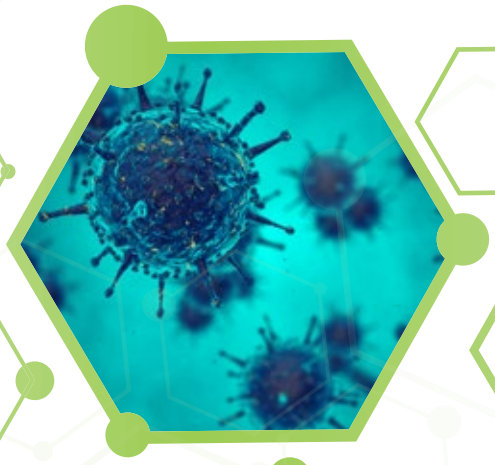
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Division of the National Health Laboratory Service

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES ANNUAL OVERVIEW

2018/19



NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

National Institute for Communicable Diseases
Annual Overview 2018/19

Contents

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
ASMR	Autonomous sensory meridian response
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 sero-positivity
VL	Viral load
VPIBD	Vaccine preventable and invasive bacterial disease
VTS-A	Vaccine induced Sero-positivity 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

Interim Executive Director's Overview

Interim Executive Director
Prof Lynn Morris

The National Institute for Communicable Diseases (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 National Department of Health (NDOH), as well as the World Health Organization (WHO), Africa Centers for Diseases Control and Prevention (CDC) and other relevant bodies, through surveillance of communicable diseases, outbreak response, specialised diagnostic services, research and training, capacity building and provincial epidemiology services.

The past financial year saw the declaration of the end of the Listeria outbreak by the then Minister of Health, Dr Aaron Motsoaledi, at a press conference held at the NICD on 3 September 2018. The Listeria outbreak highlighted the vital role of the Emergency Operations Centre (EOC) in tackling a public health crisis and the power of molecular epidemiology through next-generation sequencing to pinpoint the source of the outbreak. The resolution of the outbreak was achieved through the joint WHO/RSA Incident Management Team (IMT) and the combined efforts of WHO, NDOH, NICD and other stakeholders. For this, the NICD received the Alfred Nzo Environmental Health Excellence Award from the NDOH.

Figure 1. From left, Ms Malebona Precious Matsoso (DG of NDOH), Dr Kerrigan McCarthy (NICD) and Ms Montsheng Tsiu (MEC of Health, Free State Province).

The NICD supported the NDOH with the Joint External Evaluation (JEE) exercise of the International Health Regulations (IHR) and led the development of aspects of the JEE action plan. A medical epidemiologist was deployed to the Butembo health zone of the Democratic Republic of Congo (DRC), under the Global Outbreak Alert and Response Network (GOARN), to assist in the Ebola outbreak relief efforts.

Biosafety and biosecurity is an important and unique aspect of the NICD. A number of biosafety level (BSL) 3 laboratories and a BSL 4 laboratory housed on-site are used to diagnose and research formidable pathogens. The NICD continues to support the NDOH with the design of legislation related to hazardous biological agents and the registration of laboratories.

The Division of Public Health Surveillance and Response (DPHSR) through the GERMS-SA surveillance platform, underpins much of the surveillance activities within the seven centres at the NICD. GERMS-SA continues to expand and covered a larger number of pathogens across the country. The Notifiable Medical Conditions Surveillance System (NMCSS) designed for real-time data reporting was continued, successfully rolled-out and received over 6 500

monthly notifications from the National Health Laboratory Service (NHLS) laboratories, and private and public sector clinicians in the past year. The NICD 24-hour hotline handled over 250 calls per month from healthcare providers requesting assistance with laboratory diagnostics and advice on rabies post-exposure prophylaxis.

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. Routine surveillance by the newly established reference laboratory for Antimalarial Resistance Monitoring and Malaria Operational Research (ARMMOR) addresses the need for regular drug efficacy monitoring to ensure effective malaria treatments are in place. CEZPD is a long-standing partner of GOARN and plays an important role in alerting and responding to public health events by coordinating national, regional and global capabilities for risk assessment, management, communication, operational research, training and preparedness. In recognition of this role, the NICD was re-elected for another four-year term as a member of the GOARN Steering Committee.

The Centre for Enteric Diseases (CED) continued surveillance of acute diarrhoeal disease and national listeriosis surveillance. Nationally, the Centre actively participated in outbreak investigation and response activities for more than 20 outbreaks, providing technical and epidemiological support, as well as performing diagnostic and reference laboratory testing.

The year under review presented a number of high-profile outbreaks of neonatal sepsis in public sector hospitals. The Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses (CHARM) assisted in identifying the source of these outbreaks and piloted several interventions including a new surveillance programme (called Baby GERMS), a mobile application (APP) to detect neonatal unit outbreaks (NEO-HAI) and a plan to train healthcare workers in neonatal units.

Scientists within the Centre for HIV and Sexually Transmitted Infections (CHIVSTI) were part of the team that successfully performed a liver transplant from an HIV positive mother to her HIV negative child. This groundbreaking study creates a potential new pool of living donors that could save more lives in the future. The antenatal HIV seroprevalence survey conducted at the NICD now includes new measures of HIV incidence estimates as well as the accuracy of HIV rapid testing. An interactive web-based dashboard was developed to triangulate data from multiple sources for paediatric HIV surveillance. The STI section has focused on the monitoring of antimicrobial susceptibility profiles for the emergence of extensively drug-resistant (XDR) *Neisseria gonorrhoeae* resistance to extended-spectrum cephalosporins (ESCs).

The Centre for Respiratory Diseases and Meningitis (CRDM) through the NMCSS and syndromic surveillance platforms documented a nationwide increase in the number of pertussis cases. This data was presented to the National Advisory Group on Immunisation (NAGI) and guided policy recommendations on vaccination. CRDM also completed enrolment and follow-up for the Prospective Household Observational Cohort Study of Influenza, Respiratory Syncytial Virus and other Respiratory Pathogens Community Burden and Transmission Dynamics in South Africa (PHIRST-SA).

This is a large and intensive study of the community burden and transmission of important respiratory pathogens (influenza, respiratory syncytial virus, pertussis and pneumococcus) aimed at providing data to guide the most appropriate strategies to control and prevent these diseases.

Tuberculosis (TB) continued to be a national priority in terms of disease burden in South Africa. The Centre for Tuberculosis (CTB) completed the first ever national TB prevalence survey and data are being used to find the missing TB patients. Geospatial mapping in 21 priority districts was used to identify hotspots of TB and to guide implementation plans for targeted interventions by the NDOH and partners. CTB also defined interpretive criteria for identifying bedaquiline resistance that is being used to set global policy.

There were 50 measles cases confirmed over the past year by the Centre for Vaccines and Immunology (CVI). Since measles is targeted for elimination in the African region, each case is investigated to ensure that there is no further spread of the disease. CVI identified vaccine-derived poliovirus type 2 (VDPV2) from 57 samples in the DRC, Niger and Mozambique. A case of immune-deficiency associated vaccine derived poliovirus (iVDPV) was identified in a child born with an inherited genetic immune disorder. The event prompted an outbreak response with multiple stakeholders including the national and provincial departments of health, WHO and the United Nations Children's Fund (UNICEF).

The National Cancer Registry (NCR) continued to serve as South Africa's main source of national cancer incidence data, through pathology-based cancer surveillance. The NCR released the first Ekurhuleni Population-based Cancer Registry (EPBCR) incidence report and published key research in cancer epidemiology and genetics.

The Field Epidemiology Training Programme (FETP) was one of six in Africa to be accredited by the global Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET). This programme continued to provide specialised and in-service training through short courses in the provinces.

The NICD houses seven WHO reference laboratories and maintained South African National Accreditation System (SANAS) accreditation of all its laboratories. The proficiency testing scheme (PTS) performance reported a success rate of 96% for the past four years with 98% successful returns in the period under review. There were also a number of laboratory refurbishments and other infrastructure projects and the acquisition of a new sequencing instrument, PacBio Sequel, the first on the African continent.

Staff at the NICD continue to strive for excellence and for improvements in public health, I would like to thank them all for their hard work over the last year. The donors, partners and collaborators are acknowledged for contributing to the success of the NICD.

Deputy Director's Overview

Deputy Director's Overview

Deputy Director
Dr Natalie Mayet

The year under review reflects the significant contribution of the activities undertaken by Human Resources (HR), the division of Biosafety and Biosecurity, Communications, Information Technology (IT), and the South African Field Epidemiology Training Programme (SAFETP). The strategic objectives of the NICD could not have been achieved without the collaborative engagement of all of these essential functions. These functions provide the platform and enabling environment that allows the NICD scientific community to achieve operational excellence. The NICD operates in an environment of networks; partnerships and collaboration agreements and, has maintained and expanded its partnerships locally, regionally and internationally with multiple stakeholders.

Human Resources

The NICD has achieved its diverse range of activities through the dedication and commitment of its 507 employees; 78% of this critical skill pool held permanent positions whilst 22% were grant-funded employees. Under the leadership of HR Manager, Ms Azia Nxumalo, the human resource team recruited 76 new staff members and maintained an average staff turnover of 1.5% whilst supporting capacity building through the 318 workplace skills plan interventions and the six internal workshops on recruitment, performance management and disciplinary processes.

Biosafety and Biosecurity Division

Quality assurance remains a high priority for the NICD, by maintaining SANAS accreditation of all laboratories and the move to have all NICD support services ISO 9001 certified. The Biosafety and Biosecurity Division played a significant role in informing national legislation for the Hazardous Biological Agent Regulations of the Occupational Health and Safety Act 85 of 1993, and the regulations related to the registration of Microbiology Laboratories of the National Health Act 61 of 2003. The Division supported the upgrade of the BSL 3 and BSL 4 facilities and assisted the NDOH with inspections of BSL 3 facilities in the provinces. The division developed train-the-trainer material on Facilities and Safety: Biosafety and Biosecurity for the Southern African Development Community training for Minimum Standards for Laboratories in the SADC Region. The division represented South Africa at the Nuclear Threat Reduction Bio Global Biosecurity Dialogue in London and at the 5th Global Health Security Agenda Ministerial Meeting in Bali, Indonesia on behalf of NDOH.

International Association of National Public Health Institutes

The NICD retained its membership with the International Association of National Public Health Institutes (IANPHI) that links and strengthens public health institutes, and continues to chair the Africa IANPHI network. In this role, the Deputy Director supported the roll-

out of the Africa CDC strategic objectives; was part of the international team that drafted the Africa CDC Framework for Public Health Workforce Development and the NICD staff participated in multiple training initiatives offered by the Africa CDC. The NICD continues to collaborate with various forums of the Regional Collaborating Centre in Zambia aimed at improving global health security in SADC. Network collaborations have grown with global public health institutions, formally through a memorandum of understanding with China CDC and through maintaining research and training collaborations.

Communications

The Communications Unit expanded its capacity by employing an Editorial Specialist and a Web Content Specialist. During the year under review, media coverage grew and the unit was instrumental in the publication of 11 opinion pieces in various publications and monitored over 2 021 news items and articles.

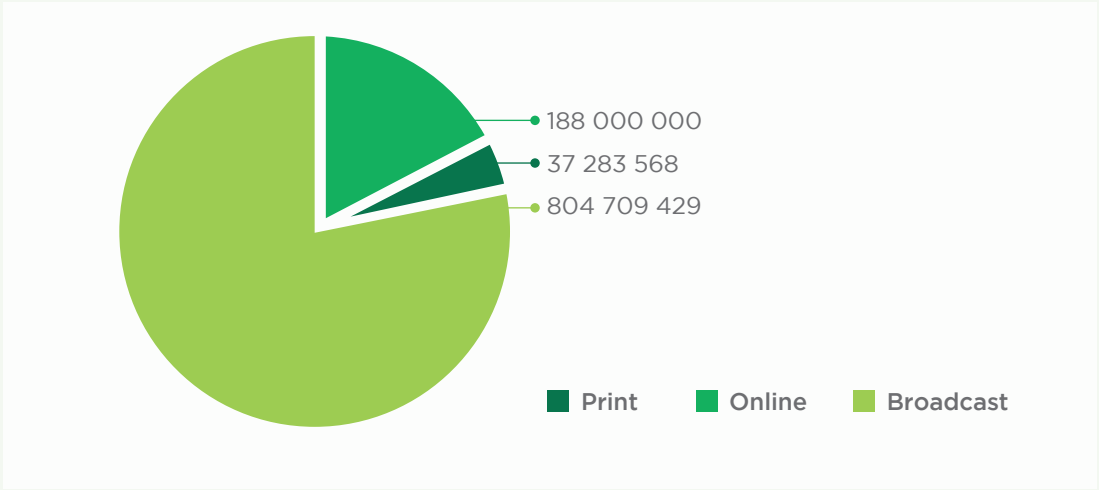


Figure 1. Media reach for the financial year 2018/19.

The NICD Pulse, an internal newsletter launched in May 2018, published four issues with a reach of 657 email users per issue. The integrated electronic newsletter, Round-Up, summarised weekly communicable diseases news and 18 pieces were circulated to staff on a weekly basis via email. Four issues of the Science Focus issues were published, profiling research excellence within the institution on a quarterly basis, with a reach of 1 657 per issue.

An integrated approach on the use of social media platforms has also enabled the institution to monitor and dispel rumours concerning communicable diseases outbreaks. Facebook reached over 54 800 users and continued to grow while Twitter reached over 335 700 users. A total of eight videos were produced, and nine audio podcasts were recorded. In addition, 72 info-graphics were produced; these were aimed at strengthening reach on communicable diseases information and engagement. The NICD's website (www.nicd.ac.za), a primary entry point for visitors, was revamped and attracted more than 109 600 visitors accessing the site under the year in review, moreover the website holds a significant repository of communicable diseases content.

Information Technology

The stability of the NICD IT infrastructure and systems availability exceeded 99% and the user satisfaction scores improved by 34% from the previous year to a final satisfaction rating of 77%. With a full complement of staff, a new local area network was established with an increase in local data throughput to 10 Gbps. Skype for Business was implemented to enable efficient unified communications and the specialist call phone for the NICD hotline was fully digitised, and a new mobile application was developed.

A number of new innovations were developed to streamline data collection for the NCR, private laboratories data and medical aid data acquisition and the replacement for the GERMS-SA Access databases.

South African Field Epidemiology Training Programme

The South Africa Field Epidemiology Training Programme (SAFETP), a 2-year, competency-based training programme, was initiated in 2006, as a collaboration between the NDOH, the NICD and the U.S. CDC, to build field epidemiology capacity for the country. SAFETP uses an established applied epidemiology curriculum, providing an accredited Masters in Public Health (MPH) degree from the University of Pretoria (UP) and a Masters in Science (MSc) degree from the University of the Witwatersrand (Wits), with mentored competency-based practical field experience. To date, the programme has trained 94 health professionals of which 83 have graduated. The programme is affiliated to the regional network AFENET - African Field Epidemiology Network and the global network TEPHINET – Training Programs in Epidemiology and Public Health Interventions Network.

In 2018, SAFETP had an intake cohort of 11 first-year and seven second-year residents. Seven residents from the 2016 cohort graduated with an MPH on April 2018, and one resident graduated in September 2018. The MPH attainment rate has increased from 51% in 2011 to the current rate of 88%.

SAFETP also builds epidemiology capacity for the provincial Departments of Health through the Frontline short course in-service training. In the year under review, 54 participants from Gauteng and Free State Departments of Health and 12 participants in Lesotho for the Lesotho Ministry of Health were trained.

SAFETP residents were involved in 25 outbreak investigations, conducted 15 large database analyses and completed six surveillance evaluation projects.

Honours and Awards

Ms Itumeleng Moema won best poster presentation at the EIS conference. Her poster was entitled 'Outbreak of culture-confirmed *Candida auris* bloodstream infection in the neonatal unit of a public-sector hospital, South Africa, July through September 2017.'

Second-year resident, Poncho Bapela, won an award for the second best oral presenter at the AFENET Conference in Maputo for her presentation, 'Investigation of clusters of malaria cases in Gauteng Province, South Africa – September to October 2017.'

Research Output

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Special Projects

SAFETP was awarded accreditation from TEPHINET in November 2018, as one of six accredited programmes in Africa.

The TEPHINET Programme Directors meeting was co-hosted by SAFETP and took place at the NICD PRF Auditorium and seminar rooms. There were 65 participants from FETPs, regional networks, partners and collaborators.

In November 2018, six staff members from the Ghana Field Epidemiology and Laboratory Training Programme (GFELTP) visited SAFETP for faculty exchange and to learn more about the South African programme.

There has been extensive engagement with the South African Local Government Association to have environmental health practitioners trained in epidemiology and it has been agreed that the provinces will host Frontline training in 2019.

Conferences

International conferences: 7
National conferences: 5

Centre for Emerging Zoonotic and Parasitic Diseases

1. Background

Centre Head
Prof Janusz Paweska

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, particularly those classified as zoonotic BSL 3 and BSL 4 agents. Many of these agents causing high rates of morbidity and/or mortality are of great public health concern, and require rapid detection to institute timely outbreak control measures and patient management.

Diagnostic, surveillance and research activities of the Centre are focusing primarily on viral haemorrhagic fevers (e.g. Ebola and Marburg diseases, Lassa fever and Lujo hemorrhagic fever), arthropod-borne diseases (e.g. Rift Valley fever (RVF), Crimean-Congo haemorrhagic fever (CCHF), yellow fever, malaria, plague), rabies, rabies-related infections, anthrax, botulism, brucellosis, leptospirosis, parasitic opportunistic infections, diarrhoeal disease in <5 year-old children, schistosomiasis and soil-transmitted helminthic diseases.

The 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. The CEZPD serves as an internationally recognised resource of expertise for referral diagnostic services, outbreak response and consultations under the mandate of the WHO Regional Reference Laboratory for Plague, and GOARN.

A variety of diagnostic assays performed by the CEZPD is accredited by SANAS for the ISO15189 standard of operation. The CEZPD houses highly specialised laboratory facilities, including the only positive-pressure suit BSL 4 in Africa, a transmission electron microscope, several BSL 3 laboratories and insectaries for housing the vectors of malaria, as well as 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.

2. Surveillance

The Special Viral Pathogens Laboratory confirmed 14 human cases of rabies in South Africa from 1 April 2018 to 31 March 2019. The increase in the number of human cases reported since 2018 was related to the resurgence of dog rabies in the KwaZulu-Natal (n=4) and Eastern Cape (n=7) provinces. In addition, cases were also recorded from the Free State (n=1), Mpumalanga (n=1) and Limpopo (n=1) provinces. In addition, 55 cases of suspected viral haemorrhagic fever were investigated during the report period, including cases referred from Namibia, Kenya and Angola. Three cases of CCHF were identified and reported from the Free State (n=2) and the Northern Cape (n=1) provinces. In addition, a case of vaccine-associated yellow fever was confirmed by laboratory testing.

The Arbovirus Reference Laboratory investigated 402 suspected endemic and exotic arboviral disease cases, including chikungunya, RVF, dengue, Ross River and Japanese encephalitis, with a total of four dengue cases detected in travellers returning from endemic areas with ongoing transmission elsewhere in the world. A number of local arboviral disease cases were detected, namely eight human cases of RVF associated with a highly localised outbreak of the disease in sheep in the Jacobsdal area on the border of the Free State and Northern Cape provinces. These findings highlight the importance of ongoing vigilance, particularly for category 1 (one) NMCs such as RVF.

The considerable public health and economic impacts of arboviruses are expected to continue in the 21st century, given limited domestic and international capabilities for rapid detection, identification, forecasting and controlling of epidemics, and lack of safe, efficacious, and affordable vaccines and chemotherapeutics. Geographic expansion or severe outbreaks of arthropod-borne viral infections, with high health and socio-economic impacts, are challenging public health systems in Africa. Insufficient surveillance and research programmes on vector-borne diseases further complicate this situation.

The majority of urban dwellers live without access to basic services. Poor urban conditions, compounded by social and economic vulnerability, result in health inequities. Despite pressing needs, urban health and urban health equity have not yet emerged as major research and policy priorities, and South Africa, like many other African countries, lag behind in addressing these issues.

There is an urgent need to address the risk of Zika virus introduction and establishment of endemicity in South Africa, considering the widespread presence of the urban vector. To address some of these challenges, the CEZPD undertook active arbovirus surveillance in the northern part of KwaZulu-Natal Province, which was identified as a potential gateway for the introduction of exotic arboviruses from Mozambique. A total of 916 patient samples were collected during the reporting period. Based on testing of hospital and clinic patients with acute febrile illness, probable diseases detected by arbovirus serology include RVF, chikungunya and cases likely related to infection with flaviviruses.

Figure 1. The CEZPD staff met with local arbovirus surveillance nurses in KwaZulu-Natal to discuss training needs on the Zika virus disease and surveillance of other arbovirus infections in the province.

Figure 1A. From the left: Dr Petrus Jansen van Vuren, Dr Liesl de Boni, Ms Veerle Msimang, and Sr Nkosi Thozama from Ngomo Clinic.

Figure 1B. From the left: Ms Veerle Msimang, Mr Mthethwa Mthokozisi, Prof Janusz Paweska and Dr Petrus Jansen van Vuren, Manguzi Hospital, KwaZulu-Natal.

As a part of ongoing active bio-surveillance programme for zoonotic pathogens in local bat populations, 2 237 oral swabs and 1 726 rectal swabs were collected from Egyptian rousette bats at the Matlapitsi cave in Limpopo, in collaboration with the Biosurveillance and Ecology of Emerging Zoonoses (BEEZ) Research Group at the Department of Medical Virology, Faculty of Health Sciences, University of Pretoria. These were tested for the presence of Marburg and Ebola virus RNA. Both serological and virological results indicate active transmission of Marburg virus in the bat colony.

Figure 2. Staff of CEZPD and of BEEZ, University of Pretoria, dissecting (Figure 2A) and trapping (Figure 2B) rousette bats in BSL 3 personal protective equipment at the Matlapitsi cave in Limpopo Province, South Africa.

The Special Bacterial Reference Laboratory continued surveillance for plague in susceptible rodent populations in the City of Johannesburg and the Nelson Mandela Bay Municipality (Coega area), in order to alert public health authorities to the possibility of increased human plague risk. More than 1 200 rodents were tested for plague anti-F1 antibodies, of which a four-striped mouse trapped in April 2018, within the Port of Ngqura, tested positive. The trapping site was approximately 2.5 km from the epicentre of the 1982 outbreak. This confirms that plague is still endemic in this area and that public health authorities should remain vigilant.

Continued surveillance of rodent and vector populations is of paramount importance. Two surveillance studies, involving patients with acute febrile illness, were conducted in collaboration with GERMS. The first study, based at Hluvukani Clinic in Mpumalanga Province, focuses on various bacterial and viral zoonoses to understand the burden of these diseases in rural South African communities. A possible leptospirosis outbreak in the Welverdiend community was reported to public health authorities after a cluster of positive cases was detected from the same area. A second study focusing on brucellosis was initiated at Tshepong Hospital in the North West Province and at Universitas Private Hospital and Pelonomi Hospital in the Free State Province. The study aims to investigate the prevalence and characteristics of brucellosis among patients with febrile illness presenting to sentinel healthcare facilities in high-risk areas.

The Parasitology Reference Laboratory (PRL) participates in sentinel site surveillance for diarrhoeal disease in children under five years old. The major parasitic contribution to diarrhoea is *Cryptosporidium hominis*, which, unlike most other cryptosporidial species, is mainly transmitted between humans.

Monitoring of quality of malaria microscopy in provincial malaria control programmes is increasingly important as the country moves towards the elimination of malaria. Nearly 3 000 blood smears from the Mpumalanga Province were tested microscopically and by polymerase chain reaction (PCR).

Routine surveillance by the newly established Reference Laboratory for Antimalarial Resistance Monitoring and Malaria Operational Research (ARMMOR) for markers of antimalarial drug resistance confirmed the absence of molecular markers associated with artemisinin resistance. However, there appears to be strong selection for markers associated with lumefantrine tolerance. This highlights the need for regular and rigorous drug efficacy monitoring to ensure effective malaria treatments are in place, and especially to help achieve South Africa's malaria elimination goals.

A total of 2 181 *Anopheles* mosquitoes was referred to the Vector Control Reference Laboratory from sentinel sites in the KwaZulu-Natal, Mpumalanga and Limpopo 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

The NICD's core transmission electron microscopy laboratory contributed to diagnostics and research at the CEZPD and the Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses (CHARM), the latter for descriptions of two species of *Blastomyces* in South Africa. Within the pathogenic domain of the CEZPD, the ultrastructure of *Burkholderia pseudomallei* and a microsporidium causing ocular keratitis took centre stage, with diagnostic input based on viral screening of clinical samples and cultured isolates (Figure 3). Measurements of both capsular thickness and toxin-containing membranous vesicles of paired *Streptococcus agalactiae* isolates continued.

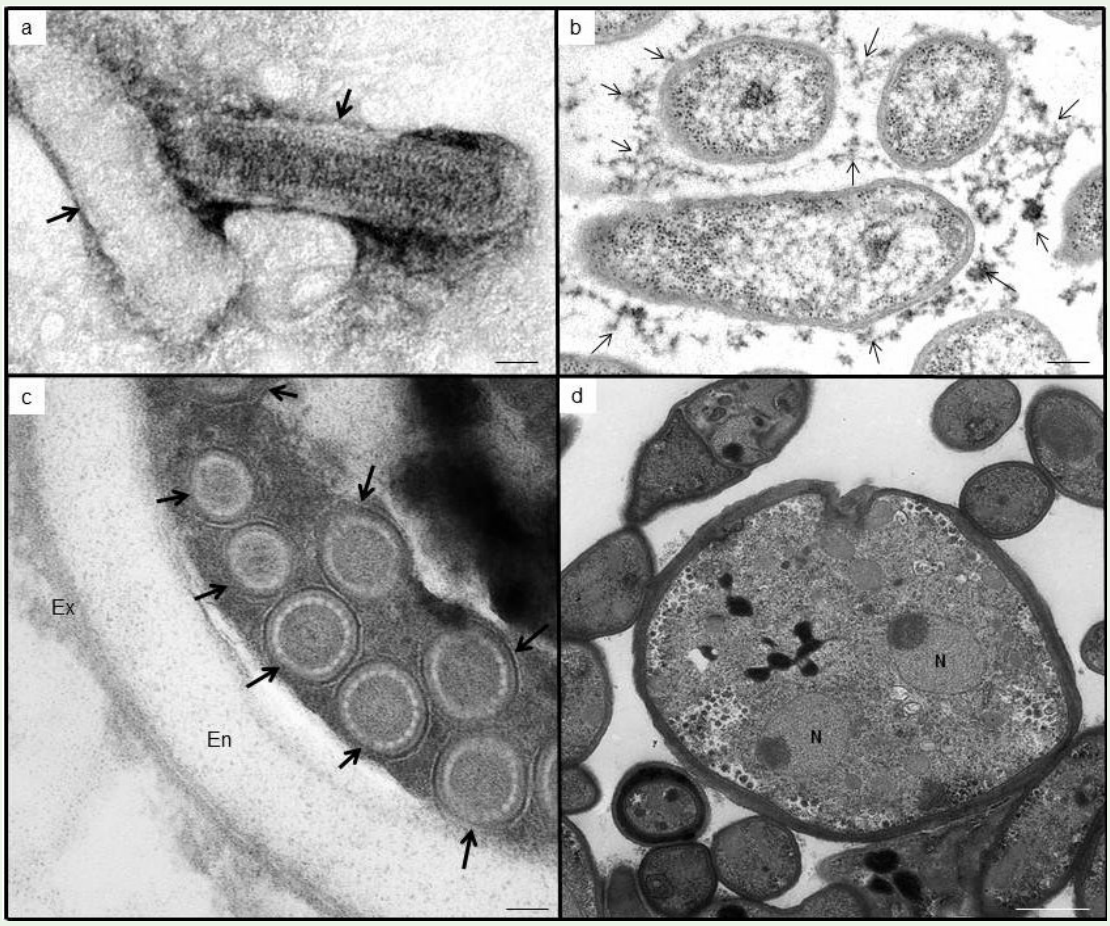

Figure 3. Transmission electron microscopy:

a. A negatively-stained virus belonging to the Rhabdoviridae, illustrating the characteristic enveloped, bullet-shaped virions (arrows) with a helical nucleocapsid;

a. *Burkholderia pseudomallei* cells sectioned and processed to illustrate the delicate capsule (arrows), a known virulence factor;

b. Section through a microsporidian spore illustrating the characteristic exospore (Ex) and endospore (En) wall layers, and the coils of the polar filament (arrows); and

a. Section through a developing, multinucleate (N), a diaspore-like cell of *Blastomyces* spp. showing enlargement and thickening of the wall, relative to the surrounding hyphal profiles.

