NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Division of the National Health Laboratory Service

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ANNUAL OVERVIEW

2019/20

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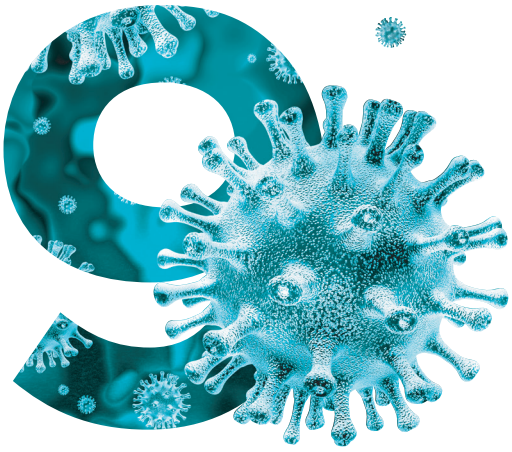

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LIST OF ABBREVIATIONS

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
CC	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
CMJAH	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
CTB	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)

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
HCC	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
HPV	Human papillomavirus
HR	High-risk
HR	Human Resources
HSRC	Human Sciences Research Council
HSV	Herpes simplex virus
HUU	HIV-unexposed and uninfected
HVTN	HIV Vaccine Trials Network
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
IgG	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

IMS	Incident management system
iNTS	Invasive nontyphoidal *Salmonella*
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	Minimal inhibitory concentration
MIR	Mortality incidence ratios
MLST	Multi-locus sequence typing
MLVA	Multiple-locus variable number tandem repeat analysis
MMed	Master of Medicine
MNORT	Multisectoral National Outbreak Response Team
MoA	Memorandum of agreement
MP	Mpumalanga Province
MPAC	Malaria Policy Advisory Committee
MPH	Master of Public Health
MPTB	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
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
PCP	*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
PT	Proficiency testing
PTS	Proficiency testing scheme
PTB	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	Rajah Muthiah Medical College 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
TB	Tuberculosis
TBF	Tick bite fever
TBSAP	Tuberculosis South Africa Project
TEPHINET	Training Programme in Epidemiology and Public Health Interventions Network
TIV	Trivalent influenza vaccine
TK	Thymidine kinase
TNM	Tumour, node, metastasis
TP	*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

Interim Executive
Director's Overview

2019/20

Prof Lynn Morrris
Interim Executive Director

1. Background

The NICD plays a vital role in the early detection, containment and response to infectious disease threats across South Africa, the Southern African Development Community (SADC) and Africa. It provides technical support to the DoH, as well as the WHO, Africa CDC and other relevant bodies, through surveillance of communicable diseases, outbreak response, specialised diagnostic services, research and training, capacity building and provincial epidemiology services.

There are seven disease-focused centres within the NICD, plus a transversal Division of Public Health Surveillance and Response (DPHSR). Core surveillance activities are funded through a conditional grant from the National Treasury and project-specific activities and research are grant-funded from external agencies and other donors. The staff complement of ~600 includes pathologists, scientists, epidemiologists, medical technologists and technicians, and surveillance officers.

Division of Public Health Surveillance and Response

The DPHSR, through the GERMS-SA surveillance platform, continues to support most of the surveillance activities within the seven NICD centres. These nationwide activities cover a broad range of pathogens and include laboratory surveillance supported by data from the CDW, enhanced surveillance at sentinel hospital sites and syndromic surveillance for respiratory and diarrhoeal disease.

The Provincial Epidemiology Team (PET), comprising of eight epidemiologists placed in eight of the nine provinces, participated in districtwide training for the National Expanded Programme on Immunisation coverage survey, provided operational management for field teams and contributed to data analysis. The PET provided regular feedback to provinces, and contributed to bi-annual surveillance bulletins detailing outbreak and surveillance activities, data analysis and reports.

In 2020, the DPHSR played a pivotal role in the national COVID-19 pandemic response with activation of the Emergency Operations Centre (EOC) within the Outbreak Response Unit (ORU) and formation of an Incident Management Team which initially comprised of the DoH, NHLS and NICD. Preparatory response activities for the expected transmission of COVID-19 into South Africa began in mid-January, with development of policy and guidance documents required for outbreak readiness, as well as screening and monitoring tools. The DPHSR also supported provincial preparedness training.

Following diagnosis of the first case of SARS-CoV-2 on 5 March 2020, activities have been ongoing, including initial contact tracing and monitoring, data management and analysis, development of reporting systems and epidemiological support, both centrally and at provincial level. The existing NICD clinicians' hotline service was significantly expanded to a full tollfree call centre. The need for a public hotline was accommodated by the NHLS and has become a significant part of the broader response to COVID-19.

The Notifiable Medical Conditions Surveillance System (NMCSS), which is designed for real-time data reporting, continued to expand across the country, receiving an average of 7 500 monthly notifications from the NHLS laboratories, and more than 3 800 private and public sector health facilities across the country. The proportion of clinical notifications submitted through the electronic case reporting platforms increased from 40% in January 2019 to about 74% in February 2020.

In March 2020, when the COVID-19 epidemic hit the country, a new module (or component) was added to the NMCSS to collect additional data elements required to guide the national response to the pandemic.
The goal of creating the COVID-19 module was to enable the system to collect enriched epidemiological data on COVID-19, incorporate real-time data feeds from private medical laboratories, and streamline the timely dissemination of the data to provinces and districts for public health action.

The Centre for Emerging Zoonotic and Parasitic Diseases

The Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD) continued to play an important role in supporting the malaria control and elimination agenda of the provincial, national and regional programmes. Several surveillance-linked research projects provided the basis for tackling residual malaria transmission in South Africa.

One of these was a community-based malaria prevalence and KAP survey that identified imported asymptomatic carriage in northern KwaZulu-Natal as a significant obstacle to malaria elimination.

Another project showed that a new approach to the control of vector mosquitoes, namely winter larviciding, is likely to add significant benefit to the reduction of malaria transmission in affected areas. This approach now forms part of South Africa's malaria control and elimination policy for the 2019 – 2023 period.

The CEZPD detected the first infant botulism case in South Africa. It was caused by a rare dual toxin-producing strain of *Clostridium botulinum* type Bf. This case illustrated the importance of maintaining a high level of clinical suspicion when assessing hypotonic infants.

A Limpopo Province resident was confirmed bacteriologically and molecularly as only the second indigenous human melioidosis case diagnosed in South Africa. Another cause of a unique opportunistic human infection was identified as the piroplasm parasite *Anthemosoma garnhami,* previously only found in wild rodents in Ethiopia and Namibia.

In collaboration with EcoHealth Alliance (USA) and a number of local institutions such as One Health, significant progress was made in understanding the ecology and epidemiology of Rift Valley fever (RVF) in South Africa, including identification of specific wetland habitats and soil properties associated with high disease mortalities and breeding habitats of RVF virus mosquito vectors.

In collaboration with UP, the CEZPD continued its bio-surveillance programme for zoonotic pathogens in local bat populations. The period of the highest Marburg virus shedding was determined by its detection in rectal swabs from Egyptian rousettes, signifying that faecal contamination of natural bat habitats represent a potential source of infection for humans. Identified genetic sequences are closely related to the Ravn strain of the virus, implying introduction of Marburg viruses from distant localities. Confirmation of the period for the highest virus exposure risk highlights the value of bio-surveillance and demonstrates that Marburg viruses continue endemic circulation in South Africa. This represents a potential threat, which needs to be communicated to at-risk communities as a part of evidence-based public health education and prevention of pathogen spill-over.

The 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 waterborne outbreaks. During the 2019/2020 financial year, the centre provided epidemiological and laboratory testing support for 32 outbreaks, and documented a further 118 outbreaks with insufficient epidemiological or sample testing data that prohibited further investigation.

In outbreaks associated with bacterial pathogens, whole-genome sequencing (WGS) of isolates was conducted to assist with investigations. In addition, the centre continued to monitor all *Listeria* cases reported to the NMC system and conduct WGS on isolates submitted to ensure early detection of any potential outbreaks following the unprecedented *Listeria* outbreak in 2017/2018.

The centre also conducts routine diarrhoeal disease sentinel surveillance at selected sites. A decline in rotavirus prevalence (11%) was noted in 2019; notably, the rotavirus was replaced by *Shigella* spp. as the leading cause of diarrhoeal hospitalisations in children <5 years in South Africa. Plans are underway to expand the current surveillance to two additional provinces and include all ages.

The centre engaged with the DoH on the Strategic Plan for Diarrhoeal Diseases, and published 10 papers in peer-reviewed journals. A paper on the *Listeria* outbreak in South Africa was published in the prestigious *New England Journal of Medicine*.

Current areas of research in the centre include:

- Increasing the capacity for WGS of enteric bacteria to improve outbreak detection and investigation;
- Improved diagnosis of common enteric infections in Africa;
- Investigating a new injectable rotavirus vaccine;
- Examining the potential infectious causes of intussusception; and
- Determining the impact of secretor status and microbiome on rotavirus susceptibility.

The 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 (CC) for AMR and is the national focal point for the WHO's Global Antimicrobial Resistance Surveillance System (GLASS). The centre's epidemiology team conducts community and healthcare-associated outbreak investigations and is involved in evaluation of large-scale public health programmes.

The centre implemented a real-time alert system to detect outbreaks of healthcare-associated bloodstream infections among neonates at secondary hospitals in four provinces. The hospital personnel were trained to use the outbreak alert mobile software application throughout 2019. Results of the pilot project will inform plans to roll out the mobile application to facilities with limited laboratory and epidemiologic capacity.

Senior members of the centre represented the NICD on the Ministerial Advisory Committee for AMR, WHO AMR Surveillance and Quality Assessment Collaborating Centres Network and the WHO Strategic and Technical Advisory Group for AMR. AMR surveillance is performed by national or sentinel isolate-based analyses for bacterial and fungal isolates, and electronic data analysis mapping AMR from patients who meet the surveillance case definitions.

The centre continued enhanced surveillance for cryptococcal meningitis to assess the impact of national reflex cryptococcal antigen screening and the use of 5-fluorocytosine (5-FC) for treatment. The centre led and participated in the investigations of several healthcare-associated outbreaks in neonatal units during the year under review. These investigations revealed that overcrowding, understaffing, sub-optimal IPC measures and lack of antimicrobial stewardship remain the driving factors for healthcare-associated outbreaks. Failure to address these underlying issues results in recurrent outbreaks.

As a WHO CC for AMR, the centre participated in the WHO AMR Surveillance and Quality Assessment CC Network, and provided external quality assessment on AMR to GLASS participants across the African continent.

The Centre for HIV and Sexually Transmitted Infections

The Centre for HIV and Sexually Transmitted Infections (CHIVSTI) consists of four sections, namely HIV Virology; Cell Biology; HIV Molecular and Serology; and Sexually Transmitted Infections, that collectively addresses the challenges of HIV and STI diseases through the following programmes:

- Surveillance of disease burden and antimicrobial resistance;
- Measurement of endpoint infections and antiviral;
- Broadly neutralising antibodies as part of prophylactic HIV vaccine and antibody-mediated protection clinical trials;
- Exploring an HIV "cure" strategy; and
- Development in large trials and cohort studies of reference diagnostics and implementation science.

HIV Surveillance

Results were released from the 27th edition of the antenatal survey conducted between 1 October and 15 November 2017 at 1,589 sentinel sites selected across South Africa. The HIV prevalence data generated from the survey continues to contribute to the Thembisa and AIM HIV models, which provide yearly national

projections on the total number of people living with HIV, new HIV infections and AIDS-related mortality in the country. Nationally, HIV prevalence among pregnant women remained stable at around 30%. The consistent decline in HIV prevalence observed among young women (15-24 years) is encouraging, as this population has traditionally been at increased risk of HIV acquisition. Knowledge of HIV status prior to the first antenatal care (ANC) visit was low, especially among young women (15-24 years), highlighting the gap in access to youth-friendly reproductive health services. The 1st and 2nd targets of the WHO 90-90-90 strategy were reached among pregnant women across all provinces, which indicates the efficiency of the PMTCT programme in identifying HIV-positive pregnant women and enrolling them for treatment.

In 2019, a nationally-representative survey of HIV drug resistance (HIVDR) was implemented in adult patients with unsuppressed VL. Next Generation Sequencing (NGS) and drug level testing (DLT) using liquid chromatography mass spectrometry was performed on random samples from 16 NHLS laboratories. Of the 8,202 VL test specimens collected, 1,053 had unsuppressed VL, of which 779 were selected for further testing. The survey showed that 72% of patients with unsuppressed VL harbour resistance to ART. DLT confirmed that 55% of specimens had detectable levels of ART. HIVDR was lower in patients that had undetectable levels of ART ($p<0.0001$), presumably due to a lack of drug selection pressure. The use of residual specimens proved advantageous in that it allowed for proportion to size sampling, and reduced collection time and cost.

STI Surveillance

The centre continued to strengthen the case-based surveillance of congenital syphilis (CS), a preventable medical condition that results from the transmission of *Treponema pallidum (T. pallidum)* infection from an infected pregnant woman to her foetus. *T. pallidum* infection has severe consequences for the foetus, resulting in early foetal deaths and stillbirths, neonatal deaths, preterm and low birthweight births and symptomatic disease in addition to asymptomatic infections. CS is a 'category two' NMC condition requiring notification within seven days of detection. The centre reported 362 cases of CS to the DoH for inclusion in the Global AIDS Monitoring (GAM) report. Although there was likely underreporting of CS, activities are underway to triangulate CS data with other data sources in a formal evaluation during the next financial year.

Aetiological surveillance of STI syndromes is essential for validating and updating the existing national STI syndromic management guidelines that are in use at PHCs throughout the country. South Africa is one of a few African countries that submits *Neisseria gonorrhoeae* antimicrobial resistance data to the WHO global antimicrobial resistance surveillance system (GLASS). The latest 2018 version of the PHC STI guidelines based on sentinel surveillance data was ratified and released, and is available on the websites of the DoH and NICD. A chapter on the management of persistent and complicated STIs was added to the national Adult Hospital Level Guidelines, which was ratified and will be disseminated in 2020.

HIV Research Activities

The HIV Virology Section continued to support preclinical vaccine development and to define the determinants of broadly neutralising antibodies, widely assumed to be key for a future HIV vaccine. Understanding B cell repertoires using extremely high-throughput technologies, was a focus supported in part through the local development of a low-cost high-performance computing cluster as an alternative approach for resource-limited bioinformatic settings. In addition, a major focus was structural characterisation of the best of the broadly neutralising antibodies and engineering of such antibodies to enhance their function or tailor them for alternative expression vectored systems for passive immunisation studies.

A single-arm clinical trial, called LEOPARD-CT, which commenced in August 2015 at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa, completed recruitment and follow up in April 2019. The trial was designed to improve the understanding of viral latency in early treated HIV-infected children to inform more effective treatment strategies with the ultimate goal of achieving a functional cure or viral remission. An observational cohort of mothers and their infants was followed in parallel, through a clinical trial called LEOPARD-O, which commenced in March 2015. Findings revealed that only half of the children attained and sustained VLs <50 RNA copies/ml, and only half of these sustained CD4% >30%. There was no difference in proportions of children attaining these endpoints according to starting ART within 48 hours or between two and 14 days of birth. Additional interventions over and above the early administration of ART must be considered to attain remission in children.

The Centre for Respiratory Diseases and Meningitis

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 DoH, healthcare providers, regional and international collaborators, to assist with the planning of public health policies and programmes, and response to respiratory disease and meningitis outbreaks.

The CRDM is also a source of capacity building and formal training within South Africa and the African region. During the year under review, the centre continued with the 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 PHCs, as well as the private general practitioner network (Viral Watch). The focus of these programmes is to describe the burden, seasonality and characteristics of influenza, respiratory syncytial virus (RSV) and *Bordetella pertussis* (pertussis). Laboratory-based surveillance programmes included long-standing pathogens under surveillance, such as the pneumococcus, meningococcus and *Haemophilus influenzae*, with a focus on outbreak detection and the impact of interventions.

The CRDM has been at the forefront of the response to COVID-19 pandemic in South Africa. Case definitions were developed for surveillance and laboratory testing of possible COVID-19 cases in January 2020. In collaboration with the DoH and other partners, COVID-19 guidelines for case-finding, diagnosis, management and public health response in South Africa, were developed and released in February 2020. These guidelines have subsequently been updated in line with the evolving epidemiology of the disease. Additional guidelines were developed for different sectors such as education, together with relevant partners.

The CRDM laboratory was the first in South Africa to implement diagnostic PCR testing for SARS-CoV-2, starting from 26 January 2020, and was the only testing laboratory in South Africa until early March 2020. The centre worked closely with laboratories to rapidly expand laboratory testing capacity in both the public and private sectors.

The CRDM laboratory became a WHO COVID-19 International 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 inter-laboratory comparisons.

Together with relevant partners, the CRDM supported a wealth of training activities on COVID-19. 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.

New pathogens (group A and group B streptococcus) were included in laboratory-based surveillance from 2019, and enhanced surveillance from April 2020. Studies of burden of disease (influenza, RSV, pertussis and pneumococcus), vaccine effectiveness (influenza) and carriage (meningococcus) were conducted to assist policy makers with the implementation of vaccine strategies.
In 2020, four postgraduate students joined the CRDM as part of the NIH-funded South Africa-Pittsburgh Public Health Genomic Epidemiology Research Training Program (SAPPHGenE), which aims to develop research in public health genomics in South Africa. Six 'category one' NMC conditions (acute rheumatic fever, COVID-19, diphtheria, meningococcal disease, pertussis and respiratory disease caused by a novel respiratory pathogen) and two 'category two' conditions (*Haemophilus influenzae* type b (Hib) and legionellosis) fall within the centre.

During the year under review, active reporting and real-time verification for the NMC programme have commenced. The CRDM responded to several outbreaks, including outbreaks of diphtheria, meningococcal disease and influenza. Pertussis alerts and updates for clinicians were published. The diphtheria and influenza guidelines were updated in 2019.

Centre for Vaccines and Immunology

The Centre for Vaccines and Immunology (CVI) was established in 2012, to provide laboratory and epidemiological support to the DoH. The centre serves as the National Surveillance Laboratory and the WHO Regional Reference Laboratory for acute flaccid paralysis (AFP), as well as measles and rubella surveillance. This includes receiving and testing samples from all nine provinces in South Africa.

In addition to testing samples from the southern block countries, namely Angola, Botswana, Lesotho, Namibia, Madagascar, Mozambique, Malawi, Zambia, Zimbabwe and Swaziland, the centre also conducts other virological and immunological research projects on TB, viral hepatitis and other vaccine-preventable diseases. During the 2019/2020 financial year, the CVI supported the African region for polio surveillance, notifying 16 countries and the WHO of results for immediate action. The centre provided laboratory support to three suspected measles outbreaks in South Africa, which enabled rapid responses by provincial health authorities. The centre furthermore conducted laboratory-based surveillance for hepatitis A and hepatitis B, reporting results to the WHO. Working together with the NMC system, the centre reported two cases of neonatal tetanus, which indicates a requirement for strengthening maternal immunisation and antenatal education.

In addition, the centre reported four cases of congenital rubella syndrome, which indicates the requirement for the introduction of the rubella vaccine into the expanded programme on immunisation. The centre also contributed modelling documents to the National Advisory Group on Immunization, to guide the timing for rubella vaccine introduction.

Regarding teaching and training, one field epidemiologist (FETP) and two intern scientists completed their rotations in the centre. Staff also established the Basic Vaccinology and Advanced Immunology Modules of the new MSc Vaccinology, which was presented for the first time at Wits in 2019.

The Centre for Tuberculosis

The Centre for Tuberculosis (CTB) serves as the National TB Reference Laboratory (NTBRL) for South Africa and as a WHO Supranational TB Reference Laboratory globally.

The results of the national TB prevalence survey provided the first direct measurement of the burden through active case finding and identified a higher burden than currently reported. This negatively impacts achievement of “The End TB Strategy” targets. Poor health-seeking behaviour among males was identified as an important issue, while TB among HIV negative patients and patients without reported symptoms are now recognised as important contributors to the gap.

Bedaquiline is a therapeutic agent to treat DR-TB and has shown significant impact on the reduction of mortality, and improvement of overall treatment success. Universal use of the agent for treatment of DR-TB raised concerns of resistance emerging. A national surveillance programme was introduced, which determined an overall baseline bedaquiline resistance prevalence of 3.8% among DR-TB patients. Emergence of resistance during treatment occurred at a frequency of 2.3%. Patient outcomes were also poorer in those with bedaquiline resistance. These findings served to guide appropriate policy decisions.
Regularised results for action (RfA) alerts were implemented for both drug susceptible and DR-TB, to drive public health action. In collaboration with external partners, the centre demonstrated the value of these data, which resulted in an improvement in the percentage of individuals with DR-TB enrolling for treatment from below 80%-95%. This evidence supported the expansion of the RfA to also include drug-susceptible TB. In addition, the re-engineered NMS Surveillance System integrated these alerts with an automated reporting system, which is a major advancement.
An inventory study is a useful approach to determine under-reporting of TB. There has been uncertainty of the true burden of TB in the private sector, which may be attributed to untraceable TB patients. In addition, the proportion of individuals diagnosed with TB but who have not enrolled for treatment, is a key concern. The centre merged data from the routine reporting of individuals on treatment and those with a laboratory-confirmed TB result in both the public and private sectors. Preliminary findings indicate that the total burden of laboratory-confirmed TB cases in the private sector is approximately 10 000, which equates to 5% or less of the total burden in SA. The project is still in progress and will also quantify the relative magnitude of loss to follow up and overall under reporting.

A critical requirement for the effective management of DR-TB, is access to a simple, user-friendly universal drug susceptibility test (DST) to guide treatment decisions. This is important as treatment involves at least four drugs with complex adverse effects. We defined criteria for a broth microdilution assay that provides phenotypic DST for 10 drugs simultaneously, which was cross-validated with WGS and demonstrated the quantitative value of the assay to guide treatment decisions.

National Cancer Registry

The National Cancer Registry (NCR) is the primary pathology-based cancer surveillance system and most extensive population-based repository of cancer data in South Africa. During the year under review, the NCR used multi-model supervised machine learning techniques to assign malignancy status to histology reports from the NHLS CDW and identify missing cancer records, which could not be identified by routine CDW algorithms. This greatly improved the completeness of the pathology-based registry for the years 2015, 2016 and 2017. Data from 2015 and 2016 were coded, cleaned and analysed and the 2015 report was published on the NCR website. The NCR created a "Stata Do" file to automate the calculation of age-standardised incidence rates and improve the timeliness of cancer incidence reports. Data for cancers diagnosed in 2017 were coded and the dataset is currently being cleaned, while 2018 data is currently being coded.

The Ekurhuleni population-based cancer registry (EPBCR) identified new data sources, and improved case finding, which was shared during a stakeholder feedback meeting. This resulted in the reporting of an additional 1324 cases (39% increase) of cancer. A total of 4695 new cancers was reported for the year 2018, and common cancers in males were prostate, colorectal, lung, melanoma and oesophageal cancers. In women, the most common cancers were breast, cervical, colorectal, uterine and lung cancers.

In the 2019/2020 financial year, the NCR published key research in cancer epidemiology. The registry also examined national cancer trends and excess cancer risk in people living with HIV compared to those who are HIV-negative. It was determined that people living with HIV are at higher risk of AIDS-defining cancers namely, Kaposi sarcoma, non-Hodgkin's lymphoma and cervical cancer. They are also at increased risk of conjunctival cancer and human papillomavirus HPV)-related cancers, which include penile, anal and vulvar cancer, compared to HIV-negative patients.

Squamous cell carcinoma of the skin was also determined to be HIV-associated. The risk of Kaposi sarcoma has declined as ART became available. The risk of conjunctival cancer and HPV-related anogenital cancers (cervical, anal, vulvar and penile cancers), however, continues to increase, despite widespread availability of ART. The findings of this study were used to inform a national HIV-associated cancer awareness campaign for the 2019 World AIDS Day.

Sequencing Core Facility

The remit of the Sequencing Core Facility is to provide high-level sequencing and analysis support, which enables multi-disciplinary research and surveillance projects to study pathogen genomes and host genetics, particularly in the context of public health priorities at the NICD. This is already ongoing with existing sequencing approaches, which include the PacBio SMRT sequel system and Illumina MiSeq sequencing platforms, as well as the most recently added Illumina NextSeq 550 instrument, which provides higher throughput capacity at a much-reduced rate.

During the 2019/2020 financial year, 4500 genomes were sequenced, with 31% focused on HIV research and surveillance, 27% on DR-TB surveillance , 17% on enteric pathogens (*Salmonella* spp., *L. monocytogenes, Shigella* sp and *V. cholerae*), 16% on respiratory pathogens (*S. pneumoniae, S. pyogenes*, influenza A and B, RSV), 7% on hospital-acquired infections, including fungal pathogens (*A. baumannii, S. aureus, K. pneumoniae* and *C. auris*) and the remaining 2% on zoonotic pathogens (arenaviruses, herpes simplex virus, *Brucella* sp.). The sequencing core facility generated the first SARS-CoV-2 genome in South Africa and is assisting other African countries through the Africa CDC partnership.

I would like to take this opportunity to thank all the staff for their commitment to keeping the NICD at the forefront of infectious disease outbreak response, surveillance and research.

Deputy Director's Overview

2019/20

Dr Natalie Mayet
Deputy Director

1. Background

The transversal functions of Biosafety and Security, Communications and Information Technology provide the universal platform for the NICD to execute its mandate of surveillance, outbreak response, operational research, specialised diagnostic services and capacity building for communicable disease and the National Cancer Registry. The South African Field Epidemiology and Training Program (SAFETP) is one of the many training programs offered by the NICD aimed at building the much needed epidemiology capacity for the country. The on-site Occupational Health services provides health and safety for NICD employees under the umbrella of our sister division, the National Institute of Occupational Health (NIOH). As a public health institute, the NICD functions within a collaborative framework of networks and partnerships at national, regional and international level. These transversal services and the extensive networks supported the preparedness of the institute for the COVID-19 response.

Division of Biosafety and Biosecurity Team Activity Highlights

The Division of Biosafety and Biosecurity (DBB) continued to provide biocontainment engineering support for the upgrading of the NICD and NHLS high and maximum containment laboratory infrastructure of BSL3 and BSL4. The DBB played a significant role in informing the national biosafety and biosecurity agenda, through active participation in various forums aimed at impacting the local, regional and international bio-risk management landscape. The team, through the Institutional Biosafety and Biosecurity Committee (IBBC), was instrumental in initiating and establishing the first multi-sectoral National Biosafety and Biosecurity Technical Working Group for implementation of International Health Regulations.

The DBB participated in the launch by the Africa Centres for Disease Control and Prevention of its initiative to Strengthen Biosecurity and Biosafety, and subsequently co-hosted the first technical workshop for the Southern Africa Regional Collaborating Centre member states with Zambia National Public Health Institute and the University of the Witwatersrand. The workshop identified priorities to improve compliance of Member States with biosecurity and biosafety-related WHO Joint External Evaluation targets, provided the framework for implementation at country-level and decided a continent-wide consensus list of high consequence agents and toxins.

DBB was involved in a number of capacity building initiatives that included: the IATA shipping course for internal NICD staff for shipping of hazardous biological agents abroad; hosting of twelve (12) intern medical scientists. The unit trained in Biorisk Management including Risk Assessments, Dual Use Research of Concern and Bioethics; provided subject matter expertise at the Middle East Scientific Institute for Security (MESIS)/ Sandia National Laboratories (SNL) workshop on perspectives for pursuing and operating high containment laboratories in Jordan; and presented at the University of Pretoria on Building Design and Engineering Approaches to Infection Control.

The team also presented at a regional meeting on Assessing the State of Laboratory Biosafety and Biosecurity in the SADC Region, co-hosted by the Academy of Science of South Africa (ASSAf) and participated in a workshop on "Engaging Young Scientists from the Global South in Biosecurity Diplomacy" hosted by the United Nations Office of Disarmament Affairs. Other activities that the team participated in include: the International Counter-proliferation Program - International Joint Bioterrorism Investigations held in Durban; NTI Global Biosafety Dialogue 2019 in Ethiopia; attendance of the European Biological Safety Association's 22nd Annual conference in Bucharest, Romania; attendance of the American Biological Safety Association's 63rd Annual Biosafety Conference in Birmingham, USA where a poster presentation was delivered on "Training interventions following exposure incidents in the public health laboratories in South Africa".

A significant achievement was the attainment of an internationally recognised qualification and the professional certification of four (4) NICD staff in Biorisk Management from the International Federation of Biosafety Associations.

International Association of National Public Health Institutes

The NICD continues to engage with other global Public Health Institutes through the Network of the International Association of National Public Health Institutes (IANPHI) and actively engages with Africa CDC and the Regional Collaborating Centre (RCC) in Zambia. Additionally, NICD employees participate in various Technical Expert Working Groups at Africa CDC. The Deputy Director, as the chairperson of the Expert Committee on National Public Health Institutes (NPHI`s) for Africa CDC, participated in the strengthening of NPHI development for SADC at a meeting hosted by the RCC in Zambia in September 2019. In the role as the chairperson of IANPHI for Africa, we engaged with the World Health Organization (WHO) to explore a closer alliance with IANPHI and WHO in meeting the global triple billion targets.

Communication

The NICD Communications Unit continued to provide strategic support to the various Centres, with the objective of delivering insightful communications solutions that packs a punch. Vital to the team's success was growing communication interaction and achieving impact through health awareness campaigns for COVID-19, Malaria, Tuberculosis and other infectious diseases. Towards the end of the reporting year, the Unit has grown to incorporate the services of a Stakeholder Relations Specialist, to anchor operations and expand relations with current and new stakeholders.

Media coverage grew fivefold from 2 021 news items in the previous financial year, to an impressive 10 962 news items in the reporting year. A noteworthy highlight for media liaison activities is media reach, which revealed that more than 1.4 billion consumers were accessed through media. These statistics support the tremendous public impact of the brand in responding to disease threats and pandemics. The production of topical communication materials, including publications, reports, multimedia and campaigns, continued to support the NICD's reputation as a forward-thinking scientific health institute.

The Communications Unit has been instrumental in raising awareness of public health matters, including malaria, AIDS, pneumonia and COVID-19, to name a few. As a result of the pandemic, the team had to be on-point in providing the South African public with credible information in order to build capacity for an informed citizenry. This included training provincial public health communicators and strengthening relations with bodies in both the public and private sectors. The strongest steel is forged by fire, and the manner in which the team executed the COVID-19 risk communications is commendable.

The NICD website attracted over 1.3 million visitors and over 7.3 million page views in the reporting period. Social media continued to grow extensively with the Facebook following increasing to 35 523 and Twitter to 53 407 at the end of March 2020.

Information Technology

The NICD continues to find innovative ways to use technology to enhance surveillance systems. This is an important part of our digital journey in ensuring that infrastructure is maintained whilst we explore new development of systems.

The most significant development was the integration of private sector laboratory data into the NICD Surveillance Data Warehouse that had to be rapidly implemented for the COVID-19 outbreak. There were a series of COVID-19 related enhancements developed for the NDoH and the NIOH.

The enhancement of the Notifiable Medical Condition System remained a focus of development throughout the year.

