-related research activities, mainly focused on the areas of burden of disease, transmission, sero-epidemiology and viral sequencing. CRDM staff participated in numerous media engagements aimed at informing the public about COVID-19 risks and how to reduce transmission, as well as to provide updates on the epidemic progression. Cheryl Cohen and Anne von Gottberg served on the COVID-19 Ministerial Advisory Committee. CRDM staff contributed to the Emergency Operations Centre and National Incident Management Team by, amongst other, providing data, epidemiology, laboratory and clinical expertise.

#### **Policy contributions**

Data on the COVID-19 pandemic were used to advise several policy recommendations such as those of the Ministerial Advisory Committee and NDoH, including topics such as case clinical management and implementation of non-pharmaceutical interventions. Influenza vaccination guidelines were updated in the light of the SARS-CoV-2 pandemic.

#### **Diagnostic services**

CRDM routinely offers molecular testing for several respiratory and meningitis-causing pathogens using a variety of in-house and commercial PCR assays, including meningitis/encephalitis, respiratory and pneumonia multi-pathogen panels. The centre also offers serotyping/grouping of bacterial pathogens (where applicable) and subtyping for influenza and RSV.

#### **Research activities**

## Estimated impact of the pneumococcal conjugate vaccine on pneumonia mortality in South Africa, 1999 through 2016: an ecological modelling study

Kleynhans J, Tempia S, Shioda K, et al. PLoS Medicine. 2021 Feb;18(2):e1003537.

National death registration data in South Africa from 1999 to 2016 were used to assess the impact of PCV introduction on all-cause pneumonia mortality in all ages using a synthetic control approach. Compared to number of deaths expected, we estimated a 22% to 33% reduction in pneumonia mortality in children aged one month to 18 years in 2012 to 2016.

#### A cost-effectiveness analysis of South Africa's seasonal influenza vaccination programme

Edoka I, Kohli-Lynch C, Fraser H, et al. Vaccine. 2021 Jan;39:412-22.

The study assessed the cost-effectiveness of South Africa's seasonal influenza vaccination programme. Influenza vaccination was cost-effective in pregnant women, people living with HIV, people with other underlying medical conditions and people aged  $\geq$ 65 years. The highest number of cases, medical consultations and deaths, averted through vaccination, were in people living with HIV and those with other underlying medical conditions.

#### Influenza economic burden among potential target risk groups for immunization in South Africa, 2013-2015

Tempia S, Moyes J, Cohen AL, et al. Vaccine. 2020 October;38:7007-14.

This study estimated that the cost of influenza-associated illness among risk groups for severe influenza accounted for 52.1% (\$140.9/\$270.5 million) of the total influenza-associated illness cost (for the entire population of South Africa), 45.2% (\$52.2/\$115.5 million) of non-medically attended illness costs, 43.3% (\$46.7/\$107.9 million) of medically-attended mild illness costs and 89.3% (\$42.0/\$47.1 million) of medically-attended severe illness costs. This study provides the foundation for future studies on the cost-effectiveness of influenza immunization among risk groups.

#### Influenza disease burden among potential target risk groups for immunization in South Africa, 2013-2015

Tempia S, Walaza S, Moyes J, et al. Vaccine. 2020 June;38:4288-97.

This study estimated that individuals in risk groups for severe influenza accounted for 43.5%, 86.8% and 94.5% of influenza-associated mild, severe-non-fatal and fatal illness episodes, respectively. Influenza immunisation of the selected risk groups has the potential to prevent a substantial number of influenza-associated severe illness. Nonetheless, because of the high number of individuals at risk, South Africa may need to further prioritise interventions among at-risk populations due to financial resources constraints. Cost-burden and cost-effectiveness estimates may assist with further prioritisation.

# Human surveillance and phylogeny of highly pathogenic avian influenza A(H5N8) during an outbreak in poultry in South Africa, 2017

Valley-Omar Z, Cloete A, Pieterse R, et al. Influenza and Other Respiratory Viruses. 2020 May;14:266-73.

During an outbreak of highly pathogenic influenza A(H5N8), active surveillance was conducted for the transmission of A(H5N8) to humans working with infected birds during the South African outbreak. Absence of A(H5N8) in humans with occupational exposure, and no clear impression of molecular adaptation for mammalian infection, suggest that this avian pathogen continues to be a low risk human pathogen.

#### Teaching registrar and training

CRDM staff provided and contributed to the following teaching and training activities during the period under review:

- Training of registrars and doctors specialising in infectious diseases
- Ongoing training at various sites for surveillance and COVID-19 special studies
- Ongoing advisory, technical and epidemiological support in-country and on the continent for the COVID-19 pandemic
- Invited talks/presentations: 14
- · Academic lectures: 4

#### Postgraduate students

Nine students were enrolled for postgraduate studies as follows:

- MSc: 3
- PhD: 6

One staff member graduated with a PhD.

#### **Research outputs**

#### Journal articles

- [1] Madhi SA, Nzenze SA, Nunes MC, et al. Residual colonization by vaccine serotypes in rural South Africa four years following initiation of pneumococcal conjugate vaccine immunization. Expert Rev. Vaccines. 2020 April;19:383–93.
- [2] Wang X, Li Y, O'Brien KL, et al. Global burden of respiratory infections associated with seasonal influenza in children under five years in 2018: a systematic review and modelling study. Lancet Glob. Heal. 2020 April;8:e497–e510.
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- [15] Pelkonen T, Urtti S, Dos Anjos E, et al. Aetiology of bacterial meningitis in infants aged <90 days: prospective surveillance in Luanda, Angola. Int. J. Infect. Dis. 2020 Aug;97:251–7.
- [16] Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic–United States, Australia, Chile, and South Africa, 2020. Morb. Mortal. Wkly. Rep. 2020 Sep;69:1305–09.
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- [33] Bennett JC, Hetrich MK, Quesada MG, et al. Changes in invasive pneumococcal disease caused by *Streptococcus pneumoniae* serotype 1 following introduction of PCV10 and PCV13: findings from the PSERENADE project. Microorganisms. 2021 Mar;9(4):696. DOI: 10.3390/microorganisms9040696.

#### Conferences

[1] International or local conferences: 8

# CENTRE FOR TUBERCULOSIS (CTB)





#### BACKGROUND

The core functions of the Centre for Tuberculosis (CTB) are to execute TB surveys and population research, conduct laboratory-based public health surveillance of TB, and contribute to the advancement of TB diagnostics, epidemiology and treatment in South Africa. In addition, the centre houses the National TB Reference Laboratory and is endorsed by the WHO as a Supranational Reference Laboratory for the region since 2016 - contributing toward both national and global TB policies and guidelines in collaboration with the NDOH and WHO.

The period under review was largely dominated by COVID-19, with key staff providing critical support for the institute's COVID-19 pandemic response by serving on the Incident Management Team. This involved compiling daily commentary reports to the Health Ministry, the Ministerial Advisory Committee and the National COVID-19 Command Council (NCCC), and coordinating the South African COVID-19 Modelling Consortium (SACMC). Despite the COVID-19 disruptions, the centre remained active, continuing its core duties and function during this period.

#### Surveillance

Routine surveillance reporting and request for action alerting (RFA)

Surveillance findings continue to be regularly analysed and reported to the national and provincial TB programmes. The weekly RfA reports cover both drug-susceptible and drug-resistant TB. Integrating the NHLS laboratory data and EDR.web has been developed, allowing transmission of data between the two data systems. This will assist to accurately estimate and monitor the total burden of drug-resistant TB in South Africa at a patient level. Quarterly reporting of the number of TB cases (drug-susceptible and drug-resistant) nationally, and further stratified by province and sub-district, are ongoing, with automated reports being emailed to the relevant stakeholders at regular intervals.

#### The impact of the COVID-19 epidemic on the laboratory investigations for TB

The COVID-19 pandemic and associated public health restrictions disrupted routine health services, including TB services, in many countries. The impact of the COVID-19 epidemic and public health restrictions on laboratory investigations and diagnosis of TB in South Africa was therefore investigated.

