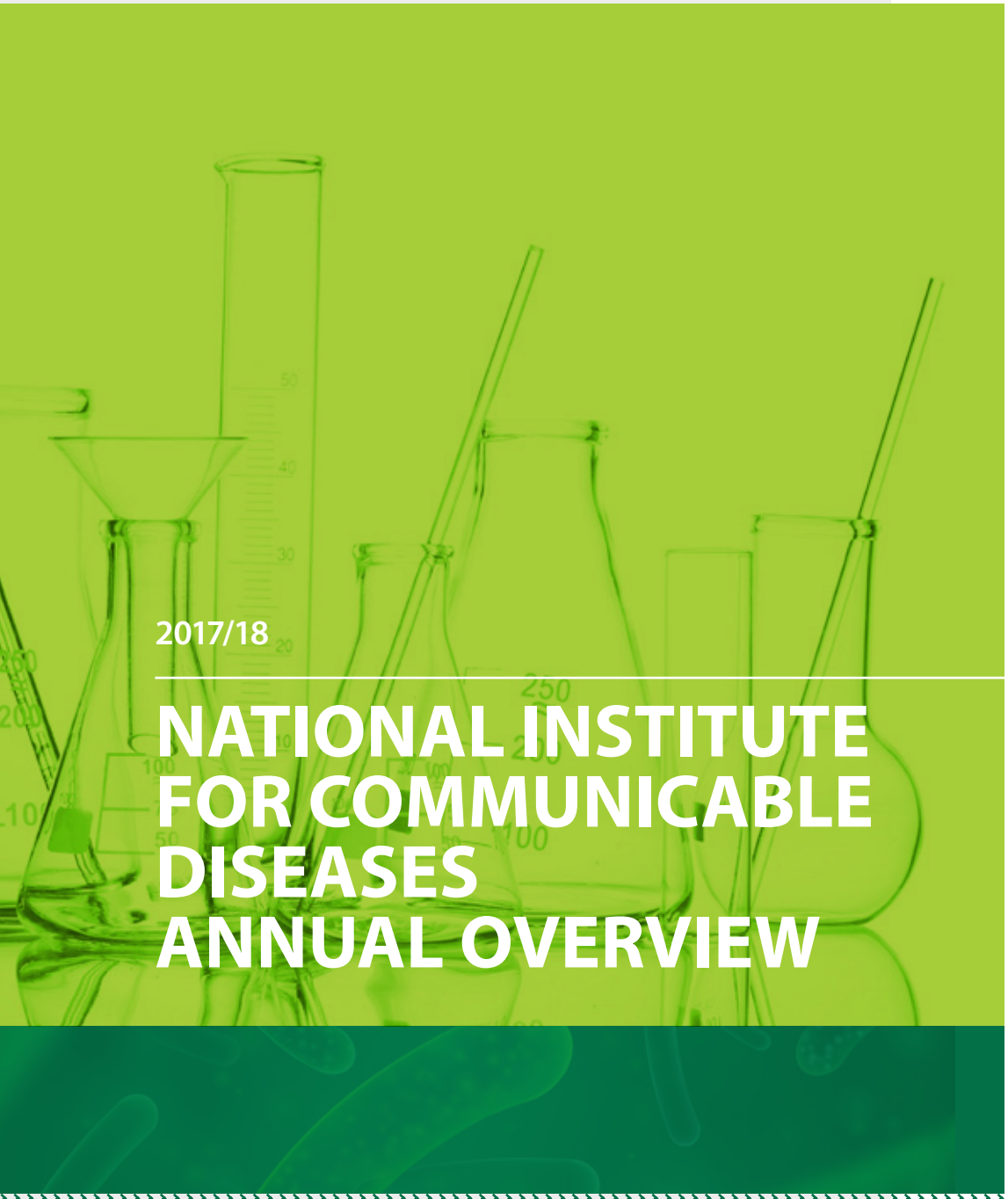
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Division of the National Health Laboratory Service



2017/18

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES ANNUAL OVERVIEW

2018

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Division of the National Health Laboratory Service

National Institute for Communicable Diseases

Annual Review 2017/18

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National Institute for Communicable Diseases Annual Overview 2017/18

CONTENTS

List of Abbreviations

ACV	Acyclovir
AAVC	Annual African Vaccinology Course
AFCRN	African Cancer Registry Network
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
ANC	Antenatal HIV survey
APP	Application
ART	Antiretroviral Therapy
ASSAf	Academy of Science of South Africa
ASIR	Age Standardised Incidence Rates
ATCC	American Type Culture Collection
BC	Breast cancer
BCAH	Burden of Cancers Attributable to HIV
BDQ	Bedaquiline
BDQ-R	BDQ-resistant
BSL3	Biosafety level 3
BSL4	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
CC	Collaborating Centre
CCHF	Crimean-Congo haemorrhagic fever
CDC	Centers for Disease Control and Prevention
CDW	Corporate Data Warehouse
CED	Centre for Enteric Diseases
CEZD	Centre for Emerging and Zoonotic Diseases
CFZ	Clofazimine
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 STIs
CHRU	Clinical HIV Research Unit
CI	Confidence Interval
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CrAg	Cryptococcal antigen
CRC	Colorectal cancer
CRDM	Centre for Respiratory Diseases and Meningitis
CRE	Carbapenem-resistant *Enterobacteriaceae*
CRS	Congenital rubella syndrome
CSF	Cerebrospinal fluid

CTB	Centre for Tuberculosis
CVI	Centre for Vaccine and Immunology
DBS	Dried blood spot
DDT	Dichlorodiphenyltrichloroethane
DHIS	District Health Information System
DNA	Deoxyribonucleic acid
DoH	Department of Health
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
ECV	Epidemiological cut-off values
EIA	Enzyme immunoassay
EID	Early infant diagnosis
ELISA	Enzyme-linked immunosorbent assay
EML	Electron Microscope Laboratory
EOC	Emergency Operations Centre
EPBCR	Ekurhuleni Population-based Cancer Registry
EPI	Expanded Programme on Immunisation
ESC	Extended spectrum cephalosporins
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species*
ESRU	Empilweni Services and Research Unit
EVD	Ebola virus disease
FDA	Food and Drug Administration (US)
FELTP	Field Epidemiology and Laboratory Training Programme
FETP	Field Epidemiology Training Programme
FIC	Fractional Inhibitory Concentration
FPD	Foundation for Professional Development
GDoH	Gauteng Department of Health
GERMS-SA	Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa
GLASS	Global Antimicrobial Resistance Surveillance System
GLI-AFRO	Global Laboratory Intiative – Africa
GOARN	Global Outbreak Alert and Response Network
GPEI	Global Polio Eradication Initiative
GUS	Genital ulcer syndrome
HAI	Healthcare-associated infection
HASA	Hospital Association of South Africa
HAstVs	Human astrovirus
HBV	Hepatitis B viral
hc2	Hybrid Capture 2
HCC	Hepatocellular carcinoma
HEU	HIV- Exposed Uninfected
HIV	Human Immunodeficiency Virus
HIVDR	HIV drug resistance
HPCSA	Health Professions Council of South Africa
HPV	Human papillomavirus
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
IAS	International AIDS Society
IBBS	Integrated HIV Bio-Behavioral Surveillance
IFI	Invasive fungal infection
IgG	Immunoglobin G
IHR	International Health Regulations
ILFU	Initial loss to follow-up
ILI	Influenza-like illness
IMD	Invasive meningococcal disease
IMGT	Immunogenetics
IMS	Incident Management System
iNTS	Nontyphoidal *Salmonella*
IPD	Invasive pneumococcal disease
IQC	Internal Quality Control
IQR	Interquartile range
IRS	Indoor Residual Insecticides
ISHS	Institute for Social and Health Sciences
ITNs	Insecticide treated bed nets
ITS	Internal transcribed spacer
IVIG	Intravenous immunoglobulin
JCS	Johannesburg Cancer Case-control Study
KCL	Kings College London
KPIS	Key population implementation science
KS	Kaposi sarcoma
KZN	KwaZulu-Natal
LARS	Laboratory-based Antimicrobial Resistance Surveillance
LDA	Linear discriminant analysis
LFA	Lateral flow assay
LMIC	Low-and middle-income countries
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	Multi-drug-resistant
MGIT	Mycobacteria Growth Indicator Tube
MHCU	Mental healthcare users
mHealth	Mobile technologies in health
MIC	Minimal inhibitory concentration
MLST	Multi-locus sequence typing
MLVA	Multiple-locus Variable Number Tandem Repeat Analysis
MMed	Master of Medicine
MPAC	Malaria Policy Advisory Committee
MPH	Master of Public Health

mPTB	Microbiologically Confirmed Pulmonary TB
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 Immunization
NAPHISA	National Public Health Institute of South Africa
NCI	National Cancer Institute
NCNGU	Non-chlamydial non-gonococcal urethritis
NCR	National Cancer Registry
NDoH	National Department of Health
Necsa	South African Nuclear Energy Corporation
NGS	Next generation sequencing
NHLS	National Health Laboratoy 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
NMMU	Nelson Mandela Metropolitan University
NNRTI	Non-nucleoside reserve transcriptase inhibitor
NP	Nucleocapsid protein
NPSP	National Pneumonia Surveillance Programme
NRF	National Research Foundation
NSP	National Strategic Plan
NTBRL	National TB Reference Laboratory
NTCP	National Tuberculosis Control and Management Programme
NTPs	National TB programmes
NTPn	Nontypeable pneumococci
OR	Odds ratio
ORU	Outbreak Response Unit
OSCC	Oesphageal squamous cell carcinoma
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
PHIRST	Prospective Household Observational Cohort Study of Influenza, Respiratory Syncytial Virus and other Respiratory
PCBTDSA	Pathogens Community Burden and Transmission Dynamics in South Africa
PHRU	Perinatal HIV Research Unit
PLHIV	People living with HIV
PMS	Post-marketing surveillance
PMTCT	Prevention of mother-to-child transmission
POC	Point-of-care
PRF	Poliomyelitis Research Foundation
PRL	Probabilistic record linkage
PS-MTM	PrimeStore Molecular Transport Medium
PT	Proficiency testing
PTLFU	Pre-treatment loss to follow up
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
REC	Human Research Ethics Committee
RedCap	Research Electronic Data Capture
RFa	Results 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
RT	Reverse transcriptase
RT-PCR	Reverse transcription polymerase chain reaction
RTQII	Rapid Test Quality Improvement Initiative
RV	Rhinovirus
RVF	Rift Valley fever
RVFV	RVF Virus
SABSMM V	South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (Fifth Wave)
SACIDS	Southern African Centre for Infectious Disease Surveillance
SADC	Southern African Development Community
SAFETP	South African Field Epidemiology Training Programme
SAM	South African HIV Cancer Match Study
SAMA	South African Medical Association
SAMHMS	South African Men's Health Monitoring Survey
SANAS	South African National Accreditation System
SANC	South African Nursing Council
SaNTHNet	South African National Travel Health Network
SARGDDC	South African Regional Global Disease Detection Centre

SARI	Severe acute respiratory infection
SASTM	South African Society of Travel Medicine
SBIMB	Sydney Brenner Institute for Molecular Bioscience
SCC	Sputum culture conversion
SCRI	Severe chronic respiratory illness
SG	Serogroup
SHEA	Society for Healthcare Epidemiology of America
SI	Serial interval
SIR	Secondary infection rate
SIT	Sterile insect technique
SNP	Single nucleotide polymorphism
SNSF	Swiss National Science Foundation
SPI-RT	Stepwise Process for Improving the Quality of HIV Rapid Testing
SRI	Severe respiratory illness
SSA	Sub-Saharan Africa
ST	Sequence type
Stats SA	Statistics South Africa
SA	South Africa
STI	Sexually transmitted infection
TAC	TaqMan Array card
TB	Tuberculosis
TBSAP	USAID Tuberculosis South Africa Project
TEPHINET	Training Programme in Epidemiology and Public Health Interventions Network
TIVs	Trivalent influenza vaccines
TK	Thymidine kinase
TP	Treponema pallidum
TWAS	The World Academy of Sciences
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
USAMRID	US Army Medical Research Institute of Infectious Diseases
VDPV	Vaccine-derived poliovirus
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
WGS	Whole genome sequencing
Wits	University of the Witwatersrand
WHO	World Health Organization
XDR	Extensively drug-resistant
ZAMPHIA	Zambia Population-based HIV Impact Assessment survey
ZIKV	Zika virus

NICD Interim Director's Overview

Prof Lynn Morris

INTRODUCTION

The National Institute for Communicable Diseases (NICD) continued to provide epidemiological and laboratory-based support to guide communicable diseases public health policy and activities in South Africa over the past year. Buoyed by a strong scientific culture, able leadership and efficient administrative and support services, the NICD works to provide accurate and timely information on infectious disease threats to the National Department of Health. The institution comprises of seven specialised centres and a Division of Public Health Surveillance and Response that has a transversal function. The NICD is set to become a division within the National Public Health Institute of South Africa (NAPHISA) and to that end, we have been engaging with the National Institute of Occupational Health (NIOH) to establish an agreement on shared services.

The strategically important role played by the NICD in tackling infectious disease threats was most admirably displayed in the recent listeria outbreak. In July 2017, an increase in laboratory-confirmed cases of listeriosis was reported to the NICD and on 5 December 2017, the Emergency Operations Centre (EOC) was activated to coordinate investigations in order to establish the source.