The Disaster recovery data warehouse appliance was upgraded as precursor to data integration platform upgrade with a focus on Cyber security improvement.

South African Field Epidemiology Training Program (SAFETP)

Established in 2006 the SAFETP hosted its fourteenth cohort of residents in 2020, with an intake of ten first-year and seven second-year residents.The program graduated a total of 92 graduates in the Advanced FETP training and 76% are retained in the public sector. Five (5) residents were awarded a Master's in Public Health in May 2020 and two (2) residents were awarded a Master's of Science in Epidemiology in July 2020. As part of their field training residents participated in the investigation of seven (7) outbreaks across the country and continue to respond to the COVID-19 pandemic at both provincial and district levels. SAFETP residents participated in COVID-19 preparedness activities, prior to the first confirmed case in South Africa. SAFETP staff and residents have been deployed to highly burdened districts during the COVID-19 pandemic supporting contact tracing, data management, and reporting efforts.

Dr Tedros Ghebreyesus, WHO Director General, requested South Africa to facilitate the training of 200 epidemiologists for the SADC region. To this end, the SAFETP collaborated with the Southern Africa Regional Collaborating Centre (RCC) of the Africa CDC, to develop a strategic plan to facilitate the training of these field epidemiologists. A workshop was held with representatives from Angola, Namibia, Malawi, Mozambique, South Africa, Zambia and Zimbabwe and a RCC-FETP Task Force was established with representatives from each country.

Residents conducted five (5) large database analyses and completed six (6) surveillance evaluation projects. Two (2) of the residents had been seconded for training from neighbouring countries, Lesotho and Malawi. Between July and November 2019, the SAFETP offered basic applied epidemiology training to 90 district and provincial level frontline health professionals, responsible for collecting and analysing surveillance data and/or responding to disease outbreaks. Ninety participants from the Free State (25), Mpumalanga (18), KwaZulu-Natal (23) and Gauteng (24) provinces completed the 12-week training, consisting of two one-week long didactic courses and a ten-week long applied field training. Participants learned and practiced the fundamental skills used in frontline surveillance, including use of case definitions, disease detection and reporting, summarising of data using simple tables and graphs, case investigation, outbreak investigation and response, data analysis and interpretation for decision-making. Completion certificates were awarded to 71 participants who successfully completed the training.

The SAFETP team continued to work with the NDoH to develop a training curriculum for national, provincial, district, and local level health professionals to facilitate the domestication of the WHO developed IDSR guidelines in South Africa. The first of these trainings, focusing on the COVID-19 response, took place in four (4) districts in the Northern Cape Province in October 2020.

Presentations

Publications: 9
International Conferences: 5, plenary session presentations: 2
National Conferences: 10

Occupational Heath

The on-site Occupational Health Service has developed Occupational Risk Exposure profiles specifically for BSL3 and BSL4 laboratories, together with medical protocols and questionnaires that mitigates against task and occupation-based risks.

Routine medical surveillance was conducted for more than 330 employees and 193 vaccines were administered mostly for hepatitis B, measles, mumps and rubella, rabies, meningitis, tetanus and hepatitis A. Due to the shortage of flu vaccine in the country, 150 doses of flu vaccine were prioritised for high risk employees.

The service reported 37 Injuries on Duty (IOD) for the period, the same as in the previous financial year and 84% of these injuries required first aid intervention, with only five (5) cases requiring medical attention and COIDA reporting.

The need for the service was emphasised with the COVID-19 outbreak. Sister Ida Jordaan was involved in the fielding of multiple calls from the public and was actively involved in the training and screening of NICD employees both on and off-site. She was also responsible for implementing the legislative requirements for the outbreak, conducting risk assessments, counselling of contacts of COVID-19 cases and the management of high-risk close contacts.

Presentations were delivered to the Centres on the management of IOD's aimed at providing general information on background and management processes.

Three (3) Automated external defibrillator (AED) machines were installed and a training video, that will enable all employees to familiarise themselves with CPR and the use of the AED, is being developed.

Centre for
Emerging Zoonotic and Parasitic Diseases

2019/20

Prof Janusz Paweska
Centre Head

1. Background

The Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD) provides national and regional capacity for the diagnosis, surveillance, and research of viral, bacterial and parasitic pathogens, including those classified as zoonotic biosafety level 3 (BSL3) and biosafety level 4 (BSL4) agents.

The diagnostic, surveillance and research activities of the Centre are primarily focused on:

- Viral haemorrhagic fevers (VHFs) such as Ebola and Marburg diseases, Lassa fever and Lujo haemorrhagic fever (LHF);
- Arthropod-borne diseases such as malaria, Rift Valley fever (RVF), Crimean-Congo haemorrhagic fever (CCHF), yellow fever, plague and rickettsioses;
- Rabies and rabies-related infections;
- Bacterial infectious diseases such as anthrax, botulism, brucellosis and leptospirosis;
- Parasitic opportunistic infections;
- Diarrhoeal disease in under-5 children;
- Schistosomiasis; and
- Soil-transmitted helminthic diseases.

CEZPD plays an important role in supporting the malaria control and elimination agenda of the provincial, national and regional malaria control programmes. It contributes to policy advice, technical support, and training of scientists, medical technologists and epidemiologists in emerging and re-emerging zoonotic and parasitic diseases.

In addition, CEZPD serves as an internationally recognised resource of expertise for referral diagnostic services, outbreak response and consultations under the mandate of the World Health Organization (WHO) regional reference laboratory for plague and the Global Outbreak Alert and Response Network (GOARN).

A number of diagnostic assays performed by CEZPD is accredited by SANAS for the ISO 15189 standard of operation. The Centre operates highly specialised laboratory facilities, including the positive-pressure suit BSL4, 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 resources for diagnosis, surveillance, outbreak response and research of priority viral, bacterial and parasitic diseases, public health threats and emerging zoonotic diseases in Africa.

During the financial year under review, a newly constructed BSL3 laboratory was successfully commissioned and fully operationalised. Together with BSL4, this facility represents the most advanced high and maximum biocontainment infrastructure in the country and in Africa. This enables diagnostic services and research on high-consequence dangerous pathogens with epidemic-prone potential, including the recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the coronavirus disease (COVID-19) pandemic.

A newly commissioned *Anopheles* mosquito mass-rearing facility will further contribute in assessing mosquito malaria vector susceptibility to insecticides and feasibility of the sterile insect technique for malaria vector control. A regional malaria slide bank operated by the centre's Parasitology Reference Laboratory has produced more than 20,000 slides for malaria microscopy training and quality assessment in southern African countries during the 2019/2020 financial year.

Figure 1a: Prof Janusz Paweska hosting the Deputy Minister of Health, Dr Joe Phaahla during his visit to the newly commissioned (August 2019) BSL3

Figure 1b: CEZPD staff in BSL3 protective equipment

Figure 2: Newly commissioned *Anopheles* mosquito mass-rearing facility

2. Surveillance

The CEZPD Special Viral Pathogens Laboratory confirmed five human cases of rabies in South Africa from 1 April 2019 to 31 March 2020. These cases was reported from KwaZulu-Natal (n=4) and Eastern Cape (n=1) provinces. A total of six probable cases were reported during the same period. These cases were not laboratory-confirmed, but presented with a clinical and epidemiological history that befits rabies. The probable cases were also reported from KwaZulu-Natal (n=3) and Eastern Cape (n=3) provinces. Cases are not laboratory-confirmed due to the lack of submission of samples, or submission of unsuitable samples for laboratory testing

From a total of 54 requests for VHF testing during the reporting period, a single case of CCHF was laboratory diagnosed. The case was reported from the North West Province and involved a veterinarian who was exposed to ticks. The patient recovered from the infection. The Arbovirus Reference Laboratory investigated suspected endemic and exotic arboviral disease cases, including chikungunya, RVF, dengue, Ross River and Japanese encephalitis. Several cases of imported dengue fever and chikungunya were identified.

In collaboration with the Biosurveillance and Ecology of Emerging Zoonoses Research Group, Department of Medical Virology, Faculty of Health Sciences, University of Pretoria (UP), the Special Viral Division of the CEZPD continued its biosurveillance programme for zoonotic pathogens in local bat populations. The period of the highest viral shedding by Marburg virus (MARV) detection in rectal swabs from Egyptian rousette bats was determined. These findings signify that faecal contamination of natural bat habitats represent a potential source of infection for humans. Identified genetic sequences are closely related to the Ravn virus of the *genus Marburgvirus,* implying introduction of MARV from distant localities and local circulation of different genetic variants. Confirmation of the period for the highest virus exposure risk (April-June) highlights the value of biosurveillance and demonstrates that MARV continue endemic circulation in South Africa. This represents a potential threat, which needs to be communicated to at-risk communities as a part of evidence-based public health education and prevention of pathogen spillover.

The Special Bacterial Pathogens Reference Laboratory continued surveillance for plague in susceptible rodent populations in the City of Johannesburg, Nelson Mandela Bay Municipality (Coega area) and eThekwini Municipality, to alert public health authorities to the possibility of increased human plague risk. A total of 1,164 rodents was tested and found to be negative for plague anti-F1 antibodies. Plague is currently in a quiescent phase in South Africa, but experience from outbreaks in other countries has shown that plague activity can resume unexpectedly after decades of quiescence.

Considering Gauteng's high malaria burden and based on the advice of WHO, certain health facilities from Gauteng Province were added to the antimalarial drug resistance surveillance programme of the Laboratory for Antimalarial Resistance Monitoring and Malaria Operational Research. A total of 4,177 malaria samples was analysed for molecular markers associated with resistance to artemisinins and lumefantrine. No markers of artemisinin resistance were detected. However, all parasites analysed carried the molecular markers associated with reduced susceptibility to lumefantrine, a component of the recommended treatment for uncomplicated malaria in South Africa. These results emphasise the requirement for regular assessment of antimalarial drug efficacy in South Africa, to ensure effective antimalarial treatment is in place.

A total of 4,997 *Anopheles* mosquitoes was referred to the Vector Control Reference Laboratory from sentinel sites in the KwaZulu-Natal and Mpumalanga provinces. The presence of four malaria vector species that were identified amongst these collections, namely *Anopheles arabiensis, An. merus, An. parensis* and *An. vaneedeni*, were demonstrated to contribute to ongoing residual malaria transmission in South Africa. During a community-based malaria prevalence and knowledge, attitude and practices (KAP) survey, the mapping of many *Anopheles* breeding sites in northern KwaZulu-Natal Province was also undertaken. This information will be used to improve the efficacy of the province's larval source management programme.

Policy contributions

During the year under review, the Centre made several contributions to the development of policies, guidelines, operating procedures and strategies as follows:

- The WHO plague guideline concerning recommendations on diagnostic techniques, case definitions, antibiotic treatment and biorisk management of plague positive cadavers;
- In the context of the current COVID-19 pandemic, it was strongly recommended that malaria control activities in South Africa are conducted in an especially timely and efficient manner, to reduce the risk of co-infection in affected communities and reduce malaria-related hospitalisations;
- The National Vector Control Strategy, with special emphasis on malaria vector control;
- The testing of fever patients for both COVID-19 and malaria in malaria endemic districts as part of the government's national COVID-19 screening programme. This strategy was employed to assist with the prompt detection of malaria cases during the lockdown when movement was restricted;
- Expansion of the single low-dose primaquine policy to include all malaria eliminating districts in South Africa to help with efforts to reduce secondary transmission in the country;
- Contributions to the review of hazardous biological agent regulations by the Department of Employment and Labour; and
- Contribution to guidelines for rabies prophylaxis in humans in South Africa.

Outbreaks

Odyssean malaria

This type of malaria is acquired in non-endemic areas by persons with no travel history and transmitted by infected mosquitoes that are probably mainly imported in road vehicles, such as minibus taxis and trucks. Seven cases were investigated by CEZPD staff, of which two were deaths, yielding a 29% mortality rate, which is more than 10 times the overall annual mortality rate of malaria in South Africa.

3. Research activities

Paramyxo- and coronaviruses in bats

NICD investigators: J Weyer, P Jansen van Vuren, A Kemp and JT Paweska
Collaborators: W Markotter, M Mortlock, M Geldenhuys, L Nel, (University of Pretoria); A Mudakikwa (Rwanda Development Board, Department of Tourism and Conservation); J Nziza (Mountain Gorilla Veterinary Project, Rwanda)
Funding: National Research Foundation

A high diversity of corona- and paramyxoviruses have been detected in different bat species worldwide, including Africa; however, no biosurveillance studies from Rwanda have been reported. Samples from bats collected from caves in Ruhengeri, Rwanda, were tested for the presence of corona- and paramyxoviral RNA. A novel betacoronavirus in two Geoffroy's horseshoe bats *(Rhinolophus clivosus)* was detected. In addition, several different paramyxoviral species were detected in various insectivorous bats, and a henipavirus-related sequence was detected in an Egyptian rousette fruit bat *(Rousettus aegyptiacus)*. These results expand the knowledge on the diversity of corona- and paramyxoviruses and their geographical distribution in Africa.

Figure 3a: CEZPD scientists and scientists from the University of Pretoria preparing to sample bats at the mouth of a volcanic cave in Ruhengeri, Rwanda

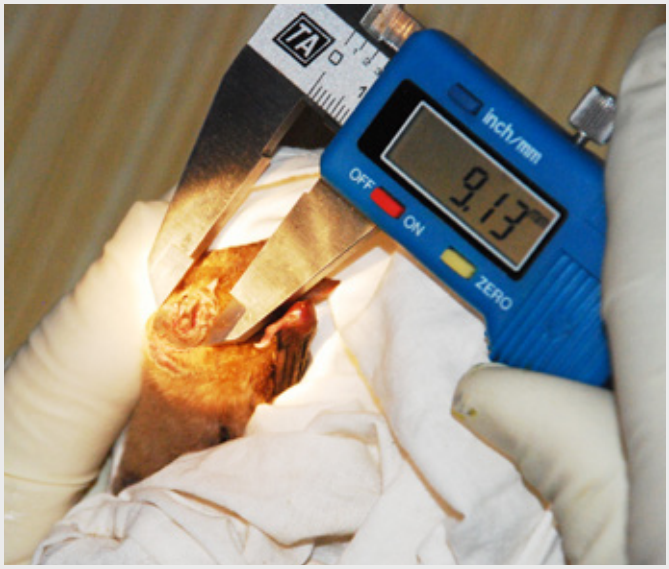

Figure 3b: Taking measurements of insectivorous Geoffroy's horseshoe bat for age estimation

Enhancing diagnostic and surveillance capacity

NICD investigators: J Weyer, N Moolla, N Storm, V Msimang, P Jansen van Vuren, and J Paweska
Collaborators: C Cêtre-Sossah (French Agricultural Research Centre for International Development); J Coertse, L Nel, W Markotter (University of Pretoria); O Conteh (Ministry of Health and Sanitation, Sierra Leone)
Funding: South African Medical Research Council

In collaboration with a number of local and international institutions, diagnostic and surveillance capacity was improved through the development and validation of a number of diagnostic platforms, including: 1. a pen-side test for the detection of nucleocapsid protein of RVF in viremic livestock, 2. a reverse transcription recombinase assay for rapid detection of canine-associated rabies, and 3. three indirect enzyme-linked immunosorbent assays for the detection of serum immunoglobin G (IgG) antibodies to Ebola virus in human sera.

Epidemiology of Rift Valley fever in South Africa

NICD investigators: V Msimang, A Kemp, P Jansen van Vuren, and J Paweska
Collaborators: Y Ngoshe, A Avenant, P Thompson (University of Pretoria); M Rostal, W Karesh, W Whitney (Ecohealth Alliance, USA); C Cordel (ExecuVet, South Africa)
Funding: U.S. Department of Defense, Defense Threat Reduction Agency

As a part of an ongoing One Health project on "Understanding of Rift Valley fever (RVF) in South Africa", a cross-sectional study was conducted on 234 randomly selected farms, to investigate the prevalence and factors associated with the presence of antibodies to RVF virus in livestock in an area heavily affected by that outbreak. The RVF seroprevalence was 42.9% in cattle, 28.0% in sheep and 9.3% in goats, showing a high degree of farm-level clustering. Seroprevalence increased with age and was higher on private versus communal land, on farms with seasonal pans (temporary, shallow wetlands) and perennial rivers, and in recently vaccinated animals. Seropositivity amongst unvaccinated animals born after the last outbreak indicates likely viral circulation during the post-epidemic period. Results indicate that the current level of herd immunity in livestock may be insufficient to prevent another large outbreak, should suitable conditions recur.

Human brucellosis: seroprevalence and exposure factors among abattoir workers in central South Africa, 2018

NICD investigators: J Rossouw, H Geyer, V Msimang, L de Boni and J Paweska
Funding: CDC Global Disease Detection Program

Brucellosis is a widespread zoonotic disease of public health importance that is often associated with occupational exposure. A cross-sectional survey was conducted to investigate the seroprevalence and factors associated with *Brucella* exposure in 382 workers in 16 abattoirs in the Free State and Northern Cape provinces. *Brucella* seroprevalence (IgG) ranged from 0% to 16.7% among abattoir workers, and overall the seroprevalence was 6.3% (24/382), with three (0.8%) workers having serological evidence of chronic infection or relapse. Multivariable analysis identified several factors associated with higher *Brucella* seroprevalence: (i) slaughtering, evisceration or dressing of carcasses, (ii) male compared to female, and (iii) consumption of undercooked meat. Several abattoir characteristics were also associated with higher seroprevalence: (i) low animal throughput, and (ii) increased size of abattoirs (number of workers). Even though a relatively low seroprevalence was observed, it was comparable with *Brucella* seroprevalence in the farming community in the same area.

Identifying the entomological drivers of malaria transmission

NICD investigators: B Brooke, G Munhenga, S Oliver, Y Dahan-Moss, M Kaiser, P Tshikae, L Koekemoer and M Coetzee
Collaborators: F Duncan (University of the Witwatersrand).
Funding: National Research Foundation and the National Health Laboratory Service Research Trust

The identification of *Anopheles* mosquitoes to the level of species is a fundamentally important precursor to incriminating specific populations in the transmission of malaria and assessing their susceptibility to insecticide. The complexity of this process and the potential for misidentification were assessed and detailed in several research manuscripts. Central to these investigations was the discovery that *Anopheles parensis,* previously assumed to be medically unimportant, contributes to ongoing malaria transmission in South Africa, and that the major vector species *An. arabiensis* does not enter a state of diapause (hibernation) during winter, providing an evidence base for the use of winter larviciding as an additional vector control strategy.

Malaria vector mosquitoes associate closely with human communities and are continually adapting to changing land use patterns and agricultural practices. Adaptive characteristics in vector mosquitoes that are important in terms of malaria transmission include breeding in aquatic sites containing various pollutants such as fertilisers, and the development of resistance to insecticides. Recent data show that larval exposure to organic and inorganic fertilisers can reduce insecticide susceptibility and affect the adult life history traits of major malaria vector species. It was also shown that gut bacteria play an important role in the adult lives of vector mosquitoes, affecting their longevities and susceptibility to insecticide.

Figure 4: Collecting *Anopheles* mosquitoes from outdoor resting traps in northern KwaZulu-Natal Province

Laboratory-based surveillance of schistosomiasis in the South African public health sector, 2011-2018

NICD investigators: L De Boni, V Msimang, and J Frean
Collaborators: Corporate Data Warehouse, National Health Laboratory Service
Funding: NICD institutional funds

Schistosomiasis is an important but neglected public health problem in South Africa. The National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW) laboratory data for schistosomiasis from public sector laboratories for the period 2011– 2018 were analysed, of which 135,627 specimens tested positive. Overall, males experienced about 3.7 times higher prevalence for urinary schistosomiasis than females. Similarly, the adjusted prevalence estimates for persons aged between 5 and 19 years were exceedingly high (all more than 100 cases per 100,000) compared to the other age groups. The initial national prevalence estimate was 31 cases per 100,000 but after adjusting for the rate of testing, this was doubled. The provinces with the highest estimated prevalence were Limpopo, Mpumalanga and KwaZulu-Natal.

4. Teaching and training

a. Undergraduate

CEZPD staff provided and contributed to the following teaching and training activities during the reporting year:

- NICD short course for registrars (June 2019);
- NICD virology and parasitology intensive courses for registrars (August 2019);
- NICD medical scientist intern rotation for virology and microbiology;
- Postgraduate Diploma in Tropical Medicine and Hygiene rotations (Universities of the Witwatersrand and London);
- One Health Module for students studying towards their Bachelor in Veterinary Science degrees (BVSc) (Faculty of Veterinary Medicine, UP);
- Collaborative MSc Tropical Animal Health (Faculty of Veterinary Medicine, UP; Institute of Tropical Medicine, Antwerp, Belgium);
- Malaria laboratory diagnosis courses for the National Malaria Control Programme and NHLS microscopists and technologists (August and November 2019);
- Malaria case sub-classification algorithm training for staff from the National Malaria Control Programme;
- A two-week training course on 'Training in *Anopheles* culturing techniques, morphological identification, sampling techniques and insecticide resistance detection' was conducted at the Vector Control Reference Laboratory (VCRL), 19-30 August 2019;
- Drs G Munhenga, P Tshikae and S Oliver hosted an introductory course on anopheline morphological identification at the KwaZulu-Natal DoH offices, 13-17 May 2019;
- Prof B Brooke participated in the WHO/DoH-mediated training course on malaria elimination in South Africa, 14-18 October 2019;
- Prof B Brooke, Dr G Munhenga and Dr P Tshikae assisted with vector control training for malaria elimination in Limpopo, Mpumalanga and KwaZulu-Natal provinces, October 2019;
- Drs Y Dahan-Moss, J Raman, M Kaiser and B Brooke conducted training in malaria biology, surveillance and control, Tshwane University of Technology (TUT), 17 July 2019;
- Plague Surveillance Training for City of Johannesburg Environmental Health Officers;
- WHO Plague Surveillance and Diagnostic Workshop (24-28 June 2019). The workshop was hosted at the NICD in collaboration with experts from WHO, US CDC and Institute Pasteur in Madagascar and was attended by 18 participants from seven African and South East Asian countries; and
- Dr Jacqueline Weyer provided guest lectures for students studying towards a MSc (Med) Vaccinology and a MSc in Epidemiology (Wits).

b. Postgraduate

During the reporting year, the Centre enrolled 20 postgraduate students for studies as follows:

- Eight for MSc; and
- 12 for PhD.

Six students from the Centre graduated with degrees as follows:

- Three with Bachelor in Social Sciences (BSS) (Honours);
- One with MSc; and
- Three with PhD.

Figure 5: Participants performing microscopy of plague during the WHO Plague Surveillance and Diagnostic Workshop, June 2019

Figure 6: Dr Nadia Storm receiving her PhD degree during the 2019 graduation ceremony at University of Pretoria; Prof Janusz Paweska, her PhD promoter, delivering laudation

Dr Nadia Strom obtained her PhD with specialisation in Microbiology based on her thesis entitled "Monitoring of humoral responses against Marburg virus and evaluation of their role in protection against re-challenge in naturally immune *Rousettus aegyptiacus* fruit bats". She was co-supervised by Dr Petrus Jansen van Vuren and Prof Wanda Markotter.

c. Professional development

- Drs Givemore Munhenga and Shune Oliver were appointed to the level of senior researcher at the Wits Research Institute for Malaria (WRIM), and Dr Munhenga received a C rating from the NRF;
- Dr Naazneen Moolla was appointed as extraordinary lecturer at the Department of Virology, UP;
- Dr Jaishree Raman was appointed as a member of the organising and scientific committees of the 3rd International Conference on Re-emerging Infectious Diseases (2020) and elected to the board of the African Pathogen Genomics Diversity Network (PDNA);
- Dr Jacqueline Weyer served as Chair to the DoH-appointed Technical Working Group for Biosafety and Biosecurity in South Africa and was appointed as a member of the Africa One Health Steering Committee;
- Dr Jacqueline Weyer completed the International Federation for Biosafety Associations' examination for international certification as a biorisk management professional;
- Prof Lizette Koekemoer was awarded the African Union Kwame Nkrumah Regional Scientists Award for her contributions to malaria vector control, allied research and capacity building in Africa;
- Prof Maureen Coetzee received an A rating by the NRF, a lifetime achievement award from the European Molecular Biology Organization (EMBO) for her contributions to vector systematics and control, and an award from the Pan African Mosquito Control Association (PAMCA) for her contributions to capacity building and research in Africa;
- Prof Janusz Paweska was nominated as a member of WHO Blueprint Rift Valley Fever Roadmap, a member of the Coalition for Epidemic Preparedness Innovation Rift Valley Fever Task Force, and a member of One Health Platform Scientific Advisory Board.

5. Research output

Journal articles and articles in books

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Conferences

1. During the year under review, staff from the Centre conducted ten presentations at international congresses and 19 presentations at local conferences.

Centre for
Enteric Diseases

2019/20

Dr Juno Thomas
Centre Head

1. 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:

1. Foodborne diseases, which are globally recognised as a threat to food safety and security;
2. Waterborne diseases, which are typically linked to the use of unsafe water and are often associated with large outbreaks;
3. Priority enteric diseases under routine surveillance, which comprise of epidemic-prone conditions such as typhoid, cholera and listeriosis; and
4. Rotavirus, which is a vaccine-preventable disease in South Africa.

The Centre comprises a small team of specialists with extensive experience in enteric diseases, and 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 year under review has been highly productive and the centre placed particular focus on stakeholder engagement to demonstrate the value of its work. To this end, the centre concentrated on several activities such as:

- Outbreak investigations, which is a key strength of the centre;
- Surveillance;
- Development of strategic documents and manuals; and
- High-level research output, which culminated in a paper being published in the New England Journal of Medicine and the completion of ten additional peer-reviewed papers.

Staff from the centre furthermore networked with both the global and local scientific communities, by attending seven international, three African and 11 national conferences. Local communities were supported through education and information on listeriosis, typhoid, hand hygiene and the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was distributed via the media.

Internal teaching and training remained a priority of the centre, and two of its staff members graduated; one with a Master of Public Health degree (MPH) and the other with a Master of Science degree (MSc). Two of the centre's medical scientists were also registered with the Health Professionals Council of South Africa (HPCSA), in the independent practice category.

2. Surveillance

a) Acute diarrhoeal diseases surveillance

The centre monitors diarrhoeal diseases in selected sentinel sites to determine hospitalisations and deaths in all ages and define the major aetiological agents and environmental factors associated with disease. In 2019, a decline of 11% in rotavirus prevalence was noted in all surveillance sites. In fact, rotavirus was no longer the leading cause of diarrhoeal hospitalisations in children <5 years, and was replaced by *Shigella* spp. (24%). In addition, comparisons between cases at urban and rural sites revealed higher prevalence of selected enteric pathogens (adenovirus, *Cryptosporidium* spp., *Campylobacter jejuni/coli* and astrovirus) and increased mixed pathogen infections in urban sites.

b) National listeriosis surveillance

The case investigation form (CIF) for listeriosis surveillance, including a comprehensive food history section, has been redesigned during the reporting period. The CIF was distributed via the website of the National Institute for Communicable Diseases (NICD) and to relevant stakeholders. New listeriosis cases, alerted by the notifiable medical conditions (NMC) surveillance system and corporate data warehouse (CDW), were followed up to ensure collection of additional data and comprehensive food history, as well as isolate referral.

All *Listeria* isolates are routinely submitted for whole-genome sequencing (WGS). Between 1 April 2019 and 31 March 2020, 86 cases of listeriosis were reported from seven provinces. Gauteng had the majority of reported cases (35%, 30/86) followed by Western Cape (30%, 26/86) and KwaZulu-Natal (12%, 16/86). No cases have been reported from Limpopo and Mpumalanga during this period.

An average of one case per week (range: 0-5 cases per week) was recorded. The majority of the cases fall within the 15-49 years age group (42%), followed by neonates ≤28 days (27%), persons aged 50-64 years (15%), the elderly (≥65 years) (12%) and children between one month and 14 years (4%).

3. Outbreaks

The centre continues to play a leading role in outbreak investigation and response to various food- and water-borne and epidemic-prone enteric pathogens. The centre's staff routinely follow up on alerts of suspected enteric disease outbreaks reported through the NMC surveillance system and provide both epidemiological and laboratory support. During the 2019/2020 period, the centre responded to 32 outbreaks.

Foodborne disease outbreaks

Outbreaks were recorded at the following institutions:

- A primary boarding school in the Capricorn District in Limpopo, in May 2019. The outbreak was caused by *Salmonella* Enteritidis-contaminated meals that affected 64 learners;
- A secondary school in Tshwane District in Gauteng in May 2019. The outbreak was caused by *Clostridium perfringens* and sickened 42 children;
- A secondary boarding school in eThekwini District in KwaZulu-Natal in May 2019. The most likely cause of the outbreak was foodborne intoxication (resulting from contamination of food with toxin-producing bacteria), which affected 77 children;
- A winter school camp that took place in Capricorn District in Limpopo in June 2019. This outbreak sickened approximately 200 learners and was most likely caused by foodborne intoxication due to toxin-producing bacteria;
- A primary school in Nkangala District in Mpumalanga in July 2019. The outbreak was more likely caused by a poisoning event than an infectious source, and affected 32 children, of whom three died;
- A long-term care facility in the City of Johannesburg in Gauteng in September 2019. A single case of *Salmonella* Typhi was reported from the facility and no additional cases were detected. However, during the investigation, a previously undetected outbreak of *Shigella flexneri* was uncovered;
- A tertiary educational institution in Tshwane District in Gauteng in September 2019. The outbreak affected 92 students and *Staphylococcus aureus* was isolated from one clinical specimen, but no additional enterotoxin testing was performed. The definitive source and cause of the outbreak were not determined;
- A psychiatric hospital in Cape Town Central District in the Western Cape in September 2019. Seven patients were affected but no definitive source and cause of the outbreak could be established;
- A retirement facility in Waterberg District in Limpopo in December 2019. The outbreak affected 50 residents and *Shigella sonnei* was identified. Epidemiologic investigation revealed that the outbreak was likely foodborne;
- A correctional facility in the City of Johannesburg in Gauteng in January 2020. Five inmates were affected, with mouldy bread the implicated food. No causative agent was determined; and
- A primary school in Vhembe District in Limpopo in February 2020. The outbreak affected 68 learners and enterotoxin-producing *S. aureus* was identified as the cause.

Outbreaks were recorded at the following events:

- A church conference which took place in the uThukela District in KwaZulu-Natal in June 2019. The outbreak affected 55 people who attended the event. Limited clinical specimens were available for testing and no enteric pathogen was detected. The most likely cause of the outbreak was foodborne intoxication due to toxin-producing bacteria;
- A traditional family event that took place in Ugu District in KwaZulu-Natal in July 2019. *S.* Typhimurium was isolated from clinical specimens and samples of goat meat served at the event;
- A funeral that took place in Chris Hani District in the Eastern Cape in August 2019. The outbreak sickened 30 people and was caused by consumption of a meal contaminated with *S.* Typhimurium;
- A church gathering that took place in eThekwini District in KwaZulu-Natal in September 2019. The outbreak affected 14 people and *S.* Newport was isolated from the case-patients;
- A housewarming that took place in eThekwini District in KwaZulu-Natal in October 2019. The outbreak affected 12 people and was caused by meat that was contaminated by *S.* Enteritidis; and
- A family gathering that took place in eThekwini District in KwaZulu-Natal in February 2020. The outbreak sickened 14 people and the pathogen that was isolated, was *S.* Enteritidis.