The CTB provided the National TB Programme with bi-weekly analysis of Xpert TB testing volumes, Xpert positive tests, positivity rate and rifampicin resistant rate to support the TB COVID-19 recovery plan. Xpert MTB/RIF Ultra (Xpert) TB testing volumes declined immediately after the implementation of the COVID-19 Level-5 lockdown in late March 2020, and remained substantially below the lower forecast confidence bound through August 2020. While there has been a partial recovery in Xpert TB testing volumes after the end of the first COVID-19 wave, September 2020 testing volumes have remained relatively subdued (Figure 1 and Figure 2).



**Figure 1:** Daily Xpert tuberculosis testing rates (navy), segmented linear regression models (green, yellow, teal and red, light green and light blue)), and 7-day smoothed COVID-19 daily cases per 100,000 population for South Africa (black dash) for the period 3 February to 1 May 2021. Grey dashed vertical lines indicate transitions between restriction levels.



Figure 2: Monthly Xpert TB tests from January 2020 to April 2021.

#### Modernising TB surveillance

The updated NMC legislation at the end of 2017 has seen significant advancement of the new system managed by the NICD. The development of the TB module on the NMC system has also been an important advancement on the public health surveillance and response front, and will provide facility-level access to the weekly alerts, and provide these on a daily basis. The application allows for near-real-time clinical notifications, and a push-based platform that provides the RfA information straight into the platform and accessible across the country and worldwide.

The landing page of the NMC TB module is shown in Figure 3. Registered users will now have access to this information to ensure that a public heath response is activated, while also allowing robust monitoring and evaluation to be automated by monitoring initial loss to follow up on a daily basis, and by providing exception notifications when actions have not been taken. Implementation has been delayed due to the COVID-19 pandemic. However, engagement with the NDoH and piloting was initiated. A phased piloting approach was performed, with the initial phase being internal testing within the organisation. In brief, testing assessed logging in, capturing a new case, editing an existing a case and being able to generate a report. During this phase, several technical bugs were identified and resolved. The second phase of the pilot is currently ongoing, with ten facility-level staff assessing the module to identify any further refinement required. The third phase will expand to several high-throughput healthcare facilities.



Figure 3: The NMC surveillance system landing page for TB.

#### Specialised Reference Mycobacteriology – National and Supranational Reference Laboratory activities

#### National bedaquiline emergent resistance surveillance

Emergence of bedaquiline (BDQ) resistance is a potential threat to its use for treatment with current and future regimens. As part of the WHO recommendations, and now also incorporated into the South African policy, is surveillance for BDQ resistance. All BDQ initiation sites have been submitting samples for baseline and follow-up resistance testing for BDQ.

Findings for the period 2015 to 2019, which included 8 041 patients (Figure 4) showed the following: Bedaquiline resistance prevalence was 3.8% (76/2023; 95%CI: 2.9%-4.6%) and associated with prior exposure to bedaquiline/clofazimine (odds ratio (OR) 7.1; 95%CI: 2.3-21.9) and RR/MDR-TB, with additional resistance to either fluoroquinolones or injectable drugs (pre-XDR-TB; OR 4.2, 95%CI: 1.7-10.5) or both (XDR-TB; OR 4.8, 95%CI: 2.0-11.7). Rv0678 mutations were the sole genetic basis of phenotypic resistance. Baseline resistance could be attributed to prior bedaquiline/clofazimine exposure in 5.3% (4/76) and primary transmission in 8.3% (6/72) of the remainder. Genetic analysis did not show primary transmission to be the dominant route (8.9%; 6/72), nor was prior exposure to BDQ/ CFZ a major contributor (5.3%; 4/76); although prior exposure to BDQ/CFZ was a significant risk factor (OR 7.1). Successful treatment

outcomes were lower among those with bedaquiline resistance at baseline (OR 0.5; 95%Cl: 0.3-1). Resistance on treatment developed in 2.3% (16/695), at a median of 90 days (IQR: 62–195) and 12/16 were pre-XDR/XDR.



**Figure 4:** Histogram over time of patients on a bedaquiline- or non-bedaquiline-based regimen compared with the first bedaquiline surveillance sample.

#### Proficiency testing scheme

Proficiency testing panels for second-line drugs susceptibility testing (including BDQ) were prepared by the centre and sent to the NHLS laboratories performing DRTB reflex testing. All participating laboratories were deemed proficient for second-line LPA, phenotypic drug susceptibility testing for levofloxacin, linezolid and bedaquiline. The Port Elizabeth laboratory is the latest laboratory to be deemed proficient in BDQ testing, and has since started routine testing of BDQ. As no formal kit for BDQ testing is available yet, prepared BDQ drug aliquots are shipped twice a year to the laboratories to enable testing locally. This has significantly improved the turn-around times for second-line phenotypic drug susceptibility testing (i.e. testing for levofloxacin, linezolid and BDQ).

#### Advancing diagnostics, epidemiology and treatment

As part of the centre's function to advance diagnostics, epidemiology and treatment, several new cutting-edge diagnostic technologies were evaluated during the period under review. These include the Xpert MTB/XDR, GeneXpert OMNI, Hain Fluorotype and BDMAX platforms for the rapid molecular detection of *M. tuberculosis* and accompanying drug resistance. Data generated were submitted to the WHO for review and used for the recent recommendations of these molecular assays. The centre also initiated assessments of next-generation sequencing technologies (NGS) for diagnostic utility in predicting drug resistance and molecular epidemiological surveillance of transmission networks, as well as an early warning system for outbreak detection in two high-burden districts in South Africa. Evaluation of targeted NGS as a potential diagnostic tool for genomic drug susceptibility prediction to current, new and repurposed drugs is in progress.

#### Regional support

On the regional front, the centre has provided support to Namibia in terms of performing additional drug susceptibility testing for patients who have a poor response to a drug-resistant TB regimen, as well as to Angola in preparing the logistic and operational detail for their National TB Drug Resistance Survey.

#### **Policy contributions**

The centre has had a busy period with contributions to recently published WHO guidelines and policies. It was involved in the review the WHO Operational Handbook on Tuberculosis: Rapid Diagnostics for Tuberculosis Detection. The centre also participated in the Guideline Development Group Meeting for Nucleic Acid Amplification Tests to Detect TB and DR-TB, which resulted in the endorsement of new nucleic acid amplification tests to detect TB and DR-TB. Rapid communications of the findings were released in January 2021, with the formal guideline document to follow.

#### **Research activities**

Microbiological and epidemiological surveillance of tuberculosis in South Africa: Application of WGS to enhance microbiological and epidemiological surveillance of drug-resistant tuberculosis in South Africa

NICD investigators: F Ismail, SV Omar, H Said, L Joseph, H Moultrie, J Mwansa, E Kachingwe

Collaborators: Centers for Disease Control, South Africa/US

There is continued need to monitor the progress of new interventions through a reliable routine surveillance system. The Centre for Tuberculosis at the NICD is recognised for the achievements delivered in producing a robust surveillance system for the country. However, the need exists to ensure that this is maintained and adapted in line with new advances and technologies. WGS of *Mycobacterium tuberculosis* (MTB) has rapidly progressed from a research tool to a clinical application for the diagnosis and management of TB in public health surveillance. Drastic reduction in costs, advances in technology, and concerted efforts to translate sequencing data into actionable information have facilitated this development. NGS would enhance the routine surveillance output by introducing a higher resolution methodology compared to the current typing methodologies, to reconstruct transmission pathways between patients, thereby allowing the detection of high-risk clusters in real-time and bring forward opportunities for breaking chains of transmission by infection control measures. Combining the genomic data with the epidemiologic metadata would create a powerful tool to direct public health interventions, due to a more holistic picture of the disease landscape.