The EOC, the Outbreak Response Unit (ORU) and the Centre for Enteric Diseases (CED) were instrumental in guiding and actively participating in the investigation to solve what became the largest listeriosis outbreak ever recorded. They collated data from all laboratory-confirmed cases, issued publically available weekly situation updates, provided technical expertise to the National Department of Health (NDoH) to guide and support outbreak investigation activities, and conducted laboratory testing that confirmed the source of the outbreak as being ready-to-eat processed meat products.

Following an announcement by the Minister of Health on 4 March 2018, a recall of affected products was initiated, and cases declined. A critical component of the investigation was the use of whole genome sequencing (WGS) data for clinical, food and environmental isolates to confirm the source of the outbreak provided by the Sequencing Core at the NICD. In collaboration with the World Health Organization (WHO), an incident management team based at the NICD was tasked with activities aimed at controlling and ending the outbreak and strengthening systems to prevent future outbreaks.

The NICD, in partnership with the national and provincial health departments, developed and implemented an integrated notifiable medical conditions surveillance system (NMCSS), that allows for rapid detection and notification of over 55 medical conditions, including listeriosis. This new system comprises a mobile and web application (APP) for real-time reporting of notifiable medical conditions (NMCs) at the point of diagnosis, and an improved paper-based notification system for use in areas with no network connectivity.

The past year saw a significant increase in the number of malaria cases. In response, the Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD) provided strategic scientific and operational support for provincial malaria control programmes, assisting them with malaria vector surveillance, and providing the clinical services with expert advice on diagnosis and treatment of malaria cases, particularly in the Limpopo Province districts.

The CEZPD houses highly specialised laboratory facilities, including the only positive-pressure suit BSL4 laboratory in Africa, BSL3 insectary and special bacterial pathogens laboratories, and breeding facilities for mosquitoes, with the latter greatly supporting 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.

The Centre for TB (CTB) conducted surveillance of resistance to bedaquiline (BDQ), the first new TB drug in 40 years. Results were published, a seminal paper describing both phenotypic and genotypic drug resistance to BDQ and established interpretive criteria which were accepted by WHO for policy formulation.

The CTB also expanded its use of specialised molecular techniques for detection and strain characterisation of *Mycobacterium tuberculosis* using next generation sequencing (NGS), to study drug resistance, as well as to identify transmission patterns. Molecular epidemiological surveillance for early detection of rifampicin resistant (RR) clusters in selected districts showed that a third of RR-TB is due to transmission, emphasising the need for improved control measures.

The Centre for HIV and STIs (CHIVSTI) led the development and implementation of the revised annual antenatal human immunodeficiency virus (HIV) survey. Results from this survey will provide key information including the 90-90-90 coverage as well as HIV prevalence and incidence rates among pregnant women. Assistance was provided with national early infant diagnosis (EID), including results for action (RFa) reporting with a self-service portal and birth testing dashboard, as well as infant HIV diagnostic support.

Sexually transmitted infection (STI) data from the national aetiological survey and the Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA), were used to revise national syndromic management guidelines for primary healthcare centres (PHCs). Research on the development of an HIV vaccine remains a major priority within the centre, with members of the team conducting validated end-point antibody and molecular diagnostic assays for HIV vaccine trials. The report of a South African child who has achieved sustained virological control for almost nine years in the absence of Antiretroviral Therapy (ART), provided important insights into the possibility of a functional cure or remission from HIV infection.

The Centre for Healthcare-Associated Infections and Antimicrobial Resistance (CHARM), incorporates national reference laboratories for antimicrobial resistance and mycoses, and houses the national biological sample collection of pathogenic bacteria and fungi. In June 2017, the centre was designated a WHO Collaborating Centre (CC) for antimicrobial resistance (AMR) and is now the national focal point for WHO's Global Antimicrobial Resistance Surveillance System (GLASS). The centre contributed to WHO guidelines for advanced HIV disease and cryptococcal meningitis, as well as national guidelines for hospital-acquired infections and *Candida auris* disease.

Ongoing syndromic surveillance for pneumonia and influenza-like illness (ILI) was conducted at sentinel sites within South Africa by the Centre for Respiratory Diseases and Meningitis (CRDM). The centre also implemented active surveillance for possible human cases of avian influenza A (H5N8), following widespread outbreaks in poultry in several areas of South Africa. Influenza virus isolates, and/or original clinical specimens were shared with WHO CC's for the important task of selecting annual vaccine strains. Laboratory-based national surveillance for causes of invasive bacterial disease and meningitis continued through the GERMS-SA platform.

In January 2018, the Centre for Vaccine and Immunology (CVI), identified a case of vaccine-derived polio virus (VDPV) serotype three in a South African child. Further investigation confirmed that the event was not due to circulating polio virus but due to inherited primary immune deficiency in the affected infant. The detection of this case signifies a success for the acute flaccid paralysis (AFP) surveillance programme, which is an essential part of the Global Polio Eradication Initiative (GPEI). The CVI also investigated measle outbreaks in three provinces in primarily vaccine-hesitant communities. South Africa is in the pre-elimination phase for measles and supports the WHO AFRO elimination target of 2020.

The national pathology-based cancer incidence for 2013 and 2014 was published by the National Cancer Registry (NCR), reducing the reporting backlog. Data showed that cancer patterns have remained stable over the two years with breast, cervix, colorectal and lung cancers being the most commonly diagnosed malignancies in the country.

The NICD continues to train and build capacity for epidemiologists, scientists, technologists and pathologists within South Africa and on the continent. The NICD maintained its membership as part of the International Association of National Public Health Institutes (IANPHI) and actively participated in endorsing the Africa CDC strategy and implementation plan with technical support from the regional CC in Zambia.

The NICD houses a number of WHO reference laboratories and maintained South African National Accreditation System (SANAS) accreditation of all its laboratories. Several infrastructure projects were completed in the last year, including the refurbishing and relocating of laboratories and offices. There was also substantial upgrades of the information technology systems and software with improvements in bandwidth, which greatly enhanced efficiency.

The past year saw the departure of Professor Shabir Madhi from the institute. We thank him for his contribution to establishing a strong foundational strategy for the NICD. I would like to acknowledge the contribution of the NHLS, our partners, donors and I would personally also like to thank all the staff at the NICD for their commitment, hard work and creativity in combating communicable diseases. It has been a year of change, but also one that presents great potential as we move towards the establishment of NAPHISA.

Centre for Enteric Diseases

Dr Juno Thomas

BACKGROUND

The Centre for Enteric Diseases (CED) focuses on the surveillance of pathogens associated with diarrhoea and enteric fevers, and actively assists with the investigation and response to enteric disease outbreaks (including food- and water-borne disease outbreaks). The CED also provides specialised reference laboratory testing for enteric bacteria and viruses, including potential causes of food- and water-borne outbreaks.

The centre staff provide policy advice and technical support to government, and the necessary expertise for strengthening outbreak preparedness and response to public health emergencies in line with International Health Regulations (IHR). The CED contributes to the training of medical professionals, including medical scientists, medical technologists, epidemiologists, public health workers, nurses and registrars.

SURVEILLANCE/DIAGNOSTIC SERVICES

Diarrhoeal surveillance

Five sentinel sites were included during 2017. Rotavirus was detected in 19% (61/327) of hospitalised diarrhoea cases in children <5 years of age, and G8P [4] strains predominated. A total of 237 stool specimens were screened for enteric viruses with adenovirus detected in 12% (29/237), norovirus GII in 8% (20/237), astrovirus in 4% (10/237) and sapovirus and norovirus GI in <1% of cases.

Outbreak investigation and response

The centre provided laboratory testing and support for several food- and waterborne disease outbreaks including typhoid fever in Limpopo Province, and the national listeriosis outbreak. The centre played a leading role in the national listeriosis outbreak investigation and response, providing critical specialised laboratory testing and epidemiological support to the NDoH during what became the largest listeriosis outbreak ever recorded.

The CED collated and analysed data on laboratory-confirmed cases and issued publically available weekly situation updates and provided technical expertise to the NDoH to guide and support outbreak investigation activities. The centre was also instrumental in guiding and actively participating in the investigation activities, as well as the subsequent laboratory testing which confirmed the source of the outbreak as being ready-to-eat processed meat products manufactured at Enterprise Foods Polokwane production facility.

An integral component of the investigation was the use of whole genome sequencing (WGS) data for clinical, food and environmental isolates, to confirm the source of the outbreak. Through close collaboration with the Sequencing Core Facility of the NICD, WGS was successfully used in real-time to guide outbreak investigation activities and identify the source.

The centre was actively engaged in media interviews during the course of the outbreak, providing a source of scientifically correct information and important health promotion messaging to the public. In addition, the centre assisted with phenotypic confirmatory testing and WGS of clinical isolates from Namibia that were suspected to be linked with the outbreak.

RESEARCH

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

NICD researchers: *N Page, S Nadan, R Netshikweta and T Kruger*
Principle investigators: *S Madhi, M Groome (DST/NRF: Vaccine Preventable Diseases, University of the Witwatersrand. Respiratory and Meningeal Pathogens Research Unit (RMPRU)*
Funding source: *Bill and Melinda Gates Foundation*

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 seven South African cities with the study ending in December 2017.

Since the start of the study, 744 stool specimens have been collected (403 cases, 294 controls and 46 unclassified cases). Roughly half of the intussusception specimens were tested, using TaqMan® Array card (TAC) real-time detection assays.

Reanalysis of stool specimens from Venda, South Africa, collected as part of the MAL-ED study, using TACs for the detection of multiple enteric pathogens

NICD researchers: *N Page and S Nadan*
Principle investigator: *Eric Houpt (University of Virginia) and Amidou Samie (University of Venda)*
Funding source: *Bill and Melinda Gates Foundation*

TAC technology was utilised to simultaneously screen stool specimens for a variety of viral, bacterial and parasitic enteric pathogens. A total of 5094 specimens from Venda were screened over an 18-month period with the University of Venda performing nucleic acid extractions and CED performing the TAC tests.

The findings of the study included: identification of the top 10 pathogens during the first two years of life, namely: *Shigella spp.*, sapovirus, rotavirus, adenovirus 40/41, enterotoxigenic *E. coli*, norovirus, astrovirus, *Campylobacter jejuni/coli, Cryptosporidium spp.* and typical *enteropathogenic E. coli.* Most *Shigella spp.* infections were non-dysenteric and while viruses predominated, especially in the first year of life, *Shigella spp.* attributed the highest burden. In addition, detection of *Shigella spp.*, enteroaggregative *E. coli, Campylobacter spp.*, and *Giardia* were negatively associated with linear growth and had a larger impact than diarrhoeal episodes.

Laboratory testing for Phase I/II double-blind, randomised, placebo-controlled, descending-age, dose-escalation study to examine the safety, tolerability and immunogenicity of the trivalent P2-VP8 subunit rotavirus vaccine in healthy South African adults, toddlers and infants

NICD researchers: *N Page and S Nadan*
Principle investigator: *M Groome (DST/NRF: Vaccine Preventable Diseases, University of the Witwatersrand (Wits). Respiratory and Meningeal Pathogens Research Unit (RMPRU)*
Funding source: *PATH Vaccine Solutions*

The trivalent P2-VP8 vaccine was administered intramuscularly to 30 adults, 30 toddlers and 450 infants with three concentrations evaluated (15µg, 30µg and 90µg). Immune responses (IgG, IgA and neutralising antibody) to the vaccine formulations were evaluated for safety and immunogenicity. All infants received Rotarix® after the third study injection, and a stool sample was obtained from a subset of infants to assess shedding of Rotarix®.

Stool specimens were also obtained from infants experiencing diarrhoea, to test for rotavirus. Stool specimens were analysed using rotavirus enzyme immunoassay (EIA). The parenteral trivalent P2-VP8 subunit vaccine was well-tolerated and immunogenic. In addition, the subunit vaccine candidate reduced shedding of Rotarix® by 40% in infants.

The epidemiology and molecular characterisation of human astroviruses in selected areas of South Africa

NICD researchers: *S Nadan*
Principle investigator: *N Page*
Funding source: *Poliomyelitis Research Foundation (PRF), the National Health Laboratory Service (NHLS) Research Trust*

Between 2009 and 2014, human astroviruses (HAstVs) were detected in 6.6% (419/6389) of stools, with 245 specimens further analysed by genotyping and sequencing of the ORF1a (serine protease protein) and ORF2 (capsid) regions. Using classic methods, canonical type HAstVs were assigned in 26% (63/245) of cases while 58% (143/245) indicated recombinant genotypes and 16% (39/245) could only be partially characterised.

Of the classic strains, genotype 1 was detected most frequently (49%), followed by type 5 (29%), type 2 (11%), type 8 (8%) and type 6 (3%). The results from WGS confirmed canonical genotypes and selected recombinant strains. WGS also identified incorrect genotypes assigned by reverse transcription polymerase chain reaction (RT-PCR), showing mis-priming of selected classic primers. The outcomes of the study suggest that the traditional typing methods and the astrovirus gene/type assignment in Genbank needs to be updated. These results highlight the urgent need to redesign the typing strategies for HAstV.

WGS and microbiome analysis to identify and characterise enteric pathogens from stool specimens

NICD researchers: *AM Smith, N Tau, M Allam and A Ismail*

Microbial WGS holds great promise for enhancing diagnostic and public health microbiology. WGS analysis of bacterial cultures is well established, but when applied directly on clinical samples, it is more challenging. The centre established and implemented WGS analysis of bacterial pathogens, including metagenomic DNA analysis. WGS and microbiome analysis was performed directly on a culture-negative stool sample from a patient presenting with haemolytic uraemic syndrome, and allowed the successful identification and characterisation of Shiga toxin-producing *E. coli*.