This dimorphic fungus was grown at 350C to initiate mould-yeast conversion. Scale bars (a) = 30 nm; (b) = 250 nm; (c) = 50 nm; (d) = 1.3 Qm.

Policy contributions

Contributions were made to several national policies, as follows:

- The National One Health Strategy of South Africa, 2019-2024. This document outlines the strategic objectives of the NDOH, Department of Agriculture, Forestry and Fisheries (DAFF) and the Department of Environmental Affairs (DEA) to achieve improved collaboration and cooperation for improved health outcomes in South Africa;
- The NDOH Strategy for the Elimination of Canine-Mediated Human Rabies in South Africa, 2019-2030. This document outlines the strategic objectives of the DAFF and NDOH for the control and prevention of rabies in South Africa;
- Revision of national rabies post-exposure guidelines was submitted to the National Essential Medicines List Committee. The revised guidelines were accepted and adopted in the Standard Treatment Guidelines and Essential Medicines List;
- A review of the Hazardous Biological Agent Regulations was conducted for the Department of Labour (DOL);
- The National Vector Control Strategy;
- The guidelines on management and control of human anthrax in South Africa;
- Participation in the One Health Day Symposium themed: 'One Health in Research and Education to Drive Policy in South Africa;'
- Addition of single low-dose primaquine, a gametocytocide, to standard malaria treatment in districts nearing malaria elimination;
- Based on local safety and efficacy data generated by ARMMOR in collaboration with Prof Karen Barnes from the University of Cape Town, the Malaria Directorate received approval from the South African Health Products Regulatory Authority (SAHPRA) to included single low-dose primaquine in its suite of elimination interventions. In January 2019, with the assistance of ARMMOR and the University of Cape Town, this policy was rolled out at 68 selected health facilities in Nkomazi Sub-District, Mpumalanga and uMkhanyakude District in KwaZulu-Natal;
- Vector control for South Africa's malaria elimination strategy, 2019 - 2023. This policy will guide South Africa's malaria vector control activities and is designed to maintain and improve its current 95%+ success rate of reducing the country's malaria incidence;
- Assessment of the production and use of dichloro-diphenyl-trichloroethane (DDT) and its alternatives for disease vector control. This report is produced under the auspices of the United Nations Environment Programme (UNEP) according to the terms of the Stockholm Convention on persistent organic pollutants (POPs).

Outbreaks

A localised outbreak of RVF in sheep was reported by the DAFF in May 2018. Follow-up investigation of residents on the affected farm revealed infection of eight farm workers that were involved in the handling of infected animals or their products. None of the patients developed any severe sequelae, and only reported mild flu-like symptoms. Although the outbreak was very small and localised, and occurred shortly before winter conditions set in, it served as a warning of the active circulation of RVF virus in the area and highlighted the

Figure 4A. Prof Janusz Paweska (left) and Dr Petrus Jansen van Vuren (right) visiting a sheep farm in Jacobsdal District in the Free State Province in South Africa that was affected by Rift Valley fever outbreak in mid-May 2018.

Figure 4B. Interviews and collecting blood for Rift Valley fever serology testing from local farming communities in the Free State Province, where sheep are the main livestock species and where major Rift Valley fever outbreaks occurred historically.

need for increased vigilance during the high-risk period of late summer and early autumn. The first case of human melioidosis in South Africa was reported in 2018. Melioidosis is a highly pathogenic disease caused by the intrinsically antimicrobial resistant bacterium, *Burkholderia pseudomallei*. A 36-year-old man in Pietermaritzburg, KwaZulu-Natal Province, presented with dizziness, nausea, weakness, coughing, and inability to walk. He was admitted to hospital with pneumonia and despite intensive medical care, he demised 11 days later. The exact source of the infection of the case is unknown, but the patient was a construction worker with possible occupational exposure to contaminated soil or water. This case and the previously reported animal case (in 1995) illustrate that improved local awareness of melioidosis is required.

The Parasitology and Vector Control reference laboratories investigated 11 cases of odyssean (also known as taxi or luggage) malaria in Gauteng Province. The first cluster occurred at Orange Farm, south of Johannesburg. Thanks to prompt diagnosis by the hospital laboratory, which examined a blood smear when a low platelet count was observed, all three cases were treated immediately and recovered fully. Unfortunately, the same was not true for the second cluster of eight cases in Mogale City, West Rand District, in which four deaths occurred. Delays in recognising odyssean malaria occurred due to unreliable history and difficulty in tracing family members. Although no malaria vector mosquitoes were found during site investigations, it is most probable that infected mosquitoes transported in vehicles from endemic zones, were responsible for transmission.

Screening of stool samples by the electron microscope laboratory confirmed the non-viral aetiology of the necrotising enterocolitis outbreak at the Rahima Moosa Mother and Child Hospital.

3. Research activities

Investigation of paramyxoviruses in rousette bat population from South Africa and description co-circulation and excretion dynamics

NICD investigators: J Weyer and JT Paweska.
Collaborators: W Markotter (University of Pretoria) and M Mortlock (University of Pretoria).
Funding: Co-funded by the Medical Research Council (MRC), Centres for Disease Control and Prevention (CDC) (USA), the NRF and Poliomyelitis Research Foundation (PRF).

Paramyxoviruses include important zoonotic viruses such as Nipah, Hendra (*Henipavirus*) and Sosuga (*Pararubulavirus*) viruses. In the past decade, the presence and diversity of many paramyxoviruses, hosted by different bat species, became evident. In this study we describe the presence and diversity of paramyxoviruses, specifically belonging to the *Orthorubula-*, *Pararubula-* and *Henipavirus* genera. In addition to the description of these viruses, including viruses that are genetically closely related to mumps and human parainfluenza 2 viruses, the co-circulation and excretion of these viruses are reported. Periods of increased virus excretion in urine was found, correlating with certain phases of the reproductive cycle and the availability of immune naïve individuals in the bat population in question. It is argued that this period of increased viral excretion may provide a high-risk period for transmission of these viruses to livestock, wildlife and human populations that may come in contact with these bats and their excretions.

Evaluation of diagnostic capacity for spotted fever rickettsiosis in South Africa

NICD investigators: A Trataris-Rebisz, J Rossouw, J Frean and J Weyer.
Collaborator: W Markotter (University of Pretoria).
Funding: NHLS Research Trust.

Spotted fever rickettsiosis, or tick bite fever (TBF), is a very common infectious disease in South Africa. This study investigated the availability and repertoire of laboratory tests for investigating TBF in South Africa. A self-administered questionnaire was used to determine tests offered in both the private and public health sectors. It was found that testing for TBF was readily available from private and public sector laboratories, but that there was no standardisation of tests or interpretation of tests offered. In the public sector no PCR testing was available for TBF, which complicates the investigation of acute cases. In addition, inter-laboratory comparison (ILC) for TBF serology was performed to determine the performance of laboratories offering these tests routinely. The outcome of the ILC indicated varied performance and interpretation of serological results for TBF. The study concluded by indicating the need for improvement of quality and standardisation of serological testing for TBF in South Africa. The utility of ILC to identify problem areas in serological testing for TBF is highlighted, and laboratories in South Africa are encouraged to use it to improve the quality of testing.

Phylodynamic analysis of Ebola disease in Sierra Leone, 2014-2015

NICD investigators: P Jansen van Vuren, J Paweska, A Grobbelaar, M Allam, A Ismail, C Le Roux, J Weyer, N Moolla, N Storm and J Kgaladi.
Collaborators: J Ladner, M Wiley, S Lovett, M Sanchez-Lochart, G Palacios from the (United States Army Medical Research Institute of Infectious Diseases (USAIMRIID) and O Conteh (Sierra Leone Ministry of Health and Sanitation).

A total of 218 previously uncharacterised Ebola virus genomes were generated from confirmed Ebola disease patients in Sierra Leone, 2014-2015. The newly characterised genomes improved coverage of available sequence data for high transmission periods, to gain further insight in the transmission dynamics in Sierra Leone. Six districts in Sierra Leone that contributed significantly to the dispersal of the virus by acting as hubs or sources, and therefore prolonged the outbreak, were identified (Figure 5). Correlations were found between case numbers, inter-district transmission events and district population sizes, confirming these factors as drivers of the outbreak.

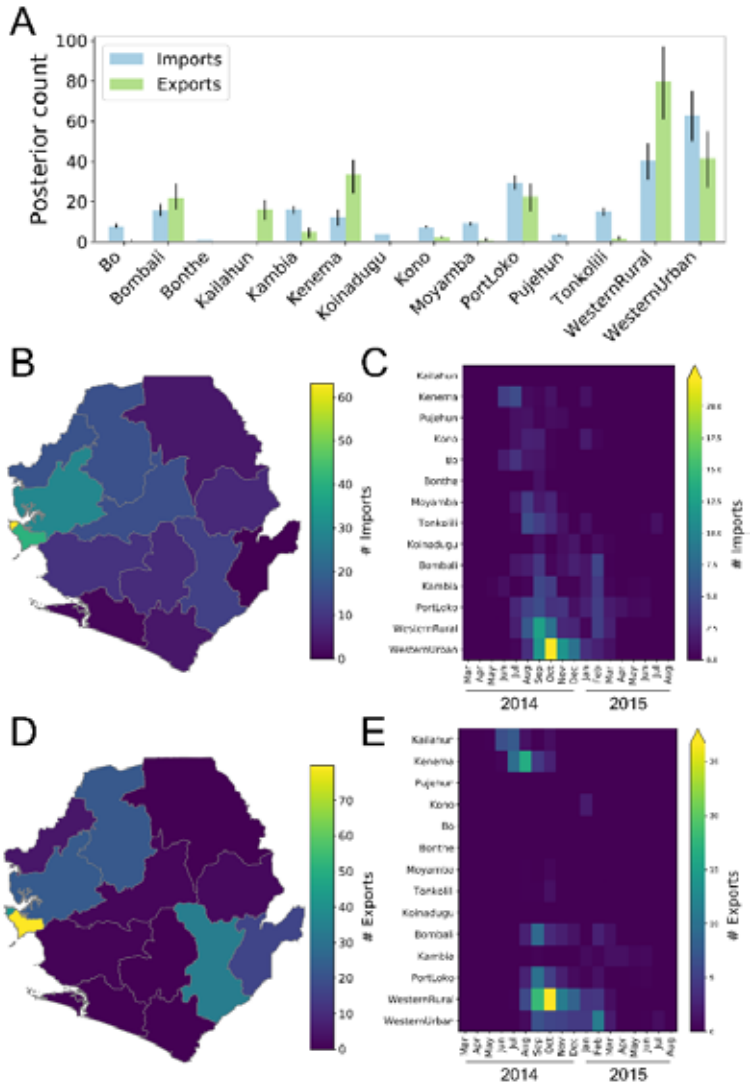

Figure 5. Sink-source dynamics of Ebola disease transmission in Sierra Leone, 2014-2015.

Identifying the entomological drivers of malaria transmission

NICD investigators: B Brooke, G Munhenga, S Oliver, Y Dahan-Moss, M Kaiser, P Tshikae, L Koekemoer, M Coetzee
Collaborators: LEO Braack (University of Pretoria) and the late F Mbokazi (Mpumalanga Malaria Control Programme).

The identification of *Anopheles* mosquitoes to species level is a fundamentally important precursor to incriminating specific populations in the transmission of malaria and assessing their susceptibilities to insecticide. The complexities of this process and the potential for misidentifications were carefully assessed and presented to the international vector control community through various forums. The necessity for accurate species identification was highlighted by data showing the changing distribution and abundance of the malaria vector *Anopheles merus* in Mpumalanga Province, and by the discovery of a population of *Anopheles rivulorum*-like, a little-known species that may be a malaria vector in Limpopo Province.

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 polluted by herbicides and metals, and the development of resistance to insecticides. Recent data show that larval exposures to herbicides and heavy metals can affect the insecticide susceptibilities and life history traits of adults of the major malaria vector species, *Anopheles arabiensis*, often leading to modified longevity and enhanced expressions of insecticide resistance.

Figure 6A. Activities that formed part of the sterile insect technique awareness campaign.

Figure 6B. Setup of mosquito traps for an *Anopheles arabiensis* population estimation in Mamfene, Jozini, in northern KwaZulu-Natal, South Africa.

4. Teaching and training

a. Undergraduate

The CEZPD staff provided and contributed to the following teaching and training activities:

- NICD Short Course for Registrars;
- NICD Virology Intensive Course for Registrars;
- NICD Medical Scientist Intern Rotation for Virology and Microbiology;
- Diploma in Tropical Medicine and Hygiene students (Universities of the Witwatersrand and London), and veterinary students (University of Pretoria);
- One Health Module for veterinary students (Faculty of Veterinary Medicine, University of Pretoria);
- The CEZPD staff also provided several guest lectures on different occasions, which were included, but are not limited to, infectious disease specialists' seminars, tutorial sessions at the Department of Medical Virology, University of Pretoria and South African Society of Travel Medicine (SASTM) Travel Medicine Course 2018, collaborators and research fellows;
- In addition, 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), 7 - 18 May 2018, and field training was conducted in Zimbabwe and Manhica Province in Mozambique as part of a WHO Vector Surveillance Capacity Building project; and
- Prof Basil Brooke participated in the Science of Eradication: Malaria leadership development course at Harvard Business School, Boston USA, 24 – 29 June 2018.

Figure 7A. Training of international research fellows and new contract researchers in serological diagnosis of Rift Valley fever for the One Health Project on Rift Valley fever in the Free State Province. From left to right: Dr Mindy Rostal (Eco-health Alliance, United States of America) and Mrs Danai Kwenda performing enzyme-linked immunosorbent assay for the detection of immunoglobin G antibody against the Rift Valley fever virus.

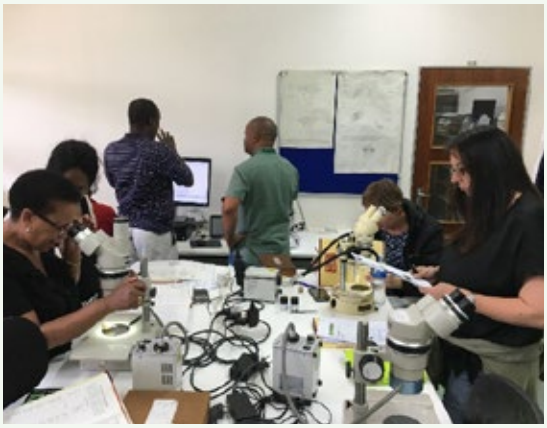

Figure 7 B. Training workshop on the identification of the Rift Valley fever virus mosquito vectors.

b. Postgraduate

- 27 postgraduate students were enrolled: Ten MSc and 17 PhD; and
- Six postgraduate students completed their studies: Two BSc Hons, one MSc and three PhD.

Figure 8. Dr Gaby Monteiro after the 2019 autumn graduation ceremony at the University of Pretoria with Prof Janusz Paweska, her PhD promoter.

Co-supervision was provided by Dr Petrus Jansen van Vuren and Prof Jeroen Kortekaas. Dr Gaby Monteiro obtained her PhD degree with specialisation in Veterinary Science: Veterinary Tropical Diseases based on her thesis entitled 'Mutation of adjacent cysteine residues in the NSs protein of Rift Valley fever results in loss of virulence in a murine model infection.'

c. Professional development

- Dr Jacqueline Weyer graduated with an MPH cum laude from the Sefako Makgatho Health Sciences University; and
- Dr Petrus Jansen van Vuren received a C2 rating from the National Research Foundation.

Awards and recognitions

- Prof Basil Brooke was re-elected as the WHO representative for the UNEP DDT Expert Group, and elected as a member of the Academy of Science of South Africa (ASSAf). He was a member of the Scientific Committee for the Annual Malaria Research Conference, hosted by the NDOH and the Southern African Development Community Secretariat 2017/2018. He officiated as a plenary speaker during the Pan Africa Mosquito Control Association Conference in Zimbabwe 2018. He also received an award for achievement in research from Wits;

- Dr Shüné Oliver received an award for achievement in research from Wits;

- Dr Givemore Munhenga was a member of the of the Scientific Committee for the 5th Pan Africa Mosquito Control Association Conference in Zimbabwe 2018 and a member of Vector Borne Diseases Epidemics Preparedness and Vector Control in Africa;

- Prof Janusz Paweska was re-elected as Deputy Director of the Southern African Centre for Infectious Disease Surveillance (SACIDS) for the next two-year term, as well as a member of the WHO Global Outbreak Alert and Response Steering Committee, for the next four-year term. He was also invited as the keynote speaker of the 59th Annual Scientific Meeting of the Japanese Society of Tropical Medicine, which took place in Nagasaki, Japan in 2018 and of the One Day Health Symposium themed: "One Health in Research and Education to Drive Policy in South Africa," which took place in Pretoria, South Africa in 2018.

5. Research outputs

Journal articles and articles in books

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Conferences

International congresses: 11
Local congresses: 7

Centre for
Enteric Diseases

1. Background

Centre Head
Dr Juno Thomas

The Centre for Enteric Diseases (CED) focuses on providing information to better understand, manage and prevent enteric diseases in South Africa. This broadly includes:

- Foodborne diseases, which have recently come under the spotlight locally and are increasingly recognised as a threat to public health and food safety and security globally;
- Waterborne diseases, which are outbreak-prone and associated with the use of unsafe water;
- Rotavirus, which is a vaccine-preventable disease of childhood; and
- Priority enteric diseases under routine surveillance (including typhoid fever, cholera and listeriosis).

Information and expertise are built from various activities, including surveillance, public health-oriented research, outbreak investigation and response, reference laboratory services, regional technical and laboratory testing assistance, and international collaborations.

The Centre provided strategic data, technical support and policy advice to the NDOH and other major stakeholders, including the WHO, during the listeriosis post-outbreak Emergency Response Plan (ERP), following the identification of the outbreak source, from April to July 2018. The Centre played a key role in the investigation of the listeriosis outbreak, which received much attention from the general public and international scientific community, and afforded an opportunity to showcase the scope of epidemiological and laboratory activities within the Centre and the institute. A national listeriosis surveillance programme was launched in the wake of the outbreak, which enabled monitoring of disease trends and early detection of possible outbreaks.

Nationally, the Centre actively participated in outbreak investigations for more than 20 other outbreaks, providing technical and epidemiological support as well as performing diagnostic and reference laboratory testing. The Centre expanded the use of whole genome sequencing (WGS) in routine listeriosis surveillance and in foodborne disease outbreak investigations, enabling case linkage and source identification whilst also building local expertise in the use of this technology. In response to the critical need to improve enteric disease outbreak detection and investigation within the region, the Centre assisted with outbreak investigations in three neighbouring countries and partnered with the WHO to train laboratorians and epidemiologists from seven countries.

2. Surveillance

a. Acute diarrhoeal disease surveillance

Monovalent rotavirus vaccine was introduced into the expanded programme on immunisation in South Africa in 2009 and led to an approximate 50% reduction in rotavirus hospitalisation in young children. Globally, there is concern that the prevalence of non-vaccine genotypes may increase, and subsequently, jeopardise vaccine effectiveness. Continued surveillance of rotavirus genotypes is required to elucidate what effect rotavirus vaccination has on circulating rotavirus strains in the country.

Existing diarrhoeal disease sentinel surveillance in children <5 years of age continued at four hospital sites (Chris Hani Baragwanath Academic Hospital and Dr George Mukhari Hospital in Gauteng Province; Pelonomi Hospital in Free State Province; and Dora Nginza Hospital in Eastern Cape Province). Rotavirus was detected in 15% (31/202) of cases, and G3P[8] strains predominated. Other enteric viruses detected in cases included norovirus GII (19%, 38/202), adenovirus (12%, 24/202), sapovirus (5%, 11/202), astrovirus (3%, 6/202) and norovirus GI (2%, 4/202).

b. National listeriosis surveillance

Following the 2017/2018 listeriosis outbreak, national surveillance was instituted. Listeriosis is a category 1 (one) notifiable medical condition (NMC) and each case is followed up by the Centre upon receipt of the NMC alert. A standardised case investigation form is used to record demographic and clinical data, and patients are interviewed to obtain a comprehensive food history. Isolates from patients routinely undergo WGS, facilitating the early detection of potential outbreaks.

Since the second week of April 2018, ≤5 new cases of listeriosis per week have been reported, which is well within the expected range for sporadic cases. No new suspected outbreaks have been identified to date. The Centre continued to perform PCR on samples referred from NHLS laboratories nationwide for *Listeria monocytogenes* to assist with diagnosis in problematic cases; a total of 247 samples were tested.

3. Policy contributions

The cholera strain responsible for the outbreak in Zimbabwe and subsequent imported cases was resistant to all antibiotics recommended in the current South African national cholera management guideline. A revised treatment recommendation and motivation for including azithromycin as a treatment option was drafted, and endorsed by the NDOH .

4. Outbreaks

South Africa

The Centre played a leading role in the national listeriosis outbreak investigation and continued to provide strategic data, technical support and policy advice to the NDOH and other major stakeholders, including the WHO, during the listeriosis post-outbreak ERP from April to July 2018.

The Centre routinely follows up on alerts of suspected enteric disease outbreaks and cases of epidemic-prone diseases reported through NMC or other sources, and provided epidemiological and laboratory testing support for over 20 outbreaks countrywide. A diverse range of outbreaks were reported, providing opportunities to identify recurring outbreak themes and risk factors:

- The importation of cholera remains a threat, with frequent outbreaks reported in neighbouring countries;
- In foodborne disease outbreaks where causative pathogens were identified, nontyphoidal salmonellosis was the most common culprit, and in most situations linked to foods of animal origin. This highlights the need to explore local surveillance strategies in a one health context to improve outbreak detection and investigation and inform food safety priorities. Health education on food safety practices in the home is an often neglected and underplayed but critical intervention that needs attention;
- The waterborne outbreaks described below are just two examples of an alarming trend of localised waterborne diarrhoeal outbreaks, likely linked to contaminated municipal potable water supply. Aging and poorly maintained water treatment and water supply infrastructure and erratic water quality monitoring culminate in diarrhoeal disease outbreaks. Additional water safety challenges are associated with the improper treatment of sewage resulting from aging infrastructure, poor maintenance, and increasing volumes of sewage due to population expansion without adequate sanitation planning; and
- Enteric disease outbreaks in healthcare facilities underscore the need for enhanced food safety for vulnerable people, and the importance of basic infection prevention and control (IPC) practices to prevent transmission.

Selected outbreaks are summarised below

a. Cholera

Three cases were reported. The first two cases (an adult and her husband who recently returned from Zimbabwe) were identified in October 2018, and both patient isolates were confirmed to be toxin-producing *Vibrio cholerae* O1 serotype Ogawa, which matched the Zimbabwean outbreak strain on WGS analysis. The third case, a male migrant worker recently returned from Zimbabwe, was identified in November 2018. The patient's isolate was confirmed to be toxin-producing *V. cholerae* O1 serotype Inaba and unrelated to the Zimbabwean outbreak strain. This was most likely an imported case, but the origin was not definitively established.

b. Foodborne disease outbreaks

- *Salmonella* Bardo outbreaks in Kwazulu-Natal Province, from July to September 2018. At least three separate *S.* Bardo outbreaks linked to the consumption of goat meat, following traditional slaughter in two districts, were identified. Thirteen isolates (from case-patients and food samples) were available for molecular typing at the CED and were shown to be genetically linked. A joint investigation by the Centre, the district DOH and the DAFF was launched to determine the provenance of the goats and elucidate common sources of *S.* Bardo zoonotic infection.
- *Salmonella* Enteritidis outbreaks in KwaZulu-Natal, in November 2018. Two concurrent outbreaks (one in patrons of a restaurant, and one in children attending a day care facility) in a single district were investigated. Isolates from ill patients with epidemiological links to the restaurant (n=10) and the day-care facility (n=3), were shown to be probably genetically related. *S.* Enteritidis was reportedly isolated from the eggs and hollandaise sauce collected at the restaurant, but testing was done at a private food laboratory and the isolates were not available for molecular typing.
- Shiga toxin-producing *Escherichia coli* (STEC) cluster in a household in Gauteng Province, in November 2018. Seven of the 13 household members developed gastroenteritis, with STEC confirmed in two cases. The source of the infection could not be established.
- *Salmonella* Enteritidis outbreak linked to a restaurant, in Free State Province in February 2019. Nine adults presented to a hospital with gastroenteritis. Stool samples from five patients yielded *Salmonella* spp. on culture; two available isolates were serotyped as *S.* Enteritidis. Food history interviews revealed that all patients ate at a common restaurant, and that eight of them ate the 'black ice cream' dessert. Samples of black ice cream collected from the restaurant and from the manufacturer tested negative for *Salmonella* spp., and the source of contamination was not identified. However, the ice cream was made using raw eggs, which was a likely source of contamination, as has been reported previously in similar outbreaks.
- *Salmonella* Heidelberg outbreak in a household in Limpopo Province, in February 2019. Seven patients presented to hospital with gastroenteritis, including a one-year-old child, who later died. The common food exposure was cooked fresh green vegetables (delele) served with pap. No food items were available for testing. *Salmonella* spp. was isolated from stool samples of three cases, of which two isolates were available for serotyping and confirmed as *Salmonella* Heidelberg. The source of the outbreak was not identified.

c. Waterborne disease outbreaks

- Diarrhoeal disease outbreak in Mpumalanga Province from July – August 2018. More than 1 700 adults and children presented with diarrhoeal disease to healthcare facilities in two areas of one subdistrict. A total of 298 stool samples were sent to the CED for multiplex PCR testing. The most commonly detected pathogens were rotavirus (34%, 103/298), *Cryptosporidium* spp. (20%, 60/292), *Shigella* spp. (17%, 51/298), norovirus GI & GII (13%, 38/298), *Giardia lamblia* (6%, 18/298) and adenovirus (5%, 16/298). Contaminated potable water supply was identified as the likely cause of the outbreak.
- Diarrhoeal disease outbreak in KwaZulu-Natal in March 2019. A total of 535 adults and children presented with diarrhoea to healthcare facilities in one municipal area. Forty-one stool samples were sent to the CED for multiplex PCR testing. The predominant pathogens detected included norovirus (39%, 16/41), *Shigella* spp. (34%, 14/41), rotavirus (32%, 13/41), adenovirus (15%, 6/41) and astrovirus (12%, 5/41). Contaminated potable water supply was identified as the likely cause of the outbreak.

d. Healthcare-associated outbreaks

- Shigellosis outbreak at a residential facility for disabled adults in Gauteng Province, in December 2018. Four cases of *Shigella flexneri*, with severe symptoms, were identified. The index case was a weekend-only resident who was ill on arrival for a weekend stay, and person-to-person transmission occurred. Strengthened IPC measures halted the outbreak.
- Shigellosis outbreak at a residential facility for neurologically disabled children in Gauteng Province, in January 2019. Six children were hospitalised with shigellosis, one of whom died. The epidemiological data suggested person-to-person transmission. Strengthened IPC measures halted the outbreak.
- *Salmonella* Enteritidis outbreak at a hospital in the Western Cape Province in November 2018. In the same week, six hospitalised adult patients developed *Salmonella* spp. gastroenteritis. The only common exposure or risk factor was meals supplied by the hospital. Isolates from all six patients were received for typing and were identified as *S.* Enteritidis. Available food samples from the hospital kitchen were tested at a private food laboratory, and *S.* Enteritidis isolated from a chicken sample. *S.* Enteritidis was isolated from one of 34 hospital food handlers screened.