## Multi-centre clinical trial to assess the performance of culture-free, end-to-end targeted NGS (tNGS) solutions for diagnosis of drug-resistant TB

#### NICD investigators: SV Omar, F Ismail

#### Collaborators: FIND (Switzerland)

Current rapid molecular assays for detection of drug-resistant TB from direct clinical samples have important limitations. They are not suited for high-throughput settings, can only be used to detect a limited number of target gene regions, and are not ideal for detection of phenotypic resistance conferred by mutations across large gene regions (e.g. pyrazinamide). Additionally, they are limited in their ability to discriminate silent mutations, resulting in imperfect specificity. Phenotypic drug susceptibility testing is dependent on high-level biosafety culture facilities and yields results only after many weeks. Culture-free, end-to-end tNGS solutions for the diagnosis of drug-resistant TB can offer higher throughput and greater accuracy across more TB drugs than current WHO-endorsed molecular assays, as well as a significantly faster time-to-result than phenotypic drug susceptibility testing. Evidence regarding the clinical diagnostic accuracy and operational characteristics of tNGS solutions is needed to comprehensively evaluate tNGS for diagnosis of drug-resistant TB among patients who have been diagnosed with TB, and will be critical to inform global and national policy.

### Investigating the usefulness of the new QuantiFERON-TB Plus assay in diagnosing latent TB infection and progression to active TB disease among healthcare workers in high-incidence settings NICD investigators: SV Omar, F Ismail, J Mwansa

Collaborators: TB Directorate, NDoH

Annually, more than 9 million new cases of active TB are occurring. This poses a significant occupational health problem. Healthcare workers specifically are at increased risk of exposure to transmissible TB, especially in a high-burden country like South Africa. The QuantiFERON-TB Gold Plus (QFT-Plus) detects latent TB infection (LTBI), and incorporates a marker that is able to potentially predict active TB cases, which has important value in detecting high-risk exposures early. This project, which is a collaboration between the TB South Africa Project and the NDoH is designed to understand and provide a baseline of the prevalence of LTBI, as well as the progression from latent to active TB among healthcare workers. Additionally, it will seek to assess the feasibility of using QFT-Plus among healthcare workers in a routine healthcare setting in the country. The site had expanded from the Pretoria West Hospital to Pelonomi Hospital in the Free State. However, as a result of the COVID-19 pandemic, the Free State site was terminated, mainly due to overburdened healthcare facilities and travel restriction, as well as temporary suspension at the Pretoria West Hospital. The study has been re-designed to factor in possible impacts of COVID-19, with new sites selected, and will recommence in Quarter 3 of 2021.

## Pre- and post-test counselling combined with a conditional cash transfer to reduce pre-treatment loss to follow-up of Xpert+ or Smear+ TB patients

#### NICD investigators: NA Ismail, J Mwansa, H Moultrie, SV Omar, F Ismail

Collaborators: Prof I Abubakar (University College London) and Dr S Moyo (HSRC)

Part of the 90-90-90 strategy is to ensure that 90% of all TB patients diagnosed are cured. A barrier to this is the combined loss associated with both pre-treatment and on-treatment follow-up. Based on early-pilot data, this is approximately 15-20%, and indicates a significant barrier to achieving the targets set for 2025 and 2035. This UK MRC Newton grant-funded project is a collaboration between NICD, HSRC and University College London. The project evaluated the impact of counselling and a cash payment of R150 per visit on the total loss to follow-up before and during TB treatment. The study was implemented across eight sites, with 4 110 participants enrolled (381 tested positive). The study ended on 26 March 2020, a few days earlier than the planned date due to the national lockdown resulting from the COVID-19 pandemic. Data cleaning is currently ongoing in preparation for the final analysis and report preparation, which will be shared with stakeholders. A modelling component is also planned to assess the potential value based on the study findings.

# Inventory study measuring the level of under-reporting and estimating incidence for TB in South Africa: An inventory study and capture-recapture analysis

#### NICD investigators: H Moultrie, F Ismail

#### **Collaborators:** Dr L Mvusi (NDoH), Dr L Anderson (WHO)

Understanding and having an accurate measure of the burden of disease is essential to successful programme planning. National TB programmes should use data collected through routine surveillance to directly measure TB incidence and track progress against global TB targets. Most high TB-burden and resource-limited countries, however, lack national TB surveillance systems that have the sufficient robustness to accomplish this. Estimated burden and what is reported is vastly different. Retrospective analysis of all TB records from the national TB programme (ETR.Net & EDRweb), the NHLS and private laboratories will be matched using specialised algorithms, as well as a manual review process. Thus far, all data sets have been compiled and the first set of linkages between the public and private sector laboratory data have been linked. Just over 10 000 laboratory-confirmed patients were identified in the private sector, with an overlap of just under half of these private sector patients also being found in the public sector. The underreporting thus attributable to the private sector seems to be relatively low. Linkages between the laboratory data and the NDOH data is underway, and will provide further insights.

#### Comprehensive resistance prediction for tuberculosis: An international consortium

NICD investigator: SV Omar, L Joseph, D Ngcamu

Collaborator: D Crook (Oxford University)

The CRyPTIC consortium seeks to establish a highly representative large database of genotype-phenotype information that is essential for the utilisation of next-generation sequencing technologies. While much is known for the common RAVs, it is only through a large study like this that the clinical relevance of rare RAVs can be reliably deciphered. Over 14 000 genotypes and 17 000 phenotypes have been collated from 10 countries, which include China, India and South Africa. Using the extensive data available interpretive criteria and geno-phenotype associations have been determined. These have confirmed what is well known for the older drugs, but have provided fascinating new insights on specific amino acid changes in the rpoB mutation at codon 491, for example. Additionally, a high-speed bioinformatics tool called 'Scalable Pathogen Pipeline Platform (SP3)' has been developed, and provides a powerful application for resistance detection and phylogenetic classification, leveraging the extensive CRyPTIC database. The study is in its final year and data are currently being cleaned and prepared for analysis.

#### Teaching and training

Training was provided on both reference mycobacteriology testing and public health aspects of TB to rotating registrars from university-based medical microbiology and public health departments in South Africa. Due to COVID-19, training was conducted on a virtual platform. CTB staff provide formal lectures to undergraduate medical students and medical microbiology registrars at the University of Pretoria, and postgraduate students at the University of Witwatersrand.

#### Postgraduate students

Five students were enrolled for postgraduate studies as follows:

- MSc: 3
- PhD: 2

#### Professional development, awards and honours

- One intern medical scientist passed the national assessment
- Two intern medical scientists are in training

#### **Research output**

#### Journal articles

- [1] Nelson KN, Jenness SM, Mathema B, et al. Social mixing and clinical features linked with transmission in a network of extensively drug-resistant tuberculosis cases in KwaZulu-Natal, South Africa. Clin. Infect. Dis. 2020 May;70(11):2396-402. DOI: 10.1093/cid/ ciz636.
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#### Conferences

[1] International conferences: 3

#### Acknowledgements

The CTB thanks the NICD/NHLS for funding and operational support, as well as PEPFAR through the CDC, under terms of agreement 1U19GH000571, the Global Disease Detection Program (U2GPS001328), and the NIAID (1R01 Al089349 and Al080737) for funding support.

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Figure 5: World TB Day 2021 outreach: donation of care packs to TB patients at Sizwe Tropical Diseases Hospital.



# CENTRE FOR VACCINES AND IMMUNOLOGY (CVI)




#### BACKGROUND

The Centre for Vaccines and Immunology is the National and WHO Regional Reference Laboratories for polio (targeted for global eradication), as well as measles, tetanus and hepatitis (targeted for regional elimination). In addition, the centre conducts projects on immune responses and immunogenetics of vaccine-preventable diseases. A biosafety level three laboratory and environmental surveillance laboratory support the Global Polio Eradication Programme. The centre provides epidemiological, virological and immunological support to the NDoH for vaccine-preventable diseases.

#### Surveillance

#### Polio surveillance

Wildtype poliovirus type 2 and 3 have been declared globally eradicated. Only wildtype poliovirus type 1 and vaccine-derived polioviruses continue to circulate. Sabin poliovirus type 2 has been withdrawn from vaccines globally, and is only used under the directive of the WHO in countries with vaccine-derived poliovirus

type 2 (VDPV2) outbreaks. Sabin poliovirus types 1 and 3 remain part of oral poliovirus vaccine administered to children in South Africa and many regions.