WGS analysis of human enteric pathogens in South Africa

NICD researchers: *AM Smith, N Tau and SL Smouse*
Collaborator: *JCD Hinton; University of Liverpool, Liverpool, UK*

WGS analysis of human enteric pathogens that were isolated in South Africa from 2004-2015, is an ongoing research project. This includes approximately 1 000 isolates of *Salmonella* species (S. Enteritidis, S. Typhimurium and S. Dublin) and approximately 600 isolates of *Shigella* species (*S. flexneri 2A and S. sonnei)*. Bacterial isolates were prepared and shipped to the University of Liverpool. WGS and analysis of WGS data is currently ongoing. WGS data analysis will provide valuable information about the pathogens, including molecular epidemiology, relatedness of isolates, emergence and spread of clones, virulence, pathogenicity, and antimicrobial resistance.

PulseNet Africa Network and molecular surveillance of diarrhoeal diseases

NICD researchers: *AM Smith, N Tau, SL Smouse and J Thomas*
Collaborators: *PulseNet Africa member laboratories and countries*

The CED is involved with ongoing activities to build and strengthen the PulseNet Africa Network. The centre's bacteriology laboratory was designated as the coordinating laboratory for PulseNet Africa. PulseNet Africa is part of PulseNet International, a network of national and regional laboratory networks. This network is dedicated to building and strengthening country and regional capacity for molecular surveillance of diarrhoeal diseases and to track foodborne/waterborne infections worldwide.

Laboratories use standardised molecular subtyping methods and share information in real-time. The resulting surveillance provides global early warning, detection and investigation of foodborne/waterborne disease outbreaks, emerging pathogens and acts of bioterrorism. Standardised molecular subtyping methods are used to analyse isolates, and results are captured on PulseNet databases. PulseNet is currently transitioning towards utilising WGS analysis as its primary analysis tool.

The centre continues to assist, advise and guide other African countries. In October 2017, the CED assisted Kenya with analysis of Vibrio cholerae O1 isolates associated with a cholera outbreak amongst guests at two hotels in Nairobi. Phenotypic characterisation was performed on 18 isolates, and genetic relatedness of the isolates was investigated, using pulsed-field gel electrophoresis (PFGE) and WGS analysis.

WGS for surveillance and outbreak investigation of *Salmonella enterica* serotype Typhi in South Africa

NICD researchers: *SL Smouse, AM Smith and N Tau*

This study was aimed at investigating WGS for outbreak detection and epidemiological surveillance of *Salmonella* Typhi in South Africa. Current molecular sub-typing tools, specifically PFGE, may be ineffective when isolates are highly clonal. WGS therefore serves as a useful tool for monitoring and identifying infectious disease outbreaks timeously.

A total of 190 isolates were selected from archived data from the period 2014 – 2017. Phylogenetic analysis was performed, based on single nucleotide polymorphism (SNP) differences between isolates. This facilitated differentiation of the major PFGE clusters into smaller subgroups, thus revealing diversity among *Salmonella* Typhi.
Two typhoid clusters from Western Cape Province that respectively consists of nine and seven isolates, were identified. The study demonstrates the effectiveness of SNP profiling as a sensitive and high-resolution analysis tool that assists in understanding the circulation of *Salmonella* Typhi strains.

TEACHING AND TRAINING

Postgraduate level

- The CED trained microbiology and virology registrars as part of the NICD registrars training course in the identification and epidemiology of enteric bacteria and viruses. Visiting public health registrars from the University of Cape Town (UCT) were also trained during the year;
- Medical intern scientists were trained as part of the NICD training courses in bacteriology and virology disciplines;
- Mrs Ntsieni Ramalwa presented on monitoring and evaluation of surveillance systems as part of the GERMS Basic Epidemiology Training Course;
- Mrs Ntsieni Ramalwa presented on the national listeriosis outbreak at the University of Pretoria's School of Health Systems and Public Health seminar; and
- Dr Thomas conducted numerous lectures and presentations regarding listeriosis to a range of postgraduate healthcare professionals during the outbreak. This included presentations to Southern African Development Community (SADC) health ministers, and WHO AFRO member countries' health ministry staff.

International courses

- Mrs Ntsieni Ramalwa attended the 13th Annual African Vaccinology Course (AAVC) in Cape Town during November 2017.

Honours

- Prof Page was reappointed as an extraordinary professor in the Department of Medical Virology, University of Pretoria (UP).

Professional development

- Five postgraduate candidates enrolled at the CED (two for a Doctor of Philospophy (PhD) and three for Master of Science (MSc) and Master of Publich Health (MPH); and
- Seven postgraduate candidates graduated from CED (two PhD's, four MSc's and one MPH).

RESEARCH OUTPUT

Publications

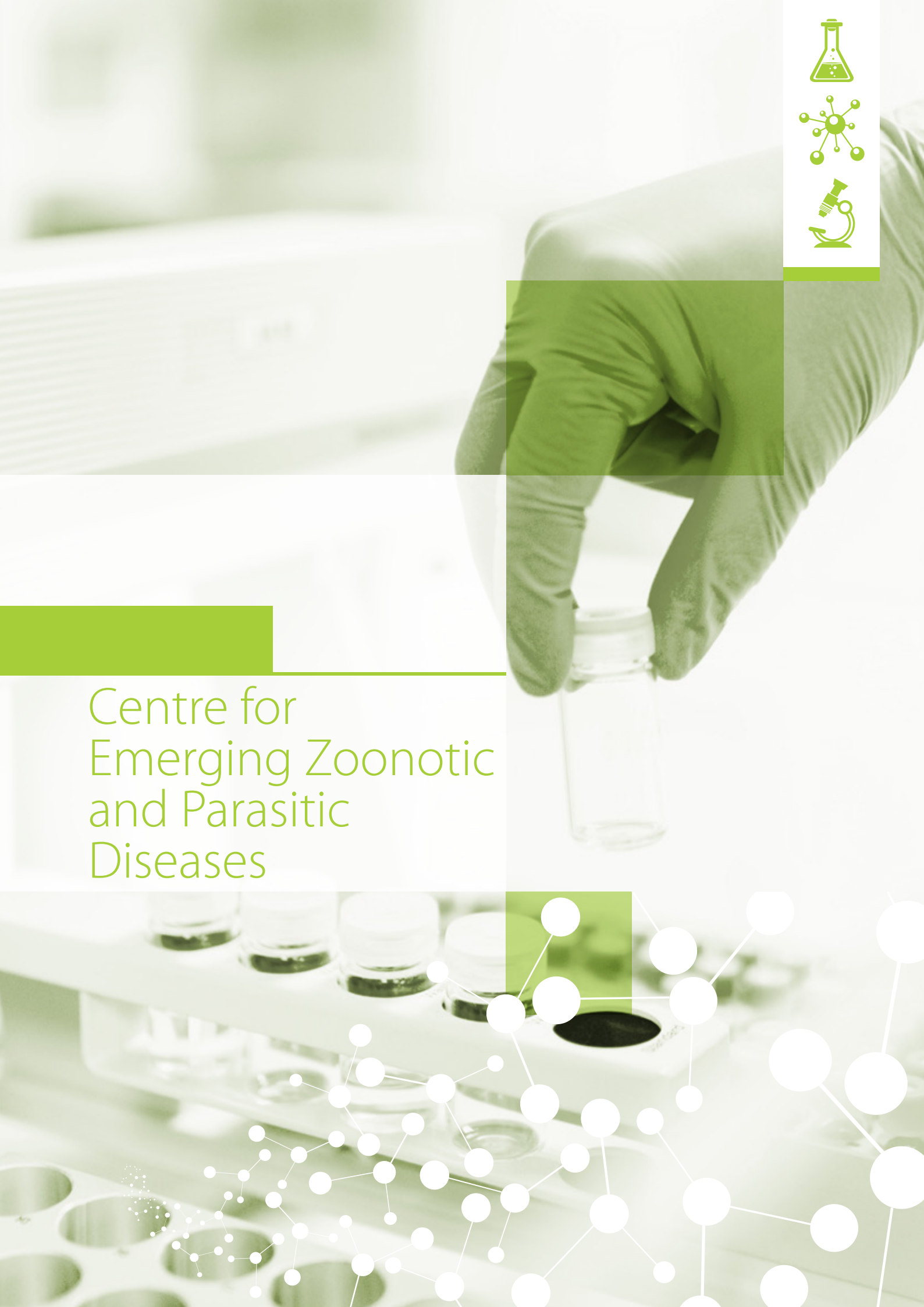
1. Page N, Groome MJ, Nadan S, Netshikweta R, Keddy KH, Poonsamy B, Moyes J, Walaza S, Kahn K, Madhi SA, Taylor MB, Mans J, Cohen C. Norovirus epidemiology in South African children <5 years hospitalised for diarrhoeal illness between 2009 and 2013. Epidemiol Infect. 2017 Jul;145(9):1942-1952.
2. Operario DJ, Platts-Mills JA, Nadan S, Page N, Seheri M, Mphahlele J, Praharaj I, Kang G, Araujo IT, Leite JPG, Cowley D, Thomas S, Kirkwood CD, Dennis F, Armah G, Mwenda JM, Wijesinghe PR, Rey G, Grabovac V, Berejena C, Simwaka CJ, Uwimana J, Sherchand JB, Thu HM, Galagoda G, Bonkoungou IJO, Jagne S, Tsolenyanu E, Diop A, Enweronu-Laryea C, Borbor SA, Liu J, McMurry T, Lopman B, Parashar U, Gentsch J, Steele AD, Cohen A, Serhan F, Houpt ER. Etiology of severe acute watery diarrhea in children in the Global Rotavirus Surveillance Network using quantitative polymerase chain reaction. J Infect Dis. 2017 Jul 15;216(2):220-227.
3. Groome MJ, Koen A, Fix A, Page N, Jose L, Madhi SA, McNeal M, Dally L, Cho I, Power M, Flores J, Cryz S. Safety and immunogenicity of a parenteral P2-VP8-P[8] subunit rotavirus vaccine in toddlers and infants in South Africa: a randomised, double-blind, placebo-controlled trial. Lancet Infect Dis. 2017 Aug;17(8):843-853.
4. João ED, Strydom A, O'Neill HG, Cuamba A, Cassocera M, Acácio S, Mandomando I, Motanyane L, Page N, de Deus N. Rotavirus A strains obtained from children with acute gastroenteritis in Mozambique, 2012-2013: G and P genotypes and phylogenetic analysis of VP7 and partial VP4 genes. Arch Virol. 2018 Jan;163(1):153-165.
5. Smith AM, Smouse SL, Tau NP, Bamford C, Moodley VM, Jacobs C, McCarthy KM, Lourens A, Keddy KH, GERMS-SA Surveillance Network. 2017. Laboratory-acquired infections of Salmonella enterica serotype Typhi in South Africa: phenotypic and genotypic analysis of isolates. BMC Infectious Diseases 17:656. doi: 10.1186/s12879-017-2757-2.
6. Smith AM, Kalule BJ, Nicol MP, Kleynhans J, McCulloch M, Duze ST, Ismail A, Allam M, Tau NP, Keddy KH. 2017. Genome sequence for Shiga toxin-producing Escherichia coli O26:H11 associated with a cluster of hemolytic uremic syndrome cases in South Africa,

2017. Genome Announcements 5(38). pii: e00989-17. doi: 10.1128/genomeA.00989-17.
7. Nadon C, Van Walle I, Chinen I, Campos J, Trees E, Gilpin B, Carleton H, Perez H, Smith AM, Concepcion-Acevedo J, Kam K-M, Moller Nielsen E, Kubota K, Takkinen J, Gerner-Smidt P. 2017. PulseNet International vision for the implementation of whole genome sequencing for global foodborne disease surveillance. Eurosurveillance 22(23):pii=30544. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2017.22.23.30544.
8. Tau N, Smith AM, Wain J, Tarupiwa A, Coulibaly KJ, Keddy KH, GERMS-SA Surveillance Network. 2017. Development and evaluation of a multiple-locus variable-number tandem-repeats analysis assay for subtyping Salmonella Typhi strains from Sub-Saharan Africa. Journal of Medical Microbiology 66:937-945. doi: 10.1099/jmm.0.000526. Epub 2017 Jul 19.
9. Muvhali M, Smith AM, Rakgantso AM, Keddy KH, GERMS-SA Surveillance Network. 2017. Investigation of Salmonella Enteritidis outbreaks in South Africa using multiple-locus variable-number tandem-repeats analysis. BMC Infectious Diseases 17:661 doi: 10.1186/s12879-017-2751-8.
10. Baker KS et al, including Smith AM. 2017. Whole genome sequencing of Shigella sonnei through PulseNet Latin America and Caribbean: advancing global surveillance of foodborne illnesses. Clinical Microbiology and Infection Apr 4. pii: S1198-743X(17)30190-8. doi: 10.1016/j.cmi.2017.03.021. [Epub ahead of print].
11. Kalule BJ, Keddy KH, Smith AM, Nicol MP, Robberts L. 2017. Development of a real-time PCR assay and comparison to CHROMagarTM STEC to screen for Shiga toxin-producing Escherichia coli in stool, Cape Town, South Africa. African Journal of Laboratory Medicine 6, a609. https://doi.org/10.4102/ajlm. v6i1.609.
12. Frean J, Blumberg L, McCarthy K, Thomas J. Plague and listeriosis: current outbreaks, and an historical South African connection. South African Journal of Infectious Disease 2018;33(1):3-4

Conference presentations

a) International congresses: 3
b) National congresses: 2
c) Local congresses: 2

Minister of Health, Dr Aaron Motsoaledi; Director General of Health, Ms Precious Matsotso; NHLS Chairperson, Prof Eric Buch; NHLS Acting CEO, Dr Kamy Chetty; and Centre for Enteric Diseases staff at the media briefing announcing that the source of the listeriosis outbreak was confirmed, 04 March 2018.