Regional support

In an ongoing effort to actively support enteric disease diagnosis and management in regional countries with limited diagnostic capacity, the Centre performed laboratory testing to assist with detection of pathogens in outbreaks of unknown aetiology, as well as confirmatory testing and molecular characterisation of outbreak strains.

- Cholera outbreak in Zimbabwe in October 2018. Twelve *Vibrio cholerae* O1 isolates were referred from the National Microbiology Reference Laboratory of Zimbabwe to the CED for molecular characterisation of the outbreak strain. Phenotypic and genotypic characterisation of the isolates, including WGS analysis, was performed. This enabled confirmation of the antibiotic susceptibility profile of the strain and guided antibiotic therapy recommendations.
- Suspected rotavirus outbreak in Botswana, in October 2018. The Centre provided laboratory support to the WHO and the South African Regional Rotavirus Reference Laboratory. Twenty outbreak-related specimens (collected between August and October 2018) and 34 surveillance specimens (collected between September 2017 and March 2018) were screened for viral, bacterial and enteric parasites. Rotavirus was detected in 80% (16/20) of the outbreak specimens. Rotavirus was also commonly detected in the surveillance specimens (41%; 14/34), although adenovirus was detected at higher levels (53%; 18/34).
- Diarrhoeal disease outbreak in Swaziland (Eswatini) in September 2018. The Centre provided laboratory support to the WHO and the South African Regional Rotavirus Reference Laboratory. A total of 51 outbreak-related specimens (collected in August and September 2018) and ten (10) surveillance specimens (collected between January and May 2018) were screened for viral, bacterial and enteric parasites. Rotavirus was detected in most of the outbreak specimens (73%; 37/51) followed by adenovirus (61%; 31/51). In the surveillance specimens, adenovirus was detected most frequently (60%; 6/10).

5. Research activities

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

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

Intussusception is a rare intestinal blockage associated with a human-simian rotavirus reassortant vaccine formulation. While current rotavirus vaccines did not demonstrate an increased risk of intussusception during large-scale vaccine trials, recent studies have indicated a low-level risk of intussusception after vaccine administration. There is currently no data on intussusception risk in African settings. Active surveillance for intussusception cases was implemented in eight South African cities, with the study ending in December 2017. A total of 96% (620/644) of specimens were screened (397 cases and 223 surgical controls) using a Taqman® Array Card (TAC) for various potential pathogens. 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.

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: ANDEMIA network investigators

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 (RTI), gastrointestinal tract infections (GTI) and acute febrile disease of unknown cause (AFDUC). Sentinel surveillance was established in three sites (Kalafong Hospital in Gauteng, and Matikwana and Mapulaneng hospitals in Mpumalanga) and enrolled patients presenting with RTI, GTI and AFDUC syndromes. From July 2018 to April 2019, 244 stool specimens were screened for enteric pathogens using molecular assays. Rotavirus was detected in 17% (41/244), *Shigella* spp. in 14% (31/214), adenovirus in 14% (30/218) and norovirus GII in 13% (31/237) of cases. The study will continue until 2021 and will begin enrolling control patients in the third quarter of 2019.

Whole-genome sequencing and cgMLST of *Salmonella enterica* isolates for surveillance and outbreak investigations

NICD investigators: AM Smith, NP Tau, S Smouse, M Ramudzulu and J Thomas.

As from 2018, whole-genome sequencing (WGS) data for *Salmonella enterica* isolates were uploaded to the EnteroBase website for data analysis, including coregenome multi-locus sequence typing (cgMLST). These included all *Salmonella* Typhi isolates and all outbreak-associated *Salmonella* spp. isolates. WGS data analysis using cgMLST provides phylogenetic context including information regarding genetic relatedness of isolates. These genomic data

complemented epidemiological data during outbreak investigations. In total, the following numbers of isolates were uploaded to EnteroBase: *Salmonella* Typhi (n=88), *Salmonella* Enteritidis (n=23), *Salmonella* Bardo (n=14), and *Salmonella* Heidelberg (n=2).

Whole-genome sequencing analysis of *Vibrio cholerae* O1 isolates from Zimbabwe, 2018

NICD investigators: AM Smith, M Ramudzulu and J Thomas.
Collaborators: F-X Weill (Institut Pasteur, France) and A Tarupiwa (National Microbiology Reference Laboratory, Zimbabwe).

Whole genome sequencing (WGS) was used to investigate *Vibrio cholerae* O1 isolates associated with a cholera outbreak in Zimbabwe, which was first reported in September 2018. A total of 19 outbreak isolates were available for extended laboratory characterisation. All isolates were confirmed as toxin-producing *Vibrio cholerae* O1 Ogawa, and showed multidrug-resistance, including the presence of extended-spectrum-lactamase (ESBL) activity. Analysis of WGS data found the isolates to be highly related and showed the presence of several antibiotic resistance genes, including the ESBL gene CTX-M15. WGS data of isolates was compared against a global collection of cholera isolates, with phylogenetic analysis showing that the Zimbabwe isolates belonged to the T13 sublineage, the most recent cholera lineage introduced into Africa.

6. Teaching and training

a. Undergraduate level
Lectures were presented to health science students.

b. Postgraduate level
Specialised NICD training courses were presented as follows:

- Pathology registrars (microbiology and virology) attending the NICD registrar training course; and
- Medical intern scientists were trained during NICD training course rotations in enteric bacteriology and virology laboratories.
- Other national training included training for SAFETP surveillance and outbreak response courses, and training for the epidemiology courses at Wits.
- International training: The Centre co-hosted a WHO/NICD training course on foodborne disease surveillance and outbreak detection in the context of listeriosis preparedness and response for 16 trainees, from seven African countries, from 15-19 October 2018.

c. Professional development
Eight postgraduate candidates were enrolled: Four PhD and four MSc/MPH. Two postgraduate candidates graduated : One MSc and one MPH.

7. Research outputs

Journal articles, books and articles in books

1. Page NA, Nadan S and Mans J. Viral Gastroenteritis. In: Eslick GD editor. Gastrointestinal diseases and their associated infections. St Louis. Elsevier Health Sciences. 2019: 135-150.

2. Nadan S, Taylor MB, Groome MJ, Cohen C, Madhi SA and Page NA. Epidemiology of human astroviruses among children younger than 5 years: Prospective hospital-based sentinel surveillance in South Africa, 2009-2014. J Med Virol 2019; 91(2): 225-234. DOI: 10.1002/jmv.25308.

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8. Smith AM, Tau NP, Smouse SL, Allam M, Ramalwa N, Disenyeng B, Ngomane and Thomas J. 2019. 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 (in press).

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16. Birkhead M, Naicker SD, Blasich NP, Rukasha I, Thomas J, Sriruttan C, Abrahams S, Mavuso GS and Govender NP. *Cryptococcus neoformans*: Diagnostic Dilemmas, Electron Microscopy and Capsular Variants. Tropical Medicine and Infectious Disease. 2018; 4(1). pii: E1. DOI: 10.3390/tropicalmed4010001.

Conferences

International congresses : 7
National congresses: 4
Local congress: 1

Centre for Healthcare Associated Infections, Antimicrobial Resistance and Mycoses

1. Background

Centre Head
Prof Nelesh Govender

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 accredited to ISO 15189: 2012 requirements, and houses the National Biological Sample Collection of pathogenic bacteria and fungi. The Centre serves as a WHO Collaborating Centre (CC) for antimicrobial resistance 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.

2. Surveillance

Healthcare-associated infections

NICD investigators: NP Govender, E van Schalkwyk, R Mathebula and S Candy.
Collaborators: T Avenant, N du Plessis, K Masemola, D Pillay, M Ngobese, C Mackay, S Mahmud Yakoob, S Abrahams, J Black, N Ramncwana, F Naby, S Haffejee, H Dawood, J Green, T Martin, A Abrahams, E Mosenye, M Maila, E Chikwuma and the NICD Surveillance Intelligence Management Unit (SIMU).

The Centre implemented a real-time alert system to detect outbreaks of healthcare-associated bloodstream infections among neonates at Kalafong Hospital (Gauteng Province), Grey's Hospital (KwaZulu-Natal Province), Dora Nginza Hospital (Eastern Cape Province) and Thelle Mogoerane Regional Hospital (Gauteng Province). The hospital personnel were trained to use the outbreak alert mobile software application. The 2019 pilot project commenced on 1 February 2019 and will continue for 12 months. Results of the pilot project will inform plans to roll out the mobile application to facilities with limited laboratory and epidemiologic capacity.

Antimicrobial resistance

NICD investigators: O Perovic, NP Govender, L Shuping, H Ismail, E van Schalkwyk, M Smith, R Mpembe, A Singh-Moodley and S Candy.
Collaborators: The GERMS-SA network and SA Society for Clinical Microbiology.

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. Several approaches are currently used by the Centre for AMR surveillance, including:

- National or sentinel isolate-based surveys: Bacterial and fungal isolates, cultured from patients who meet the surveillance case definitions, were submitted to the Centre's reference laboratories for identification, antimicrobial susceptibility testing and genotyping. During the reporting period, the Centre conducted surveillance for bacteraemia caused by carbapenem-resistant Enterobacteriaceae (2015-2019) and *Acinetobacter baumannii* (2017-2019) and all infections caused by *Candida auris* (2018-2019);

- Enhanced laboratory surveillance: Detailed clinical information was collected from patients admitted to sentinel hospitals who met the surveillance case definitions. During the reporting period, the Centre conducted enhanced surveillance for bloodstream infections caused by *Acinetobacter baumannii* and carbapenem-resistant Enterobacteriaceae; and
- Electronic laboratory surveillance: annual data were compiled on bloodstream infections caused by the ESKAPE bacterial pathogens. Line list data from public- and private-sector pathology laboratory information systems were merged by the NICD's SIMU, cleaned and made available through the NICD's AMR dashboard (www.nicd.ac.za). The dashboard displays interactive and exportable AMR maps by geographic location, pathogen, antimicrobial agent and health sector. AMR data for the public sector is available at facility level. A combined public/private AMR report on key organisms-antimicrobial agents is available from the NDOH website: http://www.health.gov.za/index.php/antimicrobial-resistance.

Mycoses

NICD investigators: NP Govender, R Mpembe, T Maphanga, S Naicker, L Shuping, H Ismail, E van Schalkwyk and R Mathebula.
Collaborators: The GERMS-SA Network and Médecins Sans Frontières (MSF).

The WHO now recommends a combination of amphotericin B and flucytosine (5-FC) as first-line treatment for patients with cryptococcal meningitis. 5-FC is not registered in South Africa. However, MSF 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 meningitis 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 will inform future registration with the South African Health Products Regulatory Authority (SAHPRA) and consideration of 5-FC for the national essential medicines list. Passive laboratory-based surveillance for rarer invasive mycoses continued.

Outbreaks

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.

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 CC Network, which was formed to support the implementation of GLASS. The NICD agreed to cooperate on activities to strengthen countries' capacity for developing and implementing AMR surveillance and external quality assessment and has delivered training to GLASS participants.

3. Research activities

Cryptococcal Antigen Screen-and-Treat National Evaluation

NICD investigators: NP Govender, G Greene, D Desanto, P Matlapeng, M Shandu and N Valashiya.
Collaborators: University of Minnesota, US CDC and Epicentre.

The Cryptococcal Antigen Screen-and-Treat National Evaluation (CAST-NET) project aims to evaluate the effectiveness of the national reflex cryptococcal antigen (CrAg) screen and treat intervention. This project is supported by a five-year NIH R01 grant. In 2018, the Centre partnered with Epicentre to image the medical records of a large cohort of CrAg+ persons, identified between February 2017 and January 2019, in 25 sub-districts and one district (in all nine provinces). The first wave of data collection was completed in one district in Gauteng and in 15 sub-districts in five other provinces (North West, Limpopo, Mpumalanga, Western Cape and Northern Cape).

Prevalence of AMR genes in animals and humans

NICD investigators: O Perovic, W Strasheim, A Singh-Moodley, Marshagne Smith and M Lowe.
Collaborators: Dr JM Mokoele and A Jonker (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.

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

NICD investigators: A Singh-Moodley and O Perovic.
Collaborators: T Thomas, T Nana and V Chibabhai (NHLS) and W Lowman (WDGMC).

Acinetobacter baumannii is a major healthcare-associated pathogen, which has acquired resistance to colistin. In this study, we aimed to estimate the prevalence of resistance to antimicrobial agents, including colistin, in *A. baumannii* isolated from patients in ICUs in public and private hospitals in Gauteng Province. We also collected outcome data.

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

NICD investigators: A Singh-Moodley and O Perovic.

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

Investigation of SCC*mec* types and the Panton-Valentine leukocidin exotoxin in bloodstream *Staphylococcus aureus* surveillance isolates, 2013-2016

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

Previous work involved the identification of 484 staphylococcal cassette chromosome *mec* (SCC*mec*) types in methicillin-resistant *S. aureus* (MRSA), but unknown typing patterns were observed among 11% of the isolates. The current study investigated these unidentified types to establish if they were truly non-typeable. This study further investigated the proportion of the lukS/F-PV gene, which encodes PVL in 768 *S. aureus isolates* from patients with a diagnosis of pneumonia, skin and soft tissue infection, bone infection and joint infection. Epidemiological data were used to classify isolates as healthcare-associated or community-associated infections and specific antimicrobial susceptibility profiles were reported by SCC*mec* type and PVL.

Molecular epidemiology of spa-type t037, t045 and t1257 healthcare-associated methicillin-resistant *S. aureus* isolates causing bacteremia in three teaching hospitals: 2013-2017

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

It was previously demonstrated that most cases of MRSA bacteremia were health care-associated in two provinces in South Africa. The most prevalent staphylococcal protein A (spa)-types were t037, t045 and t1257. MRSA isolates with the same spa-type suggest that these isolates were genetically related at some point in time. The aim of the study was to determine if healthcare-associated MRSA isolates with the same spa-type and circulating within the same hospital were genetically related.

Prevalence of AmpC-betalactamases in *Klebsiella pneumoniae* bloodstream isolates

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

We aimed to determine the prevalence of AmpC-beta-lactamases and carbapenemases in *Klebsiella pneumoniae* blood culture isolates, as well as their associated antimicrobial resistance profiles. This study will assist in guiding the choice of empirical therapy, implementing IPC measures and monitoring the circulating resistant genotypes in hospital settings.

New species of *Blastomyces*

NICD investigators: T Maphanga, M Birkhead, M Ali, A Ismail, J Frean and NP Govender.
Collaborators: The Institute of Tropical Medicine, Public Health England, University of Alberta, and Broad Institute.

The atypical clinical pattern of cutaneous and osteoarticular blastomycosis seen in South Africa may be a consequence of the disease being caused by distinct species endemic in Africa that do not possess the BAD-1 virulence gene and produce hyphal elements at 37°C.

Antifungal susceptibility testing and whole genome sequencing of *Candida auris*

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

Four hundred South African bloodstream *Candida auris* isolates were tested between 2016 and 2017. Almost all were fluconazole resistant but only 22 (6%) had amphotericin B MIC ≥2 microgram/ml and two isolates each had micafungin MICs ≥4 microgram/ml. WGS was applied to determine the molecular epidemiology and track outbreaks caused by this near-clonal pathogen. Approximately 110 South African *C. auris* strains were sequenced to date by the NICD, including 89 bloodstream isolates, 11 colonising isolates and ten environmental isolates.

Molecular epidemiology of *Cryptococcus* in South Africa

NICD investigators: S Naicker, T Maphanga, E van Schalkwyk and NP Govender.
Collaborators: Translational Genomics Research Institute, Westmead Institute for Medical Research (University of Sydney) and Universidad del Rosario (Bogota, Colombia).

We found high genetic diversity in clinical *Cryptococcus* strains from South Africa. Among cases of *Cryptococcus neoformans* disease, VNI was the major genotype, though males were more likely to be infected with a non-VNI genotype. Among cases of *Cryptococcus gattii* disease, HIV-seropositive patients and those from the northern regions of South Africa were more likely to be infected with the dominant VGIV genotype.

3. Teaching and training

a. Postgraduate

- An NICD short course was presented to registrars and ID fellows;
- A mycology workshop was presented to registrars and ID fellows;
- MSc Epidemiology and Biostatistics, Wits;
- DTM&H, Wits;
- Ambition-CM/ UCT/ Institute Pasteur medical mycology course; and
- PhD, MSc, MPH and M Med supervision.

b. Professional development

Six postgraduate candidates were enrolled : Five PhD and one MSc.

4. Research outputs

Journal articles technical reports and guidelines

1. Coetzee LM, Cassim N, Sriruttan C, Mhlanga M, Govender NP, and Glencross DK. Cryptococcal antigen positivity combined with the percentage of HIV-seropositive samples with CD4 counts <100 cells/Ql identifies districts in South Africa with advanced burden of disease. PLOS One. 2018; 13(6): e0198993.

2. Govender NP and Glencross DK. National coverage of reflex cryptococcal antigen screening: A milestone achievement in the care of persons with advanced HIV disease. South African Medical Journal 2018; 108(7): 534-535.

3. Singh-Moodley A and Perovic O. Phenotypic and genotypic correlation of carbapenememase-producing Enterobacteriaceae and problems experienced in routine screening. South African Medical Journal. 2018; 108(6): 495-501.

4. Perovic O, Ismail H, van Schalkwyk E, Lowman W, Prentice E, Senekal M and Govind CN. Antimicrobial resistance surveillance in the South African private sector report for 2016. Southern African Journal of Infectious Diseases 2018: 1–12.

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7. Rajasingham R, Wake RM, Beyene T, Katende A, Letang E and Boulware DR. Cryptococcal Meningitis Diagnostics and Screening in the Era of Point-of-Care Laboratory Testing. Journal of Clinical Microbiology. 2019; 57(1).

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12. Birkhead M, Naicker SD, Blasich NP, Rukasha I, Thomas J, Sriruttan C, Abrahams S, Mavuso GS, and Govender NP. *Cryptococcus neoformans*: Diagnostic Dilemmas, Electron Microscopy and Capsular Variants. Tropical Medicine and Infectious Disease. 2018; 4(1).

13. Hoenigl M, Gangneux JP, Segal E, Alanio A, Chakrabarti A, Chen SCA, Govender NP, Hagen F, Klimko N, Meis JF, Pasqualotto AC, Seidel D, Walsh TJ, Lagrou K, Lass-Flörl C and Cornely OA for the European Confederation of Medical Mycology (ECMM). Global Guidelines and Initiatives from the European Confederation of Medical Mycology to improve Patient Care and Research Worldwide: New Leadership is about Working Together. Mycoses. 2018; 61(11): 885-894.

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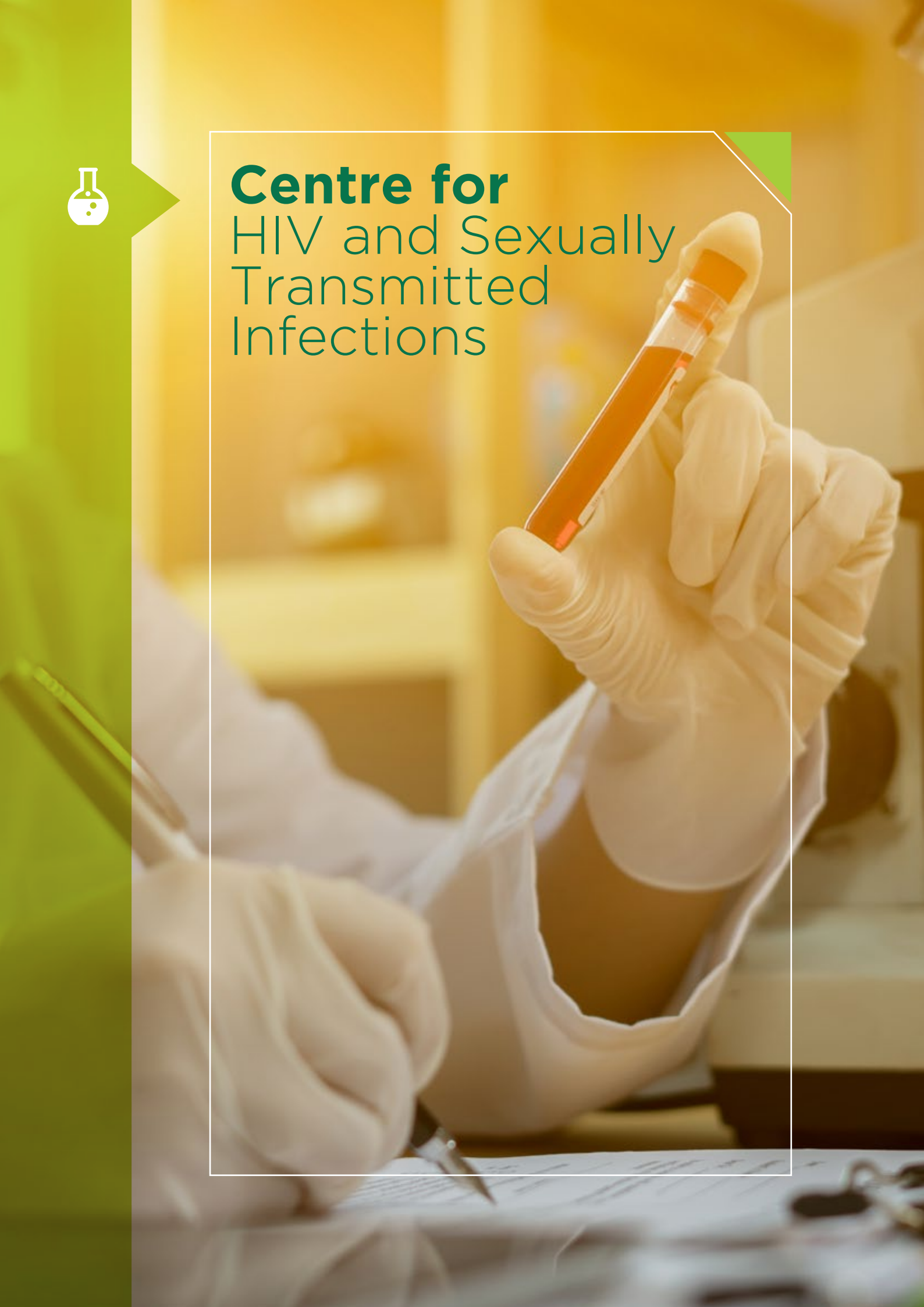
Conferences

International conferences: 6

Centre for HIV and Sexually Transmitted Infections



1. Background

Centre Head
Prof Adrian Puren

The Centre contributed to the two largest and most significant national human immunodeficiency virus (HIV) surveillance systems viz, the antenatal HIV prevalence and incidence survey and the national household HIV prevalence and incidence survey. The data presented in the case of the antenatal survey extends beyond the usual prevalence estimates, whilst paediatric and adult drug resistance data highlight the critical requirement to improve adherence in the paediatric setting. It also supports the requirement to introduce integrase inhibitor-based regimens. South Africa is likely to introduce dolutegravir as part of first-line treatment in 2019, and drug resistance monitoring will be essential.

The Centre demonstrated a keen interest in assessing systems and their impact on programmatic activities. Two examples are demonstrated: firstly, the development of a dashboard that responds to the UNAIDS 90-90-90 dashboard to measure the second and third 90s using routine HIV viral load (VL) test data. The second example is the refining of the definitions of congenital syphilis to improve reporting on the NMC system. Sexually transmitted infections (STIs), other than HIV, are often neglected and to address this issue, the Centre participated in a modelling exercise to determine the burden of STI diseases. An essential area of surveillance was the detection of gonococcal antimicrobial resistance surveillance in patients attending public health facilities and the impact on patient management. The Centre remained an essential cornerstone for HIV vaccine endpoint studies and research in broadly neutralising antibody studies.

Finally, we present an exciting example of U=U (undetectable = untransmissible) with the recent liver transplant from a virally suppressed mother to her HIV uninfected son. This precedent-setting example will influence future transplantation medicine.

2. Surveillance

HIV surveillance in adults

Antenatal HIV prevalence survey

South Africa has conducted national antenatal sentinel HIV prevalence surveys since 1990. The 2017 survey was a cross-sectional, linked-anonymous survey, involving HIV screening of selected eligible pregnant women aged between 15 - 49 years, who are attending public health facilities in South Africa. The survey aimed to measure HIV prevalence trends, HIV incidence, uptake of prevention of mother-to-child transmission (PMTCT) services, accuracy of point-of-care (POC) HIV rapid testing, and maternal syphilis screening service coverage. A nationally representative sample of 32 716 pregnant women from 1 595 public health facilities, selected from all 52 districts of South Africa, were included in the 2017 survey.