The Poliovirus Isolation laboratory serves eight countries within the southern African region in this capacity: Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, Swaziland and South Africa. The centre serves the broader African region as a Poliovirus Regional Reference Laboratory, which is only one of two poliovirus sequencing laboratories in the region.

For any acute flaccid paralysis case, stool samples are inoculated into cell cultures, and any sample with suggestive poliovirus cytopathic effects are subjected to molecular typing and characterisation to confirm poliovirus serotype/s and differentiate poliovirus subtype/s. During the period under review, 1 356 South African samples were processed for poliovirus isolation.

As the Regional Referral Laboratory, we identified vaccine-derived poliovirus type 1 (VDPV1) from four samples received from Madagascar, and VDPV2 from 892 samples received from Angola, Burkina Faso, Cote d'Ivoire, Congo, Ethiopia, Guinea, Liberia, Mali, Niger, Republic of South Sudan, Democratic Republic of Congo and Sierra Leone. Type 2 Sabin polioviruses were detected in 385 samples, all from countries using monovalent oral polio vaccine type 2 to halt VDPV2 transmission (Angola, Burkina Faso, Cote d'Ivoire, Ethiopia Guinea, Mali, Democratic Republic of Congo, Niger, Republic of South Sudan, Democratic Republic of Congo, Sierra Leone and Zambia).

The NICD has applied to host a Polio Essential Facility at its premises, one of only a handful globally. Following approval from the NDoH and a Certification of Participation issued by the Global Certification Commission for Polio Eradication, a pre-audit assessment was conducted in March 2021. The Polio Essential Facility will enable the NICD to work with poliovirus type 2 culture material under high containment, and poliovirus type 3 culture material following cessation of oral polio vaccine type 3.

The NICD provides ongoing support to WHO for environmental polio surveillance in the African Region from sewage. Of 344 environmental samples sequenced for poliovirus type 2, VDPV2 was confirmed in 258 samples from Angola, Cote d'Ivoire, Ethiopia, Niger, Democratic Republic of Congo, Republic of South Sudan, Liberia and Congo. Sabin poliovirus type 2 was confirmed in 86 environmental samples from Angola, Burkina Faso, Cote d'Ivoire, Ethiopia, Niger, Democratic Republic of Congo, Republic of South Sudan and Zambia.

From four South African environmental samples, nine Sabin poliovirus type 3, and two Sabin poliovirus type 1 were detected. Results from one of the sites in which Sabin poliovirus type 3 was detected suggested that polio vaccine coverage in the district and/or province may be suboptimal, and heightened surveillance and notification of acute flaccid paralysis (AFP) cases was recommended.

#### Measles Surveillance

CVI is the national reference laboratory for measles surveillance, and serves the southern African region as a regional reference laboratory. Serological and molecular testing for measles virus is provided by the centre in support of the global measles elimination initiative.

Laboratory results (serology, specifically the detection of measles-specific IgM antibodies, RT-PCR and genotyping) are used in conjunction with epidemiologic case investigations in the diagnosis of acute measles infection. A total of 747 South African febrile rash samples was tested during the period under review, with 12 cases classified as confirmed measles cases. No clusters were detected.

Only 40 rubella cases were identified via febrile rash surveillance. This is considerably lower than previous years, but is likely a reflection of lower health-seeking behaviour resulting from the COVID-19 pandemic, as well as lower transmission because of social distancing and lockdown measures.

As part of the WHO regional quality assurance programme, the centre retests approximately 10% of serum samples from eleven southern African countries, namely Botswana, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, ESwatini, Zambia and Zimbabwe. Only six countries sent samples during the reporting period and 374 samples were tested. There was good concordance for the measles IgM results (97.6%) and rubella IgM results (94.7%).

#### Tetanus

The centre collates and classifies tetanus cases reported through the NMC system. There have been eight suspected tetanus cases notified, of which one case was confirmed as neonatal tetanus. Investigation of the case revealed that tetanus occurred after a non-medicinal substance was placed onto the umbilical cord at home.

The remaining seven suspected tetanus cases ranged in age from eight to 85 years, comprising six confirmed and one pending classification.

There is no laboratory test for tetanus, and cases are classified after reviewing medical records. A country is certified as having eliminated neonatal tetanus if there is less than one case per 1 000 live births in every district per year. The WHO declared that South Africa had eliminated maternal and neonatal tetanus in 2002. The rate of neonatal tetanus in South Africa is still below this threshold.

#### Hepatitis

CVI, together with the NDoH, are committed to reach the 2030 viral hepatitis elimination goals. The centre performs passive laboratory-based surveillance for hepatitis A, B and C via data retrieval from the NHLS corporate data warehouse.

#### Hepatitis A

During the period under review, 118 673 cases were tested for the presence of hepatitis A IgM antibodies through NHLS laboratories countrywide. Of the cases tested, 2 523 cases were positive for hepatitis A IgM, with an overall detection rate of 2.1% (2523/118673). The Western Cape had the highest detection rate at seven per 100 000 population.

The centre responded to an outbreak in the period 1 July to 17 August 2020, when 27 cases of acute hepatitis A were recorded in the Theewaterskloof subdistrict, Overberg District, Western Cape. Of the 22 cases, 14 cases were confirmed hepatitis A IgM positive and eight cases were based on clinical diagnoses with no samples for testing. The name of facilities was reported for 20/22 cases, of which 12 were from private practice and eight from public health facilities. Age ranged from two to 61 years, with a median of 20 (IQR 15, 34 years). There were two fatalities, aged 14 and 57.

#### Hepatitis B

For the period 1 April 2020 to 31 March 2021, 613 775 cases were tested for HBsAg throughout NHLS laboratories countrywide, of which 31 844 (5.2%) tested positive. Of the 31 844 HBsAg positive cases, the majority (12 071, 38.0%) were amongst the age group of 30 to 39 years. A total of 120 cases (0.4%) were less than 12 months old. The number of incident cases (defined by a positive IgM result against hepatitis B core antigen) was 526. Hepatitis B data were shared with the National Advisory Group on Immunisation meetings held during this period.

#### Hepatitis C

We analysed data from the NHLS corporate data warehouse regarding routine diagnostic hepatitis C testing practices. From 1 April 2020 to 31 March 2021, 1 110 924 patients were tested for hepatitis C virus exposure with a hepatitis C antibody test, with a positivity rate of 2.30% (2 548). A total of 340 patients with a hepatitis C positive antibody test result also had a hepatitis C viral load test. Of the 2 548 patients who tested positive for hepatitis C exposure, 2 243 patients positive for hepatitis C exposure could not be linked to any hepatitis C nucleic acid test, showing a gap in patient care. Hepatitis C genotyping information showed circulation of genotypes 1 to 5.

#### SARS-CoV-2 environmental surveillance

The centre is leading the South African Collaborative COVID-19 Environmental Surveillance (SACCESS) network to identify and map SARS-CoV-2 distribution in sewage. For the period under review, a total of 205 wastewater samples were processed for SARS-CoV-2 surveillance - 119 samples from nine sites in Gauteng, 21 samples from two sites in Western Cape, 18 samples from two sites in Free State, 26 samples from four sites in Eastern Cape, 16 samples from two sites in KwaZulu-Natal and five samples from one site in Limpopo. SARS-CoV-2 was identified in 169 samples (82%). The 501Y.V2 variant was successfully detected in a sewage sample using next-generation sequencing. The sample was collected from a site in Eastern Cape in November 2020. To note, SARS-CoV-2 is considered non-infectious from sewage samples, but the viral RNA remains detectable. Sewage monitoring may provide accessory information to the NDOH for planning geographically localised interventions.

#### **Research activities**

#### Indoleamine 2,3 dioxygenase as a biomarker for active tuberculosis

NICD investigators: C Adu-Gyamfi, N Mlotshwa, L Makhatini, H Hong, H Ranchod, M Suchard

**Collaborators:** N Martinson (University of the Witwatersrand), T Scriba (South African TB Vaccine Initiative), S Lala (Baragwanath Hospital, University of the Witwatersrand), S Stacey (Charlotte Maxeke Academic Hospital), E Shaddock (Charlotte Maxeke Academic Hospital).