Centre for Emerging Zoonotic and Parasitic Diseases

Prof Janusz Paweska

BACKGROUND

The Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD) was established in March 2017 through the amalgamation of the former Centre for Emerging and Zoonotic Diseases and part of the Centre for Opportunistic and Tropical Hospital Infections (vector control and parasitology reference laboratories).

The CEZPD provides national and regional capacity for the diagnosis, surveillance, and research of viral, bacterial and parasitic pathogens of public health importance, particularly those classified as zoonotic biosafety level 3 (BSL3) and biosafety level 4 (BSL4) agents. This includes:

- Viral haemorrhagic fevers (e.g., Ebola and Marburg Viral Diseases, Lassa fever, Lujo haemorrhagic fever);
- Arthropod-borne diseases (e.g., Rift Valley fever, Crimean Congo haemorrhagic fever, yellow fever);
- Human rabies;
- Anthrax;
- Plague;
- Brucellosis;
- Botulism; and
- Leptospirosis.

The CEZPD also focuses on diagnosis, surveillance, and research of parasitic diseases, opportunistic infections, agents of diarrhoeal disease in under-five children, schistosomiasis and soil-transmitted helminths.

The centre, furthermore, plays an important role in supporting the malaria control and elimination agenda of the provincial, national and regional malaria control programmes. It provides policy advice and technical support to government and training of scientists, medical technologists and epidemiologists in emerging zoonotic and parasitic diseases.

It also serves as an internationally recognised resource of expertise for referral diagnostic services, outbreak response and consultations under the mandate of the WHO CC for Reference and Research on Viral Haemorrhagic Fevers and Arboviruses, Regional Reference Laboratory for Plague and Global Outbreak Alert and Response Network. A range of diagnostic tests conducted 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 BSL4 in Africa, a transmission electron microscope, BSL3 insectary and bacteriology laboratories, and breeding facilities for mosquitoes. The insectary facilities enable the Centre to render significant support 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.

SURVEILLANCE AND DIAGNOSTIC SERVICES

A total of 11 human cases of rabies were confirmed during the report period, from 1 April to 31 December 2017, five cases were confirmed from the Eastern Cape, KwaZulu-Natal (KZN), Mpumalanga and Limpopo Provinces. In the first three months of 2018, another six cases were reported from KZN (n=4) and Eastern Cape (n=2) Provinces. The rise in the number of human rabies cases relates to the resurgence of dog rabies in the latter provinces. All human cases were linked to exposure to rabid domestic dogs and cats. Apart from these locally acquired cases, rabies contracted in Zimbabawe was confirmed in a patient who was hospitalised in Johannesburg. Three human rabies cases in Namibia were also confirmed.

A total of 145 cases of suspected viral haemorrhagic fever were investigated. Six cases of Crimean-Congo haemorrhagic fever (CCHF) were identified, and reported from the Free State (n=2), Northern Cape (n=3) and Western Cape (n=1) Provinces. In addition, six Namibian cases of CCHF were diagnosed during the report period.

A total of 580 suspected cases of arboviral disease were investigated, including suspected cases of exotic arboviral infections such as Zika, dengue and Japanese encephalitis, and endemic diseases such as Sindbis, West Nile, Rift Valley fever and chikungunya. A number (13 for 2017) of dengue cases were confirmed in international travellers returning to South Africa from endemic regions. Several suspected Zika cases were also investigated in returning travellers, including pregnant women and couples attempting to conceive.

The centre continued to serve as a regional reference laboratory for arboviral diseases, including the investigation of suspected cases from Kenya, Angola and the Seychelles. Several cases of chikungunya fever were confirmed in specimens referred from Kenya, and additional testing indicated co-circulation of at least one other arbovirus, dengue which is not unexpected, considering their shared mosquito vector.

A total of 1 898 *Anopheles* mosquitoes were referred to the Vector Control Reference Laboratory from sentinel sites in KZN, Mpumalanga and Limpopo provinces. The presence of three malaria vector species - *Anopheles arabiensis, An. merus* and *An. vaneedeni* – which have previously been shown to contribute to ongoing residual malaria transmission in South Africa, were identified amongst these collections.

The CEZPD continued surveillance for plague in susceptible rodent populations in the City of Johannesburg and the surveillance programme in the historic plague-endemic area in the Nelson Mandela Bay Municipality (Coega area) was re-established. More than 900 rodents were tested for plague antibodies. Madagascar experienced a large outbreak of plague affecting major cities and other non-endemic areas from August to November 2017. South Africa was identified as one of nine priority countries in the African region for plague preparedness and readiness by having trade and travel links with Madagascar. The CEZPD supported the NDoH with the preparation of the 'Contingency plan and standard operating procedure for detection and response to plague outbreaks.'

The Parasitology Reference Laboratory provides a service that increasingly utilises molecular methods to support clinical diagnosis of cases. Surveillance projects are malaria confirmation for provincial malaria control programmes, and sentinel site surveillance for diarrhoea in under-five children. 322 clinical samples, 301 diarrhoeal samples, and 7572 malaria samples were tested. The laboratory also contributes to outbreak investigations involving the NICD. Outbreaks of malaria were for example, investigated in Shingwedzi and Mopane camps in the Kruger National Park, in May 2017.

Approximately 300 blood samples from staff, contractors and trainees were tested by microscopy and polymerase chain reaction (PCR) in the Parasitology Reference Library. Odyssean malaria (also called airport, taxi or suitcase malaria) cases were investigated (Fig. 1), in conjunction with the Vector Control Reference Laboratory and the Gauteng Department of Health (GDoH). There were 23 such cases with six deaths that equates to a mortality rate of 26%, which is more than 10 times the national case fatality rate for malaria.

Figure 1. Odyssean malaria outbreak investigations: VCRL staff members searching for mosquitoes around homes of patients.

The Parasitology Reference Library successfully bid for a regional programme funded by the global Bill & Melinda Gates Foundation which aims to support malaria surveillance for elimination in the eight Southern African countries (initially South Africa, Namibia, Botswana and Swaziland, and later Zimbabwe, Zambia, Mozambique and Angola).

The lab-based surveillance support will revolve around collecting and providing reference, training and quality assessment material for the countries' malaria reference laboratories, which will in turn support their own surveillance efforts. The startup budget is nearly R6 million over a period of one to two years, and the total duration of the programme will be five to six years, subject to continued funding.

As an NICD core service facility, the Electron Microscopy Laboratory had a constructive microscopy year that involved basic and applied research and provision of reference library images and diagnostic assistance, to requestors from a number of institutions such as:

- The NICD (CEZPD, CHARM, CED, ORU and the Communications Unit);
- NHLS (NJH);
- Wits (Faculties of Science and Health Sciences);
- University of Johannesburg (UJ) (Faculty of Health Sciences);
- Nelson Mandela Metropolitan University (NMMU) (Department of Biochemistry and Microbiology); and
- Chris Hani Baragwanath Hospital (RMDU, Paediatric Burns Unit).

Electron microscopy applications (Fig. 2) ranged from characterisation of antimicrobial silver nanoparticles to identification of environmental coliphages and other viruses isolated from diagnostic specimens and vectors. This was done through various methods that range from the use of an in-house developed protocol for pathogen capsule visualisation with both prokaryotes and eukaryotes, to ultrastructural analyses of both *Escherichia coli* (toxigenic, pathogenic and commensals). These were subjected to various pH treatments designed to simulate those of the gastro-enteric environment , and *Cryptococcus* species were subjected to various concentrations of a fungicidal, indigenous plant extract.

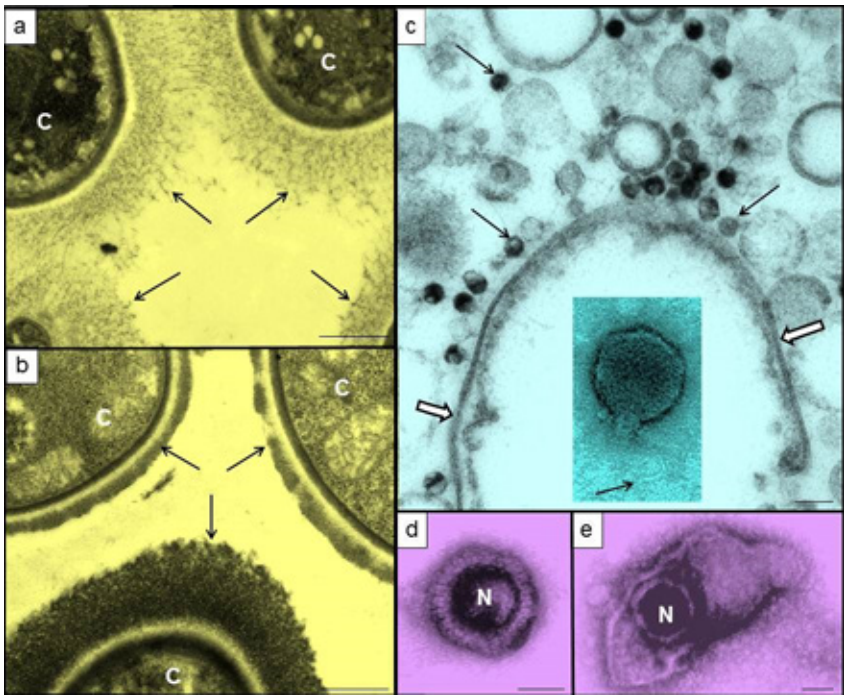


Figure 2. Transmission electron microscopy of: (a) *Cryptococcus neoformans* ATCC control cells (C) all with regularly thick, finely filigreed capsules (arrows); (b) *C. neoformans* clinical isolate not detected in the cryptococcal antigen (CrAG) lateral flow assay, but which caused invasive disease, in which cells (C) have capsules (arrows) varying in both thickness and texture; (c) section through the remains of a toxigenic *E. coli* cell (white arrows) parasitised by numerous coliphages (black arrows); inset of a negatively-stained coliphage belonging to the *Podovirales*, with an intact tail fibre (arrow); (d) the nucleocapsid (N) of a *Herpes* simplex virus identified in an outbreak in a paediatric burns unit. Note the characteristic cylindrical capsomers; (e) members of the *Herpesviridae* – the 'fried egg' virus – have an icosahedral nucleocapsid surrounded by a host-membrane-derived envelope, which readily distinguishes it from other viruses causing skin infections with similar clinical presentations. Scale bars: 400 nm (a, b); 80 nm (c); 40 nm (d, e).

RESEARCH PROJECTS

Bat-borne zoonotic pathogens in South Africa

NICD investigators: *JT Paweska, P Jansen van Vuren, N Storm and A Kemp*
Collaborators: *W Markotter (UP and G Palacios (United States Army Medical Research Institute of Infectious Diseases (USAMRID) Centre for Genome Science)*
Funding: *United States of America (US) CDC Global Disease Detection Programme, NRF and Poliomyelitis Research Foundation research grants*

As part of a biosurveillance programme in South Africa investigating the presence of viral zoonotic pathogens in bats, we tested a local population of Egyptian rousette bats residing at Matlapitsi Cave, located in the indigenous flora of Matlapitsi Valley, Limpopo Province, for evidence of Marburg virus (MARV) infection (Fig. 3).

We detected a high seroprevalence of MARV antibodies with 19.1% seroconversion in recaptured bats. Most seroconversions were detected during the period of lowest seropositivity in young bats (April - July). This indicates a period of increased risk for exposure and viral shedding.

The MARV RNA isolated, closely resembled the 1975 Ozolin strain, which was responsible for the first recognised outbreak of Marburg virus disease (MVD) in Africa, after a person hitchhiking through Zimbabwe was admitted to Johannesburg Hospital, South Africa.

Our findings indicate endemic MARV circulation in bats in South Africa and contribute to our knowledge of MARV ecologic factors that could lead to a zoonotic spillover into humans and, thus, assist in the development of evidence-based policies for MVD risk reduction. Additional testing also indicates the presence of several other potentially zoonotic viruses in the particular cave fauna, including bunyaviruses, reoviruses, paramyxoviruses, coronaviruses and adenoviruses.

Figure 3. NICD and UP teams capturing and sampling Egyptian rousette bats at Mahune Cave. The cave is located in the indigenous flora of Matlapitsi Valley on the northeast slope of Wolkberg mountain range, bordering Lekgalameetse Nature Reserve in Limpopo Province, South Africa.

Surveillance of Zika virus in South Africa

NICD investigators: *JT Paweska, V Msimang, P Jansen van Vuren, A Kemp and B Brooke*
Collaborators: *T Lo and J Fuller (US CDC)*
Funding: *US CDC Global Disease Detection Programme, NRF and PRF*

The CEZPD initiated an active surveillance project for Zika virus (ZIKV) and other arthropod-borne infections in the northern part of KZN, Umkhanyakhude Health District. As opposed to the normal modus operandi of conducting passive surveillance through the centre's reference diagnostic service, which is biased towards the more affluent part of the South African population. This new surveillance project targets a very rural area where urbanisation is increasing.

It is believed that this part of the country is at risk of introduction of Zika and other exotic arboviruses due to its close proximity to Mozambique, and a tropical climate. Hospital surveillance sites were identified, and study nurses recruited to mediate collection of specimens from patients matching the selection criteria.

Preliminary serology results on a limited number of human samples received from Manguzi hospital to date, indicate low levels of recent and past-unspecified flavivirus infections. However, due to extensive cross-reactivity in this group of viruses the specific circulating virus is yet to be identified, but might be one known to circulate in this area. Evidence of recent or past infection with chikungunya virus was also found in two patients.