Waterborne disease outbreaks

Outbreaks were recorded as follows:

- At the Lejweleputswa District in the Free State in April 2019. The outbreak was caused by non-compliant potable water, which affected over 200 adults and children. Norovirus and *Giardia lamblia* were predominant in the clinical specimens tested; and
- At the Katze Dam in Lesotho in April 2019. The outbreak affected 15 members and staff of a rowing team who were training at the dam. The main pathogens detected included *Shigella* species and norovirus.

Imported cluster

There was a cluster of *S.* Typhi in the Cape Town Central District in the Western Cape in November 2019. The cluster originated from a visiting family member from Zimbabwe (who subsequently died) and affected three other people.

In addition, the centre responded to a further nine household-based enteric outbreaks. The major pathogens included non-typhoidal *Salmonella* and *Shigella* species (*flexneri* and *sonnei*), with 67% (6/9) of these outbreaks attributed to poor food handling and hygiene practices in these households. A further 118 enteric outbreaks were noted, but further investigation was precluded by insufficient epidemiological data and/or lack of clinical, food or environmental specimen collection and testing.

4. Policy contributions

- Juno Thomas and Nicola Page participated in the development of the Strategic Plan for Diarrhoeal Diseases which is led by the DoH. The first draft of the plan was completed and is awaiting feedback; and
- Juno Thomas was invited to join the working group which is responsible for reviewing the World Health Organization (WHO) Typhoid Fever and Invasive *Salmonella* Disease Laboratory Manual.

5. Research activities

African network for improved diagnostics, epidemiology and management of common infectious agents (ANDEMIA)

NICD investigators: NA Page, J Thomas, S Nadan and J MacDonald
Collaborators: F Leendertz (Robert Koch Institut, Berlin), C Akoua-Koffi (Centre Hospitalier Universitaire Bouaké), S Ouangraoua (Centre Muraz), JJ Muyembe-Tamfum (Congo Institut National pour la Recherche Biomedicale) and M Venter (University of Pretoria)

Sub-Saharan Africa bears a disproportionately high burden of infectious diseases and associated morbidity and mortality. While European countries tend to focus research on tropical or neglected diseases due to the impact in travellers from those countries, they rarely investigate common infectious diseases like acute respiratory

tract infections (RTIs), gastrointestinal tract infections (GTIs) and acute febrile diseases of unknown cause (AFDUCs). Sentinel surveillance was established at Kalafong, Matikwana and Mapulaneng hospitals, enrolling patients presenting with RTI, GTI and AFDUC syndromes. From July 2018 to March 2020, 661 stool specimens were screened for enteric pathogens using molecular assays. *Shigella* spp. were detected in 24% (158/661), *Cryptosporidium* spp. in 14% (95/661), norovirus in 14% (90/661), rotavirus in 13% (84/661) and adenovirus in 25% (164/218), with roughly 10% enteric adenovirus strains. Control enrolment commenced in November 2019 and 62 controls are currently enrolled. The study will continue until 2021.

Post-marketing intussusception monitoring after introduction of oral rotavirus vaccine in South Africa

NICD investigators: N Page, S Nadan, R Netshikweta and T Kruger
Collaborators: S Madhi and M Groome (Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases at the University of the Witwatersrand, Respiratory and Meningeal Pathogens Research Unit)

While current rotavirus vaccines are not demonstrating an increased risk of intussusception during large-scale vaccine trials, recent studies have indicated a low-level risk of intussusception after vaccine administration. Active surveillance for intussusception cases was implemented in eight South African cities ending in December 2017. The study found no significant association between intussusception and rotavirus vaccination among infants in South Africa, and no clustering of cases occurred in any of the risk windows (1-7 days, 8-21 days, or 1-21 days) after receipt of either dose. Specimens from cases (n=397) and surgical controls (n=223) were screened for potential infectious causes, using a customised Taqman array card. Similarly to the clinical observations, rotavirus infections and rotavirus vaccine detection were not associated with intussusception. In contrast, adenovirus type C infections were detected more frequently in intussusception cases compared to surgical controls. The characterisation of the enteric pathogens detected continues.

Investigation of secretor status and the gastrointestinal microbiome in a cohort of healthy children under the age of five years in South Africa

NICD investigators: NA Page and J MacDonald
Collaborators: M Groome (Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Respiratory and Meningeal Pathogens Research Unit) and J Mans (University of Pretoria)

Similarities or differences may exist in microbiome compositions of children with different secretor phenotypes/genotypes. However, there are limited data on the gut microbiomes of South African children, and conflicting studies on whether the secretor status may or may not have a modulating effect on the microbiome. Since the gut is the site of rotavirus replication, any effects the microbiome composition and/or secretor status may have on rotavirus infection or oral vaccine replication should be investigated. Six stool specimens collected from healthy non-secretor (n=3) and secretor (n=3) children who attended a crèche in Soweto in Johannesburg in 2019, were analysed through next generation sequencing (NGS). In the pilot study, the gut microbiome of children did not show differences in microbial composition based on secretor status.
The pilot study did, however, provide valuable insights into microbiome analysis methods and pipelines. The project continues and additional specimens from paired mother-child participants will be analysed.

Snapshot of South African *Salmonella*: Development of a polymerase chain reaction assay to investigate the distribution of *Salmonella* Enteritidis clades in 2012 and 2013

NICD investigators: S Gallichan, N Ramalwa, J Thomas and AM Smith
Collaborators: N Feasey (University of Liverpool)

Salmonella Enteritidis is the most commonly reported non-typhoidal *Salmonella* serovar causing human disease worldwide. Four clades of *S.* Enteritidis have been identified worldwide: Outlier, Global, East African and West African. The distribution and epidemiology of these clades across Africa is poorly understood. To investigate this, a real-time polymerase chain reaction (PCR) assay was developed to classify (detect) these four clades.

The usefulness of this assay was demonstrated by screening 618 *S.* Enteritidis isolates from four South African provinces between 2012 and 2013. Associations between the respective clades, antimicrobial resistance and invasive disease were explored using statistical analysis. The majority of the South African isolates were classified within the paraphyletic Outlier clade (377/618, 61.00%), with fewer classified within the Global clade (240/618, 38.83%) and only one isolate classified within the West African clade (1/618, 0.16%). Of note, isolates within the Global clade were strongly associated with decreased ciprofloxacin susceptibility and invasive disease. The monitoring of *S.* Enteritidis clades in sub-Saharan Africa is important to gain an improved understanding of the distribution and epidemiology.

Whole-genome sequencing for surveillance and characterisation of enteric bacterial pathogens associated with communicable diseases

NICD investigators: AM Smith, NP Tau, S Williams and J Thomas

WGS analysis of microorganisms is poised to transform public heath microbiology. WGS is a 'one-stop technology', universally applicable to all microorganisms. The CED has secured grant funding to perform WGS on ~5000 bacterial isolates. Importantly, sequencing data for isolates will be complemented with available available epidemiological (explanatory) data, as WGS data should be interpreted within the epidemiological context. This sequencing project will mostly have a prospective focus, so that relevant and up-to-date available epidemiological data can be collected, to facilitate 'real-time' analysis. The study will investigate how WGS analysis can support and augment current methodologies used in laboratory investigations at the CED. The WGS analysis will strengthen surveillance activities at the CED and in particular, strengthen outbreak response and investigation.

6. Teaching and training

- **Community outreach**
  The centre hosted its very first World Toilet Day event in the Polio Research Foundation (PRF) Auditorium on 19 November 2019. Mr Vuyisile Malinga from SECTION27 was invited as a speaker and his presentation covered topics such as the right to sanitation and basic education, as well as health. The event attracted a large audience and contributed to much-needed continuing professional development (CPD) ethics points.

  Training was also provided to an external catering group after an outbreak was traced to the company. Three training sessions were conducted on foodborne diseases.

- **Postgraduate training**
  Staff from the centre participated in a number of specialised NICD training courses:
  - Pathology registrars (microbiology and virology) attended the NICD registrar training course; and
  - Medical intern scientists (microbiology, molecular biology and virology) were trained during NICD training course rotations in enteric bacteriology and virology laboratories.

- **Other national training included:**
  - The South African Field Epidemiology Training Programme (SAFETP) hosted by the NICD;
  - MSc epidemiology surveillance, outbreak response and scientific writing courses;
  - MSc Vaccinology and Diploma in Tropical Medicine and Hygiene (DTM&H) courses at Wits; and
  - Lectures for public health students at the University of Pretoria (UP).

- **Professional development**

  Nine postgraduate candidates from the CED were enrolled for postgraduates studies:
  - Four for Doctor of Philosophy degree (PhD);
  - Three for MSc;
  - One for MPH; and
  - One for Master of Medicine degree (MMed).

  Two postgraduate candidates graduated during the year; one with MPH and the other with MSc;
  Two intern medical scientists were registered with the HPCSA for independent practice;
  Two intern medical scientists are currently training at the CED; and
  CED staff received training on:
  - Statistical analysis (advanced epidemiology, R and advanced STATA);
  - Sequence analysis (EnteroBase);
  - The Emergency Operations Centre (EOC); and
  - Project coordination.

7. Research output

1. Mashe T., Gudza-Mugabe M., Tarupiwa A., Munemo E., Mtapuri-Zinyowera S., Smouse SL., *et al.* Laboratory characterisation of *Salmonella enterica serotype* Typhi isolates from Zimbabwe, 2009-2017. BMC Infectious Diseases. 2019 May 31;19(1):487. DOI: 10.1186/s12879-019-4114-0.
2. Smith A.M., Tau N.P., Smouse S.L., Allam M., Ismail A., Ramalwa N.R., *et al*. Outbreak of *Listeria monocytogenes* in South Africa, 2017-2018: Laboratory activities and experiences associated with whole-genome sequencing analysis of isolates. Foodborne Pathogens and Disease. 2019 Jul;16(7):524-530. DOI: 10.1089/fpd.2018.2586.
3. Karama M., Cenci-Goga B.T., Malahlela M., Smith A.M., Keddy K.H., El-Ashram S., *et al*. Virulence characteristics and antimicrobial resistance profiles of Shiga toxin-producing *Escherichia coli* Isolates from humans in South Africa: 2006-2013. Toxins (Basel). 2019 Jul 19;11(7):424. DOI: 10.3390/toxins11070424.
4. Hasso-Agopsowicz M., Ladva C.N., Lopman B., Sanderson C., Cohen A.L., Tate J.E., *et al*. Global Rotavirus Surveillance Network and Rotavirus Age Study Collaborators. Global review of the age distribution of rotavirus disease in children aged <5 years before the introduction of rotavirus vaccination. Clinical Infectious Diseases. 2019 Aug 30;69(6):1071-1078. DOI: 10.1093/cid/ciz060.
5. Van Schalkwyk E., Mpembe R.S., Thomas J., Shuping L., Ismail H., Lowman W., *et al*. Epidemiologic shift in candidemia driven by *Candida auris,* South Africa, 2016-20171. Emerging Infectious Diseases. 2019 Sep;25(9):1698-1707. DOI: 10.3201/eid2509.190040.
6. Kalule J.B., Smith A.M., Vulindhlu M., Tau N.P., Nicol M.P., Keddy K.H., *et al*. Prevalence and antibiotic susceptibility patterns of enteric bacterial pathogens in human and non-human sources in an urban informal settlement in Cape Town, South Africa. BMC Microbiology. 2019 Nov 6;19(1):244. DOI: 10.1186/s12866-019-1620-6.
7. Netshikweta R., Chidamba L., Nadan S., Taylor M.B., Page N.A. Molecular epidemiology of human bocavirus infection in hospitalized children with acute gastroenteritis in South Africa, 2009-2015. Journal of Medical Virology. 2019 Nov 22. DOI: 10.1002/jmv.25634. Epub ahead of print.
8. Smith A.M., Tau N.P., Kalule J.B., Nicol M.P., McCulloch M., Jacobs C.A., *et al*. Shiga toxin-producing *Escherichia coli* O26:H11 associated with a cluster of haemolytic uraemic syndrome cases in South Africa, 2017. Access Microbiology. 2019 Nov; 1: DOI.org/10.1099/acmi.0.000061 (https://www.microbiologyresearch.org/content/journal/acmi/10.1099/acmi.0.000061).
9. Rogawski McQuade E.T., Liu J., Kang G., Kosek M.N., Lima A.A.M., Bessong P.O., *et al*. Protection from natural immunity against enteric infections and etiology-specific diarrhoea in a longitudinal birth cohort. The Journal of Infectious Diseases. 2020 Jan 27:jiaa031. DOI: 10.1093/infdis/jiaa031. Epub ahead of print.
10. Mwape K., Kwenda G., Kalonda A., Mwaba J., Lukwesa-Musyani C., Ngulube J., *et al*. Characterisation of *Vibrio cholerae* isolates from the 2009, 2010 and 2016 cholera outbreaks in Lusaka Province, Zambia. Pan African Medical Journal. 2020 Feb 7;35:32. DOI: 10.11604/pamj.2020.35.32.18853.
11. Thomas J., Govender N., McCarthy K.M., Erasmus L.K., Doyle T.J., Allam M., *et al*. Outbreak of listeriosis in South Africa associated with processed meat. The New England Journal of Medicine. 2020 Feb 13;382(7):632-643. DOI: 10.1056/NEJMoa1907462.

Presentations

Staff from the CED conducted the following presentations during the reporting year:

- Seven international conferences or meetings: Two presentations as invited speakers, three poster presentations, one workshop presentation and one presentation at a grant holders meeting;
- Three regional/African conferences or meetings: Two oral presentations, four poster presentations, one presentation at a grant holders meeting and one presentation by an organising committee member; and
- Eleven national conferences or meetings: Eight oral presentations, four poster presentations, one presentation as a session chair, and four presentations at meetings organised by the DoH.

From left to right: Mr Vuyisile Malinga (SECTION27), Dr Juno Thomas (Centre for Enteric Diseases) and Dr Natalie Mayet (National Institute of Communicable Diseases) at the World Toilet Day

The Centre for Enteric Diseases staff at the World Toilet Day event at the Polio Research Foundation Auditorium on 19 November 2019

Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses

2019/20

Prof Nelesh Govender
Centre Head

1. Background

The Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses (CHARM) incorporates two national reference laboratories for antimicrobial resistance (AMR) and mycoses, both of which are certified to the ISO 15189: 2012 standard, and houses the National Biological Sample Collection of pathogenic bacteria and fungi.

The Centre serves as a World Health Organization (WHO) Collaborating Centre (CC) for AMR and is the national focal point for WHO's Global Antimicrobial Resistance Surveillance System (GLASS). The Centre's epidemiology team conducts community- and healthcare-associated outbreak investigations and is involved in the evaluation of large-scale public health programmes.

2. Surveillance

Healthcare-associated Infections (HAI) Surveillance

NICD investigators: Govender NP, Shuping L and Mathebula R
Collaborators: Avenant T, du Plessis N, Masemola K, Pillay D, Ngobese M, Mackay C, Mahmud Yakoob S, Abrahams S, Black J, Ramncwana N, Naby F, Haffejee S, Dawood H, Green J, Martin T, Abrahams A, Mosenye E, Maila M, Chikwuma E

The Centre implemented a real-time alert system to detect outbreaks of healthcare-associated bloodstream infections among neonates at the following hospitals: Kalafong (Gauteng), Grey's (KwaZulu-Natal), Dora Nginza (Eastern Cape) and Thelle Mogoerane (Gauteng). The hospital personnel were also trained to use the outbreak alert mobile software application. The pilot project commenced on 1 February 2019 but was halted after technical issues with the mobile application.

Antimicrobial Resistance Surveillance

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

Senior staff members from the centre represented the NICD at the following entities:

- The Ministerial Advisory Committee for AMR;
- The WHO AMR Surveillance and Quality Assessment CCs Network; and
- The WHO Strategic and Technical Advisory Group for AMR.

The centre currently uses the following approaches for AMR surveillance:

- *National or sentinel isolate-based surveys:* Bacterial and fungal isolates, cultured from patients who meet the surveillance case definitions, are submitted to the centre's reference laboratories for identification, antimicrobial susceptibility testing and genotyping. During the reporting period, the centre conducted surveillance for bacteraemia caused by carbapenem-resistant Enterobacteriaceae (2015-2020) and all infections caused by *Candida auris* (2018-2020);

- *Enhanced laboratory surveillance:* Detailed clinical information is collected from patients admitted to sentinel hospitals who meet the surveillance case definitions. During the reporting period, the centre conducted enhanced surveillance for bloodstream infections caused by carbapenem-resistant Enterobacteriaceae;

- *Electronic laboratory surveillance:* Data on bloodstream infections caused by the ESKAPE bacterial pathogens *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter* spp.) are compiled annually. Line list data from public- and private sector pathology laboratory information systems were merged, 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 were made available at facility level. A combined public/ private AMR report on key organisms-antimicrobial agents is available on the Department of Health (DoH) website at: http://www.health.gov.za/index.php/antimicrobial-resistance

Surveillance for Mycoses

NICD investigators: Govender NP, Mpembe R, Maphanga T, Naicker S, Shuping L, Ismail H, van Schalkwyk E and Mathebula R

The WHO recommends a combination of amphotericin B and flucytosine (5-FC) as first-line treatment for patients with cryptococcal meningitis, but 5-FC is still not registered in South Africa. Médecins Sans Frontières obtained 5-FC through a bulk Section 21 order and delivered this to selected hospitals (most of which are GERMS enhanced surveillance sites) for treatment of cryptococcal meningitis. 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 registration with the South African Health Products Regulatory Authority (SAPHRA) in late 2019 and the pilot project was expanded to additional hospitals in 2020. Passive laboratory-based surveillance for rarer invasive mycoses continued.

World Health Organization Collaborating Centre for Antimicrobial Resistance

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

3. Outbreaks

The centre led or participated in the investigations of several healthcare-associated outbreaks in neonatal units during the year. These investigations revealed that overcrowding, understaffing, sub-optimal infection prevention and control (IPC) measures and lack of antimicrobial stewardship remain the driving factors for healthcare-associated outbreaks. Failure to address these underlying issues results in recurrent outbreaks.

4. Research activities

CAST-NET

NICD investigators: Govender NP, Greene G, Desanto D, Matlapeng P, Shandu M, van Schalkwyk E, Paxton J, Mathebula R and Valashiya N
Collaborators: Boulware DR, Hullsiek K, Bangdiwala A, Rajasingham R, Skipper C (University of Minnesota), Cawood C, Dladla N, Kanyile D (Epicentre)

The CAST-NET project aims to evaluate the effectiveness of the national reflex cryptococcal antigen screening and treatment intervention. The project is supported by a five-year grant (NIH R01) from the National Institutes of Health (NIH). In 2018, the centre partnered with Epicentre to image the medical records of a large cohort of persons who were tested positive for the cryptococcal antigen (CrAg) between February 2017 and January 2019 in 27 sub-districts (in all nine provinces in South Africa). The first wave of data collection was completed in November 2019, and the second wave of data collection commenced in January 2020. To date, clinical data has been collected from over 2,000 CrAg-positive screened cases.

Baby GERMS-SA: Neonatal sepsis surveillance in South Africa

NICD investigators: Govender NP, Meiring S, Magobo R, van Schalkwyk E, Mathebula R, Perovic O, Smith M, Mpembe R, Quan V, von Gottberg A, de Gouveia L, Walaza S and Cohen C
Collaborators: Dramowski A (Stellenbosch University), Mackay C (Dora Nginza Hospital), Phayane R (Tembisa Hospital), Mailula T (Mankweng Hospital), Mekgoe O (Klerksdorp Hospital), Kapongo C (Queen Nandi hospital), Maphosa D, Ntuli S (Rob Ferreira Hospital)

Worldwide, neonatal mortality remains high and accounted 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. The aim of this two-tiered surveillance programme is to gain a deeper understanding of the burden and aetiological factors of neonatal sepsis in urban and rural sub-Saharan Africa. Tier 1 will serve to conduct national surveillance of laboratory-confirmed neonatal sepsis at all public sector hospitals in South Africa. Tier 2 forms part of tier 1 and will focus on a detailed characterisation of neonatal sepsis occurring at six secondary-level institutions (regional neonatal units). Data from the surveillance programme will be used to describe the pathogen-specific aetiology, antimicrobial susceptibility and clinical profile of neonatal sepsis at different levels of healthcare in South Africa. The focus will be on characterising selected multi-drug resistant bacterial and fungal pathogens in detail, through whole-genome sequencing (WGS). Funding for this programme was received by the Bill and Melinda Gates Foundation. As at the end of March 2020, national surveillance data of approximately 45,000 laboratory-confirmed neonatal sepsis cases for the period from 2014-2019 has been collated and analysed. Clinical data collection of laboratory-confirmed neonatal sepsis at six secondary-level hospitals commenced in October 2019 and is ongoing.

Prevalence of antimicrobial resistance genes in animals and humans

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

The routine use of antibiotics for therapeutic, prophylactic and growth promotion in food animals is linked to increased 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 and twenty-three production houses were sampled. In total, 113 pig faecal droppings were collected. Non-typhoidal *Salmonella* species (NTS) were not detected in any of the samples. The prevalence of *E. coli*, *Enterococcus* species (spp.) and *Campylobacter* spp. was 100% (113/113), 36% (41/113) and 21% (24/113), respectively. The dominant *Campylobacter* spp. were *C. coli* (67%; 16/24) followed by *C. hyointestinalis* (33%; 8/24). The dominant *Enterococcus* spp. was *E. hirae* (54%; 22/41), followed by *E. faecalis* (29%; 12/41), *E. faecium* (7%; 3/41), *E. durans* (5%; 2/41), *E. villorum* (2%; 1/41) and *E. casseliflavus* (2%; 1/41).

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. *Campylobacter* species were not detected from any human participant. The prevalence of *E. coli*, *Enterococcus* spp. and NTS was 78% (50/64), 7.8% (5/64) and 3% (2/64) respectively. The dominant *Enterococcus* species isolated from rectal swabs were *E. faecalis* (40%; 2/5) and *E. hirae* (40%; 2/5), followed by *E. faecium* (20%; 1/5).

Quantification of antimicrobial usage, antimicrobial susceptibility testing and further molecular testing are ongoing.

Characterisation of *Acinetobacter baumannii* strains from public- and private healthcare sector intensive care units in Gauteng Province

NICD investigators: Singh-Moodley A, Lowe M and Perovic O
Collaborators: Thomas T, Nana T and Chibabhai V (National Health Laboratory Service) and Lowman W (University of Witwatersrand Donald Gordon Medical Centre)
Acinetobacter baumannii is a major healthcare-associated pathogen that has acquired resistance to colistin. The aim of this study is 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 Province. This study is ongoing.

In vitro activity of the ceftolozane-tazobactam agent against Gram-negative bacterial isolates obtained from public hospitals

NICD investigators: Singh-Moodley A, Lowe M and Perovic O

Ceftolozane-tazobactam inhibits *P. aeruginosa* and demonstrates greater in vitro activity than other antibiotics. This study aims to evaluate the activity of ceftolozane–tazobactam against *P. aeruginosa* and extended-spectrum *β*-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*. A secondary aim of the study is to elucidate molecular mechanisms of resistance to ceftolozane-tazobactam. This study is ongoing.

Low prevalence of AmpC-ß-lactamases and the increase of carbapenemases in carbapenem-non-susceptible_*Klebsiella pneumoniae* blood culture isolates at tertiary level hospitals in South Africa

NICD investigators: Mogokotleng R, Singh-Moodley A and Perovic O

The aim of this study was to determine the prevalence of ESBL, carbapenemases and AmpC-β-lactamases in *Klebsiella pneumoniae* blood culture isolates as well as their associated AMR profiles. A low frequency of AmpC-β-lactamase genes was found, as well as evidence of multiple plasmid-mediated β-lactam resistance genes in single strains.

Establishing an external quality assessment programme for Africa

NICD investigators: Perovic O, Smith M and Badat R
Collaborators: Ondoa P (African Society for Laboratory Medicine), Inamdar L (Public Health England), Tebeje YK (Africa Centers for Diseases Control and Prevention), Hendriksen R (Danish Technical University)
The External Quality Assessment Programme for Africa (EQAFRICA) will build on identified regional capacity to establish regional external quality assessment (EQA) providers across the One Health sectors. These EQA providers (including NICD) will be supported to operate through self-sustaining business models targeting national AMR reference laboratories in the 12 Fleming Fund priority countries, plus two central African countries (Gabon and Cameroon). In addition, EQAFRICA will work to increase the demand and uptake of EQA programmes by:

- Ensuring incorporation of EQA activities into a quality management system (QMS) at facility level;
- Training and qualifying the workforce to adequately provide, run and act upon the results of EQA panels; and
- Promoting development and adoption of national laboratory quality management policies, including EQA requirements across the One Health sectors.

The NICD provides expertise and technical capacity for manufacturing, distribution and training on EQA; laboratory QMS implementation and accreditation, and laboratory policy development. The consortium will ensure country buy-in and advancement of the policy and regulation agenda, supporting the demand, uptake and effectiveness of EQA programmes. EQAFRICA will promote national laboratory quality policy development as a priority of the African Union (AU) member states, to boost participation in EQA programmes. Finally, EQAFRICA will establish mechanisms that enable sharing of regional EQA programmatic data amongst countries and regional stakeholders to inform decision-making.

Whole genome sequencing of *Candida auris*

NICD investigators: S Naicker, T Maphanga, R Mpembe, M Ali, A Ismail and NP Govender
Collaborators: Centers for Disease Control and Prevention, United States of America

Whole genome sequencing (WGS) was applied to determine the molecular epidemiology and track outbreaks caused by this near-clonal pathogen. To date, NICD has sequenced the genomes of approximately 249 South African *C. auris* isolates and analysis of the fungal genomic data is ongoing.

Molecular epidemiology of *Cryptococcus* in South Africa

NICD investigators: Naicker S, Maphanga T, van Schalkwyk E and Govender NP
Collaborators: Engelthaler D (Translational Genomics Research Institute), Meyer W (Westmead Institute for Medical Research at the University of Sydney), Firacative C (Universidad del Rosario Bogota, Colombia)

A high genetic diversity was found in clinical *Cryptococcus* strains in South Africa. This study aims to apply WGS to *Cryptococcus* molecular types which are endemic in southern Africa and to analyse their antifungal resistance and virulence patterns. Processing and analysis of genomic data is ongoing.

Development of diagnostic assays for histoplasmosis and emergomycosis

NICD investigators: Maphanga T, Naicker S and Govender NP
Collaborators: Alanio A (Institut Pasteur)

Histoplasma and *Emergomyces* are thermally-dimorphic pathogens known to be endemic to South Africa and cause human disease. The aim of this study was to validate a *Histoplasma/Emergomyces* reverse-transcriptase quantitative polymerase chain reaction (PCR) for screening of histoplasmosis/emergomycosis directly from clinical specimens. This assay was found to be highly sensitive, but cross-reacted with *Blastomyces* species and *Nannizziopsis* species. This assay will improve the diagnosis of histoplasmosis/emergomycosis in an early stage, which is important for rapid management of the disease in South Africa

Teaching and training

The centre conducted the following postgraduate teaching and training activities in the reporting year:

- An NICD short course for registrars and ID fellows;
- A mycology workshop for registrars and ID fellows;
- Lectures for a Master of Medicine Degree (MMed) (Pathology) Molecular course at Wits;
- Lectures for a Master of Science Degree (MSc) Epidemiology and Biostatistics course at Wits;
- Lectures for an MSc Vaccinology course at Wits;
- Lectures for a Diploma in Tropical Medicine and Hygiene (DTM&H) course at Wits; and
- Supervision for graduates studying towards Doctor of Philosophy (PhD), MSc, Master of Technology Degree (MTech), Master of Public Health Degree (MPH) as part of the South African Field Epidemiology Training Programme, and an MMed.

Professional development

The centre enrolled ten postgraduate students for studies as follows:

- Six for PhD;
- Two for MSc;
- One for MTech; and
- One for MPH.

Two postgraduate students also graduated during the year; one with an MSc and one with a PhD.