Indoleamine 2, 3 dioxygenase (IDO) is the rate-limiting enzyme involved in a key biochemical pathway, specifically metabolism of the amino acid tryptophan and endogenous synthesis of nicotinamide. The end products of the tryptophan metabolism pathway are thought to play a role in immune suppression – a characteristic trait of TB. By showing a link between IDO and active TB disease, our group aims to provide novel methods for TB diagnosis and monitoring. We are investigating changes of IDO activity and gene expression in TB disease. Cohorts currently being studied include HIV-negative and -positive adults, pregnant women, children and individuals with other lung diseases, including COVID-19.

#### Postgraduate students

Nine students were enrolled for postgraduate studies as follows:

- MSc: 3
- PhD: 4
- Intern scientists: 2

Five students graduated in the period under review. These comprised the following:

- FETP: 1
- PhD: 2
- Intern scientists: 2

#### Other activities

The centre provided key support to NICD COVID-19 activities in the following ways:

- Dr Villyen Motaze provided epidemiological support and NMCSS line list
- Dr Melinda Suchard acted as incident management team lead (12 October to 8 November 2020), and provided multiple media interviews related to COVID-19
- Dr Susan Malfeld supported daily reporting duties

#### **Research output**

#### Journal articles

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#### Other publications

Online Bulletin of the National Institute for Communicable Diseases

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#### Conferences

- [1] International conferences: 1
- [2] Local conferences: 1



**Figure1:** Staff of the CVI at the NICD event commemorating the one-year anniversary of detection of the first South African COVID-19 case.

## DIVISION OF PUBLIC HEALTH SURVEILLANCE AND RESPONSE (DPHSR)





Dr Michelle Groome Centre Head

#### BACKGROUND

The Division of Public Health Surveillance and Response (DPHSR) facilitates communication and data sharing between the national and provincial health departments and the NICD, and provides epidemiological input to other NICD centres through collaborative projects. It also provides support for surveillance, epidemiological and research activities, as well as outbreak responses. Epidemiology is one of the core sciences that underpin the work of the NICD to ensure evidence-based public health decision making, and to strengthen health systems at national, provincial and local level. DPHSR incorporates the GERMS-SA surveillance programme, the Provincial Epidemiology Team (PET), the Notifiable Medical Conditions (NMC) Surveillance Unit and the Outbreak Response Unit (ORU), which works closely with the Emergency Operations Centre (EOC).

GERMS-SA collaborates with all the NICD centres to implement active surveillance programmes, incorporating laboratory-based surveillance through secondary data analysis of the NHLS data; complemented by enhanced surveillance at sentinel hospital sites for specific laboratory-diagnosed conditions and syndromic surveillance for pneumonia and diarrhoea.

The PET, within the Division of Public Health Surveillance and Response of the NICD, is integral to providing epidemiological support to provincial departments of health, particularly with regards to public health surveillance and response, as well as the efficient utilisation of data. The PET works in collaboration with the NICD centres and various disease programmes in the provinces to produce outputs that inform programme performance and management decisions. It comprises eight epidemiologists based in eight of the nine South African provinces. They support provincial health departments with outbreak investigation, the epidemiological interpretation of TB, HIV, NMC data, and management activities.

The NMC Surveillance Unit coordinates the implementation of the NMC surveillance system, including support for data collection, data cleaning and reporting across the private and public sectors.

The ORU and the EOC provide technical support to national, provincial and district health departments for all aspects of communicable disease outbreaks and control, and facilitate coordination of outbreak detection, investigation and response activities, together with the appropriate NICD centres. The ORU facilitates interaction between the NHLS diagnostic laboratories and NICD centres, and the provincial and district communicable disease structures to provide appropriate laboratory diagnostic services during outbreaks and when specialised diagnostic testing is required. The Unit is also kept abreast of international developments in outbreaks and outbreak preparedness through representation on key WHO advisory committees and international interest groups. The EOC coordinates the management of high-risk public health events of national and regional concern through the use of an incident management system.

Together, these teams contribute significantly to national communicable disease surveillance and response efforts by providing systems for rapid alert and notification of diseases of public health importance, as well as technical expertise to provinces, districts and healthcare workers within South Africa. Members of the DPHSR team provide regular reports to government structures as required. Representatives from the DPHSR attend the national COVID-19 Incident Management Team meetings with the NDoH. They collaborate through various means with national and global stakeholders to enable the NICD's mandate 'to be a resource of knowledge and expertise in regionally relevant communicable diseases in order to assist in planning of policies and programmes and to support appropriate responses to communicable disease problems and issues'.

At the start of the COVID-19 pandemic, South Africa, like many low- and middle-income countries, lacked a real-time national health information system to monitor COVID-19 hospitalisations, which is vital for understanding the epidemiology of an emerging pathogen and guiding strategic policy. The NICD implemented DATCOV, a hospital surveillance system, in late March 2020. The online platform allows public- and private-sector hospitals to submit data on hospital admissions for patients diagnosed with COVID-19, and provides real-time analysis and reporting.

Despite many varied achievements, big and small, memories of this reporting period will be dominated by the preparedness and response activities for the COVID-19 pandemic. In the past year, the DPHSR has been integral to the national and provincial COVID-19 pandemic response, providing valuable epidemiological expertise in the field, as well as through the creation of data platforms to monitor trends in COVID-19 disease, hospitalisations and deaths.

#### Surveillance

#### GERMS-SA

#### Dr Vanessa Quan

Annually, approximately 250 participating NHLS and private laboratories submit isolates from cerebrospinal fluid, blood and specimens from other sites to the NICD centres, and contribute approximately 20 000 cases of communicable diseases that meet the GERMS-SA case definitions to the GERMS-SA database. Data is also obtained from the NHLS Corporate Data Warehouse/Surveillance Data Warehouse. The laboratory surveillance pathogens include *Cryptococcus* species, *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Streptococcus agalactiae, Streptococcus pyogenes, Salmonella enterica, Salmonella enterica serotype Paratyphi A, B and C, Shigella* species, *Vibrio cholerae*, diarrhoeagenic *Escherichia coli, Campylobacter* species, *Listeria* species, *Candida* species, *Mycobacterium tuberculosis*, and ESKAPE organisms (enterococci, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and Enterobacteriaceae (*Enterobacter* and *E. coli*)). An enhanced surveillance arm is operational at 25 sentinel public sector sites across the country, where nurse surveillance officers collect clinical information on patients relating to specific pathogens where additional clinical and outcome data are required to support centre outputs. These include invasive *S. pneumoniae, H. influenzae, N. meningitidis, Salmonella* Typhi; nontyphoidal *Salmonella* spp., CREs, *Acinetobacter baumannii, Cryptococcus* spp, and rifampicin-sensitive TB. The GERMS-SA core team also supports the operational side of syndromic surveillance programmes, including the pneumonia surveillance programme (with CRDM), diarrhoeal surveillance (with CED), brucellosis surveillance (with CEZPD) and neonatal sepsis (with CHARM).

GERMS-SA, together with the NICD centres, continues to use data collected through surveillance to inform and guide public health policymakers in their decisions. The objectives include estimating the burden of both community- and hospital-acquired infectious diseases under surveillance, monitoring antimicrobial susceptibility trends, monitoring the impact of treatment on HIV-associated opportunistic infections, and evaluating the impact of vaccines included in the Expanded Programme on Immunisation (EPI). GERMS-SA's work is funded through the NICD/NDOH. Some aspects of the surveillance programmes were impacted by the COVID-19 pandemic with downscaling or halting of some activities, but upscaling of others, for example COVID-19 surveillance.