Potential ZIKV vector mosquitoes were sampled in a preliminary field trip to various sites along the main routes between Jozini, Ingwavuma, Ndumo, Manguzi and Mseleni. *Aedes aegypti,* the primary vector of a number of important arboviruses including ZIKV, was found breeding in used tyres and scrapyards in urban and peri-urban settings. This species constituted the dominant mosquito species in both adult and larval collections and was distributed widely in these areas, in close association with the human population.

One Health Rift Valley fever investigation in South Africa

NICD investigators: *JT Paweska, V Msimang, A Kemp and P Jansen van Vuren*
Collaborators: *M Rostal, W Karesh, (Ecohealth), C Cordel (ExecuVet) and P Thompson (UP)*
Funding: *Ecohealth Alliance*

The One Health Rift Valley Fever (RVF) project is focussing on a part of the Free State Province that is believed to be an epicentre for large outbreaks. The project, following a One Health approach, investigates various aspects including soil, weather, vegetation, vectors, domestic livestock and wildlife and people working with animals i.e., farm workers, (para) veterinarians and game capturers, and how these contribute to the interepidemic maintenance of the RVF virus (RVFV).

A total of 2793 mosquitoes were collected, identified and tested by the PCR for RVFV, but have not yielded any isolates yet. A total of 1637 samples collected from wildlife species were tested for antibodies to RVFV, with results indicating RVFV exposure of the following species: buffalo, springbuck, blesbuck and kudu.

A total of 7865 livestock samples, including a cohort of sheep sampled on a quarterly basis, were also tested for antibodies to RVFV. Preliminary results do not suggest active circulation of RVFV during the sampling period. This might be attributed to factors such as the widespread drought in the whole of SA over recent years, but conclusions can only be made once analysis of all the samples and data is complete. A total of 883 humans (of which 823 were tested for RVFV) were surveyed during the 2015/2016 baseline. Of these humans, 276 participated again in 2017 and form the human cohort; while 396 new people participated in the 2017 cross-sectional survey.

The presence of antibodies in wildlife species, which have never been vaccinated against RVFV infection, does however suggest that the virus circulates in the area, or have in the past.

Molecular epidemiology of Ebola virus disease in West Africa and the development of diagnostic capacity

NICD investigators: *JT Paweska, N Moola, P Jansen van Vuren, J Weyer, A Grobbelaar, N Storm and G Robertson*
Collaborators: *G Palacios (USAMRID Centre for Genome Science)*
Funding: *South African Medical Research Council (MRC) Strategic Health Innovation Partnership Fund*
This project was initiated, following the Ebola virus disease (EVD) outbreak in West Africa. The project goals include investigation of serological, virological, and epidemiological aspects of the EVD outbreak in West Africa and the development and validation of recombinant protein point-of-care (POC) based tests and enzyme-linked immunosorbent assays for rapid diagnosis

Preliminary phylogenetic analyses on 218 new Ebola virus genome sequences combined with 1031 sequences from other published studies indicated that the majority of the outbreak in Freetown was the result of repeated introductions into the city, rather than extended transmission chains within the city.

More in-depth evaluation of the data that reveals the shape of the transmission curves however indicates the direction of movement (westward or eastward). Based on this, it is clear that there was both inward and outward transmission in Freetown (Fig. 4).

To date, we have successfully expressed and purified recombinant Ebola virus nucleocapsid protein (NP) and have established mammalian cell lines that stably express the NP and the glycoprotein (GP) of Ebola. These cell lines allow for the safe and convenient preparation and standardisation of IFA slides under biosafety level 2 conditions.

We also successfully used a DNA-protein prime-boost strategy to generate antibodies to the NP protein that also recognises native whole Ebola virus antigen, with high specificity. These immunoreagents will be used for the development of different immunoassays formats and POC assays for EVD diagnosis.

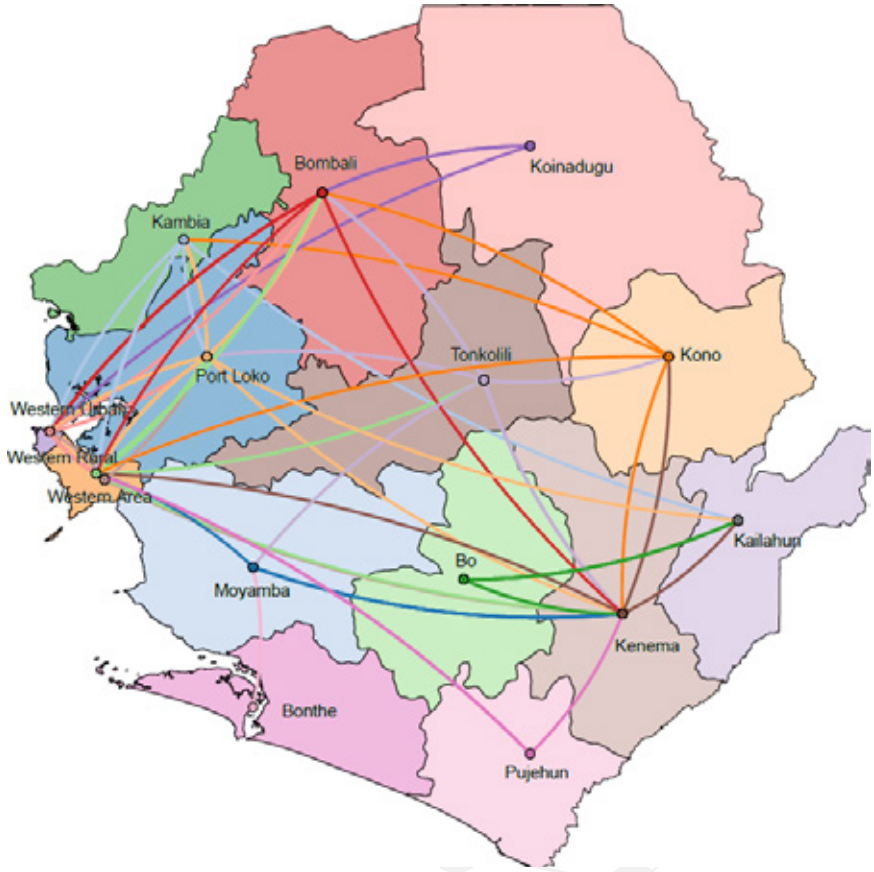


Figure 4. Phylogeographic analysis of 1249 Ebola virus genomes showing transmission throughout Sierra Leone. Upward curving transmission lines indicate eastward transmission and downward curving lines show westward transmission

Insecticide resistance in malaria vectors

NICD investigators: *B Brooke, M Coetzee and L Koekemoer*
Collaborators: *A Mnzava (WHO Global Malaria Programme)*

Malaria vector control relies principally on the use of insecticides via the distribution of insecticide treated bed nets (ITNs) or indoor spraying of residual insecticides (IRS). Wide-scale use of insecticides has, however, led to the development of insecticide resistance. The incidence of insecticide resistance in target *Anopheles malaria* vector populations is now extremely common and is increasing, especially in Sub-Saharan Africa.

Phenotypic resistance as measured using diagnostic dosages of insecticides, however, does not always translate into operational vector control failure. This is because there is no direct relationship between diagnostic dosages and the amounts of insecticide used to treat ITNs and to spray the inside walls of dwellings.

It is now evident though that measuring resistance intensity in addition to the use of diagnostic dosages, can add predictive value to the decision-making process in vector control settings, although more so in an IRS setting and especially when benchmarked against resistance phenotypes of known operational significance.

Malaria vector control and transmission dynamics

NICD investigators: *B Brooke, M Coetzee and L Koekemoer*
Collaborators: *J Gilles (International Atomic Energy Agency (IAEA), Jan-Rijn Zeevaart (South African Nuclear Energy Corporation (Necsa), F Mbokazi (Malaria Elimination Programme, Mpumalanga DoH, South Africa)*

Identifying malaria vector mosquito species and elucidating their feeding and resting behaviours is necessary for vector control and an enhanced understanding of disease epidemiology. In South Africa, where malaria incidence is low in comparison to highly-endemic regions because of intensive control operations, understanding the entomological drivers of residual malaria transmission is especially important.

To this end, an outdoor-resting population of the major vector species *Anopheles arabiensis* was incriminated in malaria transmission for the first time in South Africa, as was *An. vaneedeni*, which was previously thought to be a non-vector. The implementation of a project designed to evaluate the use of the sterile insect technique (SIT) as an alternative method of malaria vector control demonstrated that intensive mosquito surveillance over a long period of time, can provide valuable information on the population dynamics of a vector population - such as *An. arabiensis* in the Mamfene region of KZN.

Information concerning seasonal variation in the population density of this population provides an opportunity for implementation of a SIT intervention when mosquito abundance is low.

Funding: Mpumalanga and KwaZulu-Natal Malaria Control Programmes, CDC Global Diseases Detection grant, South African MRC Collaborating Centre for Multidisciplinary Research on Malaria, Division of Microbiology and Infectious Diseases, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, as part of the International Centers of Excellence for Malaria Research grant, South African DST/NRF Research Chair initiative, National Research Foundation, International Atomic Energy Agency, Industrial Development Corporation and the South African Nuclear Energy Corporation (Necsa) through its Nuclear Technologies in Medicine the Biosciences Initiative (NTeMBI) – a national platform funded by the Department of Science and Technology

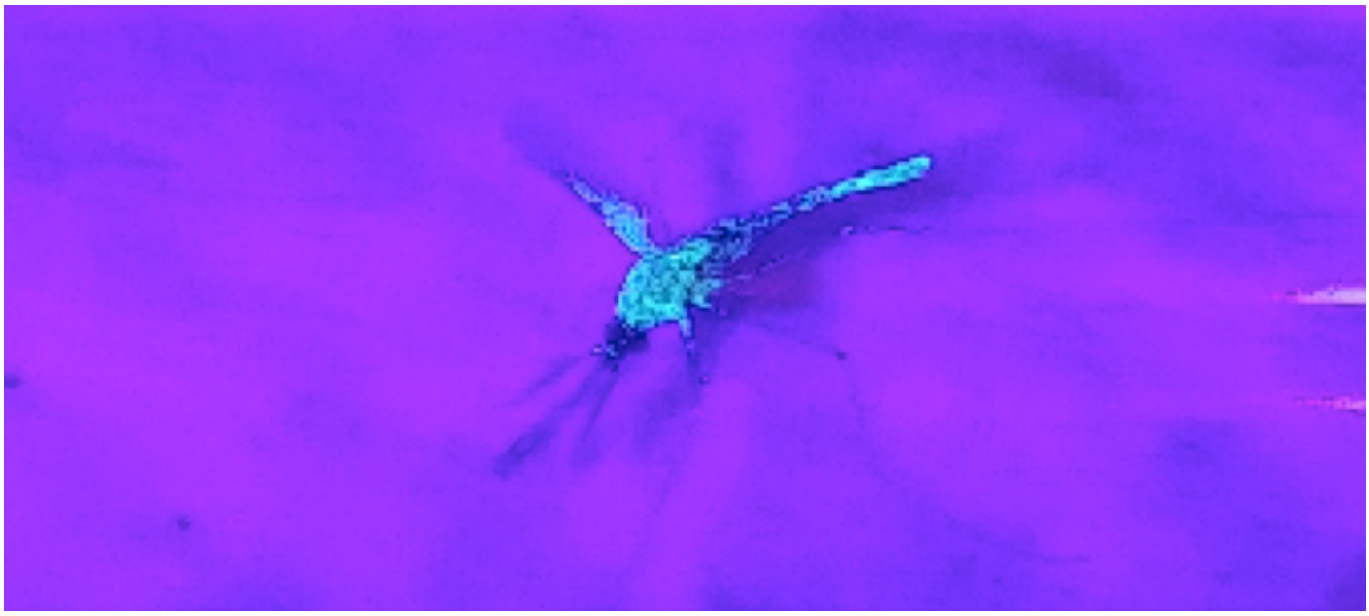


Figure 5. Fluorescent male *Anopheles arabiensis* mosquito. *Anopheles arabiensis* is a major malaria vector species. SIT is a promising non-insecticidal control method for this species. Part of the SIT project involves estimating the population size of the *Anopheles arabiensis* population at Mamfene in northern KZN. This is done by marking adult males with fluorescent dyes, so that one can utilise the mark-release-recapture method.

Figure 6. Collecting mosquitoes with a sweep net in northern KZN

Investigation of human brucellosis in South Africa

NICD investigators: *J Rossouw, J Frean, H Geyer, V Quan, V Msimang, JT Paweska*
Collaborators: *E Variava*
Funding: *US CDC Global Disease Detection Programme*

WHO declared brucellosis a neglected zoonotic disease and views appropriate needs analyses, integrated approaches and evidence-based advocacy as essential to its successful control. Brucellosis was recently listed among the top five priority zoonotic diseases in South Africa.

Despite it being a notifiable medical condition (NMC), it remains under-reported and it is often misdiagnosed. To add to the current understanding of human brucellosis in South Africa, the prevalence and exposure factors associated with human brucellosis is under investigation in different populations, which includes acute febrile illness patients presenting to two healthcare facilities, a farming population and veterinary staff in high-risk areas. The study will inform the development of a strategy for human brucellosis surveillance in South Africa.

TEACHING AND TRAINING

CEZPD was actively involved in supporting postgraduate studies in the fields of medical microbiology, virology, parasitology, entomology and public health through collaborative projects with South African and international universities and public health and research institutions.