At national level, HIV prevalence was stable since 2004 at around 30%. Prevalence in 2017 was 30.7% (95% confidence interval [CI]: 30.1% 31.3%). In the PMTCT programme, coverage of knowledge of HIV status (first 90) was 96.7%. Almost all (98.2%) of those who knew their HIV status received antiretroviral treatment (ART). Self-reported ART adherence (from three days recall) among those who reported receiving ART was 98.7%. About 61% (60.8%) of HIV-positive pregnant women were aware of their HIV status before pregnancy, of whom 91.1% reported that they commenced with ART before pregnancy. Maternal syphilis screening coverage was 96.7% at national level among enrolled pregnant women, excluding 14.1% of participants for whom these data were missing.

The consistent decline in HIV prevalence among young women (15-24 years) was encouraging, as it may reflect a positive impact of interventions targeting adolescent and young women (e.g. 'She Conquers' and 'Determined, Resilient, Empowered, AIDS-free, Mentored and Safe' (DREAMS) initiatives). The percentage of HIV-positive women who knew their HIV status prior to the current pregnancy was low, especially in the 15 to 24-year group, highlighting the gap in access to youth-friendly reproductive health services.

The achievement of the first and the second 90 targets in the PMTCT programme, despite the high percentage of women who were unaware of their HIV status prior to pregnancy, demonstrated excellent performance by the PMTCT programme in identifying and enrolling HIV-positive pregnant women for treatment. These findings suggest that PMCT services are a critical contributor to achieve HIV prevention and treatment goals in South Africa.

HIV drug resistance

Measuring acquired HIV drug resistance in paediatric patients

A national facility-based cross-sectional study was implemented in 2018 and set out to evaluate the prevalence of acquired drug resistance among children on ART and experiencing virologic failure (VF) (VL ≥1000 copies/ml) at public health facilities across the country. A sample size of 1 475 specimens was required, recruiting patients and collecting information from 33 patients at each of 45 high-burden public health facilities providing paediatric ART, in nine provinces across South Africa. All children aged from one year - ≤19 years and having been on therapy for more than one year, were eligible for inclusion. The preliminary analysis of 595 specimens showed the proportion of HIV drug resistance (HIVDR) among children on ART, with VF at 86.9% (95% CI 83.8 – 89.5).

Most of the participants (58%) harboured resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) and nucleoside reverse transcriptase inhibitors (NRTIs), 16% had resistance to NNRTIs, and 8% harboured NRTI resistance, whilst 13% were susceptible to all drug classes. Notably, 4% of participants harboured resistance to protease inhibitors (PI)+NNRTI3NRTI. Whilst there was a trend of higher levels of resistance in adolescents, there is no statistical difference in levels of resistance per age group. This data supports the need to consider new treatment strategies for children failing ART, including better PI-based regimens, as well as integrase inhibitor-based regimens.

Measuring levels of HIV drug resistance in the fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey

The fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (SABSSM V) formed part of a series of household surveys designed to determine HIV incidence, prevalence, ART exposure, VL suppression, HIVDR, risk behaviour and communication in a household-based, national representative sample of the population of South Africa. Of the 1 107 virally unsuppressed specimens, drug resistance testing and data analysis was completed in 697 samples. Resistance was detected in 27.4%, with NNRTI resistance being most commonly detected in 18.9%. Drug resistance mutations were present in 55.7% of participants failing ART, 75.9% of participants who were reported as on ART but with a negative drug level, and 22.8% of participants who were not on treatment. No significant differences by sex or age group were noted. This data echoes global findings of increasing levels of pre-treatment resistance and supports the implementation of integrase inhibitor-based regimens for first-line treatment of HIV in South Africa.

Paediatric HIV surveillance

Routine National Health Laboratory Services HIV viral load test data used to construct near real-time 90-90-90 dashboards

By 2020, South Africa must achieve the UNAIDS 90-90-90 targets: that 90% of all HIV-infected people know their status; 90% of people with known HIV-positive status receive ART and 90% of people on ART are virologically suppressed. HIV health data in the country is captured at facility level onto Tier.net and is conveyed from facility to national level via the District Health Information System (DHIS) to measure the country's 90-90-90 targets in children (aged <15 years) and adults (aged 15 years and older). However, no data is available for target populations (e.g. adolescents) or against which to regularly triangulate the DHIS data. For quarter four of the 2018/2019 reporting period, the DHIS reported that of 7 109 877 people of all ages living with HIV, 5 332 418, (75%) people knew their positive HIV status, 4 492 478 (84%) were receiving ART and 2 791 083 (62%) were virologically suppressed.

For 2017, the 5th SABSSM V survey indicated that South Africa respectively reached 85%, 71% and 88% of the 90-90-90 targets. An NICD 90-90-90 dashboard was designed to measure the second and third 90s, using routine HIV VL test data from approximately 80% of the South African population of HIV-infected patients, routinely stored by the NHLS/NICD. The latest HIV VL test per patient, performed in the past 15 months, was used as a proxy for the number of people living with HIV on ARVs (or the second 90 target). The results of these VL tests were used to measure the third 90 target (or VL suppression). The dashboard compares the DHIS and NHLS 90s for children and adults, but can also measure the targets at different age groups and sexes from district to national level.

This allows identification of high-risk populations to ensure that the targets are met in all subpopulations. These subpopulations include paediatric age breakdowns to assess subpopulations of children and adolescents, adolescent girls and young women, and women of childbearing potential, which is a critical population to monitor in order to achieve elimination of mother-to-child transmission.

Healthcare workers (HCWs) and their managers can gain access to the NICD 90-90-90 dashboard, by completing the registration process on the NICD website (http://www.nicd.ac.za/M&Edashboard) and obtaining a password. Monitoring and triangulating of the DHIS and NICD data on a regular basis, including in important subpopulations, enables the monitoring of progress, as well as the rapid identification of areas that require intervention.

STI surveillance and monitoring

Strengthening surveillance for congenital syphilis in South Africa

The global shortage of benzathine penicillin, the drug of choice for the treatment of syphilis, which commenced in 2017, the resurgence of syphilis in the west (with concerns of it becoming a global trend) and the lack of accurate and representative national level data on both maternal and congenital syphilis, highlighted a critical requirement for improved surveillance of syphilis in the country.

In collaboration with the NMC team, the Centre responded to this need by looking into strengthening 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, as well as 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.

Activities implemented during the year to improve the detection and reporting of CS include:

- Stakeholder consultations;
- Revision of case definitions;
- Development of a CS–specific case investigation form and notification procedures;
- Training of facility-based staff on the revised case definitions;
- Analysis of CS cases reported during the 2018/2019 financial year;
- Production of national estimates of CS for the Global AIDS Monitoring (GAM) report; and
- Securing funding for enhanced and active follow-up of incomplete cases, or suspected cases, until final case classification.

By yearend, the Centre reported 159 cases of CS to the NDOH, for inclusion in the GAM. Although this was likely a significant underreporting of the number of cases detected, the country was able to report estimates for the first time ever and established a baseline report against which performance of the case-based surveillance system can be measured.

Aetiological surveillance of sexually transmitted infection syndromes and gonococcal antimicrobial resistance surveillance in patients attending public health facilities in South Africa (NICD, GERMS-SA

The syndromic approach to the management of STIs in the primary healthcare centres (PHCs) is based on the identification of a group of symptoms and easily recognisable signs, associated with a number of well-defined aetiologies. Periodic aetiological surveillance of STI syndromes is critical for validating the existing treatment algorithms. Aetiological surveillance at selected sentinel primary PHCs in various provinces has been conducted under the umbrella of NICD GERMS-SA since 2015.

An important component of this programme is the monitoring of antimicrobial susceptibility profiles for the emergence of extensively drug-resistant (XDR) *Neisseria gonorrhoeae*, resistant to extended-spectrum cephalosporins (ESCs). Ceftriaxone, an ESC, is the mainstay of current therapy for gonorrhoea. In 2018, surveillance was conducted at sentinel sites in Gauteng, Free State, and Limpopo provinces. Data from the surveillance was used to revise and update the national PHC/Essential Medicines List (EML) STI syndromic management guidelines. The latest version of the guidelines (2018) was released and is available on the NDOH and NICD websites. Aggregated surveillance data was analysed and published in the NICD Public Health Surveillance Bulletin and peer-reviewed articles in both local and international journals. *Neisseria gonorrhoeae* antimicrobial resistance data was submitted to the WHO Gonococcal Antimicrobial Surveillance Programme (GASP), as well as the WHO Global Antimicrobial Resistance Surveillance System (GLASS). Additionally, with the global emergence of XDR *N. gonorrhoeae*, ceftriaxone-resistant gonorrhoea was added to the national NMC list (category 3) in December 2017.

A standard operating protocol was established to standardise the laboratory detection and reporting of ceftriaxone-resistant gonorrhoea, and disseminated to all NHLS laboratories, as well as some private laboratory service providers. This protocol includes both laboratory and clinical electronic notification forms, to facilitate confirmation of ceftriaxone resistance by the NICD STI Reference Laboratory, and for relevant public health action.

3. Research activities

HIV Research

The HIV Virology Section studies the humoral immune response to HIV infection and vaccination to contribute to the development of an HIV vaccine.

Subtype C ALVAC-HIV and bivalent subtype C gp120/MF59 HIV-1 vaccine in low-risk, HIV-uninfected, South African adults: a phase 1/2 trial

NICD Investigators: L Morris and NN Mkhize.
Collaborators: L-G Bekker (UCT), Z Moodie, KW Cohen (HVTN), GE Gray and F Laher (WITS), GD Tomaras, M Sarzotti-Kelsoe and DC Montefiori (Duke University), M Allen, M Malahleha, K Mngadi, B Daniels, C Innes, C Bentley, N Frahm, DE Morris, S Grant, C Yu, VL Mehra, MN Pensiero, S Phogat, CA DiazGranados, SW Barnett, N Kanesa-Thasan, M Koutsoukos, NL Michael, ML Robb, JG Kublin, PB Gilbert, L Corey, and MJ McElrath (Fred Hutchinson Cancer Research Centre).

Modest efficacy was previously preported for the HIV vaccine tested in the RV144 trial, which comprised a canarypox vector (ALVAC) and envelope (env) glycoprotein (gp120). These vaccine components were adapted to strains circulating in South Africa, and the adjuvant was changed to increase immunogenicity. Furthermore, a 12-month immunisation was added to improve durability. The HVTN100 trial aimed to assess this new regionally adapted regimen for advancement to efficacy testing. This was a phase 1/2, randomised controlled, double-blind trial of HIV-uninfected adults at low risk of infection. Primary outcomes included safety and immune responses associated with correlates of HIV risk in RV144. The trial enrolled 252 participants, of whom 210 were assigned to vaccine and 42 to placebo.

All vaccine recipients developed IgG binding antibodies to all three vaccine-matched gp120 antigens with significantly higher titres than the corresponding vaccine-matched responses of RV144. The IgG response to the 1086.C V1V2 env antigen was 70% lower than that of RV144. Although the IgG response to the HVTN 100 vaccine was lower, it exceeded the predicted 63% threshold needed for 50% vaccine efficacy using a V1V2 correlate of protection model. Thus, the subtype C HIV vaccine regimen qualified for phase 2b/3 efficacy testing, a critical next step of vaccine development.

HIV superinfection drives de novo antibody responses and not neutralisation breadth

NICD investigators: V Bekker, JN Bhiman, M Nonyane, L Morris and PL Moore.
Collaborators: DJ Sheward, J Marais, C Williamson and ZL Woodman (University of Cape Town), B Murrell, (University of California), K Eren (University of California), N Garrett, Q Karim Abdool and S Abdool Karim (CAPRISA).

Studies of broadly neutralising antibodies are a key focus. HIV superinfection (re-infection with a second strain following an established infection) was associated with neutralisation breadth and can provide insights into how the immune system responds to sequential exposure to distinct HIV envelope glycoproteins. A study published in Cell Host Microbe (PMID: 30269971) characterised the neutralising antibody responses in four superinfected women and revealed that superinfection does not boost memory nAb responses primed by the first infection, or promote nAb responses to epitopes conserved in both infecting viruses. Thus, sequential immunisation with heterologous Envs may thus not be sufficient to focus the immune response onto conserved epitopes, an important finding for HIV vaccine design.

V2-directed vaccine-like antibodies from HIV-1 infection identify an additional K169-binding light chain motif with broad ADCC activity

NICD investigators: C van Eeden, CK Wibmer, C Scheepers, SI Richardson, M Nonyane, B Lambson, NN Mkhize, JN Bhiman, V Bekker, T Hermanus , B Mabvakure , A Ismail, PL Moore and L Morris.
Collaborators: B Vijayakumar, H Dirr, MA Fernandes and Y Sayed (Wits University), Z Sheng and L Shapiro (Columbia University), S Stanfield-Oakley, MA Moody, K Wiehe, G Ferrari, and BF Haynes (Duke University).

In a second study, the antibody response to HIV infection was compared to vaccination. V2-directed antibodies from the RV144 HIV vaccine trial correlated with reduced HIV-1 infection risk, but were restricted to two ED-motif-encoding light chain genes. In a study published in Cell Reports (PMID:30540944), van Eeden *et al* isolated two V2-directed antibody lineages (CAP228-16H/19F and CAP228-3D) that mediate antibody dependent cell-mediated cytotoxicity. Both lineages use the IGHV5-51 heavy chain germline gene, similar to the RV144 antibody CH58, but one lineage (CAP228-16H/19F) uses a light chain without the ED motif. A cocrystal structure of CAP228-16H bound to a V2 peptide identified an IGLV3-21 gene-encoded DDxD motif that binds K169, allowing CAP228-16H to recognise more globally relevant V2 immunotypes. A follow-up structural study in Nature Communications (PMID: 30367034) showed these CAP228 antibodies recognised the same helix-coil V2 conformation as the RV144 antibody CH58, identifying a frequently sampled

alternative conformation of full-length V1V2, that exposes α4β7-binding sites, providing a functional role for non-native envelope in HIV-1 dissemination, pathogenesis, and vaccine design. Overall, this data further our understanding of cross-reactive, V2-binding, antiviral antibodies and expands the human light chain repertoire able to respond to RV144-like HIV immunogens in South Africans.

Cell biology

The first living donor liver transplant from an HIV-positive mother to her HIV-negative child – exploring the potential for HIV transmission

NICD investigators: A Haeri Mazanderani, M Paximadis and CT Tiemessen (authors representing the team at NICD).
Collaborators: J Botha, H Etheredge, J Fabian (Wits Donald Gordon Medical Centre (WDGMC) and F Conradie (Clinical HIV Research Unit, Wits University), lead investigators/ authors representing the team at WDGMC.

The first in the world - a life-saving partial liver transplantation from an HIV-infected mother (living donor) to her uninfected child, was conducted at the WDGMC in Johannesburg. This need was driven by life-threatening liver failure in the child, no available deceased or suitable living HIV-uninfected donors, and an HIV-positive mother's continued pleas for her to be allowed to save her child. This transplant was ground-breaking on two fronts. To date there have been no published reports of a living donation by an HIV-infected individual, or of an intentional transplant from an HIV-positive to an HIV-negative individual. Following on from this case, the first living donor HIV-to-HIV kidney transplant was conducted at Johns Hopkins Medicine in the USA, on 25 March 2019.

Because of the success of ART in HIV disease control, living donation of organs by HIV-positive individuals is now a possibility that did not exist in the early days when infection with HIV-1 was considered a death sentence. Furthermore, the enormous success of ARV drugs in reducing mother-to-child transmission of HIV, resulted in the majority of children born to HIV-positive mothers, escaping infection.

The question of great interest is the possible transmission of HIV-1 to the child in this unusual setting of HIV-positive to HIV-negative organ transplantation. It is now almost two years since the transplant, and both mother and child are doing well. The mother was on ART during pregnancy, and the child received standard preventative treatment. In addition, the child received ARV drugs ahead of the transplant to try to prevent infection. Both remain on treatment.

The child was HIV-negative before the transplant, but seroconverted at 43 days after the transplant. The HIV-1 antibody levels were subsequently waning, but remain detectable to date. However, HIV serology tests cannot be used to definitively diagnose HIV-1 infection in the setting of organ transplantation, as B-cells in liver or cells transferred with the graft may be the source of the antibodies produced in the child. No virus could be detected in plasma with VL tests, or in cells using ultrasensitive molecular tests. The question of the child's HIV infection status therefore remains unanswered, and will be the subject of ongoing investigations to address key knowledge gaps, as further transplants of this nature are conducted.

4. Teaching and training

a. Postgraduates

Seven postgraduate students obtained their qualifications: Three PhDs, three MScs and one BSc (Hons).

b. Professional development

Thirty three postgraduates were enrolled for qualifications: One MMed, 20 PhDs and one BSc (Hons)

5. Awards and recognition

1. The leaders of the team, Drs J Botha, F Conradie, H Etheredge and J Fabian, as well as Prof CT Tiemessen, that performed the world-first living donor liver transplant from an HIV-positive parent to her HIV-negative child, received the Innovation Award at the Congress of Business and Economics (CBE) Awards 2018.

2. Prof Penny Moore received the South African Medical Research Council (SAMRC) Silver Scientific Merit award for her outstanding scientific contributions to health research. The Awards Ceremony took place on 30 August 2018 at the MRC offices in Cape Town.

3. Prof Lynn Morris was inducted as a new Fellow of the African Academy of Sciences at an AAS General Assembly Meeting, which took place from on 10-11 December 2018 in Pretoria.

6. Research outputs

Journal articles

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Conferences

International congresses: 39
National congresses: 16
Local congresses: 25

Centre for Respiratory Diseases and Meningitis

1. Background

Centre Head
Prof Cheryl Cohen

The Centre for Respiratory Diseases and Meningitis (CRDM) 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 primary healthcare centres (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 and meningococcus, with a focus on outbreak detection and the impact of interventions.

New pathogens (Group A and Group B *Streptococcus*) were included in laboratory-based surveillance from 2019. 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.

The CRDM responded to several outbreaks, including increases in pertussis in several provinces, an outbreak of diphtheria and a cluster of cases of severe respiratory illness. Pertussis alerts and updates for clinicians were published. The diphtheria, pertussis and influenza guidelines were updated in 2018. In the year under review, active reporting and real-time verification for the NMC programme began. Five 'category one' NMC conditions (acute rheumatic fever, 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.

2. Surveillance

GERMS-SA

Through the GERMS-SA programme of national, laboratory-based, population-based, active surveillance for invasive pneumococcal and Hib disease, the CRDM evaluates the ongoing impact of both the pneumococcal conjugate vaccine (PCV) and the *Haemophilus influenzae* serotype b conjugate vaccine (Hib CV). The CRDM also contributes data on numbers and serogroups of *Neisseria meningitidis* and supports diagnostic testing and outbreak response for suspected cases of meningococcal disease. In 2019, national laboratory-based surveillance for Group A and Group B *Streptococcus* was introduced.

Syndromic surveillance for respiratory illness

The National Pneumonia Surveillance Programme (NPSP) continues 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 if needed. The NPSP continues to test for influenza, RSV and 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 two provinces. In this financial year, the process of integrating the NPSP and ILI surveillance programmes into the GERMS-SA platform commenced and this will be completed in 2019/2020. 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.

Details of the results of syndromic surveillance in 2018 were published in the Communicable Diseases Surveillance Bulletin: J Moyes, S Walaza, S Chikosha, A Buys, F Treurnicht, O Hellferscee, J Mcanerney, A von Gottberg, N Wolter, F Moosa, M du Plessis, L de Gouveia and C Cohen. Public Health Surveillance Bulletin, Vol 17 Epidemiology of respiratory pathogens from influenza-like illness and pneumonia surveillance programmes, South Africa. 2018, Issue 1, p23-46).

Figure 1. Collection of respiratory samples in the field as part of the PHIRST study of influenza community burden and transmission, Agincourt demographic surveillance site, Mpumalanga Province, 2018.

3. Policy contributions

Increases in pertussis in several provinces were noted. Pertussis alerts and updates for clinicians were published, in addition to updated pertussis guidelines. The CRDM reviewed pertussis data and presented recommendations to the National Advisory Group on Immunisation (NAGI) for possible strategies to address this increase. In response to an outbreak of diphtheria, updated diphtheria guidelines were published in 2018. Following a presentation of surveillance and research data to the NAGI, influenza vaccination recommendations were updated to prioritise vaccination of HIV-infected adults and pregnant women in 2018, and updated influenza guidelines were also published.

4. Outbreaks

The CRDM assisted in an investigation of a cluster of three cases of severe respiratory illness in the same residence, including one death, from Port Elizabeth in Eastern Cape Province, in April 2018. The Centre assisted with testing and epidemiologic investigation. Despite comprehensive testing, no common pathogen was identified as the cause of the cluster.

In addition to the general increase in laboratory-confirmed pertussis cases detected through the pneumonia and ILI surveillance programmes in 2018, clusters of pertussis cases were reported from four provinces, namely: Mpumalanga, Eastern Cape, Western Cape and KwaZulu-Natal.

The CRDM conducted laboratory testing, assisted with outbreak database management, and provided guidance on the public health management of outbreaks in a school in Emalahleni sub-district, in Mpumalanga Province (July-October 2018); and a community outbreak in Nelson Mandela Bay Health District, in Eastern Cape Province (October 2018 – ongoing), which included three infant deaths.

A laboratory-confirmed case of respiratory diphtheria was confirmed in KwaZulu-Natal in March 2018. No additional cases were identified, following extensive contact tracing and active case finding. A case of non-toxigenic cutaneous diphtheria was identified in a resident of a chronic care facility in Gauteng in February 2019.

5. Research activities

HIV infection is associated with increased meningococcal carriage acquisition amongst first year university students in South Africa

NICD investigators: S Meiring, C Cohen, L de Gouveia, M du Plessis, K Ganesh, J Kleynhans, V Quan and A von Gottberg.

In a cohort of students, testing for meningococcal carriage was conducted at two time points, six to eight weeks apart. From a baseline prevalence of 5%, meningococcal carriage increased by 63% after approximately two months on campus. At both time points, non-groupable strains predominated, followed by Y, B, C and W genogroups. Risk factors for acquiring carriage included attending nightclubs (adjusted relative risk ratio (aRRR) 2.1 (95%) confidence interval (CI) 1.1-4.0), having intimate kissing partners (aRRR 1.8, 95% CI 1.1-2.9) and being HIV-infected (aRRR 5.0, 95% CI 1.1-24.4).

Effectiveness of inactivated influenza vaccination in pregnant women for prevention of influenza-associated hospitalisation in their young infants: A case-control study

NICD investigators: S Walaza, S Meiring, S Lengana, K Bishop, Ai Mathunjwa, F Treurnicht, O Hellferscee and C Cohen.
Collaborators: US CDC and the RMPRU, South Africa.

Prior to the annual influenza seasons, from 2015 through 2018, vaccination campaigns were implemented at ante-natal clinics in two provinces. Simultaneously, hospital-based surveillance for acute respiratory or febrile illness in infants was conducted. The overall adjusted vaccine effectiveness (VE) in their infants when vaccinating pregnant women against influenza, hospitalisation in their infants was 30% (95% CI: -27-61). After stratifying for maternal HIV status in term infants, the VE was 62% (95% CI 0.1-86) in HIV-unexposed infants and 54% (95%CI: -148-92) in HIV- exposed infants aged <3 months.

Community burden of influenza in a rural and urban setting, South Africa, 2016-2017

NICD investigators: C Cohen, J Moyes, T Mkhencele, F Treurnicht, O Hellferscee, A Mathunjwa, A von Gottberg, N Wolter and J Kleynhans.
Collaborators: MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt); Perinatal HIV Research Unit, MRC Soweto Matlosana Collaborating Centre for HIV/AIDS and TB, South Africa; University of the North West andUS CDC.

A prospective cohort study was conducted to calculate the incidence of PCR-confirmed influenza infection, irrespective of symptoms, including 208 randomly selected households in an urban and a rural site in 2016 and 2017. The annual influenza attack rate (AR) was 33% (369/1118). The highest AR rate was in children <5 years of age (39%, 75/192). The urban site (adjusted odds ratio (aOR) 1.4, 95% CI 1.1–1.8) and age groups <5 years (aOR 1.9, 95% CI 1.3–2.9) and five - 18 years (aOR 1.6, 95% CI 1.1–2.1) (vs. 19–64 years) were significantly associated with influenza AR. HIV was not associated with AR (OR 0.9 95%CI 0.6–1.3).

6. Teaching and training

The Centre provided the following technical, operational and stakeholder teaching and training support:

- Assisted the Gauteng DOH with training on influenza in preparation for the National Influenza Vaccination Campaign 2018 and 2019;
- Conducted ongoing training and site visits throughout the year for surveillance and special studies, namely: Syndromic surveillance for respiratory disease, GERMS-SA, PHIRST, a maternal influenza study and the ANDEMIA study;
- Training of provincial NMC nurses related to CRDM pathogens and diseases;
- Legionella awareness activities and facility audits occurred at different sites throughout the year, and the CRDM hosted and facilitated semi-annual meetings for the national Legionella Action Group;
- Hosted the Health Professions Council of South Africa (HPCSA) medical scientist interns from other NICD departments for microbiology training as part of the NICD rotation roster, from 7-18 May 2018;

- Hosted medical registrars for training as part of the NICD three-week course, from 24 - 25 May 2018;
- The CRDM and the Fogarty International Centre from the NIH jointly hosted a training workshop on Infectious Diseases Dynamics and Evolution from 3 - 5 December 2018 at the NICD. The workshop involved 50 participants from 15 countries and included two parallel tracks on epidemiology and phylogenetics; and
- Hosted an influenza PCR training workshop (together with the WHO), for 14 participants from eight African countries, from 25 - 29 March 2019.

Academic teaching and lectures

- Prof C Cohen was the course coordinator of the infectious disease epidemiology module for the MSc Epidemiology and the Epidemiology track for the MSc Vaccinology section at Wits. She also served as an external examiner for the Diagnosis and Screening Track of the MSc Epidemiology track at the University of Stellenbosch;
- Prof C Cohen presented the annual James Gear Memorial Lecture on 12 November 2018, entitled: 'Going viral: influenza 100 years after the 1918 pandemic;'
- Prof C Cohen presented the opening lecture for the Outbreaks Exhibition at Wits Adler Museum;
- Prof A von Gottberg and C Cohen lectured at the African Advanced Vaccinology course (Afro-ADVAC), which took place at Glenburn Lodge in Muldersdrift on 7 September 2018; and
- Prof C Cohen visited the South African Centre for Epidemiologic Modelling and Analysis in Stellenbosch from 7 - 8 March 2018 and gave an invited talk entitled, 'Respiratory disease burden, transmission and modelling in South Africa.'

Professional development

- Nine postgraduates students were enrolled for qualifications: Eight PhD, three Masters and one Honours;
- Three postgraduate students graduated: One PhD and two Masters;
- One HPCSA medical scientist intern completed training and registered as a medical biological scientist with the HPCSA, two completed the first year of their internship and one new intern was registered; and
- Two NRF interns completed their one-year experiential training.

Figure 2. Participants and coordinators from the influenza PCR training workshop conducted together with the World Health Organization, involving 14 participants from 8 African countries, held at the National Institute for Communicable Diseases, 25-29 March 2019.