#### NOTIFIABLE MEDICAL CONDITIONS SURVEILLANCE

#### Dr Villyen Motaze

The NMC Surveillance Unit provides a coordinated approach to the collection, collation, analysis, interpretation and dissemination of public and private sector NMCs in South Africa. This coordinated approach is implemented through a real-time surveillance system, the NMC surveillance system (NMCSS), which was implemented to comply with the requirements of the International Health Regulations. The NMCSS provides information for targeted public health response, decision making and resource allocation. The system comprises four categories of NMCs, classified according to the timing of reporting. Since the beginning of 2020, there have been two additions to the list of NMCs: COVID-19 and multisystem inflammatory syndrome in children (MIS-C). This was done in order to improve detection and reporting of cases during the COVID-19 pandemic. An enhanced NMCSS application is currently being developed and tested, which will improve notification by heath care workers. Both the current and enhanced NMCSS applications obtain data from the NICD data warehouse. Healthcare professionals also submit notifications via a web-based or mobile health application, or through the completion and submission of a paper-based form to a designated e-mail address. Private sector laboratories submit laboratory data on COVID-19 via a designated submission portal. The specialised NICD centres review, validate and classify notified cases.

In total, 44 288 cases were notified from January to December 2020. The majority of notified cases were Category 2 conditions (82.4%). The majority of the notified cases were male (59.4%) and were between 10 and 14 years old (10.9%). Of the 36 494 Category 2 conditions, the majority were bilharzia (n=13 270, 36.4%) and hepatitis B (n=10 397, 28.5%). The provinces with the majority of clinical notifications and merged cases were KwaZulu-Natal (n=3 705/13 895, 26.7%), Gauteng (n=3 284/13 895, 23.7%), Eastern Cape (n=1 627/13 895, 11.7%), and Western Cape (n=1 600/13 895, 11.5%)

#### OUTBREAK RESPONSE UNIT

#### Dr Vivien Essel (Acting Head)

The ORU publishes a monthly Communicable Diseases Communiqué, which reports recent outbreaks and communicable disease cases or issues of relevance. This is distributed to a wide audience, including general practitioners, specialists, infectious diseases and travel medicine societies, and national and provincial public health personnel. In addition, the unit published special urgent advisories and communiqués in response to acute events requiring immediate dissemination of information. The unit co-ordinated the 24-hour emergency hotline, which serves as a resource for public and private sector healthcare workers for emergency information pertaining to the post-exposure management of rabies and other infectious disease, requests and advice for diagnostic tests for suspected epidemic-prone diseases and technical advice regarding the management of cases of infectious disease.

Prior to the identification of the first COVID-19 case in South Africa, several preparedness and response activities were undertaken, including the setting up of a national clinician and public hotline to deal with the numerous COVID-19 queries being received on the NICD hotline. As a result, the number of staff manning the hotline had to increase, as the pathologists and medically qualified staff of the NICD were not able to cope with the increase in the number of queries being received. About 120 doctors and nurses (permanent, contract, volunteers) on day/night rotations were hired to staff the hotline. The national hotline came into operation on 6 March 2020. During the period under review, 113 577 queries were attended to by ORU directly, through the NICD hotline or through the national public and clinician hotlines made available to all members of the public and healthcare workers, respectively. All queries were responded to within 24 hours. Queries reached a peak in the month of April 2020 early in the coronavirus pandemic, and then decreased steadily (Figure 1). There was a slight increase in query numbers in December 2020 and January 2021, coinciding with the second wave of COVID-19 cases in the country. Enquiries regarding COVID-19 accounted for over 99% of all queries, with queries regarding the management of rabies post-exposure prophylaxis being the most common non-COVID-19 enquiry. The majority of calls were from Gauteng (43%), followed by KwaZulu-Natal (16%) and Western Cape (13%; Figure 2).



Figure 1: Number of queries attended to on the hotline, 1 April 2020–31 March 2021.



Figure 2: Provincial origin of queries attended to from 1 April 2020–31 March 2021, n=113 264 (where caller origin was documented).

Staff from the ORU, together with the EOC and the other NICD centres, supported the country's COVID-19 response through various activities, including management of the laboratory-confirmed COVID-19 case line list, compilation of the daily commentary reports and resurgence summary statistics distributed to the Minister of Health and other key stakeholders, monitoring of the dashboard and loading of data, resolving data queries, and analysis of COVID-19 data from several sources. Provincial support included liaising with provincial teams, providing summary reports, case data harmonisation and reallocations, and attending to data queries.

ORU provided assistance with several COVID-19 cluster investigations, including the identification of clusters from the case contact database and support for the contact tracing team. Of note are the following cluster investigations:

- A description of a COVID-19 cluster in repatriated South African citizens linked to a religious gathering in Pakistan
- A cluster of COVID-19 cases amongst festival attendees at an Afro-Latin Festival in Johannesburg (12-15 March 2020)
- A cluster of COVID-19 cases in a group of 30 tourists from the Netherlands who had travelled to Eswatini and Johannesburg prior to reaching KwaZulu-Natal
- A cluster of COVID-19 cases in a group of 10 travellers who returned to SA having visited several countries: Italy, France, Austria, United Kingdom and Dubai, United Arab Emirates (7 March 2020)
- A cluster of COVID-19 cases following the 2020 Matric Rage Festival in KwaZulu-Natal (November to December 2020)

ORU was involved in internal and external meetings in preparation and response to the global COVID-19 pandemic, as well as other outbreak-related forums. In collaboration with other NICD centres, the ORU assisted with non-COVID-19 related queries, outbreaks and public health-related matters such as investigation of suspected viral haemorrhagic fever cases and foodborne disease outbreaks.

#### EMERGENCY OPERATIONS CENTRE

#### Nevashan Govender

The EOC supported the NDoH in its continued response to the COVID-19 pandemic during the period under review. Some highlights are described below.

The EOC coordinated a dedicated swab team of skilled nurses and data clerks to support the province of Gauteng as the demand for screening and testing escalated rapidly in the first surge. This included essential worker screening and testing at OR Tambo International Airport, Department of Justice, South African Reserve Bank, Chris Hani Baragwanath Academic Hospital and ESKOM. Additionally, the swab team assisted with the screening and testing at a number of quarantine sites across Gauteng, assisting in reducing the anxiety and concern amongst travellers and their families.

Epidemiologists at the EOC investigated a number of COVID-19 clusters in the past year. These investigations were often only supported by the deployment of epidemiologists to provinces or districts. The deployments of epidemiologists to support provincial and district response were coordinated through the EOC for both the first surge and the resurgence.

There were long-term deployments of epidemiologists to support Eastern Cape and Gauteng, and many shorter, specific objective deployments to KwaZulu-Natal, Limpopo, North West, Free State and Eastern Cape. Response support extends to the EOC continuing to support the national Incident Management Team, the development of the COVID-19 resurgence plan and indicators, the national and provincial review of resurgence response and the planning for subsequent COVID-19 surges.

The EOC, along with NICD IT and other colleagues, successfully developed and deployed the NMCSS line list, which acts as an outbreak response line listing system for COVID-19. The NMCSS is managed by the EOC, and provides vetted users with access to a web-based containing case data at national, provincial and district level. Case data that has undergone automated and algorithmic cleaning and manual verification are provided to users, filtered to the geographic region for timely reporting. The current NMCSS is an evolving and improving system, utilising ArcGIS geocoding to enrich district-, sub-district-, ward- and suburb-level information for cases, and hosts a number of informative dashboards (some of which are publicly available on the NICD website) generated from the available data, including a district-level resurgence indicator. The data from the NMCSS are used to inform the national COVID-19 situation, as well as a number of research, surveillance and modelling initiatives.

The EOC manager had been invited by the WHO and Africa CDC, respectively, to assist with the management of the PHEOC in Pakistan and the EOC at the Africa CDC. Furthermore, the EOC manager continues to serve as an active member of the WHO AFRO/ Africa CDC and Prevention's online community of practice for EOCs, and continued to be an active participant on the Africa CDC's Southern ECHO platform. This ensures information sharing and relationship strengthening across emergency and outbreak response leads in southern Africa. In addition, the EOC manager continues to support the Africa Taskforce for Novel Coronavirus.

When not engaged in active preparedness and response to crises, EOC staff were involved in teaching and training activities.