Postgraduate students at MSc and PhD levels were trained in routine laboratory and field-based research techniques utilised by the centre. The CEZPD also provided training to postgraduate Diploma in Tropical Medicine and Hygiene (DTM&H) students, microbiology and clinical pathology registrars, intern scientists and technologists, on an ongoing basis.

In response to the 2017 plague outbreak in Madagascar, plague preparedness and outbreak response training was given by CEZPD staff, to ensure diagnostic and surveillance efficacy, which included plague training and competency assessments of City of Johannesburg Environmental Health Practitioners.

A very successful One Health Symposium was held in November 2017 in collaboration with Onderstepoort Veterinary Research and UP, with an exceptional attendance of 160 multi-sector participants. Training on RVF laboratory serologic and molecular diagnostic techniques was provided to participants from various African countries, hosted by the National Veterinary Institute of Ethiopia and funded by the IAEA.

Two training courses on the topic: "Training in Anopheles culturing techniques, morphological identification, sampling techniques & insecticide resistance detection" were run at the Vector Control Reference Laboratory. This course is primarily designed for malaria control programme (MCP) entomologists, vector surveillance team members, Environmental Health Practitioners and researchers.

The course also offers introductory level training for postgraduate students involved in operational research projects linked to malaria vector control activities. The aim of this course is to improve the basic entomological skills of personnel associated with malaria vector control. The CEZPD also facilitated the NICD Health and Safety Representative Biorisk Management training as well as two courses on Shipping of Dangerous Goods (class 6.2).

Training was also provided through a multitude of other courses, as follows:

- 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 (Wits); and
- One Health Module, Veterinary Medicine, UP.

The CEZPD staff also provided a number of guest lectures at different occasions, which include but are not limited to: infectious disease specialists seminars, forensic services training for handling of biohazardous materials, and the Gauteng Province communicable disease coordinators outbreak workshop.

Professional development

Staff member Dr Jacqueline Weyer obtained an MPH from the Sefako Makgatho Health Sciences University. Staff member Mrs Anastasia Trataris-Rebisz was registered for a PhD in Microbiology at UP.

CEZPD staff members were involved in postgraduate training of 20 students who are enrolled at UP and Wits, primarily in the field of virology and entomology, from this cohort, three students graduated with an MSc and one with a PhD.

Postgraduate students enrolled:

Twenty (two with a Bachelor of Science (BSc) Honours, eight with an MSc and ten with a PhD).

Postgraduate students graduated:

Four; three with an MSC and one with a PhD.

Honours

- Prof Maureen Coetzee:
  - Invited by Keystone Symposia to organise a symposium on Vectors, Pathogens and Disease, 10-15 September 2017, Durban;
  - Member of the Malaria Policy Advisory Committee (MPAC) of the WHO Global Malaria Programme, 2016-2019, reporting to the Director-General, WHO; Chair; and
  - Expert Review Group on new generation bednets for MPAC and the WHO Global Malaria Programme.
- Prof Lizette Koekemoer: Promoted to Research Professor, Wits.
- Dr Jacqueline Weyer:
  - Selected as a member of the Academy of Science of South Africa (ASSAf) Standing Committee on Biosafety and Biosecurity; and
  - Appointed as an Extraordinary Lecturer to the Department of Medical Virology, Faculty of Health Sciences, UP.
- Dr Jenny Rossouw: re-appointed as a member of the International Health Regulation (2005) Roster of Experts for Pneumonic Plague.
- Dr Petrus Jansen van Vuren: appointed as an Extraordinary Lecturer, Department of Medical Virology, Faculty of Health Sciences, UP.
- Prof Basil Brooke: WHO representative for the United Nations Environment Programme (UNEP) dichloro-diphenyl-trichloroethane (DDT) Expert Group 2016-2019.
- Prof Janusz Paweska:
  - Appointed as an Extraordinary Professor, Department of Medical Virology, Faculty of Health Sciences, UP; and
  - Received a B2-rating from the NRF.

RESEARCH OUTPUT

Publications

Journal articles

1. Aly MM, Ali S, Muianga AF, Monteiro V, Gallego JG, Weyer J, Falk KI, Paweska JT, Cliff J, Gudo ES. Severe chikungunya infection in northern Mozambique: a case report BMC Res Notes 2017; 10:88.
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3. Awandu S, Raman J, Makhanthisa T, Kruger P, Frean J, Bousema T, Niemand J, Birkholtz L-M. Understanding human genetic factors influencing primaquine safety and efficacy to guide primaquine roll-out in a pre-elimination setting in southern Africa. Malaria Journal 2018; 17: 120; doi:10.1186/s12936-018-2271-z.
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6. Bażanów B, Jansen van Vuren P, Szymański P, Stygar D, Frącka A, Twardoń J, Kozdrowski R, Pawęska JT. A Survey on West Nile and Usutu viruses in horses and birds in Poland. Viruses 2018; 10: 87, doi:10.3390/v10020087.
7. Bazanow BA, Pacon J, Gadzala L, Fracka A, Welz M, Paweska J. Vector and serologic survey for Crimean-Congo haemorrhagic fever virus in Poland. Vector-borne and Zoonotic Diseases 2017; doi:10.1089/vbz.2016.2075.
8. Biggs J, Raman J, Cook J, Hlongwana K, Morris N, Seocharan I, Agubuzo E, Drakeley C, Kruger P, Mabuza A, Zitha A, Machaba E, Coetzee M, Kleinschmidt I. Serology reveals heterogeneity of Plasmodium falciparum transmission in north-eastern South Africa: implications for malaria elimination. Malaria Journal 2017; 16, 48.
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Conference presentations

1. International: 14
2. National: 33

Centre for HIV & STIs

Prof Adrian Puren

BACKGROUND

The third National Strategic Plan (NSP) for HIV, STIs and TB (2012-2016) came to an end and the fourth iteration, NSP 2017-2022 was ushered in. It is critical to understand the effectiveness of the various interventions on the HIV treatment cascade, HIV incidence and HIV drug resistance. The centre contributed to these areas and provided key laboratory testing that will contribute to the national incidence and drug resistance estimates as well as the development and implementation of a revised protocol that will inform on the treatment cascade in the case of the annual antenatal survey for 2017. New directions in HIV surveillance include the development of protocols for HIV case-based surveillance and development of cohorts for paediatric HIV. For STI surveillance, there were a range of methodological approaches to contribute understanding of the burden of STI infections in South Africa. The approaches included the use of "big data" to understand the prevalence of maternal syphilis and the implication for elimination by 2030. Laboratory testing for STIs has proven to be a mainstay of understanding individual aetiological disease-causing agents, antimicrobial drug resistance and HPV surveillance. Knowledge of the HPV genotypes in circulation will serve as an important baseline to assess the effectiveness of the vaccine programme. The centre strives to add to new knowledge, not only in the fields of surveillance and implementation science, but also the basic sciences. Of headline attention was the South African child in HIV remission, nevertheless, major studies including areas of broadly neutralising antibodies continue as do the key HIV trials of prevention mentioned in previous years. The centre provided technical support to the National Department of Health in the form of guidelines, technical support on quality assurance of HIV rapid testing and participation in expert groups. The centre had a productive year and this was reflected in the number of publications, reports and presentations and staff were recognised and appreciated for their individual efforts.

SURVEILLANCE AND DIAGNOSTIC SERVICES

Antenatal HIV Prevalence Survey

The centre coordinated the 2017 annual antenatal HIV survey between October and November 2017, aiming to enrol 36 000 pregnant women. The objectives of the survey were expanded beyond HIV prevalence to include estimation of HIV incidence and development of a continuum of care cascade that includes HIV viral load suppression and antiretroviral treatment (ART) exposure.

HIV Case-based Surveillance

WHO recommends the implementation of a HIV case-based surveillance to improve quality of care, monitoring and evaluation, and surveillance. The centre developed a project plan to pilot such an approach in Gauteng. In 2017 there were a range of stakeholder consultations.

As soon as it is fully functional, the case-based surveillance project will be integrated with the current information systems from the various health systems, namely: the District Health Information System (DHIS), Tier.net, laboratory data from the NHLS' corporate data warehouse (CDW) and vital statistics from Statistics South Africa (Stats SA).

Determined, Resilient, Empowered, AIDS-Free, Mentored and Safe Women (DREAMS)

The purpose of this study is to evaluate the impact of the DREAMS Programme on HIV incidence over time, among a household-based representative sample of adolescent girls and young women (AGYW), between the ages of 12 and 24 years, in the four or five districts in KZN and Gauteng provinces, South Africa, where DREAMS will be implemented. HIV-1 incidence and viral load testing was performed on the Dried Blood Spot (DBS) samples received.

Human Sciences Research Council (HSRC) South African National HIV Prevalence, Incidence, Behaviour and Communication SABSMM V Survey

The general population household survey is conducted every four to five years, to provide key estimates of prevalence and incidence. It is one of the foremost surveys at a national level, as these estimates are important for trend analysis and assessing key outcomes related to viral load suppression and ART coverage. The 2017 survey is the fifth in the series of surveys and the centre's primary contributions involve the incidence and drug resistance estimates and viral load testing.

HIV Drug Resistance (HIVDR)

In 2014 - 2015, the NICD established an integrated TB-HIV surveillance study building on the GERMS-SA hospital-based enhanced surveillance platform, which introduced surveillance for TB drug-resistance among persons initiating TB treatment and/or HIVDR surveillance among persons initiating ART in the same clinic.

During 2017, enrolment for the study was expanded to four clinics in three provinces in South Africa (two in KZN, one in Mpumalanga and one in the Free State). Enrolment was completed at all sites and HIVDR testing was successful in 1118 (89%) of specimens.

Non-nucleoside reverse transcriptase inhibitor (NNRTI) class resistance was detected by Sanger sequencing in 18% (198/1118) of specimens, and dual nucleoside reverse transcriptase inhibitor (N(t)RTI)/NNRTI drug resistance in 3% (36/1118). The K103N/S mutation was most commonly detected as it was present in 73% of sequences with detectable NNRTI resistance, followed by major mutations at V106 (16%), G190 (12%), P225 (11%) and Y181 (7%).

A subset of 326 specimens were further analysed according to prior ART exposure: HIVDR was present in 42% of participants reporting prior ART use, versus 11% of those with no reported prior ART exposure. There were high rates (>15%) of NNRTI resistance among patients initiating ART and even higher levels (>35%) in patients re-entering for care. This data supports the discontinuation of NNRTIs as a component of first-line treatment and the introduction of the integrase inhibitor dolutegravir.

Paediatric HIV Surveillance

The objective of this project is to ensure national early infant diagnosis (EID) through paediatric HIV surveillance, including RFa reports with a self-service portal and birth testing dashboard and infant HIV diagnostic support.

The centre distributed EID HIV PCR reports at facility level to ±200 stakeholders on a monthly basis to assist with the monitoring and prevention of mother-to-child transmission (PMTCT). HIV PCR RFa reports that details HIV PCR results in real-time, were distributed to ±80 stakeholders weekly to track and enrol HIV PCR positive children into care.

Birth testing study cohorts were established at Rahima Moosa Mother and Child and Kalafong Hospitals in collaboration with the Empilweni Research and Service Unit, Kalafong Paediatrics Department and the NDoH.

EID HIV POC testing that was performed with two different HIV PCR technologies, are under evaluation. Investigating the use of cell phone technology to close PMTCT cascade gaps for complete elimination of mother to child transmission (eMTCT) were initiated in collaboration with UNICEF.

Key Population Surveillance and Intervention Science

The centre was part of a collaboration with the HSRC and the University of California, San Francisco (UCSF) in partnership with Anova Health, that focused on surveillance in "key populations" including men who have sex with men (MSM). The centre fulfilled the following functions as part of this collaboration:

- The South African Men's Health Monitoring Survey (SAMHMS) was completed in two cities, namely Pretoria and Durban, South Africa;
- A key population implementation science (KPIS) study was completed, which involved evaluating the use of multiple interventions, including POC testing facilities to improve access to care and retention amongst MSM. As part of this study, the centre's staff conducted training and site visits in two cities, namely Springs and Port Elizabeth, in South Africa; and

- A third study was conducted that focused on people who inject drugs (PWID) in multiple locations in South Africa as part of an integrated HIV bio-behavioural study (IBBS). The objectives were to measure HIV prevalence and related risk behaviours and assess access to prevention and care services in Tshwane and Cape metros in South Africa.

Quality Assurance of HIV Rapid Testing

The centre supported the implementation of key quality assurance activities to over 2000 healthcare facilities that provide HIV point of care (POC) testing. This initiative is in line with the objectives of the National HIV/AIDS Programme which aims to ensure accuracy and reliability of the test results generated and appropriate care and management of HIV clients.

Our support encompassed the provision of Internal Quality Control (IQC), as well as assistance with the implementation of quality assurance to ensure compliance to standard requirements for HIV rapid testing of 1208 testing sites, including 653 first round and 555 second round testing sites. The external site assessments were conducted using a universal WHO-CDC stepwise process for improving the quality of HIV rapid testing checklist. In addition, the sites participated in Proficiency Testing (PT), with 1869 and 2005 testing sites respectively enrolled for PT Survey 1 and Survey 2.

STI SURVEILLANCE

Maternal Syphilis Surveillance Based on CDW Data

Analysis of laboratory test data on rapid plasma regain (RPR) positivity among women of reproductive age from the NHLS' CDW commenced in June 2017. Initial analyses were completed in September 2017. A report on the RPR sero-positivity among women aged between 15 and 49 years, for the period 2010 – 2016, by year and province, was submitted to the NDoH in October 2017. The data was included as part of the validation of the spectrum STI model that is being developed by the NDoH, WHO and NICD.