7. Research outputs

Journal articles

1. Azarian T, Mitchell PK1, Georgieva M, Thompson CM, Ghouila A, Pollard AJ, von Gottberg A, du Plessis M, Antonio M, Kwambana-Adams BA, Clarke SC, Everett D, Cornick J, Sadowy E, Hryniewicz W, Skoczynska A, Moïsi JC, McGee L, Beall B, Metcalf BJ, Breiman RF, Ho PL, Reid R, O'Brien KL, Gladstone RA and Bentley SD, Hanage WP. Global emergence and population dynamics of divergent serotype 3 CC180 pneumococci. PLOS Pathogens. 2018; 14(11): e1007438.

2. Balsells E, Dagan R, Yildirim I, Gounder PP, Steens A, Muñoz-Almagro C, Mameli C, Kandasamy R, Givon Lavi N, Daprai L, van der Ende A, Trzciński K, Nzenze SA, Meiring S, Foster D, Bulkow LR, Rudolph K, Valero-Rello A, Ducker S, Vestrheim DF, von Gottberg A, Pelton SI, Zuccotti G, Pollard AJ, Sanders EAM, Campbell H, Madhi SA, Nair H and Kyaw MH. The relative invasive disease potential of *Streptococcus pneumoniae* among children after PCV introduction: A systematic review and meta-analysis. The Journal of Infection. 2018; 77(5): 368–378.

3. Bozio CH, Vuong J, Dokubo EK, Fallah MP, McNamara LA, Potts CC, Doedeh J, Gbanya M, Retchless AC, Patel JC, Clark TA, Kohar H, Nagbe T, Clement P, Katawera V, Mahmoud N, Djingarey HM, Perrocheau A, Naidoo D, Stone M, George RN, Williams D, Gasasira A, Nyenswah T, Wang X Fox LM and Liberian Meningococcal Disease Outbreak Response Team. Outbreak of *Neisseria meningitidis* serogroup C outside the meningitis belt—Liberia, 2017: An epidemiological and laboratory investigation. The Lancet Infectious Diseases. 2018; 18(12): 1360–1367.

4. Bresee J, Fitzner J, Campbell H, Cohen C, Cozza V, Jara J, Krishnan A, Lee V and WHO Working Group on the Burden of Influenza Disease. Progress and remaining gaps in estimating the global disease burden of influenza. Emerging infectious diseases. 2018; 24(7): 1173–1177.

5. Caini S, Spreeuwenberg P, Kusznierz GF, Rudi JM, Owen R, Pennington K, Wangchuk S, Gyeltshen S, Ferreira de Almeida WA, Pessanha Henriques CM, Njouom R, Vernet MA, Fasce RA, Andrade W, Yu H, Feng L, Yang J, Peng Z, Lara J, Bruno A, de Mora D, de Lozano C, Zambon M, Pebody R, Castillo L, Clara AW, Matute ML, Kosasih H, Nurhayati, Puzelli S, Rizzo C, Kadjo HA, Daouda C, Kiyanbekova L, Ospanova A, Mott JA, Emukule GO, Heraud JM, Razanajatovo NH, Barakat A, El Falaki F, Huang SQ, Lopez L, Balmaseda A, Moreno B, Rodrigues AP, Guiomar R, Ang LW, Lee VJM, Venter M, Cohen C, Badur S, Ciblak MA, Mironenko A, Holubka O, Bresee J, Brammer L, Hoang PVM, Le MTQ, Fleming D, Séblain CE, Schellevis F, Paget J and Global Influenza B Study group. Distribution of influenza virus types by age using case-based global surveillance data from twenty-nine countries, 1999-2014. BMC Infectious Diseases. 2018; 18(1): 269.

6. Cohen C and von Gottberg A. Hib combination vaccines: Efficient and effective. The Lancet Infectious Diseases. 2018; 18(7): 700–701.

7. Dlamini SK, Madhi SA, Muloiwa R, von Gottberg A, Moosa MS, Meiring ST, Wiysonge CS, Hefer E, Mulaudzi MB, Nuttall J, Moorhouse M and Kagina BM. Guidelines for the vaccination of HIV-infected adolescents and adults in South Africa. Southern African Journal of HIV Medicine. 2018; 19(1): a839.

8. Dube FS, Ramjith J, Gardner-Lubbe S, Nduru P, Robberts FJL, Wolter N, Zar HJ and Nicol MP. Longitudinal characterization of nasopharyngeal colonization with *Streptococcus pneumoniae* in a South African birth cohort post 13-valent pneumococcal conjugate vaccine implementation. Scientific Reports. 2018; 8(1): 12497.

9. Hanifa Y, Toro Silva S, Karstaedt A, Sahid F, Charalambous S, Chihota VN, Churchyard GJ, von Gottberg A, McCarthy K, Nicol MP, Ndlovu NT, Stevens W, Fielding KL and Grant AD. What causes symptoms suggestive of tuberculosis in HIV-positive people with negative initial investigations? The International Journal of Tuberculosis and Lung Disease. 2019; 23(2): 157–165.

10. Lo SW, Gladstone RA, van Tonder AJ, Hawkins PA, Kwambana-Adams B, Cornick JE, Madhi SA, Nzenze SA, du Plessis M, Kandasamy R, Carter PE, Eser ÖK, Ho PL, Elmdaghri N, Shakoor S, Clarke SC, Antonio M, Everett DB, von Gottberg A, Klugman KP, McGee L, Breiman RF and Bentley SD. Global distribution of invasive serotype 35D *Streptococcus pneumoniae* isolates following introduction of 13-valent pneumococcal conjugate vaccine. Journal of Clinical Microbiology. 2018; 56(7).

11. McMorrow ML, Tempia S, Walaza S, Treurnicht FK, Ramkrishna W, Azziz-Baumgartner E, Madhi SA and Cohen C. Prioritization of risk groups for influenza vaccination in resource limited settings – A case study from South Africa. Vaccine. 2019; 37(1): 25–33.

12. McMorrow ML, Tempia S, Walaza S, Treurnicht FK, Moyes J, Cohen AL, Pretorius M, Hellferscee , Wolter N, von Gottberg A, Nguweneza A4, McAnerney JM, Naby F, Mekgoe O, Venter M, Madhi SA and Cohen C. The role of human immunodeficiency virus in influenza- and respiratory syncytial virus–associated hospitalizations in South African children, 2011–2016. Clinical Infectious Diseases. 2019; 68(5): 773–780.

13. Von Mollendorf C, Hellferscee O, Valley-Omar Z, Treurnicht FK, Walaza S, Martinson NA, Lebina L, Mothlaoleng K, Mahlase G, Variava E, Cohen AL, Venter M, Cohen C and Tempia S. Influenza viral shedding in a prospective cohort of HIV-infected and uninfected children and adults in 2 provinces of South Africa, 2012–2014. The Journal of Infectious Diseases. 2018; 218(8): 1228–1237.

14. Moosa F, du Plessis M, Wolter N, Carrim M, Cohen C, von Mollendorf C, Walaza S, Tempia S, Dawood H, Variava E and von Gottberg A. Challenges and clinical relevance of molecular detection of *Bordetella pertussis* in South Africa. BMC Infectious Diseases. 2019; 19(1): 276.

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16. Nadan S, Taylor MB, Groome MJ, Cohen C, Madhi SA and Page NA. Epidemiology of human astroviruses among children younger than 5 years: Prospective hospital-based sentinel surveillance in South Africa, 2009-2014. Journal of Medical Virology. 2019; 91(2): 225–234.

17. Subramoney K, Hellferscee O, Pretorius M, Tempia S, McMorrow M, von Gottberg A, Wolter N, Variava E, Dawood H, Kahn K, Walaza S, Madhi SA, Cohen C, Venter M and Treurnicht FK. Human bocavirus, coronavirus, and polyomavirus detected among patients hospitalised with severe acute respiratory illness in South Africa, 2012 to 2013. Health Science Reports. 2018. Wiley-Blackwell: e59.

18. Tempia S, Walaza S, Moyes J, Cohen AL, von Mollendorf C, McMorrow ML, Mhlanga S, Treurnicht FK, Venter M, Pretorius M, Hellferscee O, Wolter N, von Gottberg A, Nguweneza A, McAnerney JM, Dawood H, Variava E, Madhi SA and Cohen C. The effects of the attributable fraction and the duration of symptoms on burden estimates of influenza-associated respiratory illnesses in a high HIV prevalence setting, South Africa, 2013-2015. Influenza and other Respiratory Viruses. 2018; 12(3): 360–373.

19. Treurnicht FK, Buys A, Tempia S, Seleka M, Cohen AL, Walaza S, Glass AJ, Rossouw I, McAnerney J, Blumberg L, Cohen C and Venter M. Replacement of neuraminidase inhibitor-susceptible influenza A(H1N1) with resistant phenotype in 2008 and circulation of susceptible influenza A and B viruses during 2009-2013, South Africa. Influenza and other Respiratory Viruses. 2019; 13(1): 54–63.

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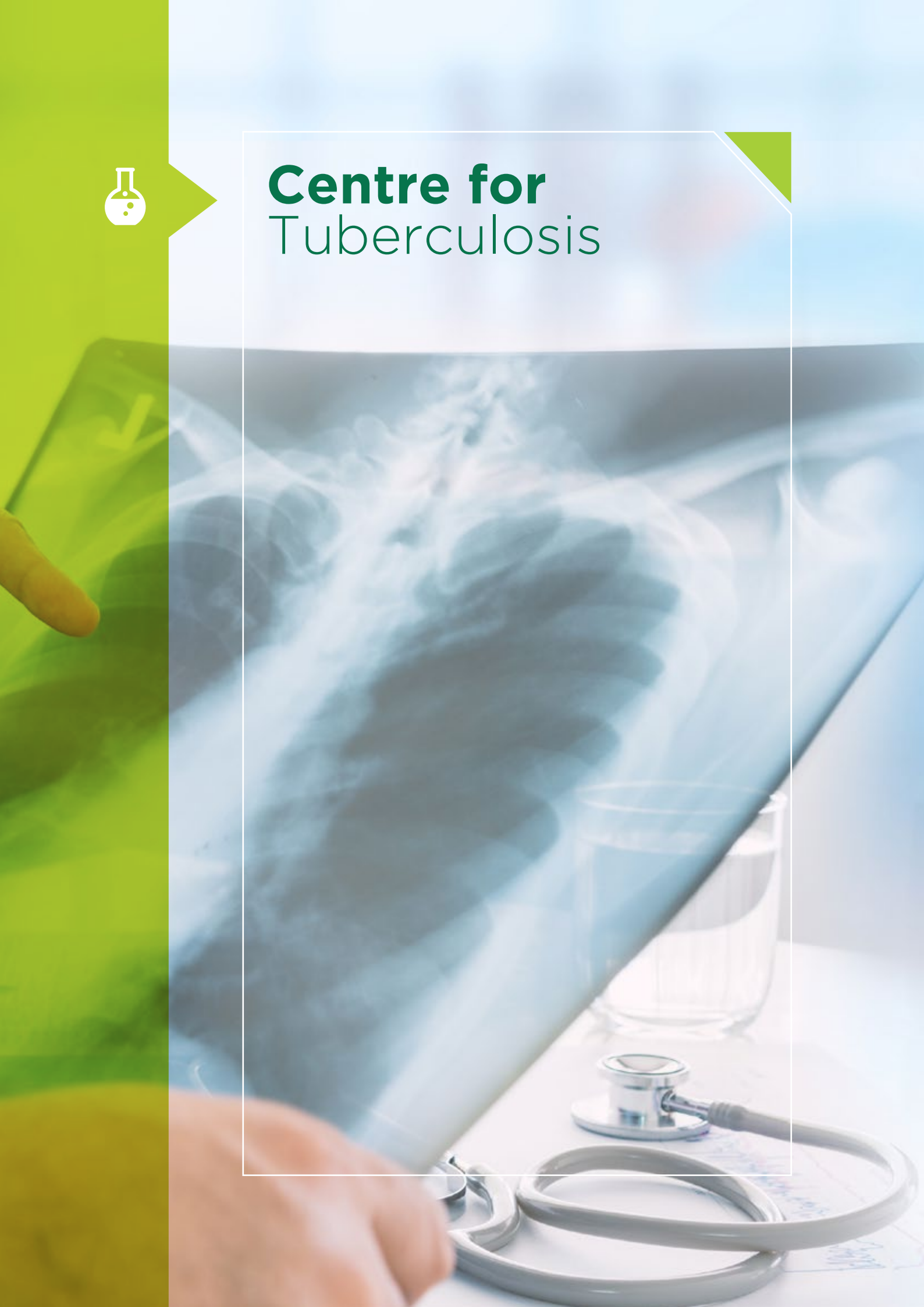
Conferences

International conferences: 34
National/local conferences: 13

Centre for Tuberculosis



1. Background

Centre Head
Prof Nazir Ismail

The year under review was a highly productive and an exciting period. The Centre for Tuberculosis (CTB) enhanced its laboratory-based public health surveillance of Tuberculosis (TB), introduced 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.

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 aimed at understanding factors that impact the TB epidemic in South Africa, and use that knowledge and insight in 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 the NDOH. An important activity this year was the development of the missing TB patient burden strategy in which the Centre played a leading role. The ongoing TB prevalence survey, coupled with the TB inventory study which the CTB leads, will be critically important in quantifying the true magnitude of the TB epidemic and refining the missing TB patients' strategy. The geospatial mapping of the TB burden facility level hotspots performed through the Centre was also incorporated into the strategic plan.

Surveillance using next generation WGS technologies continues to improve the understanding of TB transmission in a high endemic setting. The expanded use of bedaquiline (BDQ) resulted in significant reductions in mortality and improvement in treatment success among patients with drug resistant TB, but at the same time, the emergence of patients with resistance to this new drug is concerning, and ongoing surveillance is in place. The year under review has no doubt been exciting for TB management in South Africa and for the CTB at the NICD.

2. Surveillance and diagnostic services

Routine surveillance reporting and request for action alerting

Surveillance findings continue to be analysed and reported to the national and provincial TB programmes regularly and are available through an online TB surveillance dashboard. The weekly results for action (RfA) reports now cover both drug susceptible, and drug resistant TB. Several new initiatives, aimed at integrating data systems, were implemented and will help to accurately estimate and monitor the total burden of TB in South Africa. The development of the TB module on the NMC system was another important advancement on the public health surveillance and response front.

The successful implementation of the DR-TB reflex algorithm was further strengthened by incorporating phenotypic testing for resistance to new and repurposed drugs (bedaquiline, clofazimine and linezolid). The CTB played a leading role in this initiative, both locally and globally, with major contribution to WHO policy by defining criteria for resistance to these drugs and also capacitating local laboratories to test for resistance to the drugs. A global coordination of quality assurance for BDQ resistance was successfully completed this year, with CTB leading a multi-country Survival Research Laboratory (SRL) network of laboratories.

National TB Prevalence Survey

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, taking into account the considerable gap between the estimates produced by the WHO and notifications that are received through the programme.

The survey, which is a collaborative activity between the NDOH, NICD, Human Sciences Research Council (HSRC) and MRC, made major progress in this financial year, with >95% clusters completed by yearend. Major lessons were learnt through this survey, which include health seeking behaviour and the importance of asymptomatic TB. Additionally, the survey data also helped to improve the understanding of the clinical relevance of the trace positive TB detected via the new Xpert Ultra cartridge.

Modernising tuberculosis surveillance

The online TB surveillance dashboard, that was launched with the then Minister of Health on 24 March 2017, provides data for the last ten complete years and is available at: www.nicd.ac.za. It is an open access tool that allows tracking of the TB epidemic up to sub-district level, including age-gender stratification. The restricted access dashboard is also active and simplifies the availability of data to the TB programme managers.

The NMC that was updated at the end of 2017, led to significant advancement of the new system managed by the NICD. In the 2018/2019 financial year, a web-based and mobile application-based solution made provision for other pathogens, excluding TB. This was however a deliberate decision that allowed time for the comprehensive development of a TB specific module that allows near real-time clinical notifications, has a push feature that provides the RfA information directly on the platform and is accessible everywhere in the country. The landing page of the NMC TB module is shown in Figure 1 below.

Going forward, registered users will have access to this information to ensure that a public heath response is activated, while enabling robust, automated monitoring and evaluation (M&E) through monitoring initial loss to follow up on a daily basis, and providing exception notifications for actions that are not addressed. The NMC TB solution will be active in the next financial year.

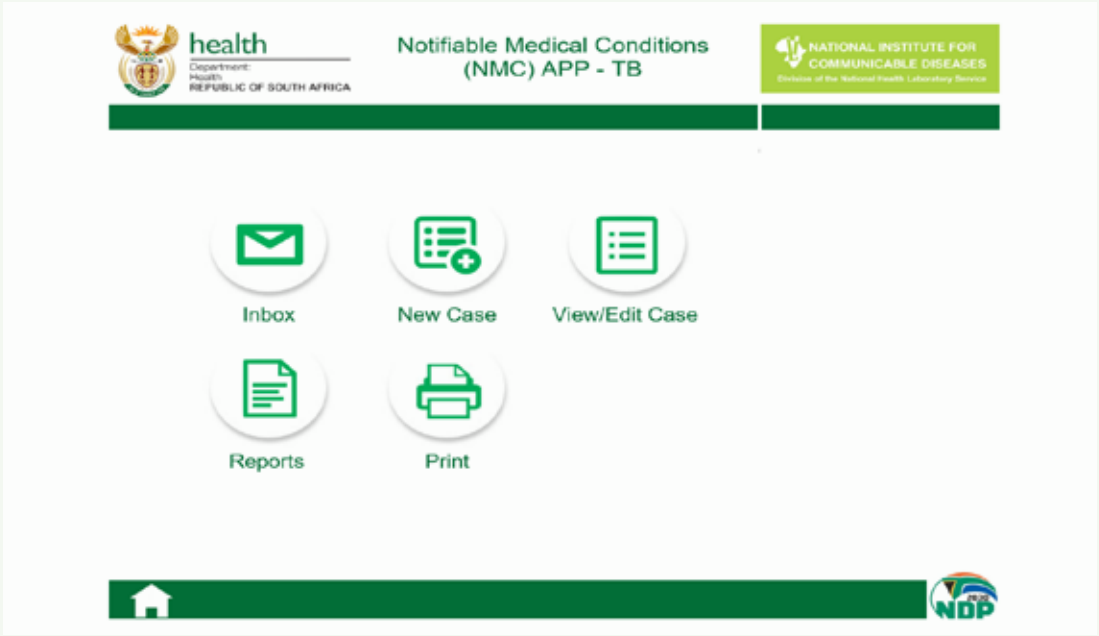


Figure 1. The web-based notifiable medical conditions surveillance system-landing page for tuberculosis.

Geospatial facility level hotspots of microbiologically confirmed tuberculosis in South Africa

The geospatial distribution of microbiologically confirmed pulmonary tuberculosis (mPTB) is highly heterogeneous at sub-district level and is even more apparent at facility level. The administrative boundaries are often arbitrary, and thus not optimal for designing geographically targeted interventions. Defining facility level hotspots has important public health relevance as it allows spatial targeting of interventions that could be highly cost-effective.

Following on the work to define the priority districts to find the missing TB patients, facility level geospatial hotspots were mapped for the 21 selected districts. An example is shown below in Figure 2. The methodology applied, identified 192 health facilities within these hotspots, with the number of facilities ranging from four to 25 per district. This is very useful and assists in further prioritisation of areas around these facilities for campaigns for active case finding activities.

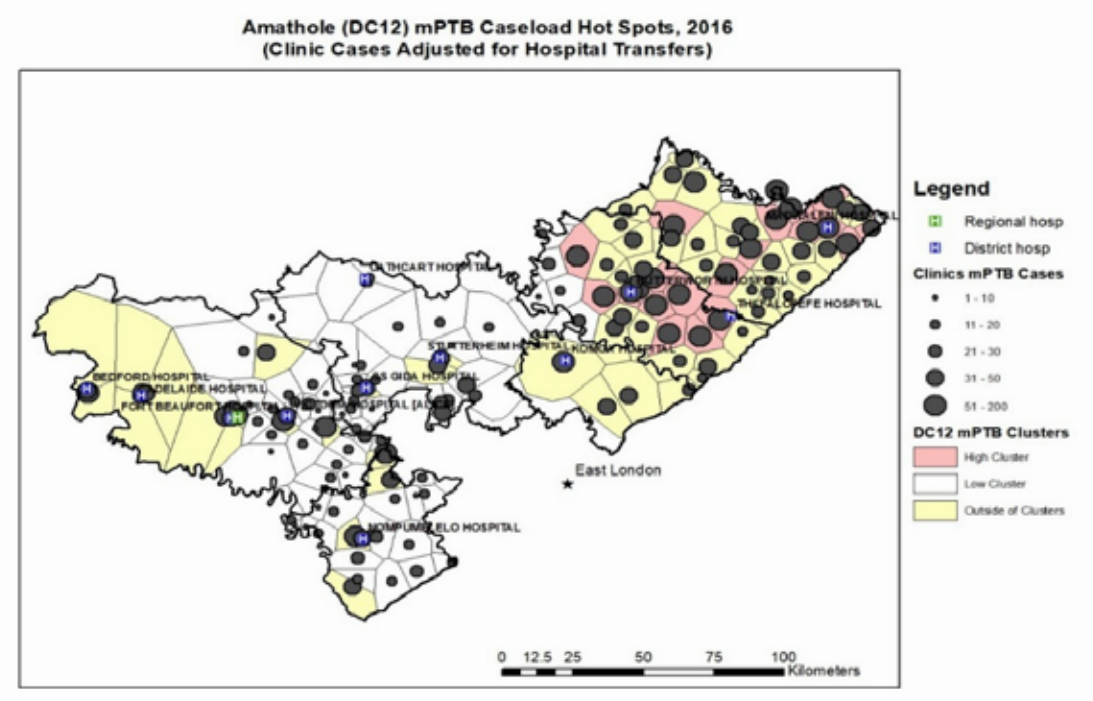


Figure 2. Clinic hotspots of microbiologically confirmed pulmonary tuberculosis burden (adjusted for hospital transfers), Amathole District, Eastern Cape Province: 2016.

Surveillance for resistance to new drugs: bedaquiline and delamanid

BDQ is a diarylquinoline anti-mycobacterial drug, which specifically inhibits mycobacterial adenosine triphosphate synthase. It is the first new drug belonging to a class with a novel mechanism of action. Since October 2014, Sirturo (BDQ) from Janssen Pharmaceutica, has been registered in South Africa for use in HIV-negative or HIV-infected ART-naïve patients, of 18 years or older, who have laboratory-confirmed MDR-TB. 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 rifampicin-resistant (RR)/MDR-TB. The new injection-free BDQ-based regimen has been administered to more than 15 000 patients.

The emergence of resistance to this drug has been seen to occur in South Africa and was detected through the BDQ surveillance programme. Many of these cases were detected among XDR-TB patients who are not responding to therapy. This results from either poor adherence, or poor regimens used. The BDQ surveillance was reduced to limited centres of excellence, while routine testing for BDQ was incorporated in selected provinces. It is planned to roll this out nationally in the coming year. To date, cases with BDQ resistance predominantly had resistance associated variants (RAVs) identified in the Rv0678 gene and none in the atpE gene. The former confers cross-resistance to clofazimine and is what was observed. Unfortunately, these RAVs are scattered across the gene, making a rapid test with preference for sequencing as the preferred approach unlikely.

Delamanid (DLM) is a dihydro-nitroimidazooxazole derivative that inhibits the synthesis of mycobacterial cell wall components, developed by Otsuka Pharmaceutical. Use of DLM (Deltyba) is approved for use in adults and children three years and older, who have drug resistant TB. The Minister of Health launched the DLM Clinical Access Programme (DCAP) on World TB Day in 2017. Surveillance was initiated alongside DCAP, with specific initiation sites chosen across different provinces. All patients initiated on DLM will submit baseline samples for testing. Those patients who remain culture positive at month three or later after initiation of treatment, will submit another specimen for further susceptibility testing. This surveillance will assist in establishment of breakpoints and detection of early emergence on resistance. Thus far, no resistance to DLM has been detected.

Specialised reference mycobacteriology – National and Supranational Reference Laboratory activities

The reference laboratory actively established standardised methodologies for BDQ resistance determination. A major multi-country study led by South Africa, across five SRLs globally (Belgium, Italy, Japan, Pakistan and South Africa), successfully completed a validation of three methods for BDQ resistance detection and the respective criteria. The Mycobacteria Growth Indicator Tube (MGIT) 960 system as well as the broth microdilution, both performed well across all RAVs. The historic agar proportion method performed sub-optimally for the detection of Rv0678 RAVs. This data and proficiency established across the DR-TB reflex testing laboratories in SA, will be shared with the WHO. Additional work was executed to ensure that these laboratories are proficient to test key second line drugs (levofloxacin and linezolid) that are now successfully used as frontline therapies for DR-TB. The Centre also provides extended drug susceptibility testing services for all patients failing on a drug resistant treatment regimen, significantly contributing to patient care around all facilities in the country.

On the regional front, we assisted Namibia with processing of their TB prevalence survey samples. We also provided quality assurance testing for a subset of samples that were part of the survey. In preparation for Angola's Drug Resistance Survey, the CTB facilitated protocol development and provided an analytical plan. Samples will be submitted to the CTB for further processing through WGS technology. The CTB is also the designated laboratory for processing samples for the Southern African Expand New Drugs for TB (ENDTB) clinical trial sites. Samples from Lesotho and Khayelitsha are sent to our laboratory for culture and DST. The clinical trial is planned to continue until 2021.

Molecular epidemiological surveillance for early detection of rifampicin-resistant tuberculosis clusters in selected districts

A review of the transmission surveillance conducted between 2015 and 2017, highlighted distinct population structures of *M. tuberculosis* strains in the different regions (Figure 3). The Beijing spoligotype predominates in the Nelson Mandela Metropolitan (Eastern Cape Province) has been replacing other strain types over time. It is often associated with high levels of resistance (e.g. XDR-TB). In the Mpumalanga region, the East African Indian spoligotype begun to emerge, highlighting its adjusted fitness in this region. Using MIRU-VNTR 24 loci for enhanced discrimination, just over half the cases were clustered with the vast majority in cluster sizes of two to five cases. Expectedly, clustering was highest among higher smear grade, while the largest clusters were associated with XDR-TB.