5. Research output

Journal articles

1. Singh-Moodley A., Strasheim W., Mogokotleng R., Ismail H., Perovic O. Unconventional SCCmec types and low prevalence of the Panton-Valentine Leukocidin exotoxin in South African blood culture *Staphylococcus aureus* surveillance isolates, 2013-2016. PLOS One 14 (11): e0225726.
2. Govender N.P., Meintjes G., Mangena P., Nel J., Potgieter S., Reddy D., *et al*. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. Southern African Journal of HIV Medicine. 2019;20(1):1-16.
3. Wake R.M., Govender N.P., Omar T., Nel C., Mazanderani A.H., Karat A.S., *et al*. Cryptococcal-related mortality despite fluconazole preemptive treatment in a cryptococcal antigen screen-and-treat program. Clinical Infectious Diseases. 2020 Apr 10;70(8):1683-1690.
4. Oladele R.O., Akase I.E., Fahal A.H., Govender N.P., Hoenigl M., Gangneux J.P., *et al*. Bridging the knowledge gap on mycoses in Africa: Setting up a Pan-African Mycology Working Group [published online ahead of print, 2019 Dec 12v. Mycoses. 2019;10.1111/myc.13044.]
5. Quan V., Toro-Silva S., Sriruttan C., Chetty V., Chihota V., Candfield S., *et al*; for GERMS-SA. Pathways to care and outcomes among hospitalised HIV-seropositive persons with cryptococcal meningitis in South Africa. PLOS One. 2019;14(12):e0225742.
6. Perovic O., Yahaya A.A., Viljoen C., Ndihokubwayo J.B., Smith M., Coulibaly S.O., *et al.* External quality assessment of bacterial identification and antimicrobial susceptibility testing in African national public health laboratories. Tropical Medicine and Infectious Disease. 2019 Dec 13;4(4). pii: E144.
7. Singh-Moodley A., Allam M., Ismail H., Perovic O., Strasheim W., Mtshali S., *et al.* Complete genome sequence of a *Staphylococcus* aureus isolate from a nasopharyngeal swab from a mine worker in South Africa. Microbiology Resource Announcements. 2019 Dec 12;8(50). pii: e01075-19.
8. Ismail H., Lowman W., Govind C.N., Swe Swe-Han K., Maloba M.R.B., Bamford C., *et al*. Surveillance and comparison of antimicrobial susceptibility patterns of ESKAPE organisms isolated from patients with bacteraemia in South Africa, 2016-2017. South African Medical Journal. 2019;109(12):934-940.
9. Lowe M., Kock M.M., Coetzee J., Hoosien E., Peirano G., Strydom K.A., *et al*. *Klebsiella pneumoniae* ST307 with blaOXA-181, South Africa, 2014-2016. Emerging Infectious Diseases. 2019; 25:739-747.
10. Perovic O., Ismail H., Quan V., Bamford C., Nana T., Chibabhai V., *et al*; for GERMS-SA. Carbapenem-resistant Enterobacteriaceae in patients with bacteraemia at tertiary hospitals in South Africa, 2015-2018. European Journal of Clinical Microbiology & Infectious Diseases. 2020 Mar 2.
11. Thomas J., Govender N., McCarthy K.M., Erasmus L.K., Doyle T.J., Allam M., *et al*. Outbreak of listeriosis in South Africa associated with processed meat. The New England Journal of Medicine. 2020 Feb 13;382(7):632-643.
12. Maphanga T.G., Birkhead M., Muñoz J.F., Allam M., Zulu T.G., *et al*. Human blastomycosis in South Africa caused by *Blastomyces percursus* and *Blastomyces emzantsi* sp. Nov., 1967-2014. Journal of Clinical Microbiology. 2020 Feb 24;58(3). pii: e01661-19.
13. Shroufi A., Govender N.P., Meintjes G., Black J., Nel J., Moosa M.Y., *et al*. Time to embrace access programmes for medicines: Lessons from the South African flucytosine access programme. International Journal of Infectious Diseases. 2020 Feb 29. pii: S1201-9712(20)30116-8. DOI: 10.1016/j.ijid.2020.02.057.
14. Van Schalkwyk E., Mhlanga M., Maphanga T.G., Mpembe R.S., Shillubane A., Iyaloo S., *et al*. Screening for invasive fungal disease using non-culture-based assays among inpatients with advanced HIV disease at a large academic hospital in South Africa.Mycoses. 2020 Mar 3. DOI: 10.1111/myc.13071.
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Technical report

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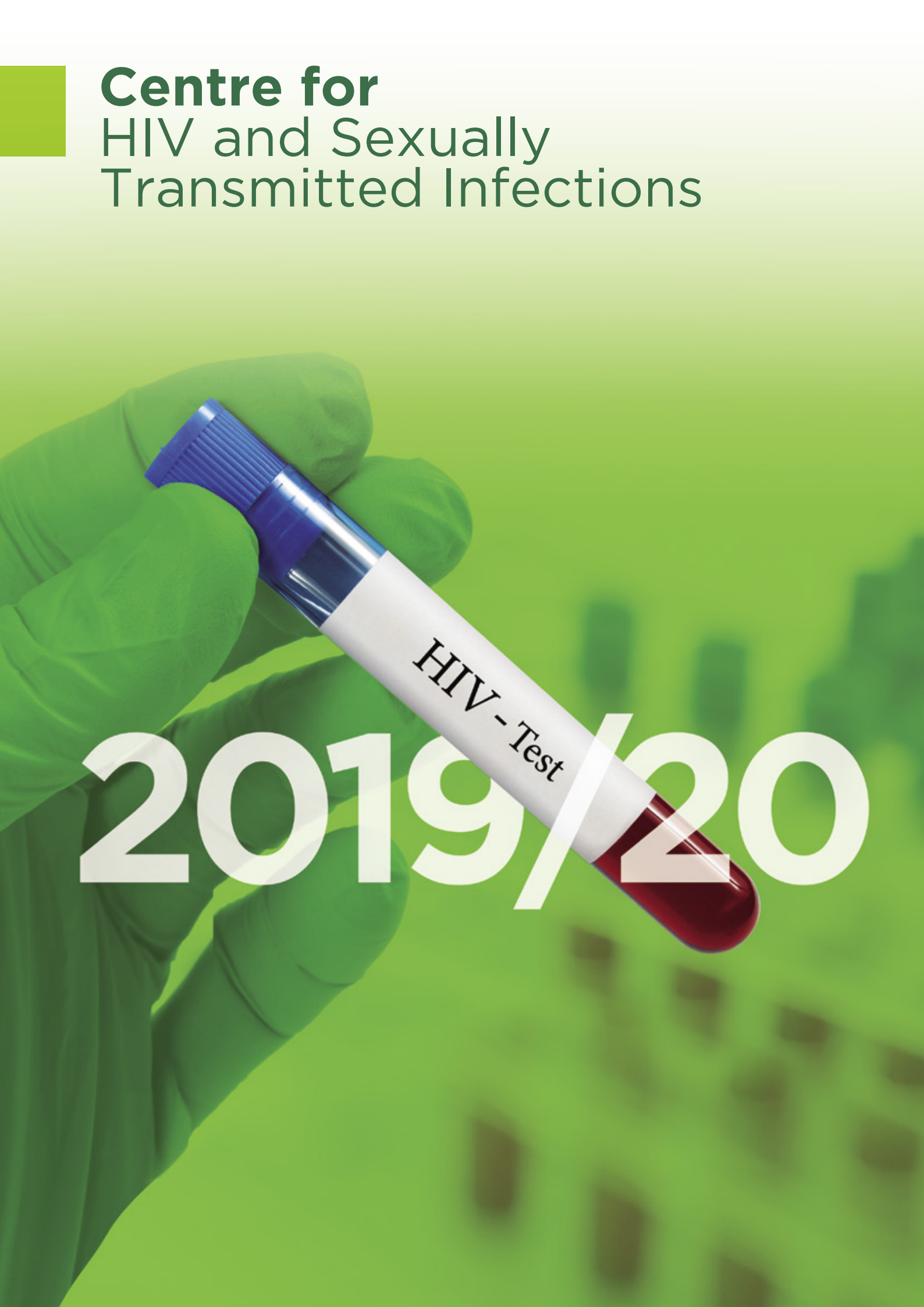
Conference presentations

During the period under review, the centre has conducted several presentations at international and national conferences as follows:

- A research and public health agenda on *Candida auris* in resource-limited settings. Understanding the biology, antifungal resistance, and clinical implications of *Candida auris*, Rockville, USA, 28-29 January 2020;
- Emergomycosis (opening plenary address). Trends in Medical Mycology Conference, Nice, France, 11-14 October 2019;
- Four decades of AIDS mycoses (keynote address). International AIDS Mycoses Conference, Cape Town, South Africa, 10-12 July 2019; and
- Federation for Infectious Diseases Societies of Southern Africa Conference, Johannesburg, South Africa, 7-9 November 2019:
    - Colistin resistance is chromosomally encoded in South African *Acinetobacter baumannii* isolates;
    - Molecular characterisation of panton-valentine leukocidin-producing methicillin-susceptible *Staphylococcus aureus* isolates from an outbreak of cutaneous abscesses at a gold mine, South Africa;
    - Daptomycin resistance in a South African clinical *Staphylococcus aureus* isolate;
    - Genotypic characterisation of carbapenemase and AmpC-β-lactamase genes among *Klebsiella pneumoniae* isolated from patients with bacteraemia, South Africa;
    - Evaluation of three phenotypic methods for the detection of carbapenemase production in Enterobacteriaceae;
    - Colistin resistance in carbapenem-resistant Enterobacteriaceae blood culture isolates submitted from sentinel surveillance sites in South Africa;
    - Rapid emergence of *Klebsiella pneumoniae* ST307 with blaOXA-181 across South Africa (2012-2016);
    - Colistin resistance is chromosomally-encoded in South African *Acinetobacter baumannii* isolates;
    - National inter-laboratory re-testing of cryptococcal antigen-screened blood samples at NHLS Microbiology and CD4 laboratories, April-December 2018;
    - Decreasing fluconazole susceptibility of clinical South African *Cryptococcus neoformans* isolates over a decade;
    - Tracking *Candida auris* in South Africa using whole genome sequencing;
    - *Acinetobacter baumannii* bacteraemia findings from GERMS surveillance data;
    - Evaluation of the RDS-1500 PRO device for reading cryptococcal antigen lateral flow assay results on plasma; and
    - A new B*lastomyces* species in South Africa.

Centre for HIV and Sexually Transmitted Infections



2019/20

Prof Adrian Puren
Centre Head

1. Background

Sexually transmitted infections (STIs), including those caused by the human immunodeficiency virus (HIV) types 1 and 2, remain a major public health problem in Africa. Published estimates of the Joint United Nations Programme on HIV/AIDS show that South Africa has the highest burden of HIV infections with recent estimates of 7.7 million people living with HIV.

The National Institute for Communicable Diseases (NICD) 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.

CHIVSTI addresses the challenges of HIV and STI diseases through various programmes:

- 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; and
- 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 fellows. The centre has well-established links and collaborations with various key national and international organisations in the field of HIV and STIs.

During the year under review, a key focus area of the centre was the various communicable diseases that are set for elimination by 2030, including HIV and congenital syphilis. In the case of HIV, the ambitious 90-90-90 targets for 2020 are to be reported. The centre revised the antenatal survey to report on the HIV treatment cascade and the results are reported for the first time. The results for the second and third components of the 90-90-90 targets are encouraging, but testing to know one's HIV status requires continued effort.

The HIV prevalence data generated from the survey contributed to both the Thembisa model and the AIDS Impact Model (AIM) which provide yearly national projections on the total number of people living with HIV, new HIV infections and AIDS-related mortality in the country.

HIV surveillance remains a priority as HIV incidence remains critical, especially in adolescent girls and young women. Results of the Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) Programme are reported. Given the substantial numbers of people living with HIV on treatment, HIV drug resistance remains a cornerstone of the centre's HIV surveillance, with a focus on various groups that are at risk, including sex workers. Children are often a neglected group when it comes to HIV surveillance. An application for reports for action for paediatric HIV was developed and is described to address the problem. The centre collaborates with the Notifiable Medical Conditions (NMC) section to enhance surveillance efforts for the elimination of congenital syphilis, the results of which are presented and are yielding useful data.

Research efforts range from implementation science e.g. the use of molecular point of care testing (POCT) for infant diagnosis, as well as the presence of drug resistance in the STI setting. Key research for HIV prevention focuses on HIV vaccine and antibody-meditated prevention (AMP) studies. The studies include understanding the role of broadly neutralising antibodies (bNAbs) and for example, how the properties of bNAbs can be enhanced. The results of antibody-mediated prevention (AMP, phase 2b HVTN 703/HPTN 081) trial and phase 2b HVTN 705/HPX2008 (Imbokodo) are keenly awaited, following the discontinuation of the Phase 2b/3 HIV vaccine study, HVTN 702.

2. Surveillance Activities

The Antenatal HIV-1 Serosurvey

The 2017 antenatal HIV survey provided the first real-world national data on progress towards the 90-90-90 UNAIDS targets to help end the AIDS pandemic among adolescent girls and young women in South Africa. Nationally, HIV prevalence among pregnant women continued to be stable at around 30%. The consistent decline in HIV prevalence observed among young women (15-24 years) is encouraging, as this population has traditionally been at increased risk of HIV acquisition. Knowledge of HIV status prior to the first antenatal care (ANC) visit was low, especially among young women (15-24 years), highlighting the gap in access to youth-friendly reproductive health services.

The first and second of the 90-90-90 targets have been reached among pregnant women across all provinces. The achievement of these targets through the prevention of mother-to-child transmission (PMTCT) programme, despite the high number of individuals who were unaware of their HIV status prior to their first ANC visit, is an indication of the effectiveness of the programme in identifying HIV-positive pregnant women and enrolling them for treatment.

The 28th edition of the antenatal survey was conducted between 1 October and 15 November 2019 in 1589 sentinel sites selected from all the various districts of South Africa. To enhance the utility of the survey for programme monitoring and policy implementation, additional key data was collected from antenatal clients to provide information about the coverage of HIV, PMTCT, and reproductive health services among this population.

Determined, Resilient, Empowered, AIDS-free, Mentored and Safe Programme

The study assessed the level of exposure to activities of the DREAMS Programme on adolescent girls and young women (AGYW) aged 12–24 living in four districts where the DREAMS interventions were implemented, with correlates of HIV incidence and sexual risk behaviours. The study was conducted from 13 March 2017 to 22 June 2018 and a total of 18,296 AGYW and 6,487 caregivers from 13,254 households were enrolled in it. A total of 10,384 AGYW and of 3,652 caregivers were from Gauteng and 7,912 AGYW and 2,853 caregivers were from KwaZulu-Natal.

HIV incidence is the number of new HIV infections in a population during a certain period and can be used as a measure of the effectiveness of interventions such as the DREAMS Programme, which aims to reduce new infections. Incidence was calculated using the recent infection testing algorithm (RITA), which is a combination of a biological measure of recent infections and post-laboratory testing modifications.

The study found that the HIV incidence rate overall in AGYW 15-24 years, in the DREAMS implementation areas, was similar to that of eThekwini and uMgungundlovu districts in KwaZulu-Natal (0.91%, 95% confidence interval (CI): 0.82–0.99%), as well as the City of Johannesburg (CoJ) and Ekurhuleni in Gauteng (0.86%, 95% CI: 0.77–0.94%). By contrast, the HIV incidence rate was lower in KwaZulu-Natal in AGYW aged 15-19 years (0.46%, 95% CI: 0.41–0.50%) compared to Gauteng (0.75%, 95% CI: 0.68–0.83%). Among AGYW 20-24 years, HIV incidence was higher in KwaZulu-Natal (1.38% 95% CI: 1.24–1.52%) compared to Gauteng (0.94% 95% CI: 0.85–1.04%). Results for the 12–14 age group are omitted, as the number of recent infections or new infections was either insignificant and/or as a result of post-natal transmission on treatment.

HIV incidence in the DREAMS Programme evaluation was lower than in previous studies amongst young women in a similar area. The HIV prevalence varied significantly by geographic region, with the KwaZulu-Natal sample having significantly higher HIV prevalence rates compared to the Gauteng sample. The performance on the first component of the UNAIDS 90-90-90 targets (proportion of those infected and know they are infected) was insufficient to meet the targets, although the data indicated that the second and third component of these targets were almost achieved by respondents in this study. The preliminary findings indicate that there is a definite need for greater coverage and targeting of interventions amongst caregivers and AGYW in these areas.

Surveillance of acquired HIV drug resistance in adult patients through routine antiretroviral therapy programme monitoring in South Africa in 2019

A nationally-representative survey of HIV drug resistance (HIVDR) was implemented using remnant viral load (VL) testing specimens from adult patients from 16 NHLS VL testing laboratories. Of the 8,202 VL test specimens collected, 1,053 had unsuppressed VL of which 779 were selected for further testing. HIVDR genotyping was performed using next generation sequencing and drug level testing (DLT) using liquid chromatography mass spectrometry as a proxy for regimen. The survey showed that 72% of patients with unsuppressed VL harbour resistance to ART. DLT confirmed that 55% of specimens had detectable levels of ART. HIVDR was lower in patients that had undetectable levels of ART ($p<0.0001$), presumably due to lack of drug selection pressure. The use of residual specimens proved advantageous in that it allowed for proportion to size sampling and reduced collection time and cost.

A national survey of HIV prevalence, continuum of care and HIV drug resistance amongst female sex workers in South Africa

A cross-sectional, national survey of 3,005 female sex workers (FSWs) was conducted between February - July 2019. 61.2% (1840/3005) of FSWs tested HIV positive. Among participants successfully genotyped (viral load > 400 copies/ml), 64.6% (431/667) had evidence of HIVDR, including 77.8% (330/424) in those ART-exposed and 41.6% (101/243) in those ART-naïve. Innovative approaches to improve adherence amongst FSWs and proactive viral load monitoring are required.

Results for action dashboard: Monitoring paediatric HIV care using HIV test data

HIV-infected children in South Africa have a poor record of being linked to and retained in care. They are seen in multiple facilities with no system in place to monitor their care. The National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW) stores all HIV tests for children in the public sector nationally.

An application (app) was developed to track every child's HIV test result across facilities to construct a facility patient list of children, flagging those 1) newly diagnosed as infected for antiretroviral initiation and 2) with a high or missed VL according to national guidelines. Clinicians can draw worklists detailing children requiring action and record their actions e.g. treatment initiated. The app applies a series of rules to flag children when the monitoring of their blood is not detected within the recommended period, to identify children at risk of loss to follow up. Other features of the app include: Real-time reporting of the number of new patients diagnosed and retained in care; viewing longitudinal patient test records; improved data quality to allow better performance of patient linking algorithms; and an audit trail.

Strengthening surveillance for congenital syphilis in South Africa

In collaboration with the NMC team, the centre continued to strengthen the case-based surveillance of congenital syphilis (CS). CS is a preventable medical condition that results from the transmission of *Treponema pallidum (T. pallidum)* infection from an infected pregnant woman to her foetus. *T. pallidum* infection has severe consequences for the foetus, resulting in early foetal deaths, and still-births, neonatal deaths, preterm and low birthweight births and symptomatic disease, in addition to asymptomatic infections. CS is a category 2 NMC condition, which means healthcare practitioners are required to notify any cases detected within seven days of detection.

During the year under review, the centre received funding from the World Health Organization (WHO) to support activities to strengthen the surveillance, prevention and control of CS. Activities implemented during the year to improve the detection and reporting of CS included:

- Hosting national stakeholder consultations;
- Revising the CS-specific case investigation form;
- Training of facility-based staff on CS case definition and notification procedures;
- Collating case investigation forms;
- Analysing CS cases notified; and
- Producing national estimates of CS for the Global AIDS Monitoring (GAM) Report.

By the end of the year, the centre had 362 cases that were reported to the DoH for inclusion in the GAM Report. Although there was likely underreporting of CS, activities are underway to triangulate CS data with other data sources in a formal evaluation during the next financial year.

3. Policy Contributions

NICD results for action (RfA) reports for early infant diagnosis (EID) and HIV VL monitoring were endorsed in the National Consolidated Guidelines for the Management of HIV.

The South African Lancet National Commission was launched in May 2017 to conduct country-specific analyses on quality of care consistent with the overall aims and objectives of the Lancet Global Health Commission on High-Quality Health Systems (HQSS Commission) in the Sustainable Development Goals (SDGs) era. As such, the following four main recommendations were made:

1. Enhance governance and leadership for quality and equity;
2. Revolutionise quality of care;
3. Invest in and transform human resources in support of a high-quality health system; and
4. Measure, monitor and evaluate to ensure a high-quality health system.

4. Research Activities

Pilot assessment of point of care testing and viral load monitoring

NICD investigators: GG Sherman, AF Haeri Mazanderani, T Murray and T Kufa-Chakezha.
Co-investigator: S Carmona (University of Witwatersrand, National Health Laboratory Service)

POCT for EID of HIV and HIV VL could transform monitoring by increasing coverage, decreasing test turnaround times (TATs), improving test result receipt rates, retention in care and decreasing time to VL suppression. Introducing decentralised POCT, however, necessitates other requirements, such as physical space for device placement, procurement of cartridges, training of staff and quality assurance, that may burden under-serviced health facilities. Accurate and timely maternal VL and birth EID POCT at four busy delivery units in Gauteng was implemented with variable success. Further scale-up will need to address health system factors at facility level and high analytical error rates. Mapping, in relation to EID requirement and capacity of GeneXpert instruments for TB testing, demonstrated that there was additional capacity to test approximately 33% of required EID volume without reducing capacity for TB testing.

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

Principal investigator: Precious Mahlangu
Co-investigators: Etienne Muller and Ranmini Kularatne

Mycoplasma genitalium is emerging as an important STI pathogen, responsible for up to 20-35% of non-chlamydial non-gonococcal (NCNGU) urethritis and cervicitis. Current treatment guidelines (adopted in 2014) recommend the use of a 1g single dose of azithromycin as first-line therapy for uncomplicated *M. genitalium* infection. Macrolide resistance is caused by mutations in region V of the 23S rRNA gene, while fluoroquinolone resistance is associated with gyrA and parC gene mutations.

To further understand the epidemiological aspects of *M. genitalium* infection and to determine associations between different *M. genitalium* types and resistance profiles, it is necessary to genetically characterise *M. genitalium* by generating DNA sequence data profiles. No macrolide resistance associated mutations were detected in *M. genitalium* from Johannesburg sentinel surveillance specimens collected between 2007-2014. Ongoing macrolide resistance surveillance is essential, as resistance may emerge, prompting a revision of STI management guidelines.

Acyclovir resistance in herpes simplex virus-2, South Africa

Principal investigator: Etienne Muller
Co-investigators: Venessa Maseko and Ranmini Kularatne

Herpes simplex virus type 2 (HSV-2) is the predominant cause of genital ulcer disease in South Africa. Acyclovir (ACV) is the drug of choice for the treatment of HSV-2 infections. HSV-2 resistance to ACV is mainly due to mutations in the viral thymidine kinase (TK) (encoded by the *UL23* gene), resulting in the defective production of TK or in the alteration of TK substrate specificity. Resistance is also associated with substitutions in conserved regions of the HSV-2 DNA-polymerase (*UL30*) gene. HSV-2 culture and phenotypic ACV resistance testing is useful to identify novel resistance-associated mutations. Comparison of phenotypic and genotypic ACV antiviral susceptibility profiles is underway to determine the prevalence of HSV-2 ACV resistance in surveillance specimens (2018 onwards). These data will inform future national management guidelines for genital ulcer disease.

Changing epidemiology of genital ulcer disease in South Africa, has donovanosis been eliminated?

Principal investigator: Etienne Muller
Co-investigator: Ranmini Kularatne

Klebsiella granulomatis, the causative agent of donovanosis, was a significant cause of genital ulceration in KwaZulu-Natal in the 1980s and early 1990s. Specific treatment for this condition is not included in the national syndromic management guidelines for genital ulcer disease (GUD). An inhouse molecular assay for *K. granulomatis* was developed to determine whether a diagnosis of donovanosis could be ascribed to GUD with no identifiable aetiology in surveillance specimens collected between 2007 and 2018 from all provinces of South Africa. A *Klebsiella* screening assay targeting the *phoE* (phosphate porin) gene was used in combination with restriction digest analysis and sequencing, to confirm the presence of *K. granulomatis*. None of the 974 specimens tested gave a positive result for *K. granulomatis* DNA. This was the first study to assess *K. granulomatis* as a cause of genital ulceration in South Africa over a 12-year period and demonstrated that this organism is no longer a prevalent cause of GUD in our population.

Comparison of gentamicin minimum inhibitory concentrations by agar dilution and Etest for clinical isolates of *Neisseria gonorrhoeae*

Principal investigator: Ranmini Kularatne
Co-investigators: Venessa Maseko, Lindy Gumede and Tendesayi Kufa-Chakezha

In South Africa, *Neisseria gonorrhoeae* is the predominant cause of male urethritis syndrome (MUS). The national MUS treatment guidelines recommend gentamicin as salvage therapy for ceftriaxone treatment failures. Gentamicin MICs obtained were ascertained and compared by agar dilution and Etest for clinical isolates of *N. gonorrhoeae* obtained from 272 MUS cases in 2017. Gentamicin MIC50 by agar dilution was significantly higher than by Etest; and the overall MIC agreement was 7.4%. Correlation with expected MICs for WHO reference strains was consistently better with Etest than agar dilution. The significant discordance between *N. gonorrhoeae* gentamicin MICs by agar dilution versus Etest highlighted the importance of standardising *N. gonorrhoeae* gentamicin susceptibility testing methodology and establishing interpretive criteria to optimise the monitoring of susceptibility trends.

5. Research activities

HIV Virology Section

Core activities as an endpoint laboratory for the HIV Vaccine Trials Network

The section conducts validated end-point antibody and molecular diagnostic assays for the HIV Vaccine Trials Network (HVTN). Specifically, sensitivity assays were performed on breakthrough infections in the antibody-mediated prevention (AMP) trial which tests the ability of a passively infused broadly neutralising antibody VRC01 to prevent HIV infection. The AMP trial will end in 2020, with unblinding scheduled for August 2020. In addition, the pharmacokinetics (PK) of VRC01 via neutralisation was measured. This information, together with the sensitivity data from breakthrough viruses will be used to measure the efficacy of VRC01 in preventing infection, and predict the protective neutralisation titer. The neutralisation assays for HVTN 100 Part B trial (a precursor of the HVTN 702 trial) was performed, which assessed durability of responses six months after protein re-boosting. Data showed higher magnitude of responses six months after re-boosting than the previous durability timepoint, suggesting boosting confers a benefit.

IgG3 enhances neutralization potency and Fc effector function of an HIV V2-specific broadly neutralizing antibody

NICD researchers: Richardson SI, Lambson BE, Scheepers C, Mkhize NN, Moore PL and Morris L
Co-investigators: Crowley AR (Dartmouth College), Bashirova A (Ragon Institute), Garrett N and Abdool Karim S (Centre for the AIDS Programme of Research in South Africa), Carrington M (Ragon Institute), Ackerman ME (Dartmouth College)

Studies of bNAbs continue to be a key focus. The efficacy of bNAbs can be enhanced through interaction with Fc receptors on immune cells. Isotype is a modulator of this, and anti-human (IgG3) antibodies mediate particularly potent Fc effector function. To examine the role of natural isotype in the context of a bNAb lineage, a bNAb donor, CAP256, was studied, who mounted a potent V2-specific bNAb response. CAP256 expressed persistently high levels of plasma IgG3 which mediated both broad neutralising activity and potent Fc function. Sequencing of germline DNA and the constant regions of V2-directed bNAbs from this donor revealed the expression of a novel IGHG3 allele as well as IGHG3*17, an allele that produces IgG3 antibodies with increased plasma half-life. IgG3 variants had significantly higher Fc function and neutralisation compared to IgG1 versions, with the length of the antibody hinge modulating both functions. This study was one of the first to show that cooperation between the variable and natural IgG3 constant regions can enhance the polyfunctionality of antibodies. This indicates the value of leveraging genetic variation for passive immunity, and was published in PLOS Pathogens.

Somatic hypermutation to counter a globally rare viral immunotype drove off-track antibodies in the CAP256-VRC26 HIV-1 V2-directed bNAb lineage

NICD researchers: Sacks D, Bhiman JN, Morris L and Moore PL
Co-investigators: Wiehe K (Duke University), Gorman J (Vaccine Research Centre, National Institutes of Health), Kwong PD (Vaccine Research Centre, National Institutes of Health)

bNAbs only develop in some HIV infected individuals, partly due to complex evolutionary pathways characterised by extensive somatic hypermutation. Furthermore, bNAbs within a lineage can form a minor subset, amidst many strain-specific “siblings”, indicating that small sequence differences between lineage members can significantly affect neutralisation. A study published in PLOS Pathogens defined the specific mutations that limit breadth in two “off-track” members of the CAP256-VRC26 bNAb lineage, and show that these occur commonly. A virus with a globally rare V2 sequence selected for these strain-specific antibodies, which highlights the complex interdependency between high levels of antibody maturation and breadth. This data shows that repeated vaccination strategies being pursued in the HIV vaccine field will require careful antigen selection to focus the humoral response to globally common epitopes.

Cell Biology

Paediatric HIV functional cure and early antiretroviral treatment

NICD researcher: Tiemessen CT
Co-investigators: Kuhn L (Columbia University), Coovadia A, Technau K, Strehlau Renate and Patel Faeezah (The LEOPARD Study Team, Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital)

A single-arm clinical trial, called LEOPARD-CT, which commenced in August 2015 at Rahima Moosa Mother and Child Hospital (RMMCH) in Johannesburg, South Africa, completed recruitment and follow up in April 2019. The trial was designed to improve the understanding of viral latency in early treated HIV-infected children to lead to more effective treatment strategies for children with the ultimate goal of achieving functional cure or viral remission. An observational cohort of mothers and their infants was followed in parallel (called LEOPARD-O, and commenced in March 2015). Findings revealed that only half of the children attained and sustained VLs <50 RNA copies/ml, and only half of these sustained CD4% >30%. There was no difference in proportions of children attaining these endpoints according to starting ART within 48 hours or between two and 14 days of birth. Additional interventions in addition to early administration of ART must be considered to attain remission in children.

Two unusual cases were described where nucleic acid diagnostic tests were initially positive in the first month of life and then negative during breastfeeding, but who became positive following cessation of breastfeeding. Based on these findings, it was hypothesized that immune/other factors in breastmilk coupled with maternal ART contributed to an undetectable virus during breastfeeding. This highlights the importance of diagnostic re-testing of HIV-exposed breast-fed infants after cessation of breastfeeding.

Grant Funding

The following organisations provided funding to support the centre's work:
- South African Medical Research Council (SAMRC);
- NHLS Research Trust (NHLS RT);
- National Research Foundation (NRF) incentive funding for rated researchers;
- NRF Professional Development Programme;
- Department of Science and Technology(DST)/NRF Chair of HIV Vaccine Translational Research;
- Poliomyelitis Research Foundation (PRF); and
- National Institutes of Health (NIH);
- President's Emergency Plan For AIDS Relief (PEFAR).

6. Teaching and Training

Professional development

During the year under review, the centre enrolled several candidates for postgraduate studies as follows:
- Five for Doctor of Philosophy degree (PhD);
- Eight for Master of Science degree (MSc); and
- Three for Bachelor of Science degree (BSc).

A number of postgraduate students from the centre graduated with the following qualifications:
- One with Master of Medicine Degree (MMed);
- Ten with PhD;
- Eight with MSc; and
- One with BSc (Honours).

Honours

J Botha, F Conradie, H Etheredge, J Fabian and CT Tiemessen from the centre received the Vice-Chancellor's Transformation Team Award for the world's first living donor liver transplant from an HIV positive parent to her HIV negative child (2019).

CT Tiemessen also received the SAMRC Gold Scientific Merit Award (2019) in recognition of research excellence.

7. Research output

Journal articles

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13. Mazanderani A.H., Sherman G.G. Evolving complexities of infant HIV diagnosis within prevention of mother-to-child transmission programs. F1000 Faculty Rev. 2019; 8: 1637.
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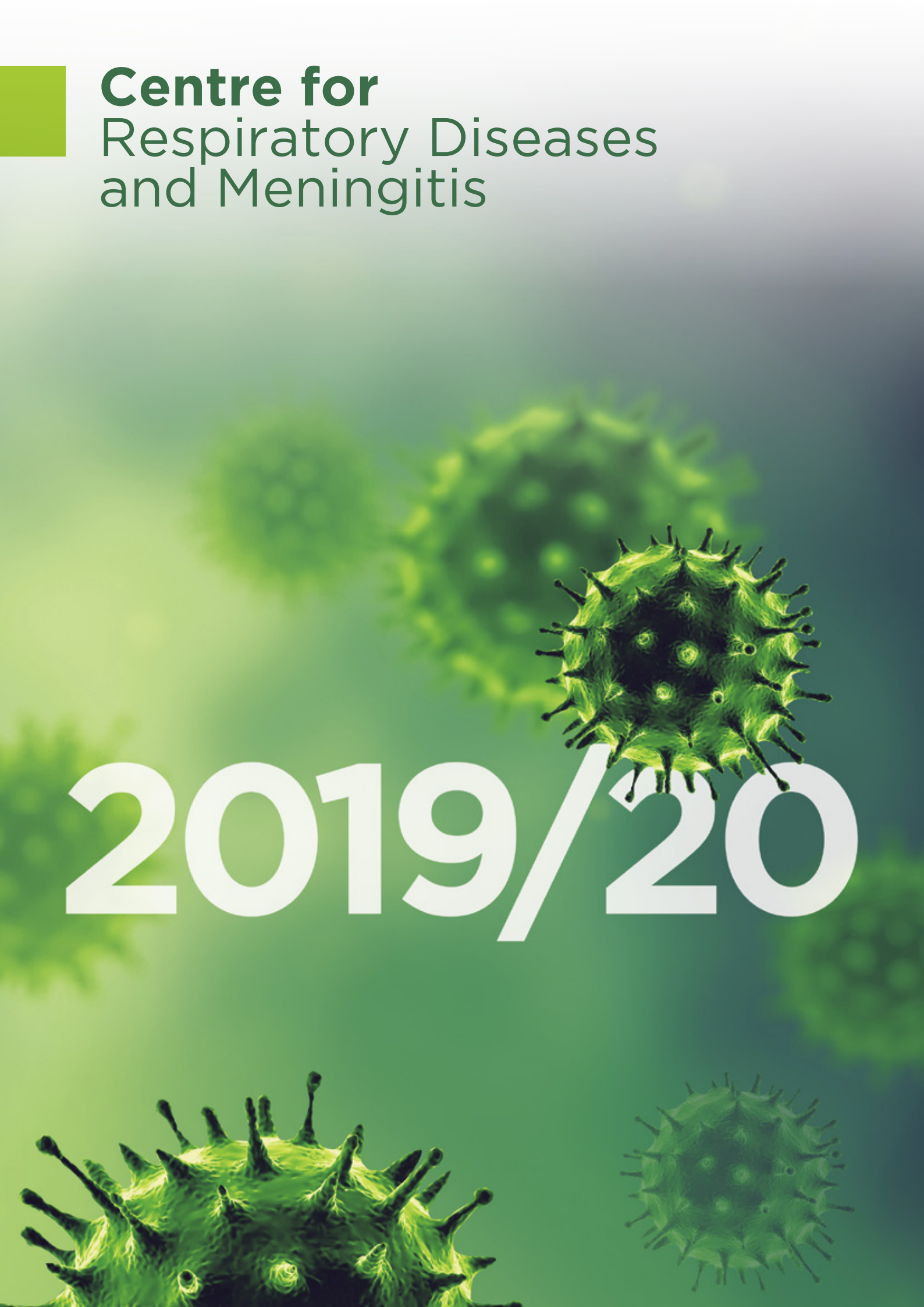
Article in books

Sherman G., Mazanderani A.H. Diagnosis of HIV infection in children and adolescents. In: Bobat R, eds. HIV Infection in Children and Adolescents. Cham: Springer, 2020: 15-22.