Aetiological Surveillance of STI 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 PHCs is based on the identification of a group of symptoms and easily recognisable signs associated with a number of well-defined aetiologies. The three major STI syndromes are male urethritis syndrome (MUS), vaginal discharge syndrome (VDS) and genital ulcer syndrome (GUS) among adult patients (>18 years). Secondary objectives are to determine:

(a) The prevalence of HIV co-infection in patients presenting with STI syndromes;
(b) The antimicrobial susceptibility of *Neisseria gonorrhoea* isolates from MUS patients to extended-spectrum cephalosporins (ESCs); and
(c) The sero-prevalence of HSV-2, infectious hepatitis B and syphilis.

Periodic aetiological surveillance of STI syndromes is critical in validating the existing treatment algorithms. Aetiological surveillance at selected sentinel sites (at least one per province) was executed under the umbrella of NICD GERMS-SA from 2015 onwards. In 2017, surveillance was conducted at various sentinel sites in the following provinces:

- Western Cape: Khayelitsha Clinics;
- Free State: Heidedal Community Health Centre (CHC);
- Eastern Cape: Zwide Clinic; and
- Gauteng: Alexandra Health Centre and University Clinic.

The findings will be published in the Quarter 4 2018 NICD Public Health Surveillance Bulletin. A report on 2016 aetiological surveillance can be found in the November 2017 NICD Public Health Surveillance Bulletin.

Sentinel Surveillance of Human Papillomavirus (HPV) Genotypes and Association with HIV Infection Among Young Women Accessing Family Planning Services at Primary Healthcare Facilities in South Africa, NICD GERMS-SA

HPV is the most common sexually transmitted infection and in women its prevalence peaks during adolescence soon after sexual debut; and decreases with age. Specific "high risk" HPV genotypes are the cause of cervical cancer. Cervical cancer is the second most common type of cancer in South African women and women co-infected with HIV are at substantially increased risk of HPV infection and HPV-associated cancers.

South Africa introduced a school-based national HPV vaccination programme in 2014, whereby girls aged between nine and 12 years are vaccinated with Cervarix HPV vaccine (which provides protection against high risk HPV 16 and 18 genotypes that are associated with 70% of cervical cancer and precancerous cervical lesions).

The main objectives of the current surveillance exercise are to determine the prevalence of HPV infection and identify individual HPV genotypes among young sexually-active women in South Africa aged 18-20 years, who access family planning services at sentinel primary healthcare facilities.

The 2017 surveillance findings from the following sentinel PHC sites: Western Cape (Khayelitsha Clinics); Free State (Heidedal CHC); Eastern Cape (Zwide Clinic) and Gauteng (Alexandra Health Centre and University Clinic), will be published in the Quarter 3 2018 NICD Public Health Surveillance Bulletin.

In 2015-2016, participants were enrolled at six primary healthcare clinics in Gauteng (Alexandra Health Centre and University Clinic), Mpumalanga (Hluvukani and Kabokweni clinics), KwaZulu-Natal (Phoenix and East Boom CHCs) and North West province (Jouberton Clinic). Findings were published in the August 2017 NICD Public Health Surveillance Bulletin.

Analysis of the Age Profile of VDS Patients and Performance of Age in Predicting the Presence of an STI

Data collected from the 2015 - 2016 STI sentinel surveillance activities were analysed to determine the demographic and clinical profiles of women with VDS and the performance of age in predicting the presence of an STI. The research showed that although rates of STIs declined with age among women with VDS, there was no age threshold that could predict the absence of an STI and that age was not a good criterion to use in the VDS treatment algorithm.

Analysis of Progress Towards the 90-90-90 Targets Among STI Service Attendees

Data from the 2017 STI sentinel surveillance was analysed for progress towards reaching the 90-90-90 targets among STI patients. The analysis served to determine the following:

- The proportion of enrolled STI patients who knew their HIV status by HIV status;
- The proportion of HIV positive STI patients who were taking ART;
- Factors that are associated with the knowledge of HIV status; and
- Factors that are associated with the misreporting of an HIV status.

HIV RESEARCH

Support for HIV Vaccine Trials

The centre conducts validated end-point antibody and molecular diagnostic assays for the HIV Vaccine Trials Network (HVTN). Data generated as part of the HVTN 100 trial, contributed to the important decision to proceed to a large-scale efficacy trial called HVTN 702 that is currently enrolling. This is the first efficacy trial in South Africa that aims to test whether a canarypox prime plus protein boost will elicit protective immune responses.

The centre was also involved in HVTN 100 Part B where participants received HIV protein at 30 months, to determine whether an additional boost can increase immune responses and enhance longevity of these responses.

Another major activity is sensitivity testing on breakthrough HIV infections in the antibody-mediated protection (AMP) trial which aims to test whether passive infusion of the broadly neutralising antibody VRC01 will provide protection from HIV infection. The two efficacy trials, namely HVTN 702 and HVTN 703 (AMP), are expected to run for the next two to three years and assessing and understanding the correlates of protection will be a major focus for the centre. Additional protocols for end-point testing included HVTN 107, 108, 111, 116, 117, 118,705, and 910.

The centre is the reference laboratory for the vaccine-induced sero-positivity (VISP) for the VISP Testing Service-Africa (VTS-A). The service is intended to provide a mechanism for testing and prevention or mitigation of social harms related to VISP.

TECHNICAL SUPPORT

HIV

HIV EIA and viral load testing was performed for the prospective household observational cohort study of influenza, respiratory syncytial virus and other respiratory pathogens community burden and transmission dynamics in South Africa (the PHIRST Study).

HIV viral load testing was also performed for the Alcohol, Tobacco and Other Drug Research Unit (MRC) project, that aims to assess the effectiveness of an alcohol-focused intervention in improving adherence to ART and HIV treatment outcomes.

The laboratory collaborated with TB HIV Care on two studies:

- An adaptive randomised evaluation of nurse-led HIV treatment retention interventions for women living with HIV; and
- Key populations and HIV epidemics in sub-Saharan Africa: primary data collection in Port Elizabeth.

HIV-1 viral load testing was performed for various SADC incidence studies:

- Swaziland Link4Health (Linkage and retention in HIV care);
- Swaziland HIV Incidence Measurement Survey (SHIMS 2);
- Swaziland Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) study; and
- MSF Mozambique and ZAMPHIA (Zambia Population-based HIV Impact Assessment survey).

In addition, the HIV drug resistance (HIVDR) laboratory performed testing for acquired and pre-treatment surveys conducted in Mozambique.

STI

The centre contributes to the following studies:

- Wits Reproductive Health & HIV Institute Unit: CHOICES study - a prospective observational study of the association between injectable contraception, HIV and other STIs among young women in South Africa. Laboratory testing over the two-year study period will include quarterly visits for serology (rapid HIV, syphilis, HSV-2) and annual molecular testing (M-PCR) of vaginal swab specimens for VDS pathogens. The study commenced in April 2016 and recruitment is ongoing;
- Foundation for Professional Development: ASPIRES Study – prevalence of STIs *(Neisseria gonorrhoea, Chlamydia trachomatis and Trichomonas vaginalis)* among school-going children (4 schools in Tshwane district). Post-intervention recruitment and testing commenced in December 2016 and the study is ongoing;
- UChoose a Star: Study of hormone (contraceptive) induced mucosal changes due to effects on the genital microbiome, and HIV susceptibility in adolescent females. Endocervical and vaginal swabs specimens for STI testing will be taken at screening; crossover (week 16) and termination (week 32). Recruitment for the screening, crossover and termination visits continued during the reporting period;
- Human papillomavirus prevalence in HIV-negative South African adolescents and young women (UCT collaboration). This study serves to investigate prevalence, incidence and clearance of cervical HPV infection in adolescents and young women in South Africa, along with the influence of other STIs [*Chlamydia trachomatis, Neisseria gonorrhoea, Trichomonas vaginalis, Mycoplasma genitalium*, herpes simplex virus-2 (HSV-2)], bacterial vaginosis (BV), sociodemographic characteristics and sexual behaviour; and
- HPV in men (HIM-SA/CANSA study): The prevalence of anogenital and oro-pharyngeal HPV infection, genotype distribution and associations with anogenital disease, according to HIV-related factors and exposure to antiretroviral treatment. The study aims to describe and report on the epidemiology of anogenital and oropharyngeal cancer patterns and trends in men, including incidence and mortality rates and differences by ethnicity in SA between 1994 and 2010. The influence of HIV status on epidemiology of these cancers will furthermore be explored.

CURRENT RESEARCH PROJECTS

STI

Molecular characterisation and detection of fluoroquinolone and macrolide resistance determinants in *Mycoplasma genitalium* in Gauteng, South Africa

Principal investigator: *E Muller*
Co-investigators: *R Kularatne, D Lewis and P Mahlangu*
Funding: *Internally funded*

Mycoplasma genitalium is responsible for 20-35% of non-chlamydial non-gonococcal (NCNGU) urethritis and cervicitis. Isolation of *M. genitalium* from clinical specimens is difficult and time consuming and diagnosis is mainly achieved by using nucleic acid amplification tests (NAATs). Due to the difficulties in culturing the organism, the antibiotic susceptibility profiles of clinical strains of *M. genitalium* is therefore limited, especially in South Africa. Known profiles have shown *M. genitalium* to be highly susceptible to macrolides but less susceptible to tetracyclines and quinolones.

Current treatment guidelines recommend the use of a 1 g single dose of azithromycin for the treatment of MUS and VDS. Macrolide resistance is caused by mutations in region V of the 23SrRNA gene, while fluoroquinolone resistance is associated with *gyrA* and *parC* gene mutations.

The centre completed testing for all *M. genitalium* positive DNA from Gauteng STI National Microbiological Surveillance (NMS) samples obtained between 2007 and 2014, as well as *M. genitalium* positive DNA obtained from HIV positive patients previously recruited at an urban HIV outpatient clinic in Johannesburg, South Africa, in 2007. We tested all stored *M. genitalium* positive DNA from these studies for specific drug resistance determinants to investigate the possible emergence of macrolide and fluoroquinolone resistance.

This research is ongoing and *M. genitalium* positive samples from STI surveillance conducted from 2015 onwards will be tested to monitor for the emergence of macrolide resistance, following the incorporation of azithromycin into the 2015 national STI syndromic management guidelines for genital discharge.

Treponema pallidum: azithromycin resistance testing and molecular typing of 2008-2016 national surveillance specimens to include all NAS/GERMS surveillance specimens

Principal investigator: *I Venter*
Co-investigators: *E Muller, R Kularatne, T Kufa and V Maseko*
Funding: *Internally funded*

Penicillin is the treatment of choice for syphilis. Macrolides (e.g., azithromycin [AZM] and erythromycin) have been used as a convenient oral and cost-effective alternative for syphilis treatment globally. High prevalence macrolide resistance, resulting in treatment failure for primary syphilis in USA, Europe and China has been attributed to an A to G substitution mutation in the 2058 or 2059 position of the Treponema pallidum (TP) 23S rRNA gene, resulting in target site alteration due to methylation.

In 2014, AZM was added to the syndromic management guidelines for genital discharge in South Africa. Individuals exposed to macrolides are twice as likely to have a resistant strain of TP within the next year. We determined the TP macrolide-resistance prevalence in GUD specimens from patients presenting to PHCs in SA, Zimbabwe and Namibia, between 2008 and 2016.

HIV Virology

Cooperation between strain-specific and broadly neutralising responses limited viral escape and prolonged the exposure of the broadly neutralising epitope

NICD researchers: *V Bekker, L Morris and PL Moore*
Collaborators: *C Anthony C (UCT), T York (UCT), D Matten (UCT), R Ferreira (UCT), NJ Garrett, Centre for the AIDS Programme of Research in South Africa (CAPRISA), SS Abdool Karim (CAPRISA), NT Wood (UCT) and C Williamson (UCT)*
Funders: *National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), NRF and MRC*

V3-glycan broadly neutralising antibodies are a focus of HIV-1 vaccine development. Understanding viral dynamics that shape their development provides insights for immunogen design. We investigated the rate of escape from V3-glycan-directed bNAbs compared to overlapping strain-specific antibodies (ssNAbs) in CAP177. Escape from the ssNAbs occurred rapidly (in 7.5 weeks) via an N334-to-N332 glycan switch.

In contrast, escape from the bNAbs took longer, first through a longer V1, which took 46 weeks, followed by an N332-to-N334 reversion, which took 66 weeks. Importantly, bNAb escape was incomplete. Selective pressure by ssNAbs may thus have constrained the bNAb escape pathway. This slower viral escape resulted in prolonged exposure of the bNAb epitope, which aided the maturation of the bNAb lineage.

Serum glycan-binding IgG antibodies in HIV-1 infection and during the development of broadly neutralising responses

NICD researchers: *C Scheepers, PL Moore, and L Morris*
Collaborators: *S Chowdhury, National Cancer Institute (NCI), WS Wright (NCI), CT Campbell (NCI), NJ Garrett, (CAPRISA), Q Abdool Karim (CAPRISA), SS Abdool Karim (CAPRISA) and JC Gildersleeve (NCI)*
Funders: *PRF, Wits Health Sciences Faculty Research Council, NRF Centre of Excellence (COE) in HIV Prevention, DST, NIH and NIAID*

The HIV-1 envelope is covered with glycans that are often bound by bNAbs. We determined whether antiglycan IgG antibodies are a general response to HIV-1 infection or specific to bNAb individuals. Sera from 20 HIV-negative and 27 HIV-positive women (including 12 who developed bNAbs) were profiled using glycan arrays. Antiglycan IgG antibodies fluctuated, irrespective of HIV infection.