#### PROVINCIAL EPIDEMIOLOGY TEAM

#### Joy Ebonwu

The critical role of the NICD epidemiologists based in the provinces became more evident and established during the COVID-19 pandemic. Epidemiological support brought about better coordinated and structured data flow, management and analysis processes within the operations of the provincial response teams. In their respective provincial Incidence Management Teams, the PET plays different roles, including data management and harmonisation, analysis and reporting, daily provincial COVID-19 situational reports, and presentation at different provincial meeting forums. In response to increasing COVID-19 case burden, trainings, technical support and capacity building were offered to the provinces. Specifically, COVID-19 contact tracing, data management and report writing training was offered in the Northern Cape, together with FETP and NDoH , to improve COVID-19 preparedness and response abilities at district/sub-district levels. The PET coordinated epidemiological support and capacity building across the five districts of the Free State, in collaboration with FETP, ORU and the WHO. The team also facilitated in the virtual FETP Frontline course on basic applied epidemiology for health practitioners, conducted in the Eastern Cape.

The PET continues to work with other stakeholders to improve data collection and reporting of COVID-19 related deaths (especially community deaths) in response to reports on excess deaths by SAMRC. The team is also implementing sentinel surveillance in four districts (Nelson Mandela Bay, Mangaung, Thabo Mofutsanyane and Frances Baard) across South Africa to strengthen the NDoH 's initiative of post-mortem COVID-19 testing on all natural deaths outside of hospitals.

#### DATCOV

#### Dr Waasila Jassat

The DATCOV system has informed understanding of the evolution of the epidemic in the different provinces of South Africa, and has served as an important mechanism to alert for COVID-19 resurgences. The data have been used to inform hospital resource needs and to identify hospitals with higher case fatality rates that require additional support. Importantly, DATCOV provided insight during the second wave of COVID-19 when the variant of concern 501Y.V2 (Beta) predominated, demonstrating higher mortality in weeks with high volumes of admissions and an increased in-hospital mortality rate. Through DATCOV, risk factors for mortality

were also identified, and showed an increased risk for COVID-19 mortality for HIV co-infected patients. Such information is critical for guiding prevention of COVID-19 in vulnerable groups, and for appropriate clinical monitoring of infected persons for interventions that include vaccine prioritisation. Analysis of COVID-19 in special groups such as paediatrics, care homes and pregnant women has informed guidelines and best practices for prevention, early alerts and care. Data have been used for reproductive rate modelling, as well as to describe 'long COVID' sequelae.

DATCOV has demonstrated the value of hospital-based surveillance, and informs understanding of technology-driven approaches that are clear in purpose, simple to administer and adaptive in the context of changing epidemic circumstances. DATCOV offers lessons for the monitoring of future epidemics that are replicable in hospitals with diverse resources in low- and middle-income settings. DATCOV data were used in modelling, and served to guide the recommendations by the Ministerial Advisory Committee and Incident Management Team with regards to levels of national restrictions. Analysis of age and comorbidities data were used in decisions around vaccine prioritisation. Data were presented in several national and international forums.

#### **Research activities**

Baby GERMS-SA: implementing a surveillance programme to describe the burden of neonatal sepsis at secondary-level hospitals in South Africa (with CHARM)

NICD investigators: S Meiring, R Mathebula, O Perovic, M Smith, R Mpembe, V Quan, A von Gottberg, L de Gouveia, S Walaza, C Cohen, E van Schalkwyk, NP Govender

Collaborators: C Mackay, R Phayane, T Mailula, O Mekgoe, C Kapongo, N Maphosa, A Dramowski

Culture-confirmed neonatal bloodstream infections and meningitis in South Africa, 2014–2019 (with CRDM)

**NICD investigators:** R Mathebula, S Meiring, E van Schalkwyk, O Perovic, V Quan, R Magobo, T Bell, A von Gottberg, C Cohen, NP Govender

Collaborators: A Dramowski, S Velaphi for Baby GERMS-SA

## Prolonged shedding of SARS-CoV-2 at a low cycle threshold value among immunocompromised HIV-infected individuals in South Africa (with CRDM)

NICD investigators: S Meiring, J Bhiman, A Buys, J Kleynhans, J Moyes, V Quan, S Walaza, N Wolter, A von Gottberg, C Cohen **Collaborators:** S Tempia, M McMorrow and the COVID-19 shedding study group

#### **Policy contributions**

During the period under review, DPHSR made the following contributions:

- Coordinating and developing national rabies post-exposure prophylaxis guidelines for South Africa, 2020/2021
- Assistance with development of several COVID-19 guidelines
- Contributor to the WHO AFRO's Public Health Emergency Operations Centre (PHEOC) Legal Framework Guide: 'A Guide for the
  Development of a Legal Framework to Authorize the Establishment and Operationalization of a PHEOC ' and ' Handbook for
  Public Health Emergency Operations Centre Operations and Management'

#### Teaching and training

DPHSR staff provided and contributed to the following teaching and training activities during the period under review:

- Training of EOC/NMC epidemiologists and community service doctors
- Teaching and training activities on Public Health Emergency Operations Centres and Incident Management System of registrars and FETP residents
- Use of the NMC programme as the field site for two Field Epidemiology Training Programme residents who currently enrolled in master's degree programs
- Presentation of postgraduate seminars: Surveillance and data management in a hospital setting (Geneva Centre for Security Policy
   – Health Security and COVID-19 module), and lecture on surveillance (University of Pretoria MPH)
- Lectures to clinical associate students at the University of the Witwatersrand on rabies, malaria, COVID-19 and an approach to a patient with fever and bleeding
- Supervising SAFETP residents during their monthly outbreak rotation

- Supervising and training public health registrars from University of Pretoria and the University of the Witwatersrand during their six-monthly outbreak rotation
- DPHSR medical scientist training rotation programme
- Teaching the SAFETP Disease Surveillance module (EPM874) to University of Pretoria MPH students
- Teaching the NICD Core three-weeks course to public health medicine and infectious disease registrars from various universities
- Training/demonstration on how to access and use the foodborne disease web app
- Campaign and awareness videos for Women's Day and World Rabies Day (ORU)

#### Postgraduate students

Two students graduated from the University of the Witwatersrand in the period under review.

- Postgraduate Diploma in Monitoring and Evaluation: 1
- MSc in Epidemiology and Biostatistics: 1

#### **Research output**

#### Journal articles

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# NATIONAL CANCER REGISTRY (NCR)





Dr Elvira Singh Centre Head

#### BACKGROUND

National pathology-based cancer surveillance and implementation of populationbased cancer registration are the primary mandates of the NCR. Despite the challenges presented by the COVID-19 pandemic, the NCR was able to meet key performance objectives, while also supporting the NICD COVID-19 response extensively. Four NCR research staff members were seconded to the NICD response for four months as part of the COVID-19 de-duplication team.

The NCR published the 2016 and 2017 national cancer incidence reports. The year 2020 proved to be a difficult year for population-based surveillance due to the COVID-19 pandemic. With hospital wards closed, outpatient clinics suspended and restrictions on movement of surveillance officers, high-quality and complete cancer data collection was hindered. Overall case finding and data collection for the year 2019 decreased by 45.8% compared with 4 695 in 2018. One of the challenges was restricted access for surveillance officers to collect cancer data in health facilities.

In the 2020/21 financial year, the NCR published key research in cancer epidemiology in 12 peer-reviewed publications. We compared cervical cancer survival rates across 13 population-based cancer registries in 11 African countries, taking human development index into account. Overall, three-year survival rates were 44.5%, compared to 73.7% in the United States. In countries with a medium or low development index, patients were four times more likely to die than those in countries with a high development index. This was a timely publication in line with the WHO cervical cancer elimination call. We also conducted research evaluating the impact of the ART programme on Kaposi's sarcoma. The ART programme was associated with a decrease of over 50% in the predicted age-standardised incidence rates of Kaposi sarcoma. This highlights the role of effective control of oncogenic infections such as HIV in cancer control in the context of high HIV prevalence in South Africa. We summarised current evidence on conjunctival cancer in people living with HIV (PLWH). 33% of squamous cell carcinoma of the conjunctiva in sub-Saharan Africa is attributed to HIV. Therefore, symptom screening of conjunctival cancer in PLWH should be encouraged.