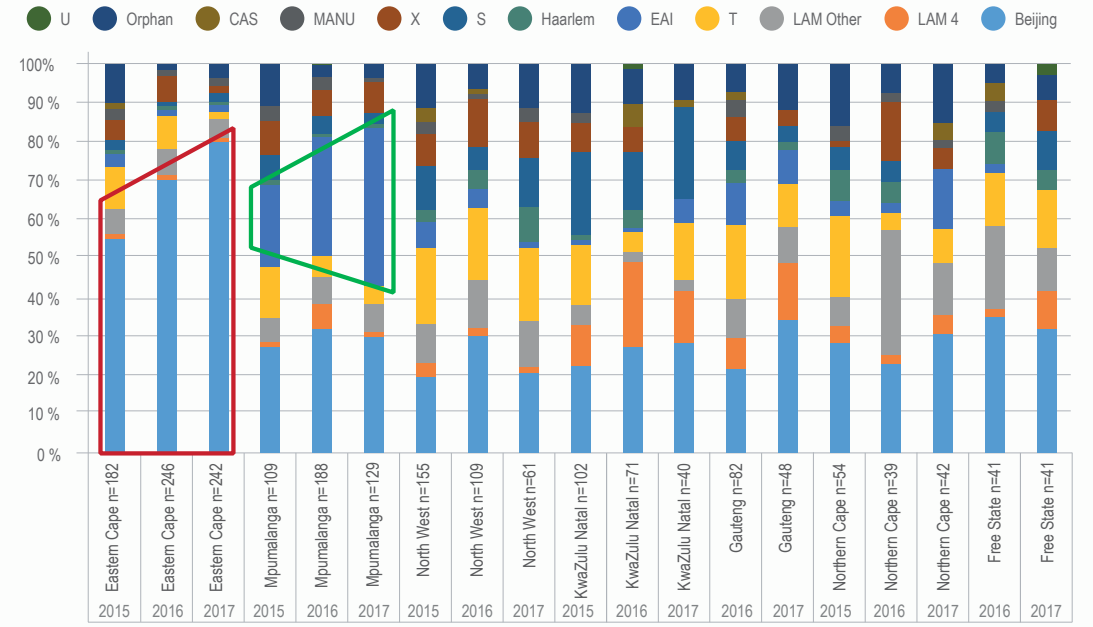


Figure 3. Spoligotype population structure in selected districts/regions among rifampicin-resistant tuberculosis: 2015-2017.

3. Policy contributions

Work executed by the Centre on phenotypic susceptibility testing for new and repurposed drugs, provided major contribution to the WHO 2018 technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant TB. The Centre further plays a significant role in contributing to the South African TB and DR TB guidelines, which are currently being updated.

4. Outbreaks

An outbreak of MDR-TB was reported by investigators from the University of Limpopo and Belgium, indicating that the outbreak strain was missed by WHO-endorsed technologies and continues to emerge. The reported cases occurred in the North West Province, with a few cases in Gauteng Province. These findings were published in a reputable journal and led to an early and rapid review, coordinated by the Centre and published as a response in the same journal, clarifying the low frequency of the mutation from surveillance data and risk of bias in the study. Vigilance for such cases is however necessary and testing is offered at the CTB, to detect this mutation. A second outbreak was reported in a specialised facility in Kwa-Zulu Natal. The concern arose from an increasing number of cases of TB seen over the years in this confined setting. Findings from the investigation revealed that the cases detected were attributed to enhanced case finding, rather than an outbreak. No clear epidemiological or microbiological evidence was found for an outbreak, but important findings related to infection control and case investigation was identified and recommendations were made.

5. Research activities

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

Collaborator: R Matji and the USAID Tuberculosis South Africa Project (TBSAP).

More than nine million new cases of active TB are occurring, and this poses a significant occupational health problem. HCWs specifically, are at increased risk of exposure to transmissible TB, especially in a high burden country like South Africa. The QuantiFERON-TB Gold Plus (QFT-Plus) detects latent tuberculosis infection (LTBI) and incorporates a marker that can potentially predict active TB cases, which has important value in the early detection of high risk exposures.

This project, which is a collaboration with the TBSAP 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. In addition, it seeks 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 Hospital, with just over half of all the hospital staff enrolled in the study. Feasibility of applying the test was complex but achievable, with both excitement and interest among participants. Two additional sites will be added in the coming year. The study is a cohort study design and will follow through on the HCWs enrolled for the total period of three years.

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

Collaborators: I Abubakar (University College London, UK) and S Moyo (HSRC 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. Based on earlier pilot data, the loss is approximately 15 - 20%. This is a significant barrier to achieving the targets set for 2025 and 2035.

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

The design applied is a multi-centre, parallel-group, open-label randomised controlled trial and is conducted in 14 clinics in Gauteng Province. Over 1 000 participants were enrolled in the trail and the use of modern technology is applied. This includes biometric capturing at all the facilities, as well as conditional mobile payments to participants. An interim analysis is scheduled for December 2019.

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

Collaborators: L Mvusi (NDOH, South Africa) and L Anderson (WHO, Switzerland).

Understanding and having an accurate measure of the burden of a 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 burdened and resource-limited countries however, lack national TB surveillance systems that have the robustness to accomplish surveillance, while the estimated burden and what is reported, differs drastically.

Retrospective analysis of all TB records from the NTP (ETR.Net & EDRweb), the NHLS and private laboratories will be matched, using specialised algorithms and a manual review process. The proportion of case overlap among sectors will be used to estimate TB incidence and estimate the under-reporting of TB notification in South Africa. Data was received, and algorithm optimisation and manual verification systems were developed. The private laboratory sector also participated successfully. Following the capture – recapture analysis, risk factors will also be analysed to understand reasons for under-reporting and measures instituted to ensure future corrective action.

Comprehensive Resistance Prediction for Tuberculosis: An International Consortium

Collaborator: D Crook (Oxford University, UK).

The Comprehensive Resistance Prediction for Tuberculosis (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 there is considerable information available on the common RAVs, it is only through a large study like this that the clinical relevance of rare RAVs can be reliably deciphered. Over 11 000 genotypes and 8 500 phenotypes were collated from nine countries, including China, India and South Africa. Innovative tools such as scanning software and crowd reading were applied to minimal inhibitory concentration (MIC) interpretations, while machine learning technology is being applied to the large combined data sources. The broader target is to reach ~30 000 whole genomes with associated phenotype, and the project is currently operational at full scale. Concepts of MIC ranges by mutation are emerging, as well as proteomic structural science based on genomic data that are providing further insights.

6. Teaching and training

The Centre provided onsite training to scientist from Eswatini's (formerly Swaziland) National TB programme for TB typing methods (spoligotyping and MIRU-VNTR) and WGS, including analysis. Onsite training for postgraduate students from the universities of Pretoria and Witwatersrand were provided on phenotypic DST for pyrazinamide and WGS respectively. In addition, a scientist from the University of Free State was trained on sample storage techniques and typing methods.

Two scientists from Sudan were trained onsite in all the routine diagnostic TB tests from microscopy and decontamination to line probe assays (LPAs) and phenotypic DST. Training was also provided on both reference mycobacteriology testing and public health aspects of TB to rotating registrars from university-based medical microbiology and public health departments in South Africa, as well as for intern scientists in the country. In addition, the Centre's pathologists and scientists provided training to undergraduate medical students and postgraduate medical microbiology students (registrars, Honours and MSc) from the University of Pretoria, by means of lectures and tutorials. The CTB also mentored a Field Epidemiology and Laboratory Training Programme (FELTP) student, further expanding capacity in epidemiology in South Africa.

Lastly, a group of scientists from the Centre developed training material for national reference laboratories in Vietnam, Philippines, Turkey and Lithuania, for performing MIC testing for BDQ and travelled to these countries to provide hands-on training.

Professional development

In line with acquiring additional skills to enhance work performance, certain staff members attended various workshops and courses such as Big Data Analytics Track of the 2018 World Bank Skills Building Programme (Pretoria) and a WHO data analysis workshop (Geneva).

Postgraduates

- Five candidates were enrolled for PhD, of which one thesis was submitted for marking, and another completed. In addition, three MSc students also graduated;
- One intern medical scientist completed training, and one is currently in training;
- Prof NA Ismail was promoted to Permanent Professor in the Department of Medical Microbiology at the University of Pretoria and Honorary Professor at the Department of Internal Medicine at the University of Witwatersrand.

7. Research outputs

Journal articles

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Conferences

International conference: 7
National conference: 6

8. Acknowledgements

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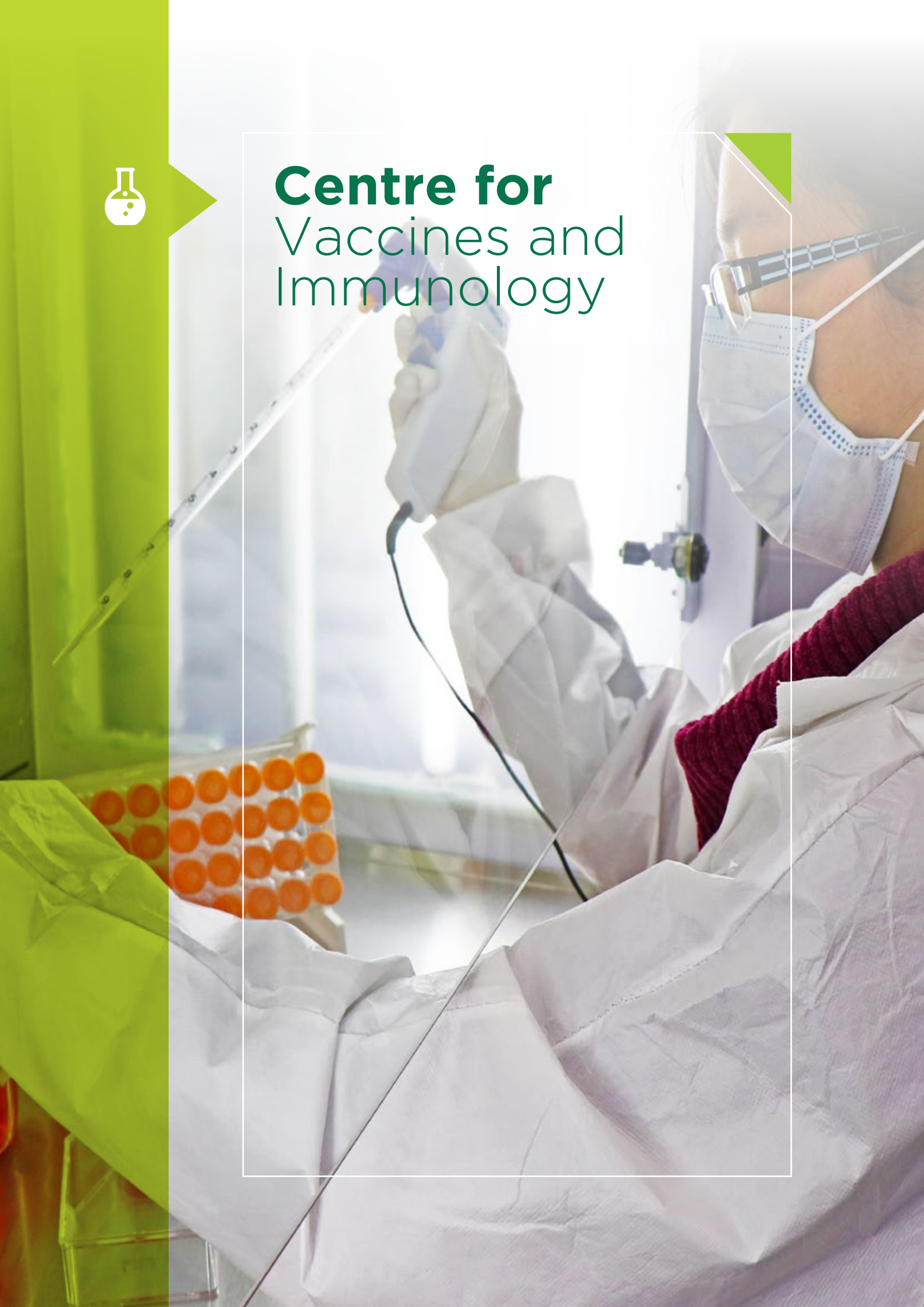
Centre for Vaccines and Immunology



1. Background

Centre Head
Dr M Suchard

The Centre for Vaccines and Immunology (CVI) comprises the National and WHO Regional Reference Laboratories for acute flaccid paralysis, and measles and rubella surveillance. In addition, the Centre conducts projects on viral hepatitis, TB and other vaccine preventable diseases. The Centre, furthermore, supports the Global Polio Eradication Initiative (GPEI) through a BSL 3 laboratory and environmental surveillance laboratory. CVI also provides epidemiological, virological and immunological support to the NDOH for vaccine preventable diseases.

2. Surveillance

Polio surveillance

The Poliovirus Isolation Laboratory serves the following eight countries within the southern African region in this capacity: Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, Eswatini (formerly Swaziland) and South Africa. The Centre serves the broader African region as a Regional Reference Laboratory. The CVI is the only poliovirus sequencing laboratory in the region.

For any acute flaccid paralysis case, stool samples are inoculated into cell cultures and any sample with suggestive poliovirus cytopathic effects are subjected to molecular typing and characterisation, to confirm poliovirus serotype and differentiate poliovirus subtype. During the reporting period, 1 390 South African samples were processed for poliovirus isolation.

In addition to processing South African samples, as the Regional Referral Laboratory, we identified vaccine derived poliovirus Type 2 (VDPV2) from 57 samples. The samples were mostly from the Democratic Republic of Congo (DRC), followed by Niger, then Mozambique. The three countries have been battling outbreaks of circulating VDPV2. Sabin polioviruses Type 2 were detected in 334 other samples, all from countries using monovalent oral polio vaccine type 2 to halt VDPV2 transmission: the DRC, Niger and Ethiopia.

The NICD applied with the NDOH to host a Polio Essential Facility (PEF), 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. Operations of the proposed PEF commenced in 2016.The application was approved by the NDOH in March 2017. The National Authority for Containment received the application for participation from the NICD as a PEF, and it is currently under review by the Global Containment Advisory Group.

The NICD provides ongoing support to the WHO for environmental polio surveillance from sewerage sites: 97 samples were received from Angola, 91 from Mozambique and 189 from Zambia. Ten samples were sequenced from other environmental laboratories in the DRC, Ethiopia, Niger, Madagascar and Uganda. Two VDPV2 from DRC were identified. The rest of the samples were either Sabin-like viruses, non-polio enteroviruses or non-enteroviruses.

Measles

The CVI is 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 measles virus, in support of the African Region's 2020 measles elimination goal and the global measles elimination initiative.

Serology, specifically the detection of measles-specific IgM antibodies, PCR and genotyping is used in conjunction with epidemiologic case investigations in the diagnosis of acute measles infection.

A total of 3 508 South African samples were tested during the reporting period. After review, 50 cases were classified as confirmed measles cases. Additional information on the measles cases was reported in the online bulletin of the NICD. 1 130 rubella cases were furthermore identified; a development that was not unexpected, as 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 nine southern African countries, namely: Botswana, Lesotho, Madagascar, Malawi, Mozambique, Namibia, Eswatini (formerly Swaziland), Zambia and Zimbabwe. A total of 393 samples were tested. There was good concordance for the measles IgM results (90-100%), with slightly poorer concordance for rubella IgM results (80-100%).

Congenital Rubella Syndrome surveillance

The CVI established a sentinel site surveillance programme for congenital rubella syndrome (CRS), which includes 28 study sites in all nine provinces of South Africa. Through the programme, seven laboratory-confirmed CRS cases were detected in four provinces (Eastern Cape = one, Free State = one, Gauteng = one and Western Cape = four). 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.

Hepatitis

The CVI, together with the NDOH, is committed to reach the 2030 viral hepatitis elimination goals. To provide accurate data on hepatitis B, data was mined from the Corporate Data Warehouse (CDW) of the NHLS. In the reporting period, 36 614 patients on the database was positive for hepatitis B. The number of incident cases (defined by anti-HBc IgM) was 2 251. The HBsAg prevalence ranged from 94/100 000 population in Gauteng Province to 29/100 000 population in Limpopo Province. Gauteng Province had the highest incidence of 6/100 000 population. In 2018/2019, there were 167 HBsAg positive cases in the zero-one age group. The data was reported via the WHO joint reporting form.

Monthly hepatitis A incidence is reported to the multinational outbreak response team (MNORT).

Outbreaks

International

Ebola: Dr NV Motaze was deployed as a GOARN consultant for the WHO from June to July 2018 and from January to March 2019. He reinforced response activities during the Ebola virus disease (EVD) outbreaks in Equateur and North Kivu provinces in the DRC.

South Africa

Polio: In October 2018, we identified a case of vaccine derived polio virus (VDPV) serotype 3, in a South African child. Detection of such an event is of international public health importance and can impact the global polio end game. This was a second case, following a similar case identified in January 2018. Notification of the case by the NICD triggered an investigation response by multiple partners, including national and provincial departments of health and the WHO. The investigation confirmed that the event was not due to circulating polio virus, but rather due to an immune deficiency in the affected infant. Close contacts of the index case, as well as community members, were tested for shedding of poliovirus in their stool, which confirmed no circulation of the virus. The index case did not respond to pocapavir treatment, an off-label use of this antiviral drug, and passed away in March 2019.

Hepatitis A: The NICD was notified of a cluster of hepatitis A cases in a paediatric ward (treating children with multidrug resistant TB and HIV) at King Dinuzulu Hospital (King George) in eThekwini, KwaZulu-Natal, from November to December 2018. During this period, seven cases positive for hepatitis A IgM were reported in the ward. All the other children (N=20) and staff (N=30) in the ward that were tested for hepatitis A IgM were found to be negative. Of the 30 staff, 26 were immune. At the time of identifying the cluster, there was a shortage of hepatitis A vaccines and immunoglobulin. It was recommended to reinforce good hygiene principles for nappy changes, strengthen hand hygiene and infection control, both in the ward and in the kitchen.

Measles: Provincial departments of health respond to every measles case through home visits and vaccination of contacts. The Centre regularly collaborates with national and provincial departments of health through meetings and teleconferences to follow up on every positive case. Clusters of cases are described in more detail in the online bulletin of the NICD.

3. Policy Contributions

Hepatitis B birth dose in South Africa – literature review and recommendations were submitted to the National Advisory Group on Immunisation in November 2018.

4. Research activities

Congenital rubella syndrome surveillance in South Africa using a sentinel site approach: A cross-sectional study

NICD investigators: NV Motaze, JM Manamela, S Smit, A Mazanderani, C Cohen and M Suchard.
Collaborators: H Rabie (Department of Paediatrics, Tygerberg Hospital, Stellenbosch University), K Harper (Department of Paediatrics, Frere Hospital), N du Plessis (Department of Paediatrics, Kalafong Hospital, University of Pretoria), G Reubenson (Department of Paediatrics & Child Health, Empilweni Service & Research Unit, Rahima Moosa Mother & Child Hospital), M Coetzee (Department of Paediatrics & Child Health, Steve Biko Academic Hospital, University of Pretoria), *et al*.

Congenital rubella syndrome (CRS) includes disorders associated with intrauterine rubella infection. Incidence of CRS is higher in countries with no rubella-containing vaccines (RCVs) in their immunisation schedules. In the WHO African region, RCVs are being introduced as part of the 2012 - 2020 global measles and rubella strategic plan. Baseline data on laboratory-confirmed CRS will enable planning and monitoring of RCV implementation in the South African EPI programme.

Figure 1. Two three-day measles and rubella serology workshops were conducted for the World Health Organization in the Poliomyelitis Research Foundation Virology Training Laboratory, from 24 - 26 September and 27 - 29 September 2018, with trainers Sheilagh Smit, Mirriam Fortuin and Lillian Makhathini.

Figure 1A. Dr NV Motaze was deployed as a Global Outbreak Alert and Response Network consultant under the World Health Organization to support the Ebola outbreak in the Democratic Republic of Congo. Here he can be seen during training of healthcare workers at points of entry along the Congo River in Brazzaville, in the Democratic Republic of Congo, in July 2018.

Figure 1B. Conversing with an Ebola survivor during an investigation of a suspected case, in Butembo in the Democratic Republic of Congo, in February 2019.

Figure 1C. Dr NV Motaze receiving the Ebola vaccine in the Democratic Republic of Congo, in 2019.

5. Teaching and training

- The CVI is a national and regional resource for training of medical scientists, technologists, registrars and field epidemiology training programme residents. Trainees acquire specialised skills in the disciplines of virology and immunology. The CVI hosted a PCR workshop on intertypic differentiation of polioviruses, from 5 November 2018 - 9 November 2018 and conducted sequencing training from 22 October 2018 to 31 October 2018.

- Two to three-day measles and rubella serology workshops were conducted for the WHO in the PRF virology training laboratory from 24 - 26 September and 27 - 29 September 2018. There were 30 participants from African anglophone countries (Botswana, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Kenya, Lesotho, Liberia, Malawi, Mozambique, Mauritius, Namibia, Nigeria, Seychelles, Sierra Leone, South Sudan, Tanzania, Uganda, Zimbabwe and Zambia) and, in preparation for the francophone training, a participant from Cote D'Ivoire. Facilitators and stakeholders were from the CVI (three), WHO (four), China CDC (two), USA CDC (three), Euroimmun (one) and Virion/Serion (two);

- Dr Suchard was a course designer and module coordinator of the MSc Vaccinology Course, which was run for the first time at Wits in 2019. Dr Suchard is also an external examiner for the Higher Certificate in Vaccinology available at Sefako Makghato University and a moderator for the HPCSA for intern scientist portfolios; and

- Dr Jallow and Dr Hong lectured students in Molecular Medicine and Haematology and MSc Vaccinology at Wits. Dr Hong also lectured University of Johannesburg Biotechnology Honours students.

Professional development

- Eight students were enrolled : Two MSc , two in FETP, one MMed and three PhD.
- One student graduated in FETP.

6. Research outputs

Journal articles

1. Mbaeyi C, Alleman MM, Ehrhardt D, Wiesen E, Burns CC, Liu H, Ewetola R, Seakamela L, Mdodo R, Ndoutabe M, Wenye PR, Riziki Y, Borus P, Kamugisha C and Wassilak SGF. Update on vaccine-derived poliovirus outbreaks — Democratic Republic of the Congo and Horn of Africa, 2017–2018. Morbidity and Mortality Weekly Report. 2019; 68: 225–230.

2. Motaze NV, Manamela J, Smit S, Rabie H, Harper K, du Plessis N, Reubenson G, Coetzee M, Ballot D, Moore D, Nuttall J, Linley L, Tooke L, Kriel J, Hallbauer U, Sutton C, Moodley P, Hardie D, Haeri Mazanderani A, Goosen F, Kyaw T, Leroux D, Hussain A, Singh R, Kelly C, Ducasse G, Muller M, Blaauw M, Hamese M, Leeuw T, Mekgoe O, Rakgole P, Dungwa N, Maphosa T, Sanyane K, Preiser W, Cohen C and Suchard M. Congenital rubella syndrome surveillance in South Africa using a sentinel site approach: A cross-sectional study. Clinical Infectious Diseases. 2018; XX: 1-7.

3. Motaze NV, Nwachukwu C and Humphreys E. Treatment interventions for diarrhoea in HIV-infected and HIV-exposed children: A systematic review. Pan African Medical Journal. 2018; 29: 208-216.

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5. Buckee CO, Cardenas MIE, Corpuz J, Ghosh A, Haque F, Karim J, Mahmud AS, Maude RJ, Mensah K, Motaze NV, Nabaggala M, Metcalf CJE, Mioramalala SA, Mubiru F, Peak CM, Pramanik S, Rakotondramanga JM, Remera E, Sinha I, Sovannaroth S, Tatem AJ and Zaw W. Productive disruption: Opportunities and challenges for innovation in infectious disease surveillance. BMJ Global Health. 2018; 3: 1-5.

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7. Thobela MD, Smith AM, Moonsamy S, du Plessis H, Govender N and Keddy KH. Detection of *Campylobacter* species in stool specimens from patients with symptoms of acute flaccid paralysis in South Africa. Journal of Infection in Developing Countries. 2018; 12: 542-549.

8. Jallow S, Agostia Y, Kgagudia P, Vandecar M , Cutlanda CL, Simões EAF, Nunes MC, Suchard MS, and Madhi SA. Transplacental transfer of respiratory syncytial virus neutralizing antibodies in HIV-infected compared to HIV-uninfected pregnant women. Clinical Infectious Diseases. 2018. ciy1071. https://DOI.org/10.1093/cid/ciy1071.

9. Howard W, Moonsamy S, Manamela MJ, Motaze V, Seakamela L, Du Plessis H, Sibiya R, Mohlala G, Maseti E, Kamupira M and Suchard MS. Acute flaccid paralysis surveillance for polio, South Africa and other African countries, 2017. Online bulletin of the National Institute for Communicable Diseases May 2018.

10. Hong HA, Makhathini L, Mashele M, Malfeld S, Motsamai T, Sikhosana L, Manamela J, Motaze NV, Smit S, Maseti E, Dlamini N, Kamupira M, McCarthy K and Suchard MS. Annual Measles and Rubella Surveillance Review, South Africa, 2017. Online bulletin of the National Institute for Communicable Diseases September 2018.