Conference Presentation

During the year under review, the centre conducted 10 presentations at international congresses; 18 presentations at national congresses and five at local congresses.

Centre for Respiratory Diseases and Meningitis



2019/20

Prof Cheryl Cohen
Centre Head

1. Background

Summary
During the financial year under review, the Centre for Respiratory Diseases and Meningitis (CRDM) continued with 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 influenza, respiratory syncytial virus (RSV) and *Bordetella pertussis* (pertussis). Laboratory-based surveillance programmes included pneumococcus, meningococcus and *Haemophilus influenzae*, with a focus on outbreak detection and the impact of interventions.

CRDM was at the forefront of the response to the coronavirus disease 2019 (COVID-19) outbreak in South Africa. The Centre developed case definitions for surveillance and laboratory testing of suspected COVID-19 cases in January 2020 and were the first in South Africa to implement diagnostic testing for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Together with strategic partners, CRDM supported the national incident management team and contributed to a substantial number of guidelines and training activities on COVID-19.

The Centre is responsible for six 'category one' notifiable medical conditions (NMCs) as follows: acute rheumatic fever, COVID-19, diphtheria, meningococcal disease, pertussis and respiratory disease caused by a novel respiratory pathogen, as well as two 'category two' conditions, namely: *Haemophilus influenzae* type b and legionellosis. Active reporting and real-time verification of the NMC programme commenced during the reporting year.

In 2020, four postgraduate students joined CRDM as part of the National Institutes of Health (NIH)-funded South Africa-Pitt Public Health Genomic Epidemiology Training Program (SAPPHGenE), which aims to build capacity and develop research in public health genomics in South Africa.

2. Surveillance

The South African Group for Enteric, Respiratory and Meningeal Disease

Through the South African Group for Enteric, Respiratory and Meningeal Disease (GERMS-SA) programme for national, laboratory- and population-based, active surveillance of invasive pneumococcal and Hib disease, CRDM continued to evaluate the ongoing impact of both the pneumococcal conjugate vaccine (PCV) and the *Haemophilus influenzae* serotype b conjugate vaccine (Hib CV).

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. Surveillance for group A and group B streptococci was enhanced from April 2020. CRDM furthermore participated in the BABY GERMS-SA Neonatal Sepsis Surveillance at six enhanced surveillance sites.

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) irrespective of duration of symptoms, and tests for pathogens of public health importance. The programme can incorporate testing for additional emerging pathogens when required. The NPSP continues to test for influenza, RSV and *B. pertussis* with the aim to describe the burden, risk groups and seasonality of these pathogens and to identify outbreaks. Additional studies allow the investigation of factors associated with severity of illness and effectiveness of vaccine programmes.

Systematic surveillance for outpatient ILI and suspected pertussis is ongoing at outpatient clinics in three provinces. A new ILI site with two clinics was initiated in Mitchell's Plain, Western Cape. Good progress was made with the integration of the NPSP and ILI surveillance programmes into the GERMS-SA platform. GERMS-SA took over the management of surveillance staff and ~90% of field surveillance staff are funded through GERMS-SA.

The Viral Watch ILI surveillance network of general practitioners continues to operate in eight provinces, providing data on viral circulation, timing of the influenza season and annual estimates of influenza vaccine effectiveness. In March 2020, the surveillance platform was expanded to include surveillance for COVID-19 at all ILI and NPSP surveillance sites. This will provide valuable, systematically collected data to describe the epidemiology and risk factors for severe COVID-19 disease in South Africa.

3. Outbreaks

Coronavirus disease 2019

Together with the National Department of Health (NDoH) and other partners, the Centre developed and released COVID-19 guidelines for case-finding, diagnosis, management and public health response in South Africa, in February 2020. These guidelines have subsequently been updated in line with the evolving epidemiology of the disease. Additional guidelines were also developed for different sectors, such as education.

From 26 January 2020 to mid-March 2020, the CRDM laboratory was the only testing laboratory that implemented diagnostic polymerase chain reaction (PCR) testing for SARS-CoV-2. CRDM worked closely with laboratories in the public and the private sector to rapidly expand laboratory testing capacity in both sectors. The CRDM laboratory was appointed as a World Health Organization (WHO) COVID-19 international regional reference laboratory and provided technical support and training to many African countries, in this capacity.

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 (MAC). CRDM staff contributed to the Emergency Operations Centre (EOC) and national Incident Management Team (IMT) by amongst other providing data, epidemiology, laboratory and clinical expertise.

Other

Throughout the financial period under review, the Centre has provided ongoing laboratory and epidemiology support to the NDoH for suspected cases of diphtheria, pertussis and meningococcus, including contact tracing.

4. Research activities

Declining incidence of invasive meningococcal disease in South Africa

NICD investigators: Meiring S, Cohen C, de Gouveia L, du Plessis M, Kularatne R, Lengana S, Seetharam S, Quan V, von Mollendorf C, von Gottberg A

This observational study described the decline in meningococcal disease in South Africa over fourteen years, in the absence of significant vaccine coverage. Data for the study was derived from the GERMS-SA national surveillance programme on invasive meningococcal disease that has been ongoing in South Africa since 2003. The study highlights the natural waxing and waning of meningococcal serogroups, describes risk factors (including HIV) for the different serogroups and demonstrates the presence of multiple serogroup clusters occurring simultaneously across the country.

Can pneumococcal meningitis surveillance be used to assess the impact of pneumococcal conjugate vaccine on total invasive pneumococcal disease? A case-study from South Africa

NICD investigators: Kleynhans J, Cohen C, de Gouveia L, du Plessis M, von Gottberg A

South Africa introduced a seven-valent pneumococcal conjugate vaccine (PCV7) in 2009 and PCV13 in 2011. The estimated impact of PCV on pneumococcal meningitis (PM) was compared to the impact of PCV on total invasive pneumococcal disease (tIPD) based on risk reduction after PCV introduction. During 2005-2016, national, laboratory-based surveillance for tIPD was conducted. Rates of PCV13 and non-PCV13 serotype disease among tIPD and PM in individuals aged <5 years and ≥5 years were estimated and compared. These rates were also compared for the period between the 2005-2008 pre-PCV introduction period and at the stage of two-time points after PCV introduction, in 2012 and 2016. By 2016, IPD caused by all serotypes decreased by 55% (95%CI 57% to 53%) for tIPD, and 54% for PM (95%CI 58% to 51%), with 0.7% difference between estimates (p = 0.7). No significant differences were observed between PCV7-serotype disease reduction in tIPD and PM in both age groups or the additional six serotypes included in PCV13 in <5 year olds in 2012 and 2016. PM showed similar reductions to tIPD seven years after PCV introduction in vaccine serotype disease in those <5 years, and increases in non-vaccine serotype disease in all ages.

The impact of human immunodeficiency virus exposure on respiratory syncytial virus–associated severe respiratory illness in South African infants

NICD investigators: Walaza S, Treurnicht FK, Moyes J, Hellferscee O, Wolter N, von Gottberg A, Nguweneza A, McAnerney JM, Cohen C

During 2011-2016, prospective surveillance for severe respiratory illness (SRI) in children aged <5 years was conducted in three South African hospitals. Nasopharyngeal aspirates were tested for influenza and RSV to estimate rates of influenza- and RSV-associated hospitalised SRI by HIV status. HIV exposure was associated with increased incidence of influenza- and RSV-associated hospitalisation in infants aged 0-5 months. HIV infection was associated with increased incidence of influenza- and RSV-associated hospitalisation in all age groups.

Quantifying how different clinical presentations, levels of severity, and healthcare attendance shape the burden of influenza-associated illness: a modeling study from South Africa

NICD investigators: Walaza S, Moyes J, Treurnicht FK, Hellferscee O, Wolter N, von Gottberg A, Cohen C

The mean annual number of influenza-associated illness episodes in South Africa from 2013-2015 was 10,737,847 (19.8% of 54,096,705 inhabitants). Of these episodes, 10,598,138 (98.7%) were mild, 128,173 (1.2%) were severe-non-fatal and 11,536 (0.1%) were fatal. A total of 2,718,140 (25.6%) mild, 56,226 (43.9%) severe-non-fatal and 4,945 (42.8%) fatal episodes were medically attended. Influenza-associated respiratory illness accounted for 99.2% (10,576,146) of any mild illness, 65.5% (83,941) of severe-non-fatal illness and 33.7% (3,893) of fatal illness.

Household transmission of seasonal influenza from HIV-infected and HIV-uninfected individuals in South Africa, 2013-2014

NICD investigators: Cohen C, Tshangela A, Valley-Omar Z, Von Mollendorf C, Walaza S, Hellferscee O, Treurnicht FK

A total of 28 HIV-infected and 57 HIV-uninfected index cases were enrolled for this study. Based on multivariable analysis, HIV-infected index cases were less likely to transmit influenza to household contacts (odds ratio (OR) 0.2 95% CI 0.1-0.6) (secondary infection risk (SIR) 16%, 18/113 vs 27%, 59/220). Factors associated with increased SIR included index age group 1-4 years (OR 3.6, 95% confidence interval (CI) 1.2-11.3), 25-44 years (OR 8.0, 95% CI 1.8-36.7) and contact age group 1-4 years (OR 3.5, 95%CI 1.2-10.3) compared to 5-14 years and sleeping with index case (OR 2.7, 95%CI 1.3-5.5). HIV infection of index cases was not associated with serial interval.

5. Teaching and training

In the reporting year, the centre provided technical, operational and stakeholder support as follows:

1. Training and site visits for surveillance and special studies, namely, syndromic surveillance for respiratory disease including the GERMS-SA surveillance programme, and the Prospective Household observational cohort study of Influenza, Respiratory Syncytial virus and other respiratory pathogens community burden and Transmission dynamics in South Africa (PHIRST), maternal influenza and African Network for improved Diagnostics, Epidemiology and Management of Common Infectious Agents (ANDEMIA) studies;
2. Ongoing training of provincial NMC nurses on topics related to CRDM pathogens and diseases;
3. Legionella awareness activities and facility audits at different sites, as well as hosting and facilitating semi-annual meetings for the national legionella action group;
4. Hosting of a hands-on workshop on invasive bacterial diseases (IBD) surveillance bacteriology and EQA laboratory training to the WHO Regional Office for Africa (WHO-AFRO) from 26-30 August 2019, which was attended by participants from 10 Southern African Development Community (SADC) countries;
5. Jinal Bhiman, Thabo Mohale, Ewalde Cutler and Anne von Gottberg from the centre formed part of the Africa CDC, WHO, NICD and Roche Diagnostics faculty that provided SARS-CoV-2 training to participants from 13 African countries at the Roche Scientific Campus in Midrand from 20-22 February 2020;
6. On 26 March 2020, Jinal Bhiman conducted online follow-up training to 100 participants on the African Society for Laboratory (ASLM) Extended Community Health Outcomes (ECHO) model and platform on laboratory diagnostics for SARS-CoV-2; and
7. Clinical, technical and epidemiological COVID-19-related support was provided on an ongoing basis.

Academic teaching and lectures

1. Cheryl Cohen was the course coordinator for the infectious diseases epidemiology module that forms part of the Master of Science (MSc) Epidemiology Degree as well as the Epidemiology track that forms part of the MSc Vaccinology Degree at the University of the Witwatersrand (Wits);
2. Orienka Hellferscee and Kedibone Ndlangisa provided lectures to Bachelor of Science Honours Degree (BSc Hons) students at the Department of Clinical Microbiology and Infectious Disease at Wits Medical School on 31 May 2019;
3. Jackie Kleynhans provided a lecture on: The importance of the laboratory during outbreak investigations, to students from the South African Field Epidemiology Training Programme (SAFETP) on 4 September 2019;
4. Amelia Buys and Anne von Gottberg lectured for the MSc Vaccinology course at Wits; and
5. Nicole Wolter lectured on Laboratory Diagnosis of SARS-CoV-2 at the University of Pretoria (UP) Symposium on 5 March 2020.

Professional development

During the financial year under review, the Centre enrolled 11 students for postgraduate studies as follows:
- Seven for Doctor of Philosophy degree (PhD);
- Three for Masters' degrees; and
- One for Honours degree.

Five students from the Centre graduated with postgraduate degrees as follows:
- Two with PhD;
- Two with MSc; and
- One with BSc (Honours) degree.

The Centre also hosted:
- Four medical scientist interns from the Health Professions Council of South Africa (HPCSA);
- One intern from the National Research Foundation (NRF);
- Two residents from the SAFETP; and
- Two PhD and two Masters' students from the South Africa-Pittsburgh Public Health Genomic Epidemiology Research Training Program (SAPPHGenE).

6. Research output

Journal articles

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Conferences

During the year under review, staff from the Centre conducted 16 presentations at international conferences and 13 presentations at national and local conferences.

Centre for
for Tuberculosis

2019/20

Prof Nazir Ismail
Centre Head

1. Background

The year under review was a highly productive and dynamic period. The Centre laid the foundations to re-invigorate its laboratory-based public health surveillance of TB, reached important milestones for several high impact projects and continued to serve a leading role both as the National TB Reference Laboratory (NTBRL) for South Africa and as a WHO Supranational TB Reference Laboratory globally.

The latter was endorsed by the World Health Organization (WHO) as a supranational reference laboratory in 2016. Global TB policies and guidelines are initiated through WHO and their formulation has included representation from the CTB which assisted in developing these strategic documents. Microbiology- and epidemiology-oriented training programmes continued, while we remained focused on one of the key functions of the CTB, which is to initiate public health research, contribute to new knowledge creation and provide insights on the TB epidemic in South Africa, with the objective of guiding policies and practices.

The South African National TB Strategic Plan for the period 2017-2021, places great emphasis on a data-driven approach to TB management and control efforts in the country, and this stream of work is co-led between the Centre and NDoH. Two important outputs have made major progress over the period. The SA TB prevalence survey was completed and the TB inventory study which CTB leads, has made major progress. The true magnitude of the TB epidemic and a more focused strategy to find the “missing TB patients” will now be possible. The geospatial mapping of the TB burden facility level hotspots has been completed and temporal associations with introduction of new technologies and seasonal influenza have been explored.

Surveillance using next generation WGS technologies continues to improve the understanding of TB transmission in a high endemic setting. The expanded use of BDQ has resulted in significant reductions in mortality and improvement in treatment success among patient with drug resistant TB, but at the same time, the emergence of the resistance has occurred. Analysis of the national BDQ resistance surveillance has provided key data on the extent of the problem and high risk categories for BDQ resistance. The year under review has no doubt been exciting for TB management in South Africa and also for the CTB at the NICD.

2. Surveillance and diagnostic services

Routine surveillance reporting and request for action alerting

Surveillance findings continue to be regularly analysed and reported to the national and provincial TB programmes and are available through an online TB surveillance dashboard. The weekly results for action (RfA) reports cover both drug susceptible and drug resistant TB. Integrating the NICD surveillance data and EDR.web has been developed and will help to accurately estimate and monitor the total burden of drug resistant TB in South Africa. The development of the TB application 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 as well and provide these on a daily basis.

The Centre has played an important role in establishing the broth microdilution assay as a new diagnostic for tuberculosis drug susceptibility testing. In addition, the Centre has contributed significantly to the development of the DR-TB and new TB guidelines.

TB prevalence survey – South Africa

The National Tuberculosis Control and Management Programme (NTCP) initiated a nationwide TB prevalence survey to establish the true burden of pulmonary TB disease in South Africa. This is becoming increasingly important, considering the wide gap between the estimates produced by WHO and what is notified through the programme.

The survey, which is a collaborative activity between the NDoH, NICD, HSRC and MRC, has been successfully completed. The CTB played a leading role in writing the short report of the TB Prevalence Survey. The estimate has confirmed the large gap between the cases notified and the true burden. Three key groups were identified as populations that have TB but are missed: men, HIV negative individuals and patients who have active TB but do not display overt symptoms. Additionally, while most people with a cough would attend a public sector facility to seek care, due to the nature of the symptoms early on, care is often delayed.

Modernising TB surveillance

The online TB surveillance dashboard was launched with the Minister of Health on 24 March 2017, and provides data for the last 10 years and is available at: www.nicd.ac.za. It is an open access tool that allows tracking of the TB epidemic to the level of sub-district and provides age-gender stratification. The restricted access dashboard is also active and simplifies the availability of data to the program managers. In the past year a revamp of the automated surveillance system, that underpins these dashboards, has been undertaken. These have gone through validation and will be incorporated so that the reporting will be more robust and regularised on the dashboard.

The updated Notifiable Medical Conditions Legislation at the end of 2017, has seen significant advancement of the new system managed by the NICD. A TB specific application has been developed that allows near real-time clinical notifications, a push-based platform that provides the RfA information straight into the platform and accessible universally in the country. The landing page of the NMC TB module is shown in Figure 1. Registered users will now have access to this information to ensure that a public heath response is activated while also allowing robust M&E to be automated by monitoring initial loss, to follow up on a daily basis and providing exception notifications when actions have not been taken. Delays in implementation were due to technical aspects and later the COVID-19 pandemic, however planning for the implementation has begun, initially prioritised to the Global Fund priority districts.

Monitoring and evaluation of microbiologically confirmed TB in South Africa

The geospatial distribution of mPTB is highly heterogeneous at sub-district level and is even more apparent at facility level. A key determinant to ensure that SA is able to effectively introduce interventions seeking to increase case finding is to ensure a robust monitoring and evaluation solution. Several options have been considered, however due to wide variations between facilities and the relatively low numbers on a daily and even weekly basis, CTB has innovated a new approach to this priority issue. A novel matrix was developed and shown in Table 1. The matrix allows monitoring of trends at facility level and takes into account the seasonal variation observed. Furthermore it classifies facilities into groups, which is very useful to assist program managers to identify and respond to areas of need, while also assessing if interventions introduced are having the necessary impact. The use of laboratory data is powerful as these are relatively objective and having a fully digital laboratory system allows data to be provided at a granular level in a near real-time system. However for practical purposes the M&E solution will be monitored monthly and quarterly.

Figure 1: The Notifiable Medical Conditions Surveillance System landing page for TB

Table 1: Trajectory analysis of monthly laboratory tuberculosis investigations, by facility and sub-district, 2019

Sub-District	Facility	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Sparkline plot	Trajectory Group
A	Facility 1	7	6	23	15	16	33	45	33	29	44	29	14		Uncertain
A	Facility 2	11	6	9	16	9	10	13	8	11	15	15	16		Increasing
A	Facility 3	9	6	20	19	17	12	13	10	8	18	6	0		Seasonal
A	Facility 4	7	15	9	7	2	18	12	19	4	3	6	3		Seasonal
A	Facility 5	5	11	4	16	7	10	7	14	7	10	8	14		Uncertain
A	Facility 6	8	7	8	7	4	8	11	11	7	14	11	9		Increasing
A	Facility 7	42	21	31	27	12	26	19	36	16	42	16	10		Uncertain
A	Facility 8	8	10	25	25	17	12	12	24	16	14	10	9		Seasonal

National Bedaquiline Resistance Surveillance Resistance

Bedaquiline (BDQ) is a diarylquinoline antimycobacterial drug that specifically inhibits mycobacterial adenosine triphosphate synthase. It is the first new drug belonging to a class with a novel mechanism of action. Improvement in patient success rates and reduction in mortality attributed to BDQ has been well documented leading to a policy shift by the NDoH to use it for all patients newly diagnosed with RR/MDR-TB. Overall, mortality was reduced threefold while patient success is reported to have surpassed 70%. The new injection-free bedaquiline-based regimen has been administered to more than 30 000 patients.

The emergence of resistance to this drug has shown to occur in South Africa and was detected through the BDQ surveillance programme. The national surveillance programme enrolled >8,000 individuals and tested just over 2,000 patients at baseline, starting a BDQ-based regimen between 2015 and 2019. Overall, 3.8% of patients had BDQ resistance at baseline and when restricted to those without prior BDQ or clofazimine (CFZ) exposure, this figure was 2.8%. No atpE mutations were observed, and the primary resistance mechanism was related to variants in the Rv0678 gene. Prior exposure to BDQ/CFZ had high odds of BDQ resistance, while other factors included increasing levels of resistance, e.g. extensively drug-resistant TB (XDR-TB). HIV neither showed an increase in odds, nor did the time-based phased implementation which included decentralisation. The occurrence of BDQ resistance had a ~50% reduction in successful outcomes.

Specialised reference mycobacteriology – National and Supranational Reference Laboratory activities

The reference laboratory has been active at establishing standardised methodologies for bedaquiline resistance determination. A major multi-country study across five SRLs globally (Belgium, Italy, Japan, Pakistan and South Africa) confirmed the appropriateness of the BDQ critical concentration criteria and assessed the reproducibility of the assays for BDQ resistance detection.

The broth microdilution assay is increasingly being used for resistance determination for *Mycobacterium tuberculosis* across multiple drugs. The major limitation has been robust criteria using this MIC method for routine use. We determined interpretive criteria and cross validated these with whole genome sequencing data. The findings were published in *Nature Scientific Reviews,* providing an important first step using this technology to provide universal DST for tuberculosis.

Proficiency testing of BDQ was completed by the NHLS laboratories performing DRTB Reflex testing. As no formal kit for BDQ testing is available as yet, prepared BDQ drug aliquots were shipped 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).

On the regional front, we have provided support to Namibia in terms of performing additional drug susceptibility testing for patients who are failing a drug-resistant TB regimen. Results provided are used to create an effective patient regimen aiming at improving treatment outcome.

Molecular epidemiological surveillance for early detection of RR clusters in selected districts

A review of the transmission surveillance conducted between 2015 and 2017 has highlighted differential clustering patterns of *M. tuberculosis* strains in the different regions (Table 2). Most of the clusters (247/300; 82%) were small in size (<5 cases), 12% (36/300) were medium sized (5-10 cases), 3.3% (10/300) were large (11-25 cases) and 2.3% (7/300) were very large with 26-270 cases. The Beijing genotype was responsible for majority of DR-TB cases in Western and Eastern Cape, while the EAI1_SOM genotype accounted for a third of DR-TB cases in Mpumalanga. The overall proportion of cases estimated to be due to transmission was 42%, with the highest estimated rate of transmission in Western Cape (64%) and the lowest in Northern Cape (9%). Large clusters contribute to the expanding burden of DR-TB in specific geographic areas such as Western Cape, Eastern Cape and Mpumalanga, highlighting the need for community-wide interventions. Most of the clusters identified in the study were small, suggesting close contact transmission events, emphasising the importance of contact case investigations and infection control as the primary interventions in SA.

Table 2: Proportion of clustered cases by provinces/districts in South Africa: 2015-2018

Provinces	No. of isolates	No. of cases clustered*	No. of clusters	Estimated proportion of cases likely due to recent transmission %	No. of clusters by cluster size			
					2-4 cases	5-10 cases	11-25 cases	≥26
WC	897	661	89	64	68	13	5	3
EC	723	435	64	51	47	11	3	3
MP	435	193	48	33	42	4	1	1
NW	358	116	42	21	38	4		
KZN	230	90	28	27	23	4	1	
GP	142	41	15	18	14	1		
NC	135	22	10	9	10			
FS	79	13	5	10	5			

3. Policy contributions

The Centre had a busy period as both the drug-susceptible and drug-resistant TB guidelines were going through an update over the period. We have provided input and developed selected sections and the guidelines for DR-TB have now been made public, while the DS-TB guidelines are still undergoing final review. The introduction of the Xpert Ultra has also added some uncertainty regarding the management of trace positive results. Following findings from the TB PS and other consultations, a memorandum was developed in consultation with the NDoH and circulated providing guidance to health professionals. Lastly, we contributed to an article in collaboration with WHO and FIND on the process and key aspects for new diagnostics for TB, to be approved by WHO.

4. Outbreaks

In June 2019, the Centre was contacted to assist with an outbreak at Bohmer Special school where three learners residing at the hostel tested positive for drug-susceptible TB by the Xpert MTB/RIF. Engagements with the provincial Departments of Health and Department of Basic Education followed. All staff and students were screened and sputum samples were collected and sent to the Centre for smear microscopy and TB culture processing. A total of 293 sputum samples were processed. None were smear positive and only one sample was culture positive. This sample belonged to the one of the index cases, thus no additional cases of TB were detected from the students or staff. Culture samples from other two cases were not obtained; they were both culture negative as samples were collected after initiating TB treatment. As a result, molecular typing was not possible.

5. Research activities

The CTB was involved in the following research projects during the year under review:

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

Collaborators: Dr Refiloe Matji and the USAID Tuberculosis South Africa Project (TBSAP)

Annually more than 9 million new cases of active TB are occurring and poses a significant occupational health problem, and HCWs specifically are at an increased risk of exposure to transmissible TB, especially in a high-burden country like South Africa. The QuantiFERON-TB Gold Plus (QFT-Plus) detects 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 with 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 HCWs. Additionally, it will seek to assess the feasibility of using QFT-Plus amongst HCWs in a routine healthcare setting in the country.

The first study site was Pretoria West with 52% (272/519) of all the hospital staff enrolled into the study. The median age was 42 years and the majority of participants were female (85%). Most participants were nurses, however the spectrum was wide and included allied health workers (e.g. radiographers) as well as clerks and cooks. Of those investigated for LTBI, just under a half (44%) were positive at baseline. Doctors and nurses had the highest LTBI prevalence 67% and 52% respectively, though the number of doctors was small. Of those without previous TB, 43% were LTBI positive. There was no difference between those with and without HIV. Participants will be followed up for three years to assess conversions and reversions over time. A second site is being prepared and enrolments will begin in the next financial year.

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

Collaborators: Prof Ibrahim Abubakar (University College London, UK) and Dr Sizulu Moyo (Human Sciences Research Council, South Africa)

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 loss to follow up and based on early pilot data is approximately 15-20%. This is a significant barrier to achieving the targets set for 2025 and 2035.

The study sought to assess the effectiveness of a combination of interventions aimed at increasing successful patient outcomes in adults undergoing investigation for pulmonary TB (PTB). It consisted of pre- and post-TB test counselling and a once-off cash transfer, on the condition that initiation of TB treatment occurred within 14 days and follow up appointments were on schedule.

The design applied was a multi-centre, parallel-group, open-label randomised controlled trial and was conducted in eight clinics in Gauteng Province. A total of about 4 000 participants was enrolled. Biometric capture of participant fingerprints, as well as mobile money payments, are the modern technological methods that had been used in the trial. While an interim futility analysis conducted in December 2019 concluded that futility boundaries had not been crossed, recruitment challenges and budgetary constraints necessitated closure of the study. The study ended on 26 March 2020. Data cleaning is currently ongoing in readiness for the final analysis. A modelling component is planned to assess the potential value.

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

Collaborators: Dr Lindiwe Mvusi (Department of Health, South Africa) and Dr Laura Anderson (World Health Organization in Switzerland)

Understanding and having an accurate measure of the burden of disease is essential to successful programme planning. National TB programmes (NTPs) 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 TB national surveillance systems that have the sufficient robustness to accomplish this, while estimated burden and what is reported is vastly different.

Retrospective analysis of all TB records from the NTP (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 being also found in the public sector. Thus the underreporting 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

Collaborator: Derrick Crook (Oxford University, UK)
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 that 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 tool bioinformatics 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.

6. 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 departments in South Africa, as well as for intern scientists in the country.

The CTB also mentored a Field Epidemiology and Laboratory Training Programme (FELTP) student, further expanding capacity in epidemiology in South Africa.

Professional development

Postgraduate candidates
Six candidates were enrolled for PhD and four for MSc. One candidate graduated with MPH, one with MSc and one with PhD.

Medical scientists

Two candidates were enrolled and two graduated.

Honours

Nazir Ahmed Ismail was awarded a prestigious silver medal for research by the Medical Research Council, South Africa. Halima Mohammed Said has been rated a C2 Scientist by the NRF.