We were awarded the Africa Oxford Development grant, funding five southern African countries (South Africa, Zimbabwe, Eswatini, Zambia and Mozambique), and taking a key role in strengthening childhood cancer registration in the region. Our funding for the ongoing South African HIV Cancer Match study was renewed for another five years until June 2026. The NCR continues to establish itself as the regional centre of excellence in cancer registration in sub-Saharan Africa.

#### Surveillance

#### Pathology-based cancer registry

In the period under review, we published 2016 and 2017 cancer incidence reports on the NCR website (<u>https://www.nicd.ac.za/</u> <u>centres/national-cancer-registry/</u>). Data on cancers diagnosed in 2018 were coded and cleaned. We are currently coding 2019 data and 117 402 reports have been coded for that year.

#### Ekurhuleni population-based cancer registry (EPBCR)

A total of 2 541 new cancer cases was registered for the year 2019. The most common cancers registered were prostate, colorectal and kidney cancers among males, and breast, cervix and uterus cancer among females. Among children (0-14 years) there were 27 cases registered for 2019. Leukaemia was the most common cancer among children. The overall case-finding and data collection for the year 2019 decreased by 45.8% compared with n=4 695 in 2018. We experienced significant challenges, as there was restricted access for EPBCR surveillance officers to collect cancer data in health facilities due to the COVID-19 pandemic.

During Level 5 of the national lockdown, there was no active data collection at the sites of all surveillance officers. At Level 4 to Level 3, challenges of active data collection included social distancing restrictions and restricted access to some areas in hospital

facilities, which had reached their legal capacity. In other instances, surveillance officers were sent home for short periods as their work areas were shut down because of positive COVID-19 cases amongst staff members. Other facilities, such as hospices, refused our surveillance officers entry to their premises where they house the elderly in palliative care who are high-risk individuals.

The 2019 Ekurhuleni Cancer Incidence Report was submitted in March 2021.

#### Childhood cancer registry

The National Cancer Registry is working towards establishing a national childhood cancer registry. Data capturing and staging of paediatric notifications has started.

The International Agency for Research on Cancer (IARC)-Global Initiative for Cancer Registry development nominated Natasha Abraham (NCR epidemiologist) as the regional expert for childhood cancers. This involves extensive virtual training by the IARC, creating training materials, and strengthening childhood cancer registration in the sub-Saharan region.

Dr Mazvita Muchengeti and Dr Max Parkin (AFCRN) were jointly awarded the Africa Oxford Development Grant (http://www.afox. ox.ac.uk/2020/12/11/afox-research-development-awards-accelerating-progress-towards-the-sdgs/) to strengthen childhood cancer registration in southern Africa (South Africa, Zimbabwe, Zambia, Eswatini and Mozambique). Natasha Abraham is leading this work. She created online training materials and trained all participating sites virtually.

#### **Research activities**

#### South African HIV Cancer Match Study (SAM)

The SAM study is a national cohort of HIV-positive people created from NHLS HIV data (HIV tests, CD4 count and HIV viral load tests) and linked probabilistically to the National Cancer Registry to determine the spectrum and risk of cancer in the HIV population.

In the period under review, NIH funding for the SAM study through the IeDEA-Southern Africa was renewed for a further five years until June 2026. A new server was procured to allow for greater computational capacity and efficiency of linkage.

HIV data were updated to include 2015–2019 data, the deduplication of the full 2004–2019 HIV data is complete and linkage with NCR is in progress.

#### Johannesburg cancer case-control study (JCS) and evolving risk factors for cancer in African populations (ERICA-SA)

The JCS is a case-control study of newly-diagnosed (<6 months) black cancer patients (1995–2016), with over 26 000 patients interviewed and over 20 000 blood samples stored to examine genetic and emerging and/or novel risk factors for cancer.

Two PhD students continued working on the ERICA study (Melitah Motlhale and Gideon Singini). They also had ongoing online meetings and supervisor consultations with Dr Elvira Singh and their external supervisor, Prof Freddy Sitas (University of Sydney).

#### Acknowledgements and collaborators

- Prof Matthias Egger, Dr Julia Bohlius, Dr Lina Bartels, Dr Eliane Rohner (Institute of Social and Preventive Medicine, University of Bern, Switzerland)
- Prof Tim Rebbeck (Harvard TH Chan School of Public Health, Harvard University, USA)
- Prof Chris Mathew (Department of Medical and Molecular Genetics, Guy's Hospital, King's College London, United Kingdom)
- Prof Debbie Bradshaw (SAMRC)
- Dr Kathryn Chu, Dr Akrem Amer (Department of General Surgery, University of Cape Town)
- Prof Paul Ruff, Dr Brendan Bebbington (Wits Donald Gordon Oncology Centre)
- Dr Donald Max Parkin (Nuffield Department of Population Health, Oxford University, United Kingdom)
- Prof Freddy Sitas (University of Sydney, Australia)
- Prof Juliet Pulliam, Cari van Schalkwyk (DST-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA, Stellenbosch University)

#### Support of the NICD COVID-19 response

- Lactatia Motsuku (NCR epidemiologist), Wenlong Chen (medical scientist), Victor Olago (SAM study data manager) and Dr Mazvita Muchengeti were seconded to the COVID-19 data de-duplication team for four months (April 2020–July 2020). Their duties included daily de-duplication of COVID-19 data, testing the new and old NMC COVID-19 app, and training NICD epidemiologists in deduplication of COVID-19 data
- Wenlong Chen and Dr Mazvita Muchengeti served on the Ministerial COVID-19 report roster since January 2021
- Babongile Ndlovu (SAFETP resident, NCR clerk specialist) and Nelisa Peter (NCR data capturer) were deployed at EOC to assist
   with the NICD COVID-19 response
- Dr Elvira Singh provided consultant cover for the COVID-19 healthcare worker hotline

#### Teaching and training

The NCR continued with monthly scientific writing meetings and journal club meetings to build capacity in scientific writing amongst junior research staff and students. Other teaching and training activities included the following:

- Dr Elvira Singh gave public health lectures to undergraduate students at the Wits School of Public Health
- Dr Mazvita Muchengeti trained NICD epidemiologists on data de-duplication of COVID data
- Ms Lactatia Motsuku gave lectures to SAFETP students on cancer surveillance
- Ms Natasha Abraham gave lectures to SAFETP students

#### Postgraduate students

During the period under review, NCR enrolled 13 postgraduate students, comprising the following:

- MSc/MPH: 6
- PhD: 7

Three students graduated in the period under review.

• MSc: 3

#### Professional development, awards and honours

- The NCR research team and students attended an online writing course offered by Dr Kali Tal through the University of Bern, Switzerland
- Dr Mazvita Muchengeti, Lactatia Motsuku and Natasha Abraham attended the SAFETP supervisors training workshop
- Dr Mazvita Muchengeti and Victor Olago attended a trainer of trainers online and ragogy course with Swiss TPH
- Lactatia Motsuku registered with SACEMA (University of Stellenbosch) to pursue a PhD in Epidemiology, supervised by
  Dr Mazvita Muchengeti and Prof Juliet Pulliam
- Victor Olago attended a course on feature engineering from Kaggle
- Natasha Abraham was appointed the IARC GICR regional expert for childhood cancer in Africa
- Dr Mazvita Muchengeti was appointed as a SACEMA Research Associate
- Dr Elvira Singh represents the NCR on the Ministerial Advisory Committee for Cancer Care and Prevention

#### **Research outputs**

#### **Journal articles**

- Muchengeti M, Bohlius J, Dhokotera TG. Conjunctival cancer in people living with HIV. Current Opinion in Infectious Diseases. 2021 Feb;34(1):1-7.
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#### Conferences

[1] International conferences: 1

### **NATIONAL HEALTH** LABORATORY SERVICE



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RP195/2021

ISBN: 978-0-621-49574-4