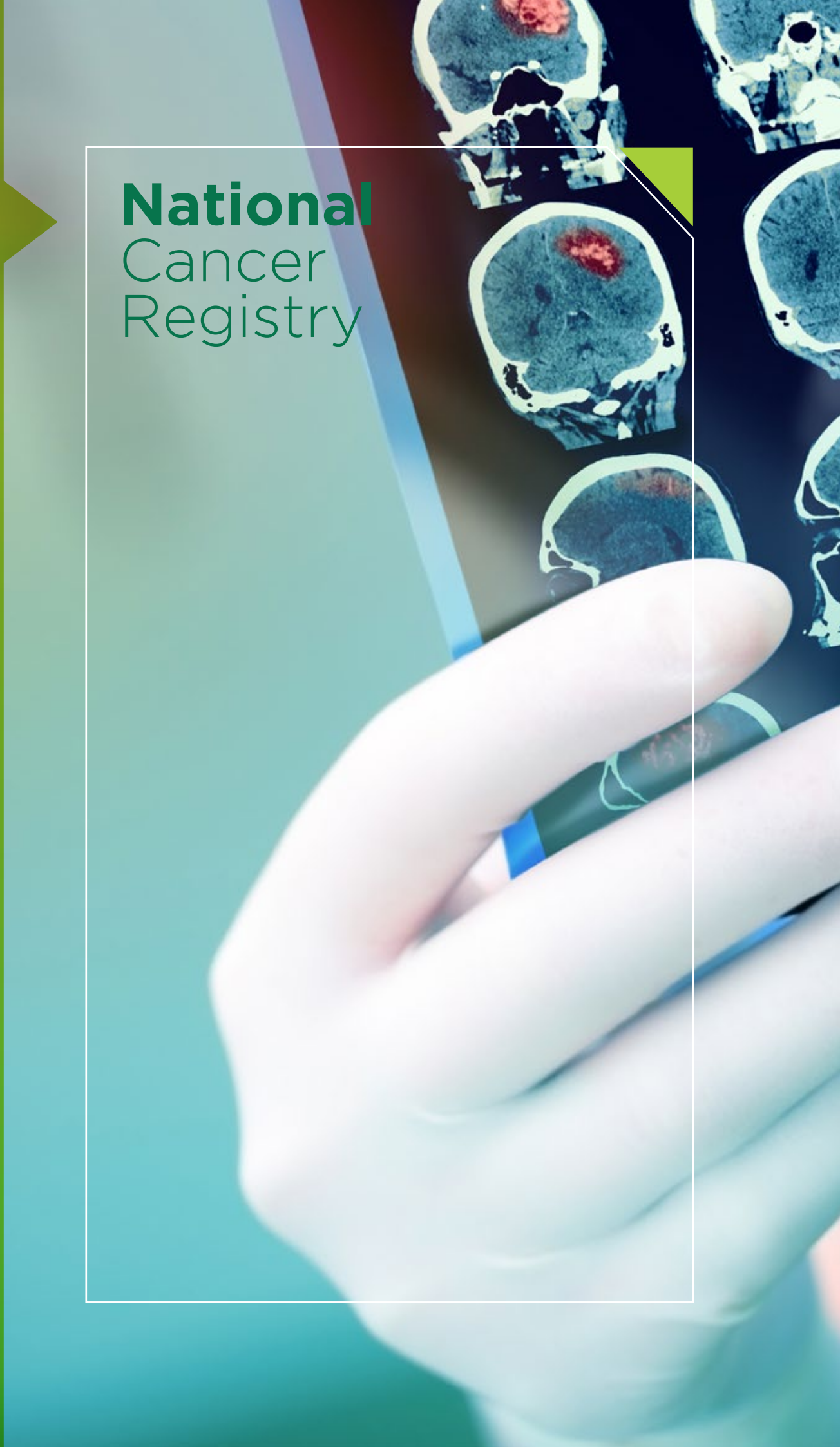
Health promotion

October 2018: Survving Polio, a documentary of 4 South African Polio Survivors, to commemorate World Polio Day 2019 https://www.youtube.com/watch?v=RW-lzRI_Nml&feature=youtu.be

Conferences

International congresses: 2
National congresses: 3

National Cancer Registry



1. Background

Centre Head
Dr Elvira Singh

The primary roles of the National Cancer Registry (NCR) are the management of the national pathology-based cancer surveillance system and implementation of population-based cancer registration. In the year under review, the NCR embarked on a case-finding optimisation project to improve completeness of the Ekurhuleni Population-based Cancer Registry (EPBCR). The EPBCR data was collected, cleaned, analysed and the first EPBCR annual incidence report was completed. The NCR improved its strategic relationships with both local and international partners in cancer surveillance. The Registry conducted a successful cancer meeting and engaged effectively with local stakeholders in cancer surveillance. We also strengthened our participation in the African Cancer Registry Network (AFCRN), which is the International Agency for Research on Cancer (IARC) regional hub for cancer surveillance in sub-Saharan Africa, through fellowships for NCR epidemiologists and participated in the AFRCN annual meeting. The NCR successfully motivated and applied for funding for population-based registration from the NDOH and the private sector.

In the 2018/2019 financial year, the NCR published key research in cancer epidemiology and genetics. Our study on temporal trends in cervical cancer epidemiology showed gross disparities in cancer mortality between black African and white women in the country. The age-standardised mortality rate was nearly six times higher in black than in white women. Another study exploring liver cancer mortality demonstrated a rising trend for this disease in middle to older aged black African men and women in the recent decade. Black Africans were more likely to die from liver cancer compared to the white population. Both studies highlighted persistent racial disparities in cancer incidence and mortality, which reflect an interplay between viral risk factors and differential access to cancer diagnosis and care.

We also investigated genetic variants from seven oesophageal squamous cell carcinoma (OSCC) risk loci identified in non-African populations, for association with OSCC in the South African black population. Only one nucleotide polymorphism in the CHEK2 gene, rs1033667, was significantly associated with OSCC. The lack of association of six of these loci with OSCC in South African populations, may reflect different genetic risk factors in non-African and African populations, or differences in the genetic architecture of African genomes. The association at CHEK2, a gene with key roles in cell cycle regulation and DNA repair in an African population, provides further support for the contribution of common genetic variants at this locus to the risk of oesophageal cancer.

Sadly, in the year under review we lost one of our longest serving cancer coders, Meriam Ramela, who passed away in May 2018.

2. Surveillance

Pathology-based cancer registry

The NCR electronic application, developed by the NICD IT-department has proved to be a success, and available NHLS cancer data were uploaded on the application. Cases from private pathology laboratories were reported in full. We did however notice that numbers of cases received from the Western Cape NHLS laboratories (Groote Schuur, Tygerberg and Red Cross) are significantly under-reported. We initiated an investigation involving SIMU, the Western Cape Laboratories, NHLS Trakcare® and other responsible parties. We are exploring novel text-mining techniques to overcome the identified challenges.

Ekurhuleni population-based cancer registry

The EPBCR team embarked on a case-finding optimisation strategy, based on lessons learnt from the Harare population-based registry in Zimbabwe. Following completion of case finding, a data quality control and assurance exercise was executed on 10% of records. Thereafter, data cleaning, data analysis and report writing was completed.

The first report of the EPBCR was completed in March 2019. A total of 3 371 cancers were registered for 2017, with 62% of cases reported from the black population. Prostate cancer was the most common cancer in men, and breast and cervical cancer were common in women.

The NCR hosted a Cancer Town Hall meeting on 5 September 2018, to engage stakeholders in the cancer community to raise awareness on the importance of cancer registration and to enhance cooperation with stakeholders. The meeting proved to be a resounding success, with the invited guests providing exciting ideas for cancer surveillance improvements and showing their support of the NCR's work.

3. Research activities

South African HIV Cancer Match Study

The South African HIV Cancer Match (SAM) Study is a national cohort of HIV-positive people created from NHLS HIV data (HIV tests, CD4 count and HIV VL tests) and linked probabilistically to the NCR, to determine the spectrum and risk of cancer in the HIV population. Data de-duplication of the HIV data and linkage to the NCR data is complete and a final de-identified dataset is under preparation. Ms T Dhokotera and Dr E Rohner presented two poster presentations on adolescents at the annual Conference on Retroviruses and Opportunistic Infections (CROI) in March 2019. Mr V Olago presented a poster on the use of supervised machine learning for linking HIV and cancer databases, at the International Workshop on HIV and Hepatitis Observational Databases (IWHOD) in March 2019. Mr Olago submitted his MSc in Research Database Management to Wits for examination.

A successful visit from our University of Bern collaborators in August 2018, allowed for important planning of the future strategic direction of the study.

Burden of Cancers Attributable to HIV (2004-2014)

The Burden of Cancers Attributable to HIV (BCAH) Study is a sub-study within the SAM study, which aims to estimate the burden of laboratory-diagnosed cancer attributable to HIV in the South African public sector. The additional cancer risk of HIV-positive people, compared to HIV-negative people in the era of ART, is also studied. The study was funded under the Beginner Investigator Grant for catalytic research in cancer awarded to Dr M Sengayi by the Civilian Research and Development Foundation (CRDF) Global, with the aim of building local capacity in cancer epidemiology.

In the year under review, our MSc Cancer Epidemiology fellow, Ms T Dhokotera, completed her MSc in Epidemiology and Biostatistics. The Wits School of Public Health (SPH) awarded a distinction for her research report entitled: 'The burden of cancers associated with HIV in the South African Public Health Sector, 2004-2014,' She wrote two manuscripts based on her MSc research work, one of which was accepted for publication in the Infectious Agents and Cancer Journal. She presented this work at AIDS 2018 and CROI 2019.

Johannesburg Cancer Case-control Study

The Johannesburg Cancer Case-control (JCS) is a case-control study of newly (<six months) diagnosed black cancer patients (1995 – 2016), with over 26 000 patients interviewed and more than 20 000 blood samples stored to examine genetic and emerging and/or novel risk factors for cancer. Several genetic and epidemiological studies are using JCS samples and data:

- **Evolving Risk Factors for Cancer in African Populations (ERICA-SA)**
  The main objective of this collaborative study is to identify genetic variants that are associated with susceptibility to breast, cervical and oesophagael cancer in African cancer patients. We recruited two PhD students (Ms M Motlhale and Mr M Singini) on the ERICA-SA study. The genotyping of all oesophagael cancer and breast cancer samples was concluded, with data analysis currently in progress.

- **Men of African Descent Cancer of the Prostate (MADCaP) Consortium**
  The MADCaP Consortium is an Africa-wide collaborative research, with US partners, to explore genetic causes of prostate cancer in men of African origin. Prospective data collection and patient recruitment is ongoing. DNA samples is submitted to the Centre for Proteomic and Genomic Research (CPGR) for microarray analysis. A database mapping exercise is ongoing, to ensure quality of the research data captured.

- **Breast Cancer in Black South African Women (Genetics)**
  This study aims to perform targeted sequencing of all known breast cancer susceptibility genes in young (<50) black South African women, diagnosed with breast cancer. Genome-wide association study (GWAS) analysis is ongoing. Targeted gene sequencing study is complete, and a manuscript is in preparation.

- **Genetic Aetiology of Oesphageal Squamous Cell Carcinoma (OSCC)**
  Mr W Chen, a medical scientist at the NCR, is conducting this study for his PhD. The aim of the project is to test the hypothesis that genetic variation in the South African black population contributes significantly to the risk of OSCC. The genetic replication paper was accepted and published in Carcinogenesis. GWAS analysis for oesophagael cancer is ongoing. Oesophagael tumour samples are in preparation for shipping to the Wellcome Trust Sanger Institute. Recruitment of oesophagael cancer patients at Chris Hani Baragwanath Hospital will commence in April 2019.

- **The impact of HIV testing policy on HIV testing patterns in cancer patients**
  This study examines the impact of the 2010 provider-initiated HIV counselling and testing policy on HIV testing patterns, in newly diagnosed cancer patients within the JCS. Our South African Field Epidemiology Training Programme (SAFETP) resident, Ms N Abraham, submitted this study for her Master's thesis and passed.

- **Ovarian cancer research project (Genetics)**
  Samples were submitted to collaborators at the University of Cape Town and DNA sequencing is in progress.

- **Hepatocellular carcinoma HBV miRNA**
  Serum samples were shipped to collaborators at the National Cancer Institute (NCI)/ NIH.

- **Pancreatic cancer research project**
  Serum samples were submitted to collaborators at the University of Cape Town and analysis is in progress.

- **Spectrum of HIV-associated cancers**
  This study seeks to explore the spectrum of HIV-associated cancers with the evolving HIV epidemic in South Africa, using JCS data. A first version of the HIV data analysis was completed in March 2019 and input from co-authors was received.

Colorectal cancer research project

This is a collaborative research project with the (WDGMC), which seeks to explore risk factors and survival of colorectal cancer (CRC) patients, using a prospective cohort of CRC patients from both private and public sectors. The first publication from this collaborative work entitled: 'Design and methodology of a study on colorectal cancer in Johannesburg, South Africa,' was published in the journal of Gastroenterology and Hepatology. Dr M Sengayi completed the analysis on a second manuscript and Prof P Ruff is preparing the draft manuscript for submission.

Anatomical Distribution of Colorectal Cancer in South Africa

This study was conducted by an MMED surgery student, Dr A Amer, in the Department of General Surgery at the University of Cape Town. The main objective of this study is to describe the anatomic location of colorectal cancer in South Africa from 2006 – 2010. This work was submitted for Masters examination to UCT.

Acknowledgements and collaborators

- Prof M Egger, Dr J Bohlius, Dr L Bartels and Dr E Rohner, Institute of Social and Preventive Medicine, University of Bern, Switzerland;
- Prof T Rebbeck (Harvard TH Chan School of Public Health, Harvard University, Boston, USA);
- Prof C Mathew, (Department of Medical & Molecular Genetics, Guy's Hospital, King's College London, United Kingdom);
- Prof D Bradshaw, (Medical Research Council of South Africa);
- Prof A Krause and Dr F Baine, (Division of Human Genetics, University of the Witwatersrand);
- Dr K Chu and Dr A Amer (Department of General Surgery, University of Cape Town);
- Prof A Kramvis and Mr D Mak (Hepatitis Virus Diversity Research Unit;
- Department of Internal Medicine, University of the Witwatersrand);
- Dr P Pisa and Dr A Chikandiwa (Wits Reproductive Health Institute, University of Witwatersrand);
- Prof Pl Ruff and Dr B Bebbington (Wits Donald Gordon Oncology Centre);
- Dr D M Parkin (Nuffield Department of Population Health, Oxford University, United Kingdom); and
- Prof F Sitas (University of Sydney, Australia).

4. Teaching and training

- Dr E Singh and Dr M Sengayi continued to teach MPH and MSc Epidemiology students at the Wits SPH. Ms L Motsuku presented lectures to SAFETP students on cancer surveillance and on introduction to programming with R software.

- Dr E Singh presented on 'Cancer Surveillance and Epidemiology in the African Region' at the China-African Public Health Collaboration Workshop, on behalf of the NICD.

- As part of our long-term plan to build capacity for cancer research at grassroots level at the NCR, we identified two NCR coders, Ms L Malakoane and Ms M Mohlala for mentoring in research. They participate in monthly journal club meetings. Ms Malakoane and Ms Mohlala attended a 'Comprehensive Statistics Course Using Stata' training session at the Centre for Epidemiology and Statistical Analysis Research (CESAR), from 25-29 March 2019. Ms L Malakoane passed her Honours degree in Life Sciences with distinction, in March 2019.

- Dr M Sengayi presented lectures on data analysis and presentation to members of the AFRCN at the AFCRN meeting in Entebbe, Uganda.

- Dr M Sengayi conducted induction lectures on data analysis to newly employed NICD provincial epidemiologists and NMC epidemiologists.

- Dr M Sengayi chaired a postgraduate assessor group meeting for MSc epidemiology student protocols at Wits SPH on 21 November 2018 and was the senior academic discussant for a PhD protocol presentation on 23 November 2018.

- Ms B Ndlovu attended a course on essential Tumour, Node, Metastasis (TNM) staging, which was organised by the AFCRN and IARC from 26 – 30 November 2018 in Addis Ababa, Ethiopia.

- Mr V Olago attended the African Union writing workshop in Uganda, from 26 - 30 Nov 2018.

Professional development

- Dr E Singh and Dr M Sengayi attended the AFCRN annual meeting in Entebbe, Uganda, in October 2018.

- Dr M Sengayi was awarded the African Oxford Travel Grant in May 2018, to travel to the Cancer Epidemiology Unit, Nuffield Department of Population Health, Oxford University to work on cervical cancer survival in African populations under the mentorship of Dr DM Parkin, coordinator of the African Cancer Registry Network. She travelled to Oxford from 7 July – 5 August 2018. Analysis is complete and a mature draft manuscript is ready for submission.

Students supervised and registered during 2018/2019

We had six PhD students in the period under review (Mr M Singini, Ms M Motlhale, Mr C Chen, Mr D Mak, Mr W Mapanga and Dr A Chikandiwa). Mr Daniel Mak, Mr Witness Maphanga, Dr Admire Chikandiwa and Mr W Mapanga completed their PhDs this year.

Eight students were registered for MSc/MPH/MMed degrees (Dr Akrem Amer, Ms Tafadzwa Dhokotera, Mr Victor Olago, Ms Babongile Ndlovu, Ms Lerato Khoali, Ms Natasha Abraham, Ms Evidence Majaya, and Ms Carole Temdemnou Metekoua). Ms Tafadzwa Dhokotera (with distinction) and Ms N Abraham completed their Masters' degrees in the period under review.

Two students were registered for honours degrees (Ms M Mohlala and Ms L Malakoane). Ms L Malakoane completed her Honours degree (with distinction) in the period under review.

Honours

- Mr WC Chen was awarded a renewal of the NRF-Thuthuka grant, to the value of R250000.00 per annum, for oesophageal cancer related work;

- Ms L Motsuku was awarded USD $2000, by the Union for International Cancer Control, to fund a one-day workshop on cancer registration for stakeholders and gatekeepers from EPBCR data sources and sites;

- Ms T Dhokotera was awarded a distinction for her MSc research report entitled: 'The burden of cancers associated with HIV in the South African Public Health Sector, 2004-2014;

- Ms T Dhokotera was awarded the Young Investigator Award at CROI 2019 for her abstract entitled: 'HIV and Cancer amongst adolescents and young adults living with HIV in South Africa.' She was also interviewed at AIDS 2018 as part of the young investigator panel (https://www.youtube.com/watch?v=HHyYiudUTb4);
- Ms T Dhokotera was awarded the Swiss School of Public Health Plus PhD scholarship for 2019 and will undertake her PhD work on 'The cervical cancer cascade of care' at the NCR; and

- Dr M Sengayi was awarded the African Oxford Travel Grant to travel to Oxford University and work on 'Cervical cancer survival in African women' under the mentorship of Dr DM Parkin, coordinator of the African Cancer Registry Network.

5. Research outputs

Journal articles

1. Bebington B, Singh E, Fabian J, Kruger CJ, Prodehl L, Surridge D, and Ruff PP. Design and methodology of a study on colorectal cancer in Johannesburg, South Africa. JGH Open. 2018; 1–5. https://DOI.org/10.1002/jgh3.12061.

2. Olorunfemi G, Ndlovu N, Masukume G, Chikandiwa A, Pisa PT and Singh E. Temporal trends in the epidemiology of cervical cancer in South Africa (1994–2012). International Journal of Cancer. 2018. DOI: 10.1002/ijc.31610.

3. Mak D, Babb de Villiers C, Chasela C, Urban MI and Kramvis A. Analysis of risk factors associated with hepatocellular carcinoma in Black South Africans: 2000-2012. PLOS One. 2018; 13 (5): e0196057. https://DOI.org/10.1371/journal.

4. Mak D, Sengayi M, Chen W, Babb de Villiers C , Singh E and Kramvis A. Liver cancer mortality trends in South Africa: 1999-2015. BMC Cancer. 2018. DOI: 10.1186/s12885-018-4695-9.

5. Andrews C, Fortier B, Hayward A, Lederman R, Petersen L, McBride J, Petersen DC, Ajayi O, Kachambwa P, Seutloali M, Shoko A, Mokhosi M, Hiller R, Adams M, Ongaco C, Pugh E, Romm J, Shelford T, Chinegwundoh F, Adusei B, Mante S, Snyper NY, Agalliu I, Lounsbury DW, Rohan T, Orfanos A, Quintana Y, Jacobson JS, Neugut AI, Gelmann E, Lachance J, Dial C, Diallo TA, Jalloh M, Gueye SM, Kane PMS, Diop H, Ndiaye AJ, Sall AS, Toure-Kane NC, Onyemata E, Abimiku A, Adjei AA, Biritwum R, Gyasi R, Kyei M, Mensah JE, Okine J, Okyne V, Rockson I, Tay E, Tettey Y, Yeboah E, Chen WC, Singh E, Cook MB, Duffy CN, Hsing A, Soo CC, Fernandez P, Irusen H, Aisuodionoe-Shadrach O, Jamda AM, Olabode PO, Nwegbu MM, Ajibola OH, Ajamu OJ, Ambuwa YG, Adebiyi AO, Asuzu M, Ogunbiyi O, Popoola O, Shittu O, Amodu O, Odiaka E, Makinde I, Joffe M, Pentz A and Rebbeck TR. Development, evaluation, and implementation of a Pan-African cancer research network: Men of African descent and carcinoma of the prostate. Journal of Global Oncology. 2018; (4): 1-14. DOI: 10.1200/JGO.18.00063.

6. Odiaka E, Lounsbury DW, Jalloh M, Adusei B, Diallo TA, Kane PMS, Rockson I, Okyne V, Irusen H, Pentz A, Makinde I, Ajibola OH, Petersen L, McBride J, Petersen DC, Mante S, Agalliu I, Adebiyi AO, Popoola O, Yeboah E, Mensah JE, Hsing A, Fernandez P, Aisuodionoe-Shadrach O, Joffe M, Singh E, Gueye SM, Quintana Y, Fortier B, Rebbeck TR and Andrews C. Effective project management of a Pan-African cancer research network: Men of African descent and carcinoma of the prostate (MADCaP). Journal of Global Oncology. 2018; (4): 1-12. DOI: 10.1200/JGO.18.00062.

7. Chikandiwa A, Pisa PT, Sengayi M, Singh E and Delany-Moretlwe S. Patterns and trends of HPV-related cancers other than cervix in South Africa from 1994–2013. Cancer Epidemiology. 2019; 121–129. https://DOI.org/10.1016/j.canep.2018.12.004.

8. Rohner E, Bütikofer L, Schmidlin K, Sengayi M, Maskew M, Giddy J, Moore RD, Goedert JJ, Gill MJ, Silverberg MJ, Patel P, Castilho J, Hoy J, Sohn A, Bani-Sadr F, Taylor N, Paparizos V, Le Moing V, Bonnet F, Verbon A, Vehreschild JJ, Post FA, Sabin C, Mocroft A, Dronda F, Obel N, Grabar S, Spagnuolo V, Antinori A, Quiros-Roldan E, Mussini C, Miro JM, Meyer L, Hasse B, Konopnicki D, Roca B, Boué F, Barger D, Raben D, Clifford GM, Franceschi S, Brockmeyer N, Egger M and Bohlius J1. Non-Hodgkin lymphoma risk in adults living with HIV across five continents. AIDS. 2018; 32(18): 1. https://DOI.org/10.1097/QAD.0000000000002003.

9. Chen WC, Bye H, Matejcic M, Amar A, Govender D, Khew YW, Beynon V, Kerr R, Singh E and Mathew CG. Association of genetic variants in CHEK2 with oesophagael squamous cell carcinoma in the South African Black population. Carcinogenesis. 2019. DOI: 10.1093/carcin/bgz026.

Conferences

International conference: 5
National conference: 4

Division of Public Health Surveillance and Response

1. Background

Centre Head
Dr Kerrigan McCarthy

The Division of Public Health Surveillance and Response (DPHSR) includes the GERMS-SA surveillance programme, the Provincial Epidemiology Team (PET), the Notifiable Medical Conditions Surveillance Unit (NMCSU), the Outbreak Response Unit (ORU) that is responsible for the Emergency Operations Centre (EOC) and the Surveillance Intelligence Management Unit (SIMU). The roles and responsibilities of each are outlined below.

GERMS-SA

In collaboration with the NICD, the GERMS-SA surveillance programme centres conduct laboratory-based and syndromic surveillance through secondary data analysis of the NHLS data, which is complemented by sentinel site surveillance for specific laboratory-diagnosed conditions, pneumonia and diarrhoeal surveillance.

Provincial Epidemiology Team

The PET comprises eight epidemiologists who are stationed at eight of the nine South African provinces and who support provincial health departments with epidemiological interpretation of TB, HIV, NMC data, and outbreak investigation and management support.

Notifiable Medical Conditions Surveillance Unit

The NMCSU coordinates the rollout and uptake of the new 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, and 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 through the use of 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 Surveillance Intelligence Management Unit

The SIMU developed and continues to expand a surveillance intelligence platform that provides sustainable and reliable real-time analytics, monitoring and reporting for public health and research in South Africa. Work to date includes the development of a data warehouse, reports for action (RfA) and dashboards for the TB, HIV and cryptococcal programmes, and the data management solution that underpins the NMC surveillance system.

The technical expertise of the NICD is made available to provinces and districts within South Africa through multiple arms of the DPHSR:

- Provincial epidemiologists are based in the provinces and support analysis of routine provincial TB, HIV and NMC data and support provincial outbreak investigation and management;
- An NMC short message service (SMS) and email alerts are triggered when data enters the NMC application from the NHLS laboratory information system (LIS) and/or cases are notified by clinicians in public sector health facilities. This ensures that district and provincial communicable disease staff are timeously informed about cases of disease;
- The ORU staff provides support for appropriate public health interventions on request and in response to NMC alerts;
- The 24-hour hotline staffed by NICD pathologists and doctors and coordinated by the DPHSR, provides a forum for rapid alert and notification of diseases of public health importance, as well as provision of technical advice for a range of infectious conditions;
- Disease intelligence derived from NICD surveillance activities is reported regularly through the Multisectoral National Outbreak Response Team (MNORT), and to other government structures as the need arises; and
- RfA related to the TB, HIV and cryptococcal screening programme are made available to provincial and district through the data warehouse infrastructure developed and maintained by the SIMU.

Nationally, members of the DPHSR teams collaborate and cooperate through various means with national and provincial departments of health, the DAFF, DEA, the National Disaster Management Centre (NDMC), the National Joint Operations Committee (NATJOINTS), and the private health sector (medical aids, hospital groups and laboratories) to support preservation of public health.

Globally, the division supports the NICD's contribution to capacitating South Africa's adherence to the International Health Regulations (IHR, 2005). This document guides countries on policies, structures and activities that must be in place to support prevention, detection and response to communicable disease, chemical and radiation events. The DPHSR, together with certain NICD centres, provides technical support for most health security components of the IHR, including antimicrobial stewardship, zoonotic disease, food safety, biosafety and security, immunisation, real-time surveillance, workforce development, preparedness, emergency operations and support for simulation activities. The NDOH hosted a 'Joint External Evaluation' (JEE) of adherence to requirements of the IHR, in November 2017, and is currently completing the 'national action plan for public health security' (NAPHS), based on the JEE findings.

On account of this capacity and these relationships, the DPHSR supports the NICD's role as a key player in national, regional and international responses to public health threats. The year ending 31 March 2019, saw significant strengthening of DPHSR contributions in the above areas, and notably to the NMC surveillance system, the growth in experience and reach of the EOC and the growing capacity of the SIMU, to support surveillance data management. The foundational role of the GERMS-SA surveillance programme remains pivotal to the capacity of the NICD to provide communicable disease surveillance.

GERMS-SA

The GERMS-SA surveillance programme is coordinated by a core team within the division who works closely with the NICD centres to implement laboratory-based and enhanced surveillance systems, syndromic surveillance, and various centre-specific surveillance programmes.

The objectives of these surveillance programmes 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 EPI.

The work of the GERMS-SA is funded by the NICD and the NDOH. Data from the GERMS-SA programme is published in the GERMS-SA annual report, peer-reviewed journals, and closed reports to various government structures. It is also used by the NICD centres to inform and guide public health policymakers in their decisions.

Laboratory-based surveillance

GERMS-SA is an active surveillance programme in which the core team uses data from the SIMU warehouse to identify cases of disease under surveillance. Participating NHLS and private laboratories submit isolates to NICD centres for characterisation and additional testing.

Pathogens under surveillance in the laboratory-based surveillance programme include:

- *Candida auris;*
- *Salmonella* Typhi*;*
- *Salmonella enterica* serotype Paratyphi (A, B and C);
- Nontyphoidal *Salmonella* spp;
- *Shigella* spp;
- *Listeria* spp;
- *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);
- *Acineotobacter baumannii;* and
- *Cryptococcus* spp.

Approximately 250 laboratories (NHLS and private) that do cultures on cerebrospinal fluid and blood and send specimens to the NICD centres on an annual basis. Around 18 500 cases of communicable disease are collated annually into the GERMS-SA database.

Enhanced surveillance

With the network of laboratories participating in laboratory-based surveillance, an enhanced-surveillance programme is operational at 25 sentinel public sector sites across the country. As part of the programme, nurse surveillance officers collect clinical information, including risk factors, clinical presentation, treatment and outcome data on patients, relating to specific pathogens where this additional data is required to support epidemiological analyses.

Included in this programme are cases of disease caused by *S. pneumoniae, H. influenzae, N. meningitidis, Salmonella* Typhi; nontyphoidal *Salmonella* spp., CREs, *Acinetobacter baumannii, Cryptococcus* spp. and rifampicin-sensitive TB. In addition, brucellosis surveillance using acute febrile illness as a case definition was instituted together with the CEZPD in Free State and North West provinces.

Clinic-based surveillance for sexually transmitted infections and HIV

GERMS-SA staff assist with the paediatric HIV drug-resistance survey conducted by the centre for STIs and HIV. GERMS-SA continues to support STI surveillance to monitor aetiology of STIs, as well as *Neisseria gonorrhoea* antimicrobial resistance. Surveillance of the human papilloma virus (HPV) among young women attending family planning services, was also included. Surveillance was conducted in the Northern Cape and Limpopo provinces.

Surveillance for zoonoses amongst persons with acute febrile illness

The acute febrile illness surveillance project continues at a site in the Mnisi area, in rural Mpumalanga, in collaboration with veterinary practitioners and researchers from the University of Pretoria 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. The area is situated on the border of the Kruger National Park and frequent contact occurs between wildlife, livestock and humans. Laboratory testing includes PCR and serology for brucellosis, *Bartonella* infections, leptospirosis, Q-fever, tick bite fever, West Nile virus, Sindbis virus, RVF and chikungunya virus infections. Study data published indicates a high seroprevalence of tick bite fever, Q fever and leptospirosis, in parallel with significant exposures at the human/animal interface.

Syndromic surveillance for respiratory and diarrhoeal disease

Over the course of the 2018/2019 financial period, plans have been made to integrate syndromic surveillance programmes from the CRDM (severe acute respiratory illness, influenza-like illness), and the CED (diarrhoeal disease in adults and children) with the GERMS-SA surveillance network. This will facilitate integrated management of human resources and data management, and contribute to consolidated and reduced expenditure. These programmes are expected to be fully integrated towards the end of 2019.

Notifiable medical conditions surveillance

Following the signage of a memorandum of agreement (MoA) with the NDOH in October 2015, the NICD became responsible for the development, implementation and management of the national NMC surveillance system. In December 2017, regulations pertaining to the National Health Act were amended to update the list of NMCs. The paper notification form was revised, updated and rolled out across the country in August 2017.

Comprehensive standard operating procedures (SOPs) and case definitions were developed to assist nurses and doctors to notify correctly. Together with SIMU and outsourced developers, an online web-based and mobile application was developed to support notification and reporting of the 51 NMCs.

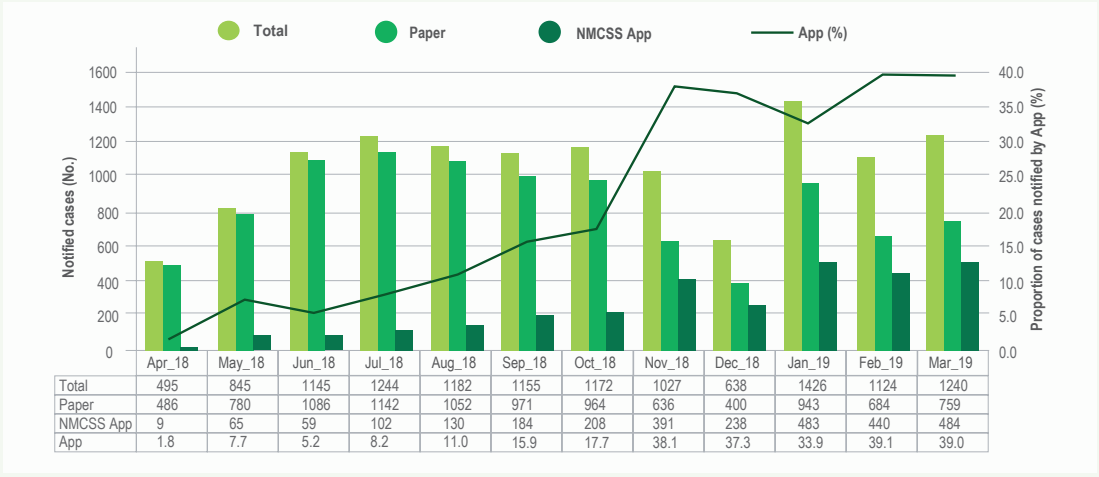
The application facilitates transmission of case data by SMS and email alerts to all relevant disease control personnel at local, provincial and national levels, as soon as a case is logged. The application also has a dashboard that provides summary statistics for NMC disease burden and trends. Following a pilot study, implementation of the application commenced in March 2018.

The following activities were conducted in the 2018/2019 financial year:

- The total number of HCWs trained from August 2017 to August 2018 was 7 711. By the end of February 2019, representatives from 35% of all health facilities in South Africa were trained in reporting procedures for NMCs (Figure 1);
- The web and mobile-based application was rolled out for routine use in Gauteng (6 April 2018), Limpopo (17 May 2018), Free State (29 May 2018), KwaZulu-Natal (20 August 2018) and North West provinces (11 October 2018);
- Over 5 00 cases are received monthly through the NHLS LIS, via an automated data download, and through clinician-based notifications from the public and private sectors submitted through the web-based portal, mobile application or captured by NICD data capturers after submission on paper notification forms. These are collated, and duplicates matched and merged. The number of cases notified by clinicians exceeds 1000/month (Figure 2);
- All case-definitions, SOPs, notification forms and access to the web-based portal are made available on the NICD website at http://www.nicd.ac.za/nmc-overview/; and
- From November 2018 to date, four reports have been published and distributed to stakeholders monthly. This includes the epidemiology report (case burden and epidemiological interpretation), training report, data quality report and application utilisation report.

	Aug_18	Sep_18	Oct_18	Nov_18	Dec_18	Jan_19	Feb_19
New facilities trained	1241	132	151	250	34	94	173
Cumulative facilities trained	1241	1373	1524	1774	1808	1902	2075
Proportion trained (%)	21.4	23.7	26.3	30.6	31.1	32.8	35.7

Figure 1. The number of health facilities represented in notifiable medical conditions trainings sessions from August 2017 to February 2019. *This includes all hospitals, community health centres, and primary healthcare clinics; both public and private.



	Apr_18	May_18	Jun_18	Jul_18	Aug_18	Sep_18	Oct_18	Nov_18	Dec_18	Jan_19	Feb_19	Mar_19
Total	495	845	1145	1244	1182	1155	1172	1027	638	1426	1124	1240
Paper	486	780	1086	1142	1052	971	964	636	400	943	684	759
NMCSS App	9	65	59	102	130	184	208	391	238	483	440	484
App	1.8	7.7	5.2	8.2	11.0	15.9	17.7	38.1	37.3	33.9	39.1	39.0

Figure 2. Statistics of cases notified by public and private sector clinicians (excluding cases notified through the NHLS laboratory information system) by month, by method of notification, and the proportion notified through the application.

Development on the NMC system is ongoing in several areas. Incorporation of private sector data is progressing. The NMC team, together with medical aid groups and private laboratories, is developing data formats and transfer mechanisms to support direct data downloads into the NICD data warehouse of NMCs identified through the private sector. Integration of the NMC system with vertical programmes for malaria control and TB is in progress through discussions at national and provincial level. The NICD centres are integrally involved in the NMC case review. Ongoing discussions and collaborative activity with the centres is underway. This includes the development of processes and procedures for data review, and enhancements to the application to support improved reporting according to epidemiological case definitions.

Provincial Epidemiology Team

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.

As at the end of the 2018/2019 financial year, the PET had a full complement of eight provincial epidemiologists, as well as one manager. The only province that is excluded is the Northern Cape.

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 timely. 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.

A strategic plan for 2018 – 2020 was developed which details how PET can best support the provincial departments, based on their epidemiology requirements. It also outlines how PET aims to fulfil its objectives and deliver on its mandate, in alignment with the broader NICD functions. The plan serves as a road map to guide the epidemiologists' activities in the provinces.

A standardised data specification document was developed to ensure that public health data is obtained from the various NICD centres in a structured and systematic manner, so that it can be made available to provincial epidemiologists for use within their respective provinces. The document also defines the frequency of receipt of the datasets, as well as the objectives of the data analysis. Standard reporting templates were also developed to ensure uniform output of the datasets by both the NICD and the DOH.

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. Province-specific data analyses to monitor trends and epidemics were conducted for listeriosis, hepatitis, pertussis, legionnaire's disease, *Haemophilus influenzae* type B, typhoid, malaria and measles. For feedback purposes, province-specific surveillance output were compiled into quarterly bulletins and distributed to relevant stakeholders in the Western Cape, Eastern Cape and Limpopo provinces respectively, by the CDC programme managers.

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 tracking, mapping of cases, data analysis and report writing. Their contribution is evident in the responses to:

- The nationwide listeriosis outbreak;
- The vaccine-derived poliovirus in Western Cape and Gauteng provinces;
- The human rabies cases in Eastern Cape and Mpumalanga provinces; and
- The pertussis outbreaks in Mpumalanga and Eastern Cape provinces.

In addition, the PET contributed to the following:

- Cholera cases identified in Limpopo and Gauteng provinces;
- The diarrhoea outbreak in Mpumalanga Province;
- The typhoid outbreak in Limpopo Province;
- The TB outbreak in a psychiatric hospital in KwaZulu-Natal Province;
- The measles outbreak in the Free State Province;
- The cluster of leptospirosis cases in Mpumalanga Province; and
- Several food-borne outbreaks across all provinces.

The outbreak investigation reports were published in the monthly NICD Communicable Disease Communiqué.

In support of the National Strategic Plan for HIV, TB and STIs 2017 - 2022, the PET uses PCR results to provide 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 RR TB data was analysed to determine treatment uptake and reasons for non-initiation of treatment in 2018.

Other contributions by the PET during the year under review include:

- The provincial epidemiologists are members of the provincial specific antimicrobial resistance (AMR) stewardship committees where they have a pivotal role in supporting analysis and interpretation of AMR data;
- The Gauteng Province epidemiologist conducted a detailed analysis of the epidemiology of malaria over a two-year cycle;
- The Western Cape Province epidemiologist presented on the epidemiology and public health responses to legionnaire's disease at the NICD Epi-Forum which took place in the province, in August;
- The PET supported the implementation of the South Africa Expanded Programme on Immunisation coverage survey;
- The PET participated in the NAPHISA district public hearings;
- The Mpumalanga and Limpopo provincial epidemiologists presented on the burden of disease at the Municipal Health Services Summit that was held at Gert Sibande (Mpumalanga) and Waterberg (Limpopo) districts respectively;
- On behalf of the NICD Centre for TB, the PET presented at the 'Finding the missing TB patients' roadshows conducted by the NDOH in all the provinces;
- The team also conducted several oral presentations at conferences;
    - 'Linkage to care for rifampicin-resistant tuberculosis patients in Johannesburg, Gauteng – 2017,' (5th SA TB Conference, June 2018);
    - 'A review of linkage to care among Xpert MTB/RIF diagnosed rifampicin resistant tuberculosis patients in the Eastern Cape, January to September 2017,' (5th SA TB Conference, Durban, June 2018);
    - 'Investigation of typhoid fever outbreak in Sekhukhune District, 2017,' (Limpopo research day, October 2018); and
    - 'Utility of GeneXpert MTB/RIF-diagnosed rifampicin resistant tuberculosis alerts for linkage to care in Gauteng, South Africa, 2017,' (ASLM Conference, Abuja (December 2018).

Outbreak Response Unit

The Outbreak Response Unit (ORU) provides technical support for all aspects of communicable disease outbreaks and control in South Africa. Through close collaboration with provincial and national 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 also remains abreast of international developments in outbreaks and outbreak preparedness through representation on key WHO advisory committees and international interest groups. Representatives from the unit attend the monthly Multisectoral National Outbreak Response Team (MNORT) meeting, and report on surveillance and outbreak investigation activities.

The ORU coordinates the provision of the 24-hour emergency hotline, which is 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 HCWs 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.

The ORU continues to publish its monthly Communicable Diseases Communiqué, which reports recent outbreaks and communicable disease cases and 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.

During the reporting period, 1 236 outbreak verification calls were attended to by the ORU directly, or through the NICD hotline, and all (100%) were responded to within 24 hours. Table 1 represents the number of calls per category, indicating that enquiries regarding the management of rabies post-exposure prophylaxis followed by investigation of persons with suspected infectious disease account for over 70% of calls. Most calls to the ORU originated from Gauteng Province, followed by KwaZulu-Natal Province and the Western Cape Province (Table 1).

Category	Number of calls
Administrative	29
Animal/environmental health	6
Food/water-borne disease investigation	29
Infection control	10
Lab-confirmed case for clinical/public health management	37
Media/journalist	4
Non-rabies post-exposure prophylaxis	5
Other	100
Patient(s) investigation (diagnostic/clinical advice)	186
Pre-exposure prophylaxis	23
Rabies post-exposure prophylaxis	780
Vaccination-related enquiry	27
Grand Total	**1 236**

Table 1. Category of 1 236 outbreak verification events attended to by NICD 24-hour hotline from 1 April 2018 – 31 March 2019.

The ORU, together with the NICD centres, attended to the following public health events over the course of the last year:

1. A nationwide listeriosis outbreak. Technical support and advice regarding development of the incident response plans for the information/epidemiology team during the EOC activation /joint response between the RSA and WHO, with support from the GOARN team, in April 2018. The outbreak was contained by the recall of the implicated products, as issued by the various government entities that formed part of the multi-sectoral task team;

2. Investigation of a foodborne illness at a correctional service facility in Gauteng Province, in May 2018. The ORU supported the province through health promotional activities to the facility, which included the proper preparation and storage of food;

3. Investigation of an outbreak of Rift Valley fever (RVF) on a farm in Free State Province, in May 2018. The NICD supported the provincial communicable disease control unit in screening and testing of farm workers who were exposed;

4. Investigation of a diphtheria outbreak in KwaZulu-Natal Province, May and June 2018. A cluster of three respiratory diphtheria cases was reported. Two cases were laboratory-confirmed with toxin-producing *Corynebacterium diphtheriae,* and a third probable case was epidemiologically linked to one of the laboratory-confirmed cases (resided in the same house and attended the same school). Health promotion activities included vaccination and administration of chemoprophylaxis in school contacts and the teachers of the affected school. A mass vaccination campaign was conducted for scholars aged 6-18 years at additional schools in the area;

5. Investigation of an outbreak of necrotising enterocolitis (NEC) in neonates admitted at a tertiary hospital in Gauteng Province, in June 2018;

6. Investigation of an outbreak of pertussis in Mpumalanga Province, between July and August 2018. The NICD ORU and CRDM supported diagnostics, provision of case-report forms, clinical guidelines and public health response;

7. Technical support and advice on a cluster of measles cases in a healthcare facility in Gauteng Province, in August 2018;

8. Investigation of an increase of diarrhoeal cases in Mpumalanga province, in August 2018, likely linked to contaminated potable water;

9. Follow-up of organophosphate poisoning cases in Gauteng Province, in September 2018;

10. Technical support and advice regarding a laboratory-confirmed measles case in Free State Province, in September 2018;

11. Investigation of a *Klebsiella pneumoniae* bacteraemia outbreak at a regional hospital in Gauteng Province, in September 2018;

12. Investigation of a case of immunodeficiency-related vaccine-derived poliovirus in Gauteng Province, in October 2018. As part of a multi-stakeholder response, stool samples from close contacts of the case and the local community were tested, and a vaccine coverage survey was conducted. In addition, active search for AFP cases in healthcare facilities within the metropolitan municipality where the case was detected was conducted;

13. Technical advice and support on a *Klebsiella pneumoniae* outbreak in a neonatal intensive care unit in Gauteng Province, in October 2018;

14. Investigation of an astrovirus gastroenteritis outbreak in multiple branches of a crèche chain in Gauteng Province, in November 2018. A total of 243 children and 36 staff members across the ten branches presented with diarrhoea. Of the nine clinical specimens collected, seven were positive for astrovirus (from three branches);

15. Investigation of a household cluster of Shiga toxin-producing (STEC) *Escherichia coli* in Gauteng Province, in November 2018;

16. Technical support and advice on a suspected cluster of pertussis cases in KwaZulu-Natal Province, in November 2018. The NICD ORU and CRDM supported diagnostics, provision of case-report forms, clinical guidelines and public health response;

17. Technical support and advice on two concurrent *Salmonella enteritidis* outbreaks in KwaZulu-Natal Province, November 2018;

18. Investigation of an outbreak of pertussis in the Eastern Cape Province, between November and December 2018. The NICD ORU and CRDM supported diagnostics, provision of case-report forms, clinical guidelines and public health response;

19. Investigation of a suspected TB outbreak at a psychiatric hospital in KwaZulu-Natal Province, in November 2018. Staff and patients at the hospital were screened for active TB disease. Molecular typing was not performed on the sputum specimens, and it was not possible to definitively conclude if this was an institutional outbreak;

20. Investigation, support and advice of a case of brucellosis in Limpopo Province, in January 2019;

21. Follow-up and technical advice on a suspected outbreak of *Acinetobacter baumanni* at a hospital in Gauteng Province, in January 2019;

22. Investigation, technical advice and support of a suspected *Klebsiella pneumoniae* carbapenem resistant Enterobacteriaceae (CRE) at a psychiatric hospital in Eastern Cape Province, in January 2019;

23. Investigation of a suspected CRE outbreak at a hospital in Western Cape Province, in February 2019;

24. Technical support and advice on a foodborne *Salmonella enteritidis* outbreak at a restaurant in Free State Province, in February 2019; and

25. Investigation of a suspected outbreak of enterovirus meningitis in Western Cape and Eastern Cape Provinces.

Emergency Operations centre

The NICD EOC supported the South African NDOH to respond to two events of national significance over the period from 1 April 2018 – 31 March 2019. On 9 April 2018, a WHO GOARN support team of technical experts in the field of risk communication, EOC management, food safety, incident management and epidemiology joined South African government officials to implement a project plan with the aim of controlling and ending the listeriosis outbreak. The EOC provided incident management assistance through its incident management system and resourcing of the outbreak responses, including finance, human resources, administration, data management and logistics.

The EOC team of national experts in environmental health and international technical experts developed material to conduct food processing plant risk assessments, and to train district environmental health inspectors in all aspects of food safety. Risk assessments and sampling of all processed meat producing facilities in the country were conducted over a four-month period, along with retraining of environmental health practitioners in all provinces on conducting inspections and sampling. In addition, risk communication workshops were conducted in every province on general food safety and *Listeria*-specific communication. The project activities successfully culminated in the announcement of the end of the listeriosis outbreak by the Minister of Health, in September 2018.

The second event supported by the EOC followed on anecdotal reports of counterfeit and expired foods being sold across South Africa. On the request of the Minister of Health, the

EOC managed a call centre for the reporting of counterfeit and expired foods that are sold to the public. Data pertaining to these calls were collated and shared with the responsible local municipalities for action. When not engaged in supporting responses to national crises, the EOC and ORU staff participated in several international meetings and consultative workshops, including:

- Africa CDC Epidemic Response Team Training;
- Global Food Network Listeriosis and Foodborne Pathogens Training Workshop;
- WHO-AFRO's Review of Public Health Emergency Operations Centre (PHEOC) training and technical materials;
- Public Health Emergency Management Workshop;
- JEE National Action Plan for Health Security; and
- WHO-AFRO/Africa CDC Public Health Emergency Operations Centre Evaluation of the Zambian EOC.

Surveillance Intelligence Management Unit

The SIMU was created in 2016, with the mission to develop a surveillance intelligence platform to provide sustainable and reliable, real-time analytics, monitoring and reporting for public health and research in South Africa.

From 2016 - 2018, the unit established the NICD surveillance data warehouse (SDW) through acquisition of a data warehouse appliance server to host a MicroStrategy web/mobile business intelligence environment. This warehouse was established to create a direct data-feed from the NHLS LIS. Numerous technical positions were approved and filled, including a principal health data analyst, an NMC information manager, a geographic information specialist (GIS), a junior analyst/developer, a system administrator and a data scientist. A position remains vacant for an extract, transform and load (ETL) specialist.

In the 2018/2019 financial period, the SIMU team, together with outsourced developers, supported and expanded on existing reports and dashboards including the TB dashboard, the HIV dashboard, the anti-microbial resistance dashboard, and the cryptococcal antigen (CrAg) screening dashboard. RfA pertaining to linkage to care for newly identified cases of drug-resistant TB and perinatally-transmitted HIV infection, were developed further. A self-service environment for CrAg reporting was also developed.

Early in 2019, the data source for these reporting tools was migrated from the NHLS central data warehouse (CDW) to the NICD data warehouse. District boundary demarcation and facility location data were improved. Following development of the NMC application by outsourced developers in early 2018, the application was rolled out to public and private hospitals as described above.

Maintenance of this system is ongoing, with the continuous addition of new developments to improve functionality and user experience, data cleaning and reporting. Additional modules to improve reporting and case investigations are currently in development. An application to support clinician-based surveillance for nosocomial infections in intensive care units is currently being piloted with the CHARM.

2. Research activities

Exploring patterns in antibiotic use in a rural community in a One Health context

Investigators: BC Mejia, V Quan, M Sande, L Blumberg, J Frean, M Oosthuizen and I Wijk.
Collaborators: The University of Pretoria and Institute of Tropical Medicine, Antwerp, Belgium.

The aim of this project is to explore and understand patterns and drivers of antibiotic use in humans and animals of the same community, over the same period, and to generate preliminary data to develop One Health research, and further, to assess the role of antibiotic use as a risk factor for antimicrobial resistance and to support developing and testing targeted interventions.

Development and evaluation of a mHealth application for tracking and managing foodborne illness outbreaks in South Africa (ongoing)

Investigators: G Ntshoe, E Webb, K McCarthy and NA Page.

This project entails the development, pilot implementation and evaluation of a mHealth application to track and manage foodborne illness (FBI) outbreaks. A systematic review of the role of mHealth applications in the context of outbreaks is underway. A situation-assessment of current procedures for the investigation of FBI outbreaks across South Africa is underway. A mHealth application is being developed, that will provide decision support and data management for FBI outbreaks. The application will integrate with the NMC software that is currently being rolled out by the NICD. Before and after the pilot implementation, feasibility, user-friendliness and acceptability by district staff will be assessed. A cost-effectiveness evaluation will be conducted following the pilot application.

Representation on committees and advisory groups

Prof Lucille Blumberg serves on several committees and advisory groups as follows:

- WHO Scientific Advisory Group for the Blueprint on Research and Development Preparedness for Emerging Pathogens, which conducted the following activities:
  1. Prioritisation of emerging diseases for preparedness planning;
  2. Research and development pertaining to vaccines and therapy; and
  3. Developing of funding opportunities to support preparedness activities.
- WHO International Health Regulations Emergency Committee pertaining to EVD, which had responsibility for declaration and rescinding the status of 'Public Health Emergency of International Concern' in respect of the Ebola virus outbreak in West Africa;
- EDCARN: A clinical network with global representation under the aegis of the WHO Epidemic Response Cluster, which focuses on providing clinical guidelines for the management of epidemic-prone diseases, mainly the viral haemorrhagic fevers;
- Elected as chair of the WHO Scientific and Technical Advisory Group on Yellow Fever Risk Mapping;
- Member of Strategic Advisory Group of Expert on Immunisation Working Group on Rabies Vaccines and Rabies Immunoglobulins;

- Elected as a commissioner in the Lancet One Health Commission. Co-chairs: Professor A Winkler, Centre for Global Health, at the University of Oslo and Dr J Amuasi, Kumasi Centre for Collaborative Research in Tropical Medicine, Ghana, invited her to participate in this commission; and
- Elected Chair of the South African Malaria Elimination Committee (SAMEC)

Dr Kerrigan McCarthy serves as a member of the following platforms:

- GOARN of the WHO;
- South African National Immunisation Safety Committee (NISEC);
- Technical Working Group for Diarrhoeal Diseases;
- Advisory Scientific Committee for the 3rd Pathology Research and Development (PathRed) Congress 2019; and
- Steering Committee (SC) for the South African DST-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA).

Sue Candy is a member of the Ministerial Advisory Committee on Antimicrobial Resistance.

Travel health

This unit fulfils the following functions:

- Consultation to health practitioners on issues such as pre-travel for travellers and clinical consultations for returning travellers with suspected infectious diseases;
- The development of guidelines for a number of travel-related diseases and neglected diseases;
- A point of contact and liaison internationally for infectious diseases acquired in Southern Africa, and
- Assistance with the training of travel health practitioners and those studying tropical diseases.

There is a focus on zoonotic diseases and emerging pathogens through the One Health approach, derived from interaction between animal and human health and the environment. The unit is also a Geosentinel Programme member, reporting travel-related infections as part of a global surveillance.

South African National Travel Health Network
http://www.santhnet.co.za

The South African National Travel Health Network (SaNTHNet) is a travel health network run by the DOH, the NICD and the SASTM. The SaNTHNet provides up-to-date information on health risks for travel in the Southern African region, with a primarily South African focus, by developing and providing guidelines on communicable diseases and up-to-date information on disease outbreaks.

Health at Mass Gatherings
http://www.who.int/ihr/publications/mass_gatherings/en/

Following the communicable disease surveillance and risk assessment for the 2010 FIFA World Cup, the DPHSR is now part of the WHO Mass Gatherings Collaborating Centre Network, which includes the Disaster Research Centre, Flinders University, Australia; Public Health England, United Kingdom; NICD, South Africa; Institute of Public Health of Vojvodina, Serbia; School of Public Health, University of Washington, United States of America; and the Ministry of Health, Saudi Arabia.

3. Teaching and training

Staff of the DPHSR delivered lectures for training activities related to communicable diseases for the national and provincial departments of health to under- and postgraduate students of the Wits School of Public Health (Departments of Medicine, Obstetrics and Gynaecology, Community and Family Medicine, Diploma in Tropical Medicine and Hygiene), University of Pretoria, Onderstepoort Veterinary Institute, North West University (School of Pharmacology) and Stellenbosch University (Department of Medicine). The unit collectively supervised 15 FETP residents and four public health registrars from the Universities of the Witwatersrand and Pretoria, on rotation, through the unit.

Professional development

- Dr K McCarthy, J Ebonwu and Dr S Meiring (Wits School of Public Health), and G Ntshoe (University of Pretoria) are registered for PhDs,
- Dr L Erasmus (Wits School of Public Health) is registered for an MSc in Biostatistics and Epidemiology; and
- N Legare (University of Pretoria) is registered for an MPH.

Awards and recognitions

The NICD was awarded the Alfred Nzo Award for Environmental Health at the NDOH Environmental Health Conference on 26 September 2018, in recognition of capacity building activities conducted during the Listeria outbreak.

4. Research outputs

Publications

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Honours

Prof Blumberg was appointed as one of the editors for the Oxford Handbook of Tropical Medicine 5e.

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National conference: 7


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1 Modderfontein Road
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