7. Research output

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3. Dean A.S., Zignol M., Cabibbe A.M., Falzon D., Glaziou P., Cirillo D.M., Köser C.U., Gonzalez-Angulo L.Y., Tosas-Auget O., Ismail N., Tahseen S., Ama M.C.G., Skrahina A., Alikhanova N., Mostofa Kamal S.M,. Floyd K., Prevalence and genetic profiles of isoniazid resistance in tuberculosis patients: A multicountry analysis of cross-sectional data. PLoS Med 2020;17(1):e1003008
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5. Jamieson L., Evans D., Berhanu R., Ismail N., Aucock S., Wallengren K & Long L., Data quality of drug-resistant tuberculosis and antiretroviral therapy electronic registers in South Africa. BMC Public Health 2019;19(1): 1638.
6. Mwansa-Kambafwile J.R.M., Chasela C., Ismail N., Menezes C., Initial loss to follow up among tuberculosis patients: the role of Ward-Based Outreach Teams and short message service (SMS) technology (research proposal). BMC Res Notes 2019;12(1):737.
7. Brown T.S., Challagundla L., Baugh E.H., Omar S.V., Mustaev A., Auld S.C., Shah N.S., Kreiswirth B.N., Brust J.C.M., Nelson K.N., Narechania A., Kurepina N., Mlisana K., Bonneau R., Eldholm V., Ismail N., Kolokotronis S., Robinson D.A., Gandhi N.R., Mathema B., Pre-detection history of extensively drug-resistant tuberculosis in KwaZulu-Natal, South Africa. Proceedings of the National Academy of Sciences 10/2019;116(46):201906636., DOI:10.1073/pnas.1906636116
8. Georghiou S.B., Schumacher S.G., Rodwell T.C., Colman R.E., Miotto P., Gilpin C., Ismail N., Rodrigues C., Warren R., Weyer K., Zignol M., Arafah S., Cirillo D.M., Denkinger C.M., Guidance for Studies Evaluating the Accuracy of Rapid Tuberculosis Drug-Susceptibility Tests. The Journal of Infectious Diseases 10/2019;220(Supplement_3):S126-S135.,DOI:10.1093/infdis/jiz106
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10. Wake R.M., Govender N.P., Omar T., Nel C., Mazanderani A.H., Karat A.S., Ismail N.A., Tiemessen C.T., Jarvis J.N., Harrison T.S., Cryptococcal-related mortality despite fluconazole pre-emptive treatment in a cryptococcal antigen (CrAg) screen-and-treat programme. Clinical Infectious Diseases 06/2019;,DOI:10.1093/cid/ciz485
11. Ismail N., Ismail N.A., Omar S.V., Peters R.P.H., Stepwise acquisition of rv0678 and atpE mutations conferring bedaquiline resistance: an in vitro study. Antimicrobial Agents and Chemotherapy 05/2019;,DOI:10.1128/AAC.00292-19
12. Ismail N.A., Said H.M., Rodrigues C., Omar S.V., Ajbani K., Sukhadiad N., Kohl T.A., Niemann S., Kranzer K., Diels M., Rigouts L., Rüsch-Gerdes S., Siddiqi S., Multicentre study to establish interpretive criteria for clofazimine drug susceptibility testing. The International Journal of Tuberculosis and Lung Disease 05/2019;23(5):594-599.,DOI:10.5588/ijtld.18.0417

13. Mwansa-Kambafwile J.R.M., Jewett S. Chasela C., Ismail N., Menezes C., Initial loss to follow up of tuberculosis patients in South Africa: perspectives of program managers. BMC Public Health 20, 622 (2020).https://doi.org/10.1186/s12889-020-08739-w.

Conference presentations

- International: Six oral presentations and one poster
- National: Five oral presentations and three posters

International Conferences

Oral	
International Union for TB and Lung Disease, Hyderabad, November 2019	Emerging Drug Resistance in SA
International Union for TB and Lung Disease, Hyderabad, November 2019	Applications and implications of using Xpert Ultra in prevalence surveys
International Union for TB and Lung Disease, Hyderabad, November 2019	How individualised should individualised treatment be? Laboratory perspective.
International Union for TB and Lung Disease, Hyderabad, November 2019	Universal drug susceptibility testing
International Union for TB and Lung Disease, Hyderabad, Nov 2019	Repurposing routine TB data for research

Poster	
International Union for TB and Lung Disease, Hyderabad, November 2019	Prevalence of Linezolid resistance and associated mutations amongst pre-XDR and XDR isolates requiring drug susceptibility testing at the South African National TB Reference Laboratory

National Conferences

Oral	
PathRed, Johannesburg, July 2019	TB algorithm update: A focus on DR-TB
PathRed, Johannesburg, July 2019	The role of research in improving TB care
PathRed, Johannesburg, July 2019	Use of Xpert Ultra in SA National TB prevalence survey key findings SA TB Prevalence Survey: A first for SA – lessons thus far
PathRed , Johannesburg, July 2019	The Role of research in improving TB care
South African Thoracic Society Congress, August 2019	DR-TB in South Africa
FIDSSA, Johannesburg, November 2019	DR-TB
Ekurhuleni Research Conference, November 2019	Counselling and Conditional Cash Transfer TB Study (CCCT TB Study)
Ekurhuleni Research Conference, November 2019	Efficacy of mobile payments for conditional cash transfers

Poster	
SAAIDs conference, June 2019	Low coverage of ART and poor retention among young adults initiating treatment for tuberculosis
HPCSA Conference, August 2019	Latent TB infection in healthcare workers

Acknowledgements

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Centre for
Vaccines and Immunology

2019/20

Dr M Suchard
Centre Head

1. Background

The Centre for Vaccines and Immunology (CVI) houses the national and World Health Organization (WHO) regional reference laboratories for polio, which is targeted for global eradication, as well as measles, tetanus and hepatitis which are targeted for regional elimination. In addition, the centre executes 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 also provides epidemiological, virological and immunological support to the National Department of Health (NDoH) for vaccine-preventable diseases.

2. Surveillance

Polio surveillance

Wildtype poliovirus type 2 and 3 have been globally eradicated. Only wildtype poliovirus type 1 and vaccine-derived polioviruses (VDPVs) continue to circulate. Any finding of a poliovirus type 2 is noteworthy. Sabin poliovirus type 2 has been withdrawn from vaccines globally and is only used in campaigns. Sabin poliovirus types 1 and 3 remain part of oral poliovirus vaccines administered to children in South Africa and many regions.

The Poliovirus Isolation Laboratory serves the following 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 (AFP) case, stool samples are inoculated into cell cultures and any sample with suggestive poliovirus cytopathic effects is subjected to molecular typing and characterisation, to confirm the poliovirus serotype and differentiate the poliovirus subtypes. During the reporting period, 1 356 South African samples were processed for poliovirus isolation.

As the regional referral laboratory, the Centre identified VDPV type 2 (VDPV2) from 617 samples. The samples were mostly from Angola, followed by the Democratic Republic of Congo (DRC), and then Ethiopia. Several VDPV2 samples were also identified from Niger, Malawi, Cote d'Ivoire, Central African Republic, Burkina Faso and Zambia. These countries have been experiencing outbreaks of circulating VDPV2, and the NICD continues to receive samples for poliovirus type 2 genotyping from them. Type 2 Sabin polioviruses were detected in 448 other samples, all from countries using monovalent oral polio vaccine type 2 to halt VDPV2 transmission, namely DRC, Niger, Angola, Cameroon, Malawi, Mozambique, Zambia and Ethiopia. VDPV type 1 (VDPV1) was detected in two cases from Mozambique.

NICD received approval from the NDoH to host a Polio Essential Facility (PEF), which will be one of only a handful globally. The PEF will enable the NICD to work with poliovirus type 2 culture material under high containment, following global certification of eradication. The National Authority for Containment and Global Containment Advisory Group approved the NICD's application for participation as a PEF and a certificate of participation was issued accordingly.

The NICD provides ongoing support to the WHO for environmental polio surveillance from sewerage sites. Two hundred and eleven (211) poliovirus type 2 samples were sequenced from environmental samples from Ethiopia, Cameroon, Cote d'Ivoire, Angola and Zambia. One hundred and thirty nine (139) VDPV2 were identified from Cameroon, Angola, Cote d'Ivoire and Ethiopia. Sabin poliovirus type 2 was detected in 72 other samples from Angola, Zambia, Cameroon, Ethiopia and Cote d'Ivoire. Eight (8) Sabin poliovirus type 3 and one (1) Sabin poliovirus type 1 samples were sequenced from environmental samples from South Africa.

Measles

The CVI houses the national reference laboratory for measles surveillance and serves the southern African region as a regional reference laboratory. The centre provides serological and molecular testing for the measles virus, in support of the global measles elimination initiative.

Serology, specifically the detection of measles-specific immunoglobin M (IgM) antibodies, real-time polymerase chain reaction (RT-PCR) and genotyping are used in conjunction with epidemiologic case investigations in the diagnosis of acute measles infection.

A total of 4 633 South African febrile rash samples was tested during the reporting period, with 65 cases classified as confirmed measles cases. Three suspected measles clusters were detected; however, on review, two of these clusters were later considered to be due to rubella rather than measles. The third cluster was limited to one family and considered to be imported. For this reason, no outbreak was declared. Additional information on the measles cases was reported in the NICD online bulletin.

Furthermore, 1 512 rubella cases were identified via febrile rash surveillance. This is not unexpected, as rubella circulates widely and there is no rubella vaccine in the national Expanded Programme on Immunisation (EPI) schedule.

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. Five hundred and eighty-one (581) samples were tested during the reporting period. There was good concordance for the measles IgM results (94.7%) and rubella IgM results (97.1%).

Congenital Rubella Syndrome surveillance

The Centre runs a sentinel site surveillance programme for congenital rubella syndrome (CRS) surveillance, which includes 28 study sites nationally. Four laboratory-confirmed CRS cases were detected through the sentinel site surveillance programme. The rubella vaccine is not yet included in the South African EPI. Such data are required to inform timelines and targeted age groups for future introduction.

Tetanus

The centre collates and classifies tetanus cases reported through the Notifiable Medical Conditions (NMC) system. During the year under review, 20 suspected tetanus cases have been reported, of which three cases were confirmed as neonatal tetanus. Investigation of the cases revealed that all the cases occurred after a non-medicinal substance was placed onto the umbilical cord at home.

The remaining 15 suspected tetanus cases were among people ranging in age from 5 to 74 years, with statuses as follows: five confirmed, three probable and seven discarded. There were also two cases pending classification.

There is no laboratory test for tetanus and cases are classified after reviewing medical records. Prior to implementation of the new NMC system, five neonatal tetanus cases were reported between 2014 and 2017 (two in 2014, two in 2015 and one in 2017) (data courtesy of WHO).

The WHO declared that South Africa eliminated maternal and neonatal tetanus in 2002. A country is certified as having eliminated neonatal tetanus when there is <1 case per 1,000 live births in every district per year. The rate of neonatal tetanus in South Africa is still below this threshold.

Hepatitis

The 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 (CDW).

Hepatitis A
During the reporting period, 13 6917 cases have been tested for the presence of hepatitis A IgM antibodies at NHLS laboratories countrywide. Of the cases tested, 2 514 were positive for hepatitis A IgM, with an overall detection rate of 1.8% (2514/136917). Monthly hepatitis A incidence is reported to the multinational outbreak response team (MNORT).

Hepatitis B
During the reporting period, 39 795 patients have tested positive for HBsAg. The number of incident cases (defined by a positive IgM result against hepatitis B core antigen) was 1 985. Kwazulu-Natal had the highest incidence of 6/100000 population. The HBsAg prevalence ranged from 100/100000 population in Gauteng to 20/100000 population in Limpopo. There were 145 HBsAg positive cases among children under 12 months of age. Monthly hepatitis B prevalence is reported to the MNORT and shared with the National Advisory Group on Immunisation.

Hepatitis C
A total of 13 9217 patients countrywide has been tested for hepatitis C by the NHLS during the reporting period. Of those tested, 2 893 patients (2.1%) were seropositive for hepatitis C, of which 72.6% were males. A more in-depth analysis was published in the NICD online bulletin.

3. Policy contributions

The Centre contributed to the national Guidelines for the Management of Viral Hepatitis, National Department of Health, that was issued in January 2020.

The centre contributed rubella epidemiological information to the National Advisory Group to inform decisions regarding the introduction of a rubella vaccine in the EPI.

4. Research activities

Indoleamine 2,3 dioxygenase as a biomarker for active tuberculosis
NICD investigators: C Adu-Gyamfi, L Makhatini, H Hong, H Ranchod and M Suchard
Collaborators: Neil Martinson (University of the Witwatersrand), Thomas Scriba (South African TB Vaccine Initiative, Cape Town), Sanjay Lala (Baragwanath Hospital, University of the Witwatersrand), Sarah Stacey (Charlotte Maxeke Johannesburg Academic Hospital).

Indoleamine 2,3-dioxygenase is an enzyme responsible for degradation of tryptophan towards synthesis of nicotinamide adenine dinucleotide, a cellular cofactor involved in cellular metabolism. The aim of this study is to investigate various patient groups to determine whether measurement of activity of the enzyme can be used to diagnose tuberculosis (TB) or act as a prognostic marker for survival. Cohorts to be studied include HIV-negative and positive adults, pregnant women and children.

5. Teaching and training

The Centre is a national and regional resource for the training of medical scientists, technologists, registrars and field epidemiology training programme residents. Trainees acquire specialised skills in the disciplines of virology and immunology.

The Centre hosted an environmental workshop on concentration of sewage samples for identification of polioviruses from 12-16 August 2019.

Mirriam Fortuin facilitated at the WHO measles/rubella molecular training for participants from African countries, which was held in Rwanda from 11-21 November 2019.

Lillian Makhathini conducted measles/rubella training for staff of the Rwanda National Laboratory from 19-23 August 2019.

S. Smit attended the WHO Regional Office for Africa (WHO-AFRO) regional measles and rubella meeting in Uganda, from 26-29 February 2020.

M. Suchard coordinated the Basic Vaccinology and Advanced Immunology modules for students studying towards their Master of Science degree (MSc) in Vaccinology at the University of the Witwatersrand (Wits).

Professional development

Fhatuwani Ghavi completed the South African Field Epidemiology Training Programme.

The centre enrolled nine candidates for postgraduate studies as follows:

Four for MSc (Ndlovu Lindokuhle, Sibongiseni Ndlovu, Innocencia Cuamba and Kenneth Akuwe);
One for Master of Medicine degree (MMed) (Bonolo Mashishi); and
Four for Doctor of Philosophy degree (PhD) (NV Motaze, M. Suchard, C Adu-Gyamfi and S Moonsamy).

The centre also took in three intern scientists, namely: Emmanuel Phahlane; Lindokuhle Ndlovu and Daniel Simelane.

W. Howard attended the China ModPad+ course in Beijing, China from 7 July to 29 September 2019. This course involved the detection and analysis of new and emerging viral pathogens, and the molecular techniques available for the study of these pathogens.

6. Research output

Journal articles

1. Adu-Gyamfi C.G., Savulescu D.M., George J,A., Suchard M.S. Indoleamine 2, 3-dioxygenase (IDO)-mediated tryptophan catabolism: A leading star or supporting act in the tuberculosis and HIV pas-de-deux? Frontiers Cellular and Infection Microbiology. 2019; 9:372 https://doi.org/10.3389/fcimb.2019.00372.21.
2. Moonsamy S., Suchard M., Madhi S.A. Effect of HIV-exposure and timing of anti-retroviral treatment on immunogenicity of trivalent live-attenuated polio vaccine in infants. PLOS One. 2019; 14: e0215079. https://doi.org/10.1371/journal.pone.0215079.
3. Moonsamy S., Suchard M., Madhi S.A. Immunogenicity of a combined schedule of trivalent oral and inactivated polio vaccines in South African infants. Expert Review of Vaccines. 2019;18:751-54 https://doi: 10.1080/14760584.2019.1627878.
4. Jallow S., Wilmshurst J.M., Howard W., Copelyn J., Seakamela L., Chan K.W., *et al*. Accelerated immunodeficiency-associated vaccine-derived poliovirus serotype 3 sequence evolution rate in an 11-week-old boy with x-linked agammaglobulinemia and perinatal human immunodeficiency virus exposure. Clinical Infectious Diseases. 2020; 70:132-135 https://doi: 10.1093/cid/ciz361. PMID: 31086993.
5. Patel S.M., Jallow S., Boiditswe S., Madhi S.A., Feemster K.A., Steenhoff A.P., *et al*. Placental transfer of respiratory syncytial virus antibody among HIV-exposed, uninfected infants. Journal of the Pediatric Infectious Diseases Society. 2019; 24 https://doi: 10.1093/jpids/piz056.
6. Jallow S., Agosti Y., Kgagudi P., Vandecar M., Cutland C.L., Simões E.A.F., *et al*. Impaired transplacental transfer of respiratory syncytial virus (RSV) neutralizing antibodies in HIV-infected compared to HIV-uninfected pregnant women. Clinical Infectious Diseases. 2019; 69:151–154 https://doi: 10.1093/cid/ciy1071.
7. Scheibe A., Young K., Moses L., Basson R.L., Versfeld A., Spearman C.W., *et al*. Understanding hepatitis B, hepatitis C and HIV among people who inject drugs in South Africa: Findings from a three-city cross-sectional survey. Harm Reduction Journal. 2019;16:28 https:// doi.org/10.1186/s12954-019-0298-2.

8. Prabdial-Sing N., Makhathini L., Smit S.B., Manamela M.J., Motaze N.V., Cohen C., *et al*. Hepatitis B sero-prevalence in children under 15 years of age in South Africa using residual samples from community-based febrile rash surveillance. PLOS One. 2019; 14:1-9 https://doi.org/ 10.1371/journal.pone.0217415.
9. Keating P., Martín A.I.C., Blake A., Lechevalier P., Uzzeni F., Gignoux E., *et al*. Measles seroprevalence after reactive vaccination campaigns during the 2015 measles outbreak in four health zones of the former Katanga Province, Democratic Republic of Congo. BMC Public Health. 2019; 19: 1053-1064.
10. Mbaeyi C., Alleman M.M, Ehrhardt D., Wiesen E., Burns C.C., Liu H., *et al*. Update on vaccine-derived poliovirus outbreaks - Democratic Republic of the Congo and Horn of Africa, 2017-2018. Morbidity and Mortality Weekly Report. 2019, 68 (No. 9):225-230.
11. Suchard M.S., Tomori O., Blumberg L. Extra time and penalties in the polio end game. Invited editorial. Journal of Infectious Diseases. 2020. https://doi.org/10.1016/j.ijid.2019.12.009.

Other publications

1. Hong H.A., Suchard M.S. Measles in South Africa in the era of vaccine hesitancy. Paediatric Focus. Aug 2019; 10(2):3-4.
2. Blumberg L., Tomori O., Suchard M.S. Our polio eradication journal – the end is in site. Rotary Africa. 2019; Oct 14-15.

Online bulletin of the National Institute for Communicable Diseases

1. October 2019. Shelina Moonsamy, Nishi Prabdial-Singh, Nkengafak Villyen Motaze, Diana Hardie, Cheryl Cohen, Melinda Suchard. Laboratory-based hepatitis B surveillance in South Africa 2018.
2. October 2019. Heather Hong, Lillian Makhathini, Mirriam Mashele, Sheilagh Smit, Susan Malfeld, Tshepo Motsamai, Dipolelo Tselana, Fhatuwani Gavhi, Jack Manamela, Nkengafac Villyen Motaze, Genevie Ntshoe, Elizabeth Maseti, Nonhlanhla Dlamini, Mercy Kamupira, Kerrigan McCarthy, Melinda Suchard. Annual Measles and rubella surveillance review, South Africa, 2018.
3. December 2019. Lerato Seakamela, Jack Manamela, Villyen Motaze, Wayne Howard, Heleen du Plessis, Sabelle Jallow, Genevie Ntshoe, Mercy Kamupira, Esther Khosa-Lesola, Sibongile Mokoena, Thulasizwe Buthelezi, Bontle Motloung, Elizabeth Maseti, Nonhlanhla Dlamini, Ntombi Mazibuko, Babalwa Mtuze-Magodla, David Moore, Shelina Moonsamy, Melinda Suchard. Acute Flaccid Paralysis Surveillance for Polio, South Africa and other African Countries, 2019.
4. December 2019. Ndlovu B, Prabdial-Sing, Suchard MS, Motaze V, McCarthy K, Blumberg L, Govender N and Moipone SA. An outbreak of hepatitis A at a residential care facility for senior citizens in Johannesburg, Gauteng Province South Africa.

Public engagement

MS Suchard delivered the 14th annual James Gear Memorial Public Lecture - James Gear address at NICD entitled "Harnessing the Immune Response – To Measles Elimination and Beyond."

Conference presentations

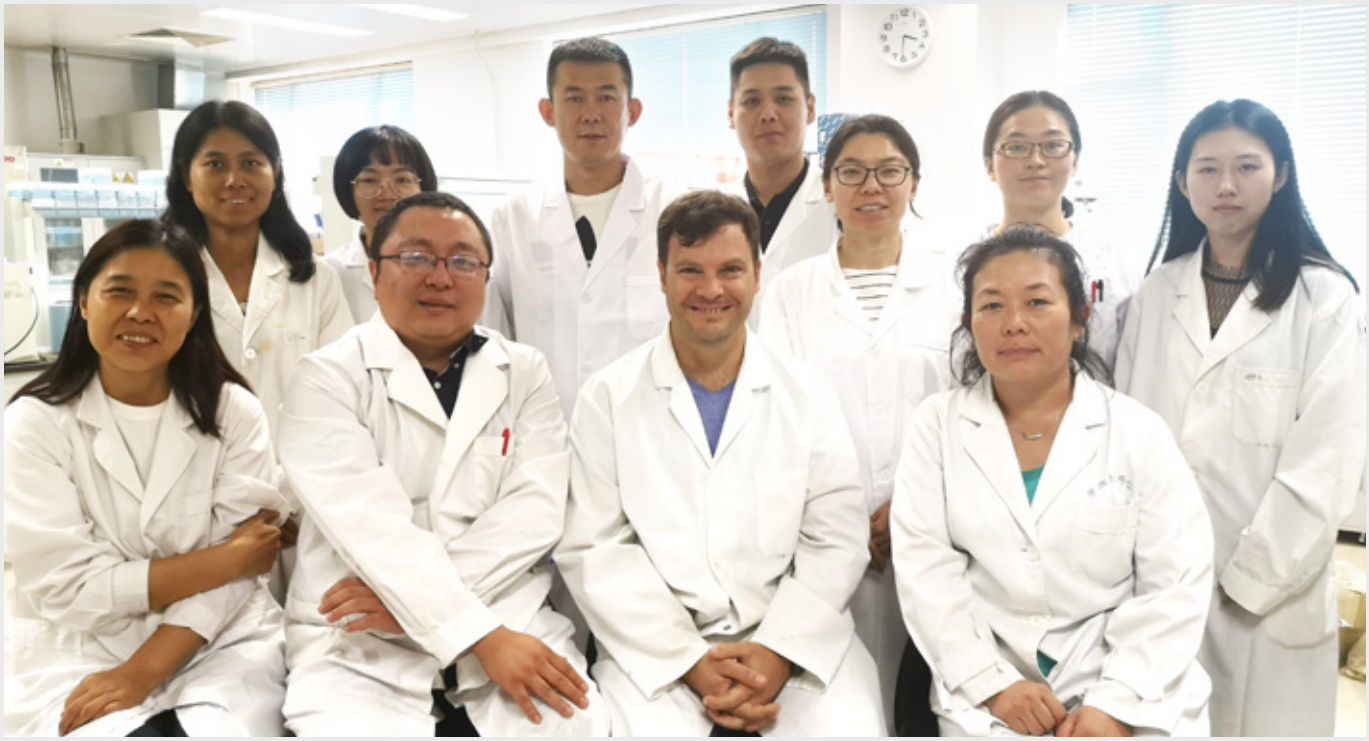
International congresses:

1. Savulescu D.M., Groome M., Malfeld S.C.K., Madhi S., Koen A., Jones S., *et al.* HLA antibody repertoire in infants suggests selectivity in transplacental crossing. Poster presentation. Optimmunize: Improving the Beneficial Effects of Vaccines conference, Cambridge, UK, 19-21 Feb 2020.
2. Prabdial-Sing N., Gaelejwe L., Manamela M., Malfeld S., Spearman W., Sonderup M., *et al.* The performance of dried blood spots (DBS) compared to plasma for hepatitis C viral load on seropositive key populations in Cape Town. Abstract 23. Conference on Liver Disease in Africa (COLDA) 2019, Cairo, Egypt, 6-8 September 2019.

National congresses:

1. Motaze N.V. Ebola: Delivering vaccine at the rockface. Vaccinology Scientific Meeting. Magaliesberg. 20-22 October 2020.
2. Suchard M.S. Review of South African immune deficiency vaccine-derived poliovirus cases. Vaccinology Scientific Meeting. Magaliesberg. 20-22 October 2020.

3. Mashishi B., Makatini Z., Venter M., Mahomed A., Prabdial-Sing N. Evaluation of dried blood spots for hepatitis C virus (HCV) molecular testing: A pilot validation in a clinic setting. Abstract:10368. ePoster, 9th Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) Conference, Johannesburg, 7-9 November 2019.
4. Ndlovu N., Ntlhamu N.T., Mufhandu H., Scheibe A., Young K., Hausler H., *et al.* Preliminary results on baseline hepatitis C NS5A gene resistance associated substitutions (RAS) among persons who inject/use drugs (PWID/UD), men who have sex with men (MSM) and blood donors. Poster. Molecular Biosciences Research Trust Postgraduate Research Day, Wits, 28 November 2019.
5. Jallow S. 3rd Pathology Research and Development Congress (PathReD) 2019 Johannesburg, 18-21 July 2019.
6. Jallow S. VIIth South African Immunological Society Congress.; Umhlanga, KZN, 18-20 June 2019.



W Howard (Middle front row) with the team from the Viral Encephalitis Laboratory, China Centre for Disease Control, Beijing, China

W Howard with the participants of the China ModPad+ course, along with a next generation sequencing specialist from the China CDC.

National Cancer Registry

2019/20

Dr Elvira Singh
Centre Head

1. Background

The primary roles of the National Cancer Registry (NCR) are national pathology-based cancer surveillance and implementation of population-based cancer registration. During the year under review, the NCR used multi-model supervised machine learning techniques to assign malignancy status to histology reports from the National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW) and identify missing cancer records, which could not be identified by routine CDW algorithms. This significantly improved the completeness of the pathology-based registry for the years 2015, 2016 and 2017.

Data from 2015 and 2016 were coded, cleaned and analysed and the 2015 report was published on the NCR website. The NCR created a Stata Do file to automate the calculation of age-standardised incidence rates and improve the timeliness of cancer incidence reports. Data for cancers diagnosed in 2017 were coded and the dataset is currently being cleaned, while 2018 data is currently being coded.

The Ekurhuleni population-based cancer registry (EPBCR) identified new data sources, improved case finding and held a stakeholder feedback meeting. This resulted in an additional 1 324 cases (39% increase) of cancer reported. A total of 4 695 new cancers were reported for the year 2018, and common cancers in males were prostate, colorectal, lung, melanoma and oesophageal cancers. In women, the most common cancers were breast, cervical, colorectal, uterine and lung cancers.

During the 2019/2020 financial year, the NCR published key research in cancer epidemiology. The NCR examined national cancer trends and excess cancer risk in people living with HIV compared to those who are HIV-negative. As expected, people living with HIV were at higher risk of AIDS-defining cancers namely, Kaposi sarcoma, non-Hodgkin's lymphoma and cervical cancer. They were also at increased risk of conjunctival cancer and human papillomavirus (HPV)-related cancers which include: Penile, anal and vulvar cancer, compared to HIV-negative patients. Squamous cell carcinoma of the skin was also found to be HIV-associated. The risk of Kaposi sarcoma has declined as antiretroviral therapy (ART) became available. However, the risk of conjunctival cancer and HPV-related ano-genital cancers (cervical, anal, vulvar and penile cancers) continues to rise, despite widespread availability of ART. The findings of our study were used to inform a national HIV-associated cancer awareness campaign for the 2019 World AIDS Day.

The NCR also published work summarising the wealth of evidence arising from the Johannesburg Cancer Study (JCS) over a 20-year period. The work also presents the JCS as a global resource for investigation of the intersection of infectious, non-communicable, lifestyle, hormonal, social and genetic risk factors for cancer in a black African urban population.

Dr Elvira Singh and Dr Mazvita Muchengeti contributed to the World Health Organization (WHO) and International Agency for Research in Cancer (IARC) publication entitled "Cancer in Sub-Saharan Africa III," describing cancer incidence and mortality patterns on the continent. Dr Singh represents the NCR on the Ministerial Advisory Committee on Cancer Prevention and Control.

2. Surveillance programmes

Pathology-based cancer registry

In the previous financial year, the NCR noted that the number of cases received from the Western Cape NHLS laboratories (Groote Schuur, Tygerberg and Red Cross) were significantly under-reported for the years 2015 and 2016. During the period under review, the NCR used multi-model supervised machine learning techniques to assign malignancy status to histology reports from the NHLS CDW and identify the missing cancer records, which could not be identified by routine CDW algorithms. This significantly improved the completeness of the pathology-based registry for the years 2015, 2016 and 2017. Data from 2015 and 2016 were coded, cleaned and analysed and the 2015 report was published on the NCR website. The 2016 report was completed and was undergoing internal quality checks and will be published early in the next financial year. Data for cancers diagnosed in 2017 was coded and is currently being cleaned. The coders are currently working on 2018 data.

In the past, the NCR has outsourced calculation of annual age-standardised cancer incidence rates, which were calculated in Excel format. During the year under review, the NCR created a Stata Do file to automate the analysis of the annual cancer incidence and improve the timeliness of cancer incidence reports. The NCR conducted a two-day workshop to train all epidemiologists and NCR students on how to calculate age-standardised incidence rates. This also allowed capacity for dual analysis. In practise, this means that two people are able to independently conduct the cancer incidence analysis and compare the results for quality purposes. Dual analysis was performed on the 2016 annual report.

Ms Gerniene Myles, a data capturer, resigned from the NCR and was replaced by Ms Nthabiseng Mampa.

Ekurhuleni population-based cancer registry (EPBCR)

On 30 May 2019, the NCR successfully hosted a one-day workshop at Genesis Hotel, through funding from the Union for International Cancer Control (UICC) that was awarded to Ms Lactatia Motsuku, an Epidemiologist at the registry. The workshop was aimed at providing feedback on the 2017 EPBCR annual report and to solicit advice from stakeholders to strengthen the data collection process at different health facilities in Ekurhuleni. The workshop was attended by ten data source officials from Ekurhuleni district, eight surveillance officers and two NCR data capturers. Five NCR staff members conducted presentations at the workshop.

Several new data sources were identified and added to the EPBCR. This includes passive surveillance data sources like Ampath laboratory data for 2018, as well as active surveillance data sources such as the N17 Netcare hospital and Parklands Netcare hospitals in Springs. Data was collected from urologists, specialist surgeons, paediatricians, and a dermatologist who has not previously been included in the registry.

A total of 4 695 new cancer cases, of which 1 324 were new cases (an increase of 39% from the previous financial year), were registered for 2018 in Ekurhuleni District. 52% were female. The majority of cases were diagnosed in the white population (52%), followed by 46% in the black population. Common cancers in men (ranked by age-standardised incidence rates) were prostate, colorectal, lung, melanoma and oesophageal cancers. The top five cancers in women were breast, cervical, colorectal, uterine and lung cancers.

The 2018 Ekurhuleni Cancer Incidence Report was published and submitted to Mr Maphale Moloi as evidence of the NCR's key performance indicator (KPI).

Grant funding for the EPBR has ended. The NCR received additional funding from the National Department of Health (NDoH) for the new financial year, to fund the activities of the registry.

Childhood cancer registry

Ms Natasha Abraham (NCR epidemiologist) joined the NCR on 1 April 2019 and was given the responsibility of establishing a national childhood cancer registry. The NCR aims to establish this registry in line with the International Classification of Childhood Cancers (ICCC-3), as recommended by the International Agency for Research on Cancer (IARC). The registry has applied for the African-Oxford Research Development Grant for training on childhood cancer surveillance in Southern Africa in collaboration with the African Cancer Registry Network (AFCRN), and the outcome of the grant application is awaited.

3. Selected research projects

South African HIV Cancer Match Study

The South African HIV Cancer Match (SAM) Study is based on a national cohort of HIV-positive people created from NHLS HIV data (HIV tests, CD4 counts and HIV viral load (VL) tests) that is probabilistically linked to the NCR data, to determine the spectrum and risk of cancer in the HIV population.

During the year under review, ethics approval for the study was renewed for a further five years, until June 2024. The NCR received carryover funds to the value of $100 000 from the Swiss National Foundation and the International Epidemiology Databases to Evaluate AIDS (IeDEA) Southern Africa, to employ Mr. Victor Olago as Data Manager of the SAM Study for two years.