HIV-positive individuals however had elevated binding to 40 components on the array. Competition experiments confirmed that a proportion of these glycan-binding IgG antibodies were HIV-1-specific. HIV-1 infection is associated with elevated levels of IgG antibodies to specific glycans. Some antiglycan IgG antibodies were furthermore more abundant in individuals with bNAbs, suggesting a unique phenotype that may be informative for HIV vaccine design.

Phenotypic deficits in the HIV-1 envelope are associated with the maturation of a V2-directed broadly neutralising antibody lineage

NICD researchers: *L Morris and PL Moore*
Collaborators: *L Reh (University of Zurich), C Magnus (ETH Zurich), C Kadelka (University of Zurich), D Kuhnert (University Hospital Zurich), T Uhr (University of Zurich), J Weber (University of Zurich) and A Trkola (University of Zurich)*
Funders: *Swiss National Science Foundation (SNSF), Marie Heim-VoÈgtlin and MRC*

We followed the evolution of the VRC26 bNAb lineage in CAP256 to investigate viral phenotypic changes during bNAb induction. The VRC26-resistant primary infecting virus, the VRC26-sensitive superinfecting virus and recombinants showed substantial phenotypic changes, with a switch in Env properties coinciding with early resistance to VRC26. Decreased sensitivity resulted in reduced infectivity, altered entry kinetics and lower sensitivity to neutralisation.

VRC26 maintained neutralisation activity against cell-associated virus, indicating that cell-cell transmission is not a dominant escape pathway. Reduced fitness of the early escape variants and sustained sensitivity in cell-cell transmission both limit virus replication, thereby impeding rapid escape. This supports a scenario where VRC26 allowed only partial viral escape for a prolonged period, increasing the time for bNAb maturation.

Cross sectional surveillance of HIVDR in paediatric patients receiving antiretroviral therapy in South Africa

NICD researchers: *G Hunt, M Yousif, J Ledwaba, G Sherman, T Kufa and L Morris*
Collaborators: *L Levin (Right to Care), S Carmona (NHLS), K Steegen (NHLS), G Aynalem (CDC-SA), K Ayalew (CDC-SA), K Diallo (CDC-SA), G Kindra (CDC-SA) and E Raizes (CDC-USA)*
Funders: *CDC-RFA-GH15_1575*

A national facility-based study of HIVDR among children who are failing was implemented in February 2017. A sample size of 1475 specimens is required. Patients were recruited and information was collected from 33 patients at 45 high burden public health facilities in nine provinces.

The preliminary analysis of the 185 participants who enrolled, showed a mean most recent VL result of 164770 copies/ml (95% CI: 40516 – 289025 copies/ml). Most (61%) participants received a PI-based regimen, 34% were receiving EFV/NVP/RPV-based regimens, and 5% were on 3TC monotherapy. Of 165 specimens successfully amplified (89%), 17% of participants harboured no resistance mutations, 49% had dual NNRTI+NRTI resistance, 13% had NNRTI resistance, 14% had NRTI resistance, 2% had dual PI+NRTI resistance and 4% harboured triple class resistance.

Cell Biology

Paediatric HIV functional cure and early ART

Collaborators: *L Kuhn (Columbia University), A Coovadia, Empilweni Services and Research Unit (ESRU), Rajah Muthiah, Medical College Hospital (RMMCH), K Technau (ESRU), R Strehlau (ESRU), F Patel (ESRU), the LEOPARD study team and the NEVEREST study team*
Funded as a NIH UO1 grant: *PI Louise Kuhn, RSA PIs CT Tiemessen, R Strehlau*

A single-arm clinical trial, called LEOPARD-CT, commenced in August 2015 at RMMCH in Johannesburg, South Africa. The trial was designed to improve the understanding of viral latency in early treated HIV-infected children, to lead to more effective treatment strategies for children, with the ultimate goal of achieving functional cure or viral remission.

In parallel, we have been recruiting an observational cohort of mothers and their infants (called LEOPARD-O, which commenced in March 2015) where there has been a delay in treatment to the infant (i.e., it did not start within 48 hours of birth as per the LEOPARD-CT protocol).

To date, 75 birth-identified HIV-1 infected infants have been enrolled, 30 of whom started treatment within 48 hours of birth. Testing of select longitudinal samples to assess the HIV reservoir through quantitating total cell-associated HIV-1 DNA by a semi-nested PCR assay is underway. This assay was first tested on the NEVEREST cohort samples, highlighting that smaller reservoirs are associated with earlier administration of ART. Four flow cytometry panels were utilised to characterise longitudinally in infants where all the known T cell subsets can serve as reservoirs for HIV, as well as B cell subsets.

Simultaneously, a small group of HIV-exposed uninfected (HEU) infants have been recruited as controls. Immunophenotyping by flow cytometry is being conducted at birth (mother and infant) and at four weeks, 12 weeks and 18 months (infant). We enrolled 27 HIV-1 infected infants and 25 HEU infants for this component of the study and expect to complete follow up of these participants in the first half of 2018.

The South African child in HIV remission

Collaborators: *A Violari, Perinatal HIV Research Unit (PHRU), Wits, M Cotton (Stellenbosch University), L Kuhn (Columbia University), J McIntyre (Anova Health Institute), A Babiker and Diana Gibb (MRC, Clinical Trials Unit, University College London)*

The recent finding of a South African 9.5 year old child who has achieved sustained virological control for 8.75 years post-ART interruption was reported at the 9th IAS Conference on HIV Science 2017 in Paris, providing further hope for the possibility of a functional cure/HIV remission.

To gain further insight into specific characteristics of this case, detailed virological, immunological and genetic studies were undertaken on blood samples from the child at 9.5 years of age, and some viral studies were conducted on stored samples collected at 50 weeks of age at the time of ART interruption.

The child is HIV-negative on standard diagnostic enzyme-linked immunosorbent assay (ELISA) and qualitative DNA PCR. Ultrasensitive PCR assays to detect HIV-1 provirus were positive, confirming the presence of a small cell-associated HIV-1 DNA reservoir.

Studies are ongoing to understand the events that may have resulted in this remarkable outcome. The importance of continued study of a single unique case such as this child (or any similar cases that may emerge) lies in the hypotheses that are generated, that can then be tested in cohorts of HIV-1 infected adults and children.

South African HIV-1 infected long term nonprogressors and elite controllers

Collaborators: *N Martinson (PHRU), D Spencer (Right to Care), P Ive, Clinical HIV Research Unit (CHRU), M Ramsay, Sydney Brenner Institute for Molecular Bioscience (SBIMB), P Kiepiela (MRC), M Vermeulen (SANBS), M Papathanosopoulos (Wits)*

This study explores natural control of HIV-1 that occurs in rare individuals called elite controllers, and includes other phenotypic groups of patients that may control their disease progression through different mechanisms, to identify viral and host targets that can be developed for functional cure strategies in our populations.

The approach includes establishing biosignatures (combinations of host, viral, bacterial, environmental factors) that will ultimately distinguish different clinical phenotypes of HIV-1 control, and the incorporation of unbiased systems biology approaches such as whole genome DNA sequencing, whole genome transcriptional profiling of mRNA and microRNA.

In 2017, we continued to identify and recruit HIV-1 controllers and progressors across South Africa. To date, we have samples from approximately 240 elite controllers (182 from SANBS testing), 500 viraemic controllers, 1032 progressors, and 11 high viral load long term nonprogressors (a very rare group among HIV-1 infected adults; >10,000 RNA copies/ml and healthy CD4 T cell counts for > 7 years). Assays were established and analyses are ongoing with an initial focus on a cohort from Johannesburg/Soweto. Given the implementation of the test and treat programme, we will in future only recruit HIV-1 infected elite controllers that are referred to the project.

Utilising samples from the Johannesburg cohort (n=124 total: a group of 11 elite controllers, 30 viraemic controllers, 11 high VL LTNPs and 72 progressors), allowed us to establish and optimise the many assays to be used in this project, provided some important insights into immune processes important in HIV-1 control in our populations, and revealed some additional complexities unique to our populations along some host axes that need to be resolved.

To date, the focus has been on genetic factors (*HLA* class I A, B and *C; KIR; CCR5; CCL3* haplotypes; *CCL3L and CCL4L; CXCR6; RICH2;* Tetherin and functional FcγR gene variants), soluble plasma factors/metabolic and host functional assays (sCD26, HIV-specific antibodies, antibody dependent cytotoxic and phagocytoic responses) and virological studies which included the development of HIV-1 subtype C reservoir assays and monitored viral escape in progressive infection (HIV-1 Gag, Vif, Vpu, Vpr).

TEACHING AND TRAINING

The centre contributed scientist and specialist registrar training that encompassed topics on surveillance of HIV and STIs, antimicrobial drug resistance, diagnostics for HIV and STIs and HIV vaccine developments.

Lectures in medical microbiology were given to undergraduate medical and dental/pharmacy/nursing students; as well as to postgraduate students enrolled for the DTM&H at Wits.

In the area of epidemiology, lectures were provided to the FETP and the Epidemiology and Biostatistics Programme at the Wits School of Public Health. Dr Tendesayi Kufa, served as a protocol assessor at the Wits School of Public Health during the year.

Technical trainings were also provided to various organisations in the fields of DBS for surveillance and HIV incidence testing.

POLICY FORMULATION

The centre contributed data for policy formulation as well as written recommendations for incorporation into national STI syndromic management guidelines at meetings of the Essential Medicines List of the NDoH. This includes:

1. The Standard Treatment Guidelines and Essential Medicines List for Primary Healthcare; and
2. The Standard Treatment Guidelines and Essential Medicines List for Adult Hospital Level of Care.

The centre also contributed to the national HIV self-testing guidelines.

GRANT FUNDING

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

1. British Society for Antimicrobial Chemotherapy (BSAC);
2. DST/NRF Foundation Chair of HIV Vaccine Translational Research;
3. MRC;
4. NHLS Research Trust;
5. National Research Foundation Incentive Funding for Rated Researchers;
6. National Research Foundation Professional Development Programme;
7. NIH;
8. PRF;
9. PEPFAR; and
10. WHO, Department of Reproductive Health and Research.

PROFESSIONAL DEVELOPMENT

Postgraduate Training

The centre currently has a number of postgraduates registered as follows:

1. Four for a PhD;
2. Five for an MSc;
3. One for a BSc Hons;
4. Six for an MSc;
5. Two for an MSc in Epidemiology; and
6. One for a Master of Medicine (MMed).

The centre also supports six postdoctoral fellows.

Graduations

Two students graduated with a PhD, two with a BSc Hons and one with a Bachelor of Technology.

Honours

1. Prof Lynn Morris received the Harry Oppenheimer Award which is awarded annually by the Oppenheimer Memorial Trust. It is considered the top award for research on the African continent. Professor Morris was also awarded with The World Academy of Sciences (TWAS) Prize in Medical Sciences for 2018;
2. Prof Tiemessen was awarded the Wits Vice-Chancellor's Research Award for 2017.
3. Prof Gayle Sherman was appointed as Professor (Department of Paediatrics and Child Health, Faculty of Health Sciences, Wits);
4. Prof Penny Moore was elected as a new Member of ASSAf;
5. Dr Cathrine Scheepers was invited to serve on a panel of Immunogenetics (IMGT) experts to provide guidance for studies involved in human Ig repertoires and standardisation;
6. Rutendo Ziki received the Merck Award for Best MSc student in Biotechnology in the School of Molecular and Cell Biology at Wits. She completed her Masters with distinction in 2015;
7. David Sacks received the Bronze Prize for his talk at the Molecular Biosciences Research Thrust (MBRT) Postgraduate Research Day, which took place at Wits on 30 November 2017; and
8. Batsirai Mabvakure (PhD), Alaine Marsden (MSc) and Holly Spencer (BSc Hons) received merit awards from Wits to cover their 2018 tuition fees.

RESEARCH OUTPUT

Journal articles

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Conference Presentations

- International Congresses: 29
- National Congresses: 28
- Local Congresses: 12

Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses

Prof Nelesh Govender

BACKGROUND

The centre was created in April 2017 to serve as a national hub of expertise in the priority areas of healthcare-associated infections (HAIs), AMR and mycoses. The centre incorporates two national reference laboratories for 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.

In June 2017, the centre was designated a WHO CC for AMR and is now the national focal point for WHO's GLASS. The centre's epidemiology team helps to drive the surveillance/public health research agenda and conducts community- and healthcare-associated outbreak investigations.

The centre is also involved in the evaluation of large-scale public health programmes. In the field of laboratory quality improvement, the centre has played an active role in reporting on clinical laboratory capacity in the WHO African region for the past 15 years.

SURVEILLANCE/OUTBREAK ACTIVITIES

HAI surveillance

Collaborators: *T Avenant, N du Plessis, K Masemola, D Pillay, M Ngobese, C Mackay, S Mahmud Yakoob, S Abrahams, J Black, N Ramncwana, Eastern Cape DoH, F Naby, S Haffejee, H Dawood, J Green, T Martin; GERMS-SA network, South African Regional Global Disease Detection Centre, NICD; Surveillance Information Management Unit (SIMU) and the NICD*

Limited data exists on the burden of HAIs in South Africa and there is currently no national HAI surveillance system. Over the last year, the centre prepared for establishing a pilot surveillance project focused on bloodstream infections (BSIs) in neonates. This includes a real-time alert system to detect potential HAI outbreaks.

The surveillance project will establish the baseline prevalence and incidence density of BSIs among neonates and will facilitate development of simplified surveillance case definitions for use