Mr Victor Olago developed a data-clustering pipeline for data deduplication, using natural language processing and density-based spatial clustering of applications with noise (DBSCAN) to improve linkage efficiency.

Results from the SAM Study were presented at several forums, including: The International Conference on Malignancies (ICMH) in HIV/AIDS 2019, IeDEA Southern Africa Steering Group meeting and at the 2019 African Organization for Research and Training in Cancer (AORTIC) conference. Virtual presentations were also conducted at the Conference on Retroviruses and Opportunistic Infections (CROI) 2020. One publication on the study was completed and several others are in progress.

Johannesburg Cancer Case-control and Evolving Risk Factors for Cancer in African Populations studies

The Johannesburg Cancer Case-control study (JCS) is a case-control study of newly (<6 months) diagnosed 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. This study will be completed within the new financial year.

Two students who are enrolled for their Doctor of Philosophy degrees (PhDs), namely Ms Melitah Motlhale and Mr Gideon Singini, are furthermore working on the Evolving Risk Factors for Cancer in African Populations (ERICA) study. Both received postgraduate and ethics approval from the Human Research Ethics Committee of the University of the Witwatersrand (Wits). They also had meetings and supervisor consultations with their external supervisors, who are Prof Freddy Sitas from the University of Sydney and Dr Debbie Bradshaw from the University of Cape Town (UCT) and the South African Medical Research Council (SAMRC); as well as an internal supervisor from the NCR, Dr Elvira Singh.

During the period under review, one article from the JCS study was published and several others are in progress.

Acknowledgements and collaborators

1. Prof Matthias Egger, Dr Julia Bohlius, Dr Lina Bartels and Dr Eliane Rohner, Institute of Social and Preventive Medicine, University of Bern, Switzerland;
2. Prof Tim Rebbeck, Harvard TH Chan School of Public Health, Harvard University, Boston, USA;
3. Prof Chris Mathew, Department of Medical & Molecular Genetics, Guy's Hospital, King's College London, United Kingdom;
4. Prof Debbie Bradshaw, SAMRC;
5. Dr Kathryn Chu, Department of General Surgery, UCT;
6. Prof Paul Ruff and Dr Brendan Bebbington, Wits Donald Gordon Oncology Centre;
7. Dr Donald Max Parkin, Nuffield Department of Population Health, Oxford University, United Kingdom;
8. Prof Freddy Sitas, University of Sydney, Australia; and
9. Prof Juliet Pulliam, Prof Alex Welte and Dr. Roxanne Beauclair, Department of Science and Technology (DST)/National Research Foundation (NRF) Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, South Africa.

4. Teaching and training

The NCR had monthly journal club meetings and scientific writing meetings to build capacity in scientific writing amongst junior research staff and students.

Dr Elvira Singh and Dr Mazvita Muchengeti continued to teach Master of Public Health (MPH) and MSc Epidemiology students at the Wits School of Public Health. Ms Lactatia Motsuku gave lectures on cancer surveillance to students from the South African Field Epidemiology Training Programme (SAFETP). Ms Natasha Abraham conducted training on Epi-Info for SAFETP students.

Dr Elvira Singh attended the IARC Summer School in Lyon, France, from 17 June to 7 July 2019.

Mrs Lerato Khoali and Dr Elvira Singh attended the NHLS Leadership and Management course from 15-16 August 2019, as part of the Workplace Skills Programme (WSP).

Mr Victor Olago attended the Deep Learning Indaba 2019 at Kenyatta University, Nairobi, Kenya, from 25-30 August 2019.

Ms Londiwe Mhlungu (surveillance officer) attended the Time Management course on 10 September 2019, as part of the WSP.

Ms Tafadzwa Dhokotera received basic training on geographic information systems (GIS) mapping from 15-19 July 2019 and attended the Tim Albert scientific writing course from 16-18 September 2019.

Mr Victor Olago attended datab management and integration training on the new multi-regional format for data harmonization at the IeDEA All Africa meeting in Johannesburg, in October 2019.

Natasha Abraham attended the Global Initiative on Childhood Cancers (GICC) workshop on Registration of Childhood Cancers: Registration and Opportunities on 22 October 2019 at the IARC in Lyon, France. She received financial assistance from IARC to attend this workshop.

Natasha attended the REDCap advanced workshop from 29-31 October 2019 at Wits, as part of her skills development plan.

Dr Mazvita Muchengeti chaired a postgraduate assessor group meeting for MSc epidemiology student protocols at University of Witwatersrand School of Public Health on 20 November 2019.

Dr Mazvita Muchengeti gave a two-day training workshop to NCR research staff and students on how to calculate age-standardised cancer incidence rates using Stata from 3-4 March 2020.

Babongile Ndlovu obtained a competency certificate after attending a Project Management course.

Babongile Ndlovu delivered a training course for NCR staff on tumour-node-metastasis (TNM) staging of cancers.

Victor Olago attended the Winter School on Machine Learning in Murren from 2-6 March 2020. He also worked with the Institute of Social and Preventive Medicine (ISPM) on comparing various linkages from 9-13 March 2020, at the University of Bern, Switzerland.

Professional development

Dr Elvira Singh, Dr Mazvita Muchengeti and Ms Natasha Abraham attended the AFCRN annual meeting in Maputo, Mozambique in November 2019.

Students supervised and registered during 2018/2019

The NCR had four PhD students in the period under review (Mr Mwiza Singini, Ms Melitah Motlhale, Ms Okechinyere Achilonu and Mr Carl Chen).

Eight students were registered for MSc, MPH and Master of Medicine (MMed) degrees, namely: Ms Tafadzwa Dhokotera, Mr Victor Olago, Ms Babongile Ndlovu, Ms Lerato Khoali, Ms Natasha Abraham, Ms Evidence Majaya, Ms Anishka Ramadhar, Mr Sandile Ndabezitha and Ms Carole Temdemnou Metekoua.

During the period under review, Ms Tafadzwa Dhokotera completed her degree with distinction, and Ms Natasha Abraham and Mr Victor Olago graduated with their Masters degrees. Ms Evidence Majaya and Ms Babongile Ndlovu completed their Masters degrees and are awaiting graduation. Ms Carole Temdemnou submitted her thesis for examination and is awaiting her results.

Honours

Lactatia Motsuku was awarded a scholarship from the University of Stellenbosch to undertake her PhD with the South African Centre for Epidemiological Modelling and Analysis (SACEMA).

5. Research output

Top publications

1. Dhokotera T., Bohlius J., Spoerri A., Egger M., Ncayiyana J., Olago V., Singh E., Sengayi M., The burden of cancers associated with HIV in the South African Public Health Sector, 2004-2014: a record linkage study. Infectious Agents and Cancer.

   This study examined national cancer trends and excess cancer risk in people living with HIV compared to those who are HIV-negative. The study found that people living with HIV are at higher risk of AIDS-defining cancers, namely Kaposi sarcoma, non-Hodgkin's lymphoma and cervical cancer. They are also at increased risk of conjunctival cancer and human papillomavirus (HPV) related cancers, which include penile, anal and vulvar cancer, compared to HIV-negative patients. Squamous cell carcinoma of the skin was also found to be HIV-associated. The risk of Kaposi sarcoma has declined as antiretroviral therapy (ART) became available. However, the risk of conjunctival cancer and HPV-related ano-genital cancers (cervical, anal, vulvar and penile cancers) continues to rise, despite widespread availability of ART.

The findings of this study were used to inform a national HIV-associated cancer awareness campaign in collaboration with the Cancer Association of South Africa (CANSA) for the 2019 World AIDS Day, the details of which can be found at the following link: https://www.cansa.org.za/cansa-encourages-hiv-patients-to-know-their-cancer-risk.

2. Chen W.C., Singh E., Muchengeti M., Bradshaw D., Mathew C.G., Babb de Villiers C., *et al*. Johannesburg Cancer Study (JCS): Contribution to knowledge and opportunities arising from 20 years of data collection in an African setting. Cancer Epidemiology. 2020;65(March):101701.
   This summarises the wealth of evidence that arose from the study over a 20-year period. The work also presents the JCS as a global resource for investigation of the impact of infectious diseases (such as HIV, the human papillomavirus, herpes virus, etc.), non-communicable diseases (such as hypertension, diabetes, obesity, etc.), lifestyle (such as smoking, alcohol use, etc.), hormonal (contraceptive use, parity, etc.), social (such as education, employment, etc.) and genetic risk factors on cancer development in a black African urban population. This is an invaluable resource for cancer research in this under-studied population.

3. "Cancer in Sub-Saharan Africa Volume III" Edited by D.M. Parkin, A. Jemal, F. Bray, A.R. Korir, B. Kamaté, E. Singh, W.Y. Joko, M. Sengayi-Muchengeti, B. Liu and J. Ferlay

   This is a WHO and IARC publication in collaboration with the AFCRN which aims to describe patterns of cancer incidence and mortality on the sub-continent. Dr Elvira Singh and Dr Mazvita Muchengeti were invited as editors on this publication and contributed chapters on prostate cancer, oesophageal cancer and cancer of the cervix.

List of publications

1. Dhokotera T., Bohlius J., Spoerri A., Egger M., Ncayiyana J., Olago V., *et al*. The burden of cancers associated with HIV in the South African Public Health Sector, 2004-2014: a record linkage study. Infectious Agents and Cancer.
2. Rohner *et al*. Cervical cancer risk in women living with HIV across four continents. International Journal of Cancer. Dr Mazvita Sengayi is a co-author.
3. Tod B.M., Kellett P.E., Singh E., Visser W. I., Lombard C.J., Wright, C.Y. The incidence of melanoma in South Africa: An exploratory analysis of National Cancer Registry data from 2005 to 2013 with a specific focus on melanoma in black Africans. South African Medical Journal. 2019.
4. Ayeni O.A., Chen W.C., *et al*. The multimorbidity profile of South African women newly diagnosed with breast cancer. International Journal of Cancer. 2019 Oct. Doi:10.1002/ijc.32727.
5. O'Neil D.S., Chen W.C., Ayeni O.A., *et al*. Quality of breast cancer care in five public hospitals in South Africa: Evaluation using American Society of Clinical Oncology measures. International Journal of Global Oncology. 2019 Nov. Doi:10.1200/JGO.19.00171.
6. Chen W.C., Singh E., Muchengeti M., Bradshaw D., Mathew C.G., Babb de Villiers C., *et al*. Johannesburg Cancer Study (JCS): Contribution to knowledge and opportunities arising from 20 years of data collection in an African setting. Cancer Epidemiology. 2020;65(March):101701. Available from: https://doi.org/10.1016/j.canep.2020.101701.
7. Kamiza A.B., Kamiza S., Singini M.G., Mathew C.G., Association of TP53 rs1042522 with cervical cancer in sub-Saharan Africa population: A meta-analysis. Tropical Medicine and International Health. 2020.

Books

"Cancer in Sub-Saharan Africa Volume III" Edited by D.M. Parkin, A. Jemal, F. Bray, A.R. Korir, B. Kamaté, E. Singh, W.Y. Joko, M. Sengayi-Muchengeti, B. Liu and J. Ferlay
https://issuu.com/uicc.org/docs/afcrn_cancer_in_sub_saharan_africa

NICD Bulletin

Babongile Ndlovu, Patricia Kellett, Lazarus Kuonza, Mazvita Sengayi, Elvira Singh. Histological subtypes, anatomical sites, and incidence trends of non-melanoma skin cancers in South Africa, 1993-2014.

Conferences

1. In October 2019, Tafadzwa Dhokotera conducted an oral presentation entitled "Cervical Cancer Incidence in Women Living with HIV in South Africa, 2004-2014" at the International Conference on Malignancies in HIV in Maryland, USA.
2. Tafadzwa Dhokotera and Victor Olago participated in the IeDEA All Africa meeting through two poster presentations, and Tafadzwa attended an analysis of longitudinal data training workshop from 30-31 October.
3. The NCR team presented five poster presentations, one oral presentation and two invited talks at the 2019 AORTIC International Conference on Cancer in Maputo, Mozambique in November 2019.
4. Tafadzwa Dhokotera conducted a virtual oral presentation on her abstract titled "Conjunctival cancer in people living with HIV" at the annual Conference on Retroviruses and Opportunistic Infections (CROI) which took place from 8-11 March 2020. Masa Davidovic conducted a virtual poster presentation titled "Breast cancer risk in women living with HIV in South Africa: The SAM Study" at the same conference. Both abstracts are from the South African HIV Cancer Match Study.
5. Victor Olago was selected to conduct an oral presentation at the International Workshop on HIV Observational Databases (IWHOD) 2020 which was set to take place from 26-28 March 2020, but was cancelled due to the coronavirus disease 2019 (COVID-19) pandemic.
6. Babongile Ndlovu's abstract titled "Skin cancer risk factors among black South Africans - The Johannesburg Cancer Study, 1995–2016" was accepted for a poster presentation at the Epidemic Intelligence Service (EIS) conference in Atlanta, Georgia (USA), which was scheduled to take place from 4-7 May 2020, but was also cancelled due to the COVID-19 pandemic.

NICD COVID-19 response support

Lactatia Motsuku (NCR epidemiologist), Babongile Ndlovu (SAFETP resident and NCR clerk specialist), Grace Mapisa (NCR clerk specialist), Nellie Peters (NCR data capturer), Mazvita Muchengeti and Wenlong Chen were deployed to the Emergency Operations Centre (EOC) to assist with the NICD COVID-19 response.

Division of Public Health
Surveillance and Response

2019/20

Dr Linda Erasmus
Acting Centre Head

1. Background

The National Institute for Communicable Diseases (NICD) Division of Public Health Surveillance and Response (DPHSR) incorporates the GERMS-SA surveillance programme, the Provincial Epidemiology Team (PET), the Notifiable Medical Conditions Surveillance Unit (NMCSU) and the Outbreak Response Unit (ORU) that works closely with the Emergency Operations Centre (EOC). The roles and responsibilities of each are outlined below.

GERMS-SA

GERMS-SA collaborates with all NICD centres to provide an active surveillance programme incorporating laboratory-based surveillance through secondary data analysis of the National Health Laboratory Service (NHLS) data, complemented by enhanced surveillance at sentinel hospital sites for specific laboratory-diagnosed conditions. Sentinel pneumonia and diarrhoeal syndromic surveillance were also integrated into the programme, for optimal efficiency.

Provincial Epidemiology Team

The PET comprises of eight epidemiologists based in eight of the nine South African provinces. They support provincial health departments with epidemiological interpretation of TB, HIV and NMC data, and support outbreak investigation and management activities.

Notifiable Medical Conditions Surveillance Unit

The NMCSU coordinates the implementation of the NMC surveillance system. The unit supports data collection, data cleaning and reporting across the private and public sectors.

Outbreak Response Unit for the Emergency Operations Centre

The ORU and the EOC provide technical support to provincial and district health departments. Where necessary, they facilitate coordination of outbreak responses, together with the appropriate NICD centres. The NICD EOC coordinates the management of high-risk public health events of national and regional concern, using an incident management system. When the EOC is not activated, ORU/EOC staff support preparedness activities in response to local and international public health threats.

The activities of the DPHSR provide systems for rapid alert and notification of diseases of public health importance and avail the technical expertise of the NICD to provinces, districts and healthcare workers within South Africa. Members of the DPHSR team provide regular reports to the Multisectoral National Outbreak Response Team (MNORT), and to other government structures as required. 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".

Apart from a multitude of achievements of varying scales, the preparedness and response activities for the coronavirus disease 2019 (COVID-19) pandemic were a significant highlight of this reporting period.

2. Germs-SA

Lead: Dr Vanessa Quan

Surveillance

The GERMS-SA surveillance programme has been operational since 2002 and is coordinated by a core team within the DPHSR that works closely with the NICD centres to implement both laboratory-based and enhanced surveillance systems.

The laboratory surveillance pathogens include:

- *Candida auris;*
- *Salmonella typhi;*
- *Salmonella enterica* serotype Paratyphi (A, B and C);
- Nontyphoidal *Salmonella* spp.;
- *Shigella spp., Listeria spp.* and *Campylobacter spp.;*
- Diarrhoeagenic *E. coli;*
- *Streptococcus pneumoniae;*
- *Haemophilus influenzae;*
- *Neisseria meningitidis;*
- Group A streptococcus *(Streptococcus pyogenes);*
- Group B streptococcus *(Streptococcus agalactiae);*
- Carbapenem-resistant enterobacteriaceae (CRE), including *Acinetobacter baumanni; and*
- *Cryptococcus spp.*

GERMS-SA is an active surveillance programme and relies on participating laboratories to submit isolates as well as data from the NHLS Corporate Data Warehouse (CDW) to ensure that all cases that meet the case definitions are included in the database. Annually, approximately 250 laboratories (NHLS and private) that perform cultures on cerebrospinal fluid and blood, send specimens to the NICD centres. These laboratories contribute approximately 16,000 cases of communicable diseases that meet the case definitions to be submitted into the GERMS-SA database. Within this network, an enhanced surveillance arm is operational at 25 sentinel public sector sites across the country. As part of enhanced surveillance, nurse surveillance officers collect clinical information on patients relating to specific pathogens, where additional clinical and outcome data is required to support centre outputs, namely 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 operations of the syndromic surveillance programmes viz. pneumonia surveillance programme (with CRDM), diarrhoeal surveillance (with CED) and brucellosis surveillance (with CEZPD), using acute febrile illness as a case definition. In addition, all surveillance officers at enhanced sites assist with NMC training and outbreaks upon request.

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 main 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).

The work of GERMS-SA is funded by the NICD and the National Department of Health (NDoH).

Support to the Centre for HIV/STI surveillance programme

GERMS-SA surveillance officers supported the Centre for HIV/STI (CHIVSTI) surveillance programme through a multi-country evaluation of two dual syphilis/HIV point-of-care (POC) tests. The studies included pregnant women presenting at two primary healthcare facilities in Mpumalanga and KwaZulu-Natal provinces and ended in December 2019.

Acute febrile illness surveillance for zoonoses

The acute febrile illness surveillance project with the Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD) continues at one clinic site in rural Mpumalanga. The Mnisi area is bordered by the Kruger National Park and contact between wildlife, livestock and humans is frequent. This surveillance initiative is a One Health project and is executed in collaboration with veterinary practitioners and researchers from the University of Pretoria (UP) Veterinary Faculty.

The aim is to describe the prevalence of zoonotic infections in adult patients presenting with acute febrile illness and for whom the clinic sisters would do a malaria test. Laboratory testing includes polymerase chain reaction (PCR) and serology for brucellosis, *Bartonella* infections, leptospirosis, Q-fever, tick bite fever, West Nile virus, Sindbis, Rift Valley fever and Chikungunya virus infections. Study data published show a high seroprevalence of tick bite fever, Q-fever and leptospirosis, parallel to significant exposure at the human/animal interface.

3. Notifiable Medical Conditions Surveillance

Lead: Dr Lazarus Kuonza

Background

The Notifiable Medical Condition (NMC) 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, which is one of the core capacity requirements stipulated by the International Health Regulations (IHR, 2005). The NMC surveillance system (NMCSS) provides information for targeted public health response, decision making and resource allocation.

Surveillance

Uptake in use of the electronic application

Since the last reporting period, there has been a significant increase in the use of the NMCSS electronic application (app) for reporting from private and public sector health facilities across the country. More than half, 4 055 (51,9%), of the current 7 816 users of the NMCSS were registered during the reporting period (1 April 2019 - 31 March 2020). As demonstrated in Figure 1 below, there has been a marked increase of monthly registrations on the NMCSS since the implementation of the enhanced NMCSS web and mobile application platforms in October 2019. There has also been a gradual increase in the number of new users registering on the NMCSS since the outbreak of the COVID-19 epidemic in the country in January 2020.

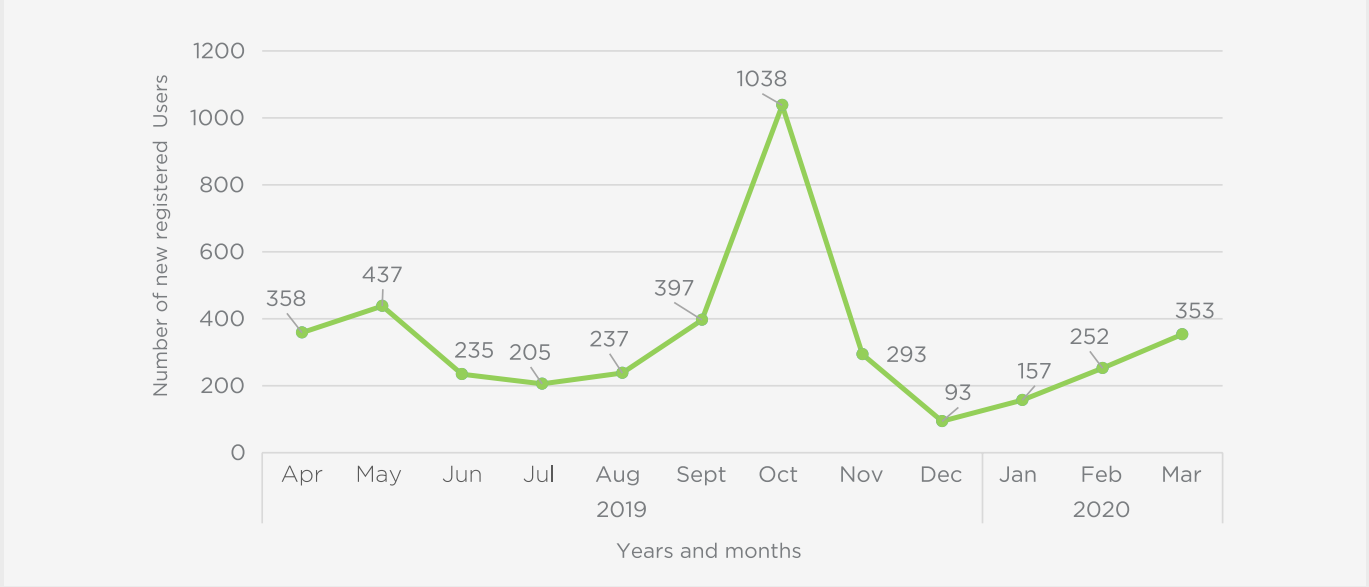


Figure 1: Number of new users registered on the NMCSS electronic reporting platform from April 2019 to March 2020

Overall, there has been a steady increase in the number of notifiable cases reported via the NMCSS electronic platforms (vs. paper-based notifications), since the introduction of the web and mobile electronic applications in April 2018. During the reporting period, the number of electronic notifications increased from 40% in April 2019 to 81% in March 2020. Conversely, the number of clinical cases reported through the paper-based platform, has decreased over time (Figure 2). KwaZulu-Natal and Free State provinces achieved and sustained the highest rates of electronic application utilisation, throughout the reporting period (Figure 3)

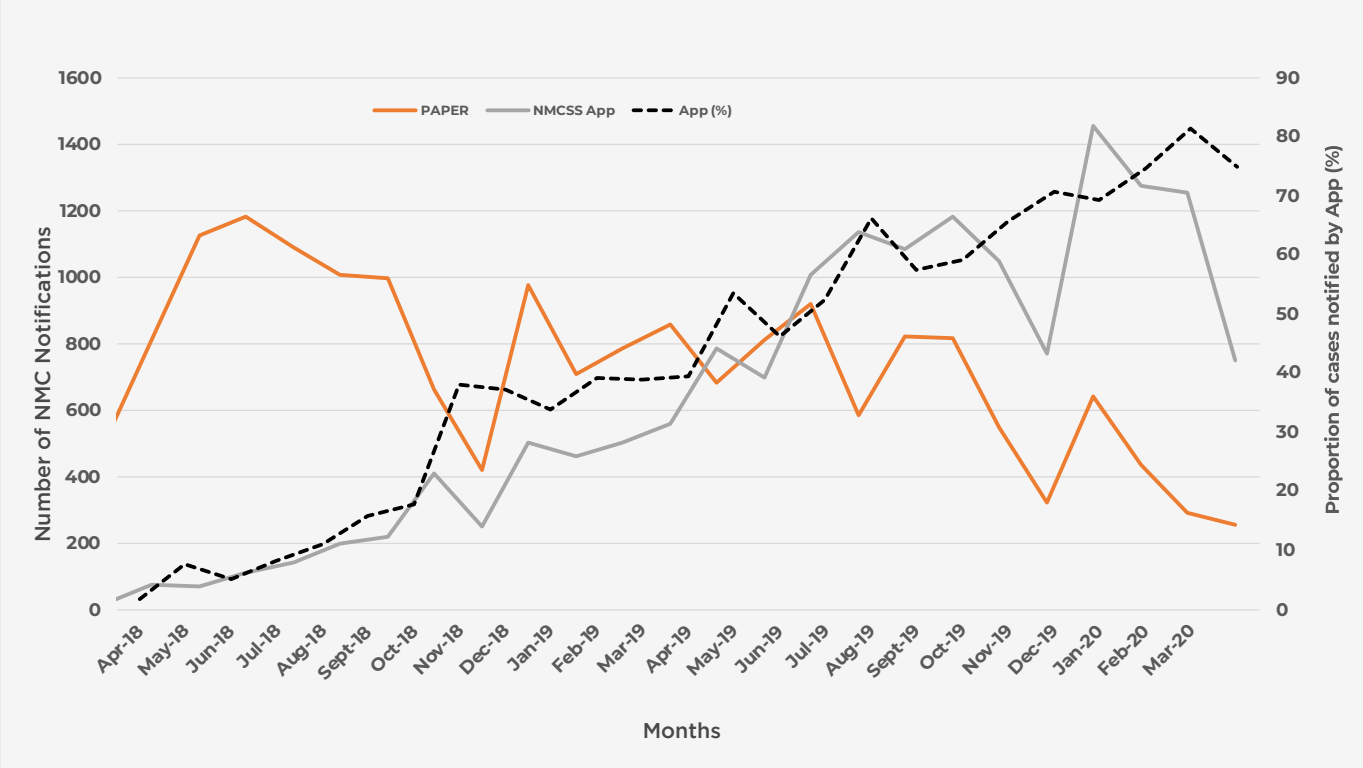


Figure 2: Utilisation of the NMCSS electronic applications for case notification from April 2018 to March 2020

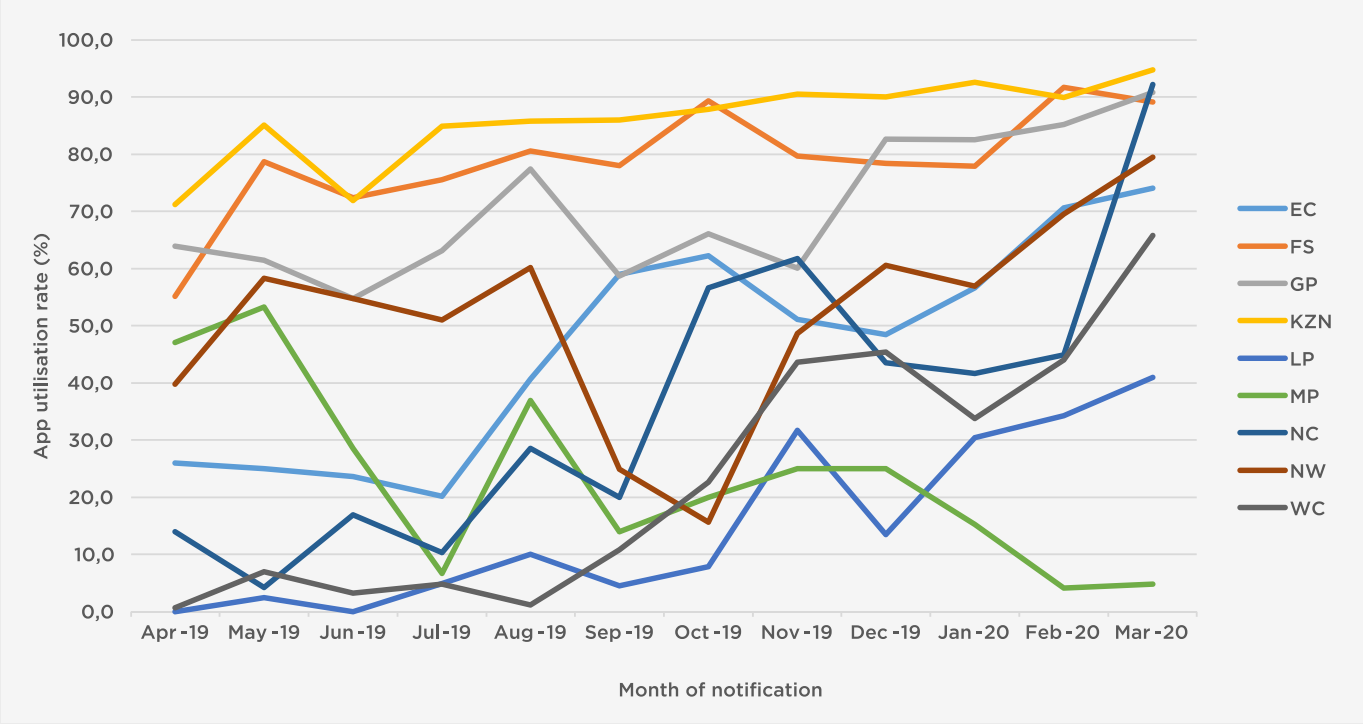


Figure 3: NMCSS electronic application utilisation rates by province, April 2019 to March 2020

The NMCSS web and mobile electronic reporting platforms were officially rolled out across all nine provinces in the country. KwaZulu-Natal, Western Cape and Free State provinces have successfully whitelisted the NMCSS web application on their provincial government intranet platforms, with the aim to expand access to the system in public health facilities. This has contributed to an increase in the use of the electronic NMCSS platform in these provinces. The continued engagement of provincial Department of Health (DoH) stakeholders also played a pivotal role in improving access to and use of the NMCSS electronic tools. This included the hosting of two meetings for stakeholders of the Centers for Disease Control and Prevention (CDC) in South Africa, during the reporting period.

Data harmonisation with the national Malaria Control Programme

The Malaria Control programme (MCP) and the NMC had several discussions about integrating the NMCSS and District Heath Information System (DHIS2). Differences in data formats resulted in delays in such an integration. The MCP has however commenced with utilising NMCSS data to enrich data collected through the DIHS2 system and for the purposes of data triangulation.

Private sector laboratory data feeds

According to the latest NMC Regulations, all clinical laboratories are required to report selected medical conditions on the NMCSS. During the reporting period, significant progress was made in the development of a web-based service to enable electronic data transfer from the private laboratories into the NMCSS data mart. By the end of March 2020, at least six private laboratories were submitting COVID-19 test results on the NMCSS, through this service. Developments to include the remaining NMCs into the web service are still in progress.

NMC case definitions and epidemiological classifications

The NMCSS team worked closely with NICD centres to revise several of the NMC case definitions and updated case definitions for 'category 1' NMCs were issued in June 2019. In addition to training healthcare providers on the notification tools and processes, the provincial NMCSS team incorporated NMC case definitions as part of their standard training curriculum.

The NMCSS team collaborated with selected NICD centres to ensure that the case investigation forms (CIFs) submitted by healthcare providers into the NMCSS are relayed to the relevant centres for capturing. The data flow diagram presented in Figure 4 provides an example of the flow of congenital syphilis notifications and CIFs through the NMCSS to the Centre for HIV and STIs (CHIVSTI).

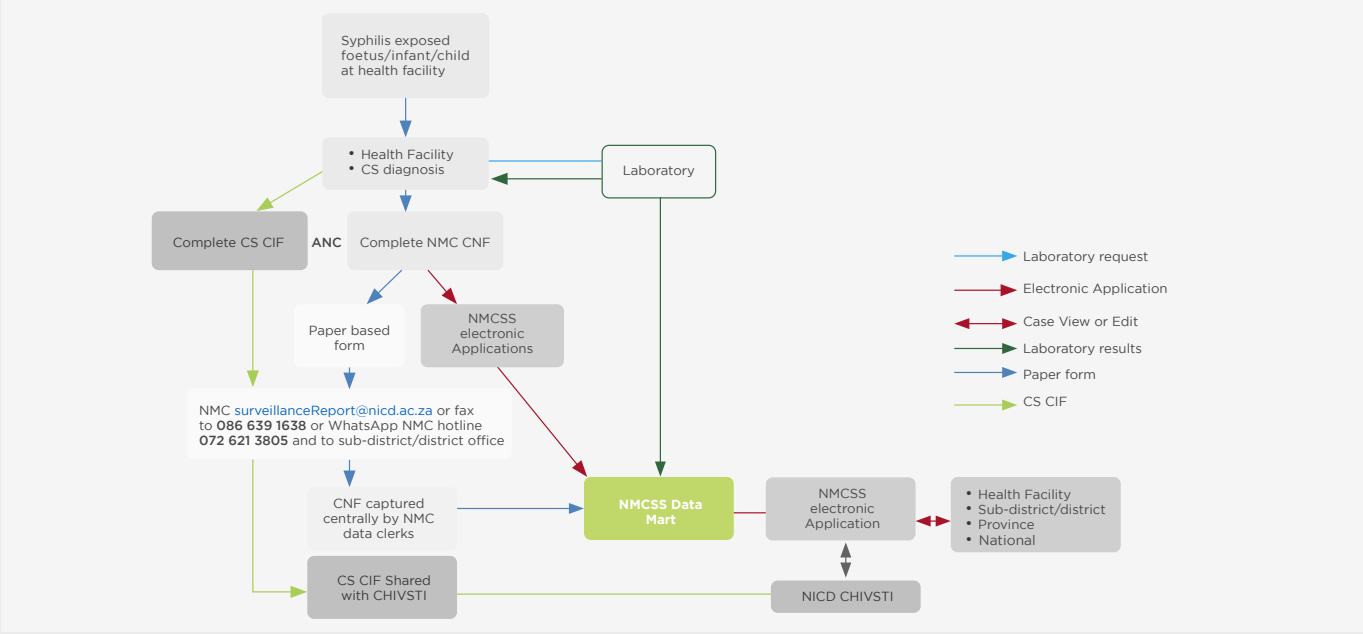


Figure 4: Congenital syphilis case data flow

During the reporting year, there were numerous collaborations between the NMCSS team and the other NICD centres, which amongst other, resulted in the following output:

- Review of 'category 1' NMC case definitions by respective NICD centres. The case definition flipchart has been published on the NICD website (since June 2019) to make it easily accessible to healthcare providers;
- Incorporation of a database-embedded editable case line list with the NMCSS web application to enable epidemiological classification of notified cases by experts within the centres; and
- Continued revision of NMC case definitions to ensure that the data collected through the NMCSS addresses the country's public health requirements. Case definitions for hepatitis A and B, were, for example revised to ensure that the correct cases are drawn from the clinical laboratories.

Outbreaks

In March 2020, a new COVID-19 module was added to the NMCSS to collect additional data elements required to guide the national response to the pandemic. The COVID-19 module enables the system to collect enriched epidemiological data on COVID-19, incorporate real-time data feeds from private medical laboratories, and streamline the timely dissemination of the data to provinces and districts for public health action. The NMC team also developed an enhanced paper-based case notification form, new standard operating procedure (SOP) documents, and relevant training materials for the implementation of the COVID-19 module.

Policy contributions

The NMC team worked closely with representatives from the South African Medical Research Council (SAMRC)'s Environment & Health Research Unit, the University of Cape Town Poisons Information Centre, and other stakeholders to develop case definitions for agricultural stock remedy poisoning, lead poisoning and mercury poisoning. The case definitions were still under review at the end of the reporting period.

4. Outbreak Response Unit

Lead: Dr Ann Mathews

Background

The Outbreak Response Unit (ORU) provides technical support for all aspects of communicable disease outbreaks and control in South Africa. Through close collaboration with the national and provincial departments of health and other stakeholders, and together with systems for early detection and improved reporting of epidemic-prone communicable diseases, the ORU functions as a source of technical expertise for outbreak detection, investigation and response activities.

The ORU facilitates interaction between the NHLS diagnostic laboratories and NICD centres, as well as the provincial and district communicable disease structures, to provide appropriate laboratory diagnostic services during outbreaks and when specialised diagnostic testing is required. The unit remains abreast of international developments in outbreaks and outbreak preparedness through representation on key World Health Organization (WHO) advisory committees and international interest groups. Representatives from the unit attend the monthly Multisectoral National Outbreak Response meeting and report on surveillance and outbreak investigation activities.

The ORU continues to publish its monthly Communicable Diseases Communiqué, which reports recent outbreaks and communicable disease cases/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 that required immediate dissemination of information.

The unit furthermore coordinates the 24-hour emergency hotline, staffed on a rotational basis by pathologists and medically qualified staff of the NICD. The hotline 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 disease; and
- Technical advice regarding the management of cases of infectious disease.

On 30 January 2020, the Emergency Committee convened by the WHO Director-General declared the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC).

South Africa reported its first COVID-19 case on 5 March 2020. Prior to this, several COVID-19 preparedness and response activities were undertaken by the ORU/EOC, NHLS and other NICD centres. This included the establishment of a national clinician and public hotline on 6 March 2020, to deal with the large volumes of COVID-19 queries referred to the NICD hotline. About 120 doctors and nurses (permanent, contract, or volunteers) were hired to support this expanded service, on a day and night rotating shift schedule.

During the reporting period, 43,730 queries were directly handled by the ORU, through the NICD hotline or the national public and clinician hotlines made available to all members of the public and healthcare workers respectively, in response to the COVID-19 pandemic. All queries (100%) were responded to within 24 hours.

Figure 5 shows the number of queries received over the reporting period, with a sharp increase in the month of March 2020, due to the coronavirus pandemic. Table 1 represents the number of calls received per category, indicating that 90% of all queries were COVID-19 related, followed by queries regarding the management of rabies post-exposure prophylaxis. In instances where caller origin was documented (n=43 704), most calls were from Gauteng Province (43%, 18,732), followed by KwaZulu-Natal Province (15%, 6,545) and the Western Cape Province (14%, 6 296) (Figure 6).

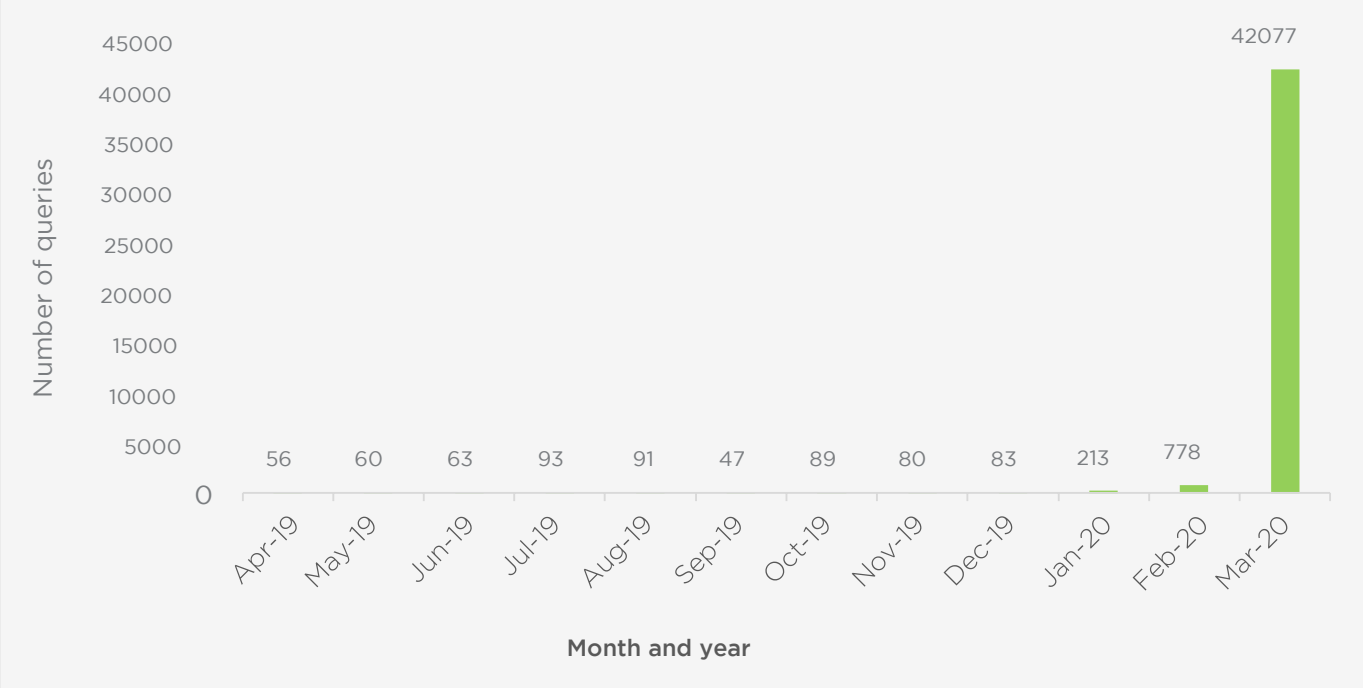


Figure 5: Number of queries attended to on the hotline from 1 April 2019 – 31 March 2020

Table 1: Number of queries attended to on the hotline by category from 1 April 2019 – 31 March 2020

Category	Number of queries
Administrative	20
Animal/environmental health	4
COVID-19	42 905
Food/Waterborne disease investigation	5
Infection control	8
Laboratory-confirmed cases for clinical/public health management	25
Media/journalists	2
Non-rabies post-exposure prophylaxis	7
Other	39
Patient(s) investigation (diagnostic/clinical advice)	106
Pre-exposure prophylaxis	17
Rabies post-exposure prophylaxis	566
Vaccination-related	26
Grand total	**43 730**

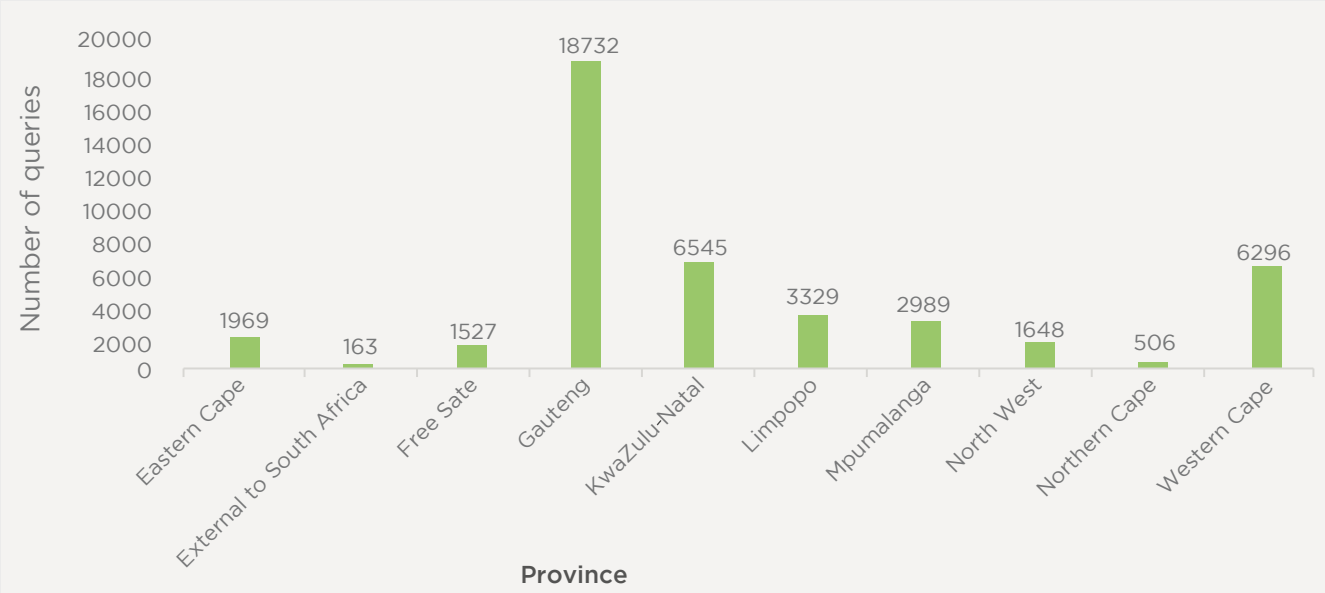


Figure 6: Provincial origin of queries attended to from 1 April 2019 – 31 March 2020, n=43 704.

Outbreaks

The ORU, together with the NICD centres, attended to several potentially major public health events over the course of the year, including the following:

1. An enterovirus meningitis outbreak in Western and Eastern Cape provinces between 2018 and 2019: The ORU assisted and provided support on data management;
2. A suspected hepatitis A outbreak at an old age home in Gauteng Province, April 2019: The team lead on this investigation was from the ORU;
3. A methicillin-resistant *Staphylococcus aureus* (MRSA) outbreak at a neonatal ward in a district hospital in Gauteng Province from June to July 2019: The ORU and the Centre for Healthcare-associated Infections, Antimicrobial Resistance and Mycoses (CHARM) supported the hospital in investigating this outbreak;
4. Several suspected outbreaks were verified and support was rendered to the provinces in question, as follows:
    a. A suspected diphtheria case which was identified in KwaZulu-Natal Province in August 2019
    b. A suspected diphtheria case which was identified in Gauteng Province from July to September 2019
    c. A suspected increase in pertussis cases which occurred in the Western Cape Province from July to September 2019

5. A suspected foodborne disease outbreak at a school in Limpopo Province in May 2019: A total of 88 learners, including some staff who resided in the school's boarding hostel reported diarrhoea and abdominal cramps. As all of them ate a common food, recommendations were provided for the safe and thorough cooking of food, as well as hand hygiene;
6. A suspected foodborne disease outbreak among learners attending a winter camp in Limpopo Province (April to June 2019);
7. A suspected outbreak of viral haemorrhagic fever at a hospital in Gauteng Province in June 2019: A patient with advanced immunocompromise disease passed away in the hospital. Further investigation and testing ruled out Ebola;
8. A mumps outbreak at a school in Ngaka Modiri Molema District in North West Province in May 2020: The ORU assisted the provincial epidemiologist with the investigation;
9. Follow-up on food poisoning reports reported via NMC notifications from 1 April to 12 September 2019 (this role was taken over by the Centre for Enteric Diseases (CED) from September 2019);
10. Investigation of a cluster of three cases presenting as possible meningitis in Limpopo Province in August 2019: Meningitis was ruled out. There were no positive results and no further cases;
11. Investigation of a pertussis case in Limpopo Province (July to September 2019);
12. Together with the Centre for Vaccines and Immunology (CVI), ORU staff supported the North West Provincial DoH in investigating a cluster of three cases of possible acute flaccid paralysis (AFP) identified in the North West Province in August 2019: Polio was excluded and there were no further cases;
13. Investigation of a cluster of meningococcal meningitis cases in the City of Tshwane District in Gauteng Province from July to September 2019;
14. Investigation of an outbreak of 'rash' in KwaZulu-Natal Province in August 2019: About 200 learners from a primary school in uThukela District complained of an itchy rash with no other symptoms. The presentation did not meet the measles case definition. The learners were treated symptomatically, and the symptoms spontaneously resolved. No definitive cause was found;
15. The ORU investigated two cases of infant deaths at crèches in Gauteng Province in August 2019: The deaths were reported by the forensic pathologist. Both cases tested positive for *Streptococcus pneumoniae*, but they were not epidemiologically linked;
16. ORU staff provided technical support in the investigation of a suspected measles outbreak in Bojanala District in North West Province in October 2019;
17. ORU staff provided technical support in the investigation of a meningococcal disease case at the North West Province University in October 2019;
18. ORU staff provided support in relation to the Lesotho Cross-border SIMEX in November 2019: This was a simulation exercise of a suspected Ebola virus disease case, which led to a media scare. A report was released explaining the situation;
19. Technical support and supervision was provided to the South African Field Epidemiology Training Programme (SAFETP) and an investigation of a foodborne disease outbreak was conducted at two schools in City of Johannesburg, Gauteng Province in October 2019;
20. Together with the CVI, ORU staff provided technical support in investigating a dual measles and rubella IgM-positive case in the Eastern Cape Province in December 2019;
21. The ORU supported CHARM in the initial investigation of a *Candida auris* outbreak at a neonatal unit in a tertiary hospital in Gauteng Province in January 2020;
22. Technical support was provided to the Kwazulu-Natal Provincial Communicable Disease Control manager regarding a suspected food poisoning in a family in eThekwini District Municipality from July – September 2019; and
23. Technical support/advice was provided to the CED regarding a suspected food/waterborne illness outbreak in Johannesburg in Gauteng Province in August 2019.

Other

During the year under review, the unit participated in a number of stakeholder engagements. From April to June 2019, ORU staff participated in quarterly meetings as part of the Joint External Evaluation (JEE) working groups who contribute to the NDoH's National Action Plan for Health Security (NAPHS) for the implementation of the IHR.

From August to October 2019, ORU staff, together with relevant stakeholders, participated in several activities relating to Ebola preparedness in South Africa, which included attending Ebola country risk assessment meetings. The unit also assisted with compiling the standard operating procedure (SOP) document for the detection and response to an Ebola virus disease outbreak in South Africa. In addition, the ORU assisted with identifying and compiling a list of organisations that may deploy or have workers in the Democratic Republic of Congo (DRC). Staff from the unit furthermore participated in Ebola meetings on vaccines and therapeutics with the aim to develop a protocol for an Ebola vaccine trial in South Africa.

Staff from the unit attend the weekly Africa Centres for Disease Control and Prevention's (Africa CDC) Southern African ECHO teleconferences to discuss and report outbreaks and events of importance occurring in the region.

ORU staff plays an integral role at CVI's two-monthly measles situational report (sitrep) meetings held at the NICD. The unit also assists the centre with measles notifications reported via the NMCSS. In July 2019, staff from the unit led the coordination and development of a national rabies post-exposure prophylaxis guideline document for South Africa. Additionally, staff from the unit are members of the NICD's Institutional Biosafety and Biosecurity Committee (IBBC) which meets quarterly to discuss mitigating factors associated with work-related risks, e.g. dealing with human pathogens in the laboratory environment.

From January to March 2020, the ORU was involved in various meetings and activities in response to the global COVID-19 pandemic, including the following;

a. Assisting with EOC preparation and response to the global COVID-19 pandemic;
b. Managing the 24/7 clinician and public hotlines, including call centre nurses, 12 community service doctors and several volunteer doctors from the Aurum Institute and Anova Health Institute;
c. Attending and participating in the weekly epidemiology and surveillance workstream regarding COVID-19 preparedness and response activities;
d. Attending and participating in the weekly provincial communicable disease control coordinators (CDCC) Zoom meetings regarding COVID-19 response activities;
e. Attending and participating in the contact tracing team meetings regarding COVID-19 public health response;
f. Reviewing of reports relating to surveillance at ports of entry regarding traveller health questionnaires;
g. Presenting of data on traveller health questionnaires completed at ports of entry at a COVID-19 port health training session in March 2020;
h. Compilation and review of COVID-19 preparedness and response documents;
i. COVID-19 document archiving and version control;
j. Assisting with contact tracing and monitoring of symptoms as part of the epidemiology and surveillance track of the incident management team (IMT);
k. Maintaining and analysing COVID-19 case line lists, and providing daily feedback reports to members of the IMT; and
l. Notifying provinces of COVID-19 confirmed cases on a daily basis, liaising with provinces and coordinating of data harmonisation.

5. Emergency Operations Centre

Lead: Nevashan Govender

The NICD EOC supported the NDoH to prepare for and respond to a number of events of significance during the period from 1 April 2019 to 31 March 2020. Some highlights are described below.

The EOC manager formed part of the South African Medics Team established by the NDoH and was deployed to Mozambique in response to the effects of Cyclone Idai in April 2019. The NICD received a letter of appreciation from the former Minister of Health, Dr Aaron Motsoaledi, for the assistance and expertise provided to Malawi, Mozambique and Zimbabwe in response to the effects of this cyclone.

The EOC also assisted with the response to a chemical factory fire in KwaZulu-Natal. Coordination meetings were convened at the EOC and a situational update was written.

EOC staff participated in the coordination of Ebola preparedness in South Africa, in response to the tenth Ebola outbreak in the DRC. This included preparation and contribution to key meetings, documents and briefs, on vaccines and therapeutics, hospital preparedness, personal protective equipment (PPE) and general Ebola response preparedness. The EOC manager participated in a WHO workshop hosted by the Sultanate of Oman on the topic of development of information systems for Public Health Emergency Operation Centres (PHEOCs), as PHEOCS play an integral coordination role during an emergency.

Following the WHO declaration of COVID-19 as a Public Health Emergency of International Concern on 30 January 2020, the EOC was officially activated and an incident management team comprising the NDoH, NICD, NHLS and other stakeholders was formed. EOC activities included:

- Rendering logistics and operational support;
- Preparing one-pager situational updates;
- Monitoring data from media and social media;
- Monitoring data from Port Health;
- Conducting a rapid hospital readiness assessment;
- Establishing a dedicated swab team for essential worker screening and testing;
- Collecting of selected specimen;
- Conducing of cluster investigations; and
- Recruiting and managing epidemiologists for provincial support.

Other

In the reporting year, EOC manager Nevashan Govender contributed and participated in a number of activities. This included the writing and review of the following WHO documents for EOCs:

- Handbook for developing a public health emergency operations centre Part A: Policy, plans and procedures; and
- Handbook for developing a public health emergency operations centre Part C: Training and exercises.

Mr Govender successfully completed the regional training of trainer's workshop on PHEOCs, making him one of only thirty-one individuals from the WHO Regional Office in Africa (WHO-AFRO) and the WHO Eastern Mediterranean Regional Office (WHO EMRO) who are certified to train on PHEOCs.

He was also invited to assist with the evaluation of the EOCs in Georgia, Serbia, Germany and Tajikistan, as well as the development of SOPs and policies for the Zambian EOC. In addition, he was responsible for the review of a number of draft documents for application of African EOCs and was invited to become a member of the WHO-AFRO CDC's online community of practice for EOCs.

Mr Govender furthermore helped to ensure EOC compliance with WHO mandatory reporting through participation in the IHR NAPHS and review and validation of the Global Health Security (GHS) Index.

He also remains an active participant on the Africa CDC's ECHO platform, ensuring information sharing and relationship strengthening across emergency and outbreak response leads in Southern Africa.

6. Provincial Epidemiology Team

Lead: Joy Ebonwu

Epidemiology is one of the core sciences that underpin the work of the NICD, to ensure evidence-based public health decision-making and strengthen health systems at national, provincial and local departments of health. Since 2014, the reach of the NICD in the provinces has expanded considerably, through the establishment of the Provincial Epidemiology Team (PET), which involves the placement of one epidemiologist in every province of South Africa. By the end of the 2019/2020 financial year, the PET had a complement of eight provincial epidemiologists, as well as one manager. The only province where there is no PET epidemiologist, is the Northern Cape, which is supported centrally from NICD.

The main goal of the PET is to ensure that the NICD's core services of surveillance, outbreak response, specialist microbiology and public health research are available at all levels of health departments, in a timely manner. The provincial epidemiologists work in collaboration with the NICD centres and various disease programmes in the provinces to produce output that inform programme performance and management decisions.

To date, the provincial epidemiologists have played a key role in strengthening surveillance of infectious diseases through routine analyses of surveillance data to assess disease burden and pattern, and to identify and address gaps in data collection. In support of the National Strategic Plan for HIV, TB and STIs 2017-2022, they provided epidemiological support for prompt linkage of laboratory-diagnosed drug-resistant TB and early infant diagnosis (EID) of HIV, to healthcare services. Results from epidemiological analyses of TB data helped to identify TB hotspots and high-risk groups in the provinces and GeneXpert-diagnosed rifampicin-resistant (RR) TB data was analysed to determine treatment uptake and reasons for non-initiation of treatment.

As part of the provincial outbreak response teams, the provincial epidemiologists support outbreak investigations in collaboration with the NICD ORU and relevant centres, by ensuring thoroughness of case investigations, contact tracing, mapping of cases, data analysis and report writing. The outbreak investigation reports were published in the monthly NICD Communicable Disease Communiqué. The significance of their contribution is evident in the current national response to the COVID-19 outbreak.

Other

During the year under review, the PET also participated and contributed to the following activities:

- Ongoing assistance with the national response to the COVID-19 outbreak in varying roles as part of the provincial IMTs;
- Conducting of a rapid preparedness assessment for the Ebola viral disease (EVD) in 11 designated hospitals in South Africa, in collaboration with the Hospital Directorate of the NDoH;
- Support for the implementation of the Expanded Programme on Immunisation in South Africa (EPI-SA) coverage survey, including training of field workers and analysis of data; and
- Facilitating a SAFETP frontline course on Basic Applied Epidemiology for Health Practitioners in Free State, Mpumalanga and KwaZulu-Natal provinces.

Professional Development

During the year under review, staff from DPHSR were enrolled for postgraduate degrees as follows:

- Dr Kerrigan McCarthy, Joy Ebonwu and Dr Susan Meiring for Doctor of Philosophy degrees (PhDs) at the University of Witwatersrand (Wits) School of Public Health;
- Genevie Ntshoe for PhD at UP;
- Dr Linda Erasmus for Master of Science degree (MSc) in Biostatistics and Epidemiology at the Wits School of Public Health; and
- Neo Legare for Master of Public Health degree (MPH) at UP.

One ORU staff member was enrolled for the postgraduate Diploma in Monitoring and Evaluation at Wits and two ORU staff members were enrolled for the South African Travel Medicine course 2020, which was postponed to 2021, due to the COVID-19 pandemic.

7. Research Output

Teaching and training

The NMC team participated in numerous frontline epidemiology training courses that were offered by the NICD to public sector healthcare professionals in Gauteng, Free State, Mpumalanga and KwaZulu-Natal Provinces. The NMC team also facilitated several surveillance and outbreak management courses that were offered to postgraduate students from UP and Wits.

In addition, the NMCSS Unit served as a field placement site for two SAFETP residents, as part of the Masters' degree training in field epidemiology. The first resident successfully completed field training in December 2019, and the second resident commenced with field placement in January 2020. The NMCSS team also served as co-supervisors to six postgraduate students from UP, Wits and the University of Johannesburg (UJ). Various staff of the ORU were involved in the following teaching and training activities:

- Undergraduate level:
  a. A lecture to second-year clinical associate students at Wits on rabies, malaria, COVID-19 and an approach to a patient with fever and bleeding in February 2020
- Postgraduate level:
  a. Supervising SAFETP residents during their monthly outbreak rotation at the ORU
  b. Supervising public health registrars from UP and Wits during their six-monthly outbreak rotation at the ORU
  c. Teaching the SAFETP outbreak module (CDS871) to MPH students at UP on:
     i. Laboratory investigations during an outbreak, May 2019
     ii. Outbreak report writing, May 2019
     iii. Outbreak management – overview of the steps, May 2019
     iv. Analysing data in outbreaks: descriptive epidemiology and hypothesis generation, May 2019
     v. Composition of an outbreak response team, May 2019
     vi. Communication during an outbreak, May 2019
  d. Training healthcare workers on the South African Society of Travel Medicine (SASTM) 2019 course module on 'Rabies guidelines', May 2019;
  e. Teaching the NICD core three-week course to public health medicine and infectious disease registrars from various universities on 'An introduction to outbreak investigation and response', May 2019;
  f. Training SAFETP students on setting threshold limit values, June 2019;
  g. Training public health registrars on the 'Steps to outbreak investigation' (theory and practical approach), June 2019;
  h. Training of provincial and district staff in North West Province on malaria, rabies and Ebola, September 2019;
  i. Training staff from the National Education, Health and Allied Workers' Union (NEHAWU) on the prevention of communicable diseases, September 2019;
  j. Teaching provincial CDCCs on surveillance during outbreaks, in the context of the Integrated Disease Surveillance and Response (IDSR), September 2020;
  k. Training and teaching SAFETP students on public health response to a measles case/outbreak, October 2019;
  l. Training SAFETP students on foodborne disease outbreak investigation, October 2019;
  m. Training of NICD staff on the foundational incident management system (IMS) together with the EOC manager, 10-11 December 2019;
  n. Teaching the SAFETP module on 'Introduction to Field Epidemiology and Biostatistics concept: measures of association/effect,' to first-year students, January 2020;
  o. Several teaching and training sessions for global COVID-19 pandemic preparedness and response from January to March 2020, including:
     i. Presentation on COVID-19 outbreak at the Civil Aviation Authority Conference, January 2020
     ii. Presentation on contact tracing regarding COVID-19 at the IHR meeting held in Pretoria, March 2020
  p. ORU staff coordinated and compiled the DPHSR medical scientist training rotation programme for 2020;
  q. Four ORU staff members completed the IMS Tier 1 online course, 8 November 2019;
  r. Four ORU staff members attended and completed the Public Health Emergency Management (PHEM) 100 – Foundational IMS Training, 12-13 November 2019;
  s. Four ORU staff members attended and completed the PHEM 450 - Train the trainer, 14-15 November 2019;
  t. One ORU staff member attended the International Joint Bioterrorism Course held in Cape Town in the Western Cape Province, August 2019;
  u. One ORU staff member attended the Vaccinology Scientific Conference held in Gauteng Province, October 2019; and
  v. Staff members participated in the US CDC Skype video meeting on Epidemic intelligence, Response and the EOC, June 2019.

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Internal publications

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3. Seakamela L., Manamela J., Motaze V., Howard W., du Plessis H., Jallow S., *et al.* Acute flaccid paralysis surveillance for polio, South Africa and other African countries, 2018. NICD Public Health Surveillance Bulletin.2019;(3).

Honours

Prof Lucille Blumberg is set to receive an honorary degree (Doctor of Medicine) from Wits for her lifetime contribution and excellent leadership in the early intervention, detection, control and surveillance of infectious disease outbreaks for over two decades.

Susan Meiring won the Institut Merieux Young Investigator Award for her work in public health and surveillance.

Andronica Shonhiwa received a Best Flash Presentation Award for her “Hepatitis A outbreak” abstract oral flash presentation at the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) conference which took place in Johannesburg from 7-9 November 2019.

Dr Kerrigan McCarthy was appointed as a member of the PathReD Organising Committee.

Conferences

1. During the year under review, the division participated in eight international conferences and 32 national conferences. Abstracts were also accepted for presentation at two international conferences, which were cancelled due to the COVID-19 pandemic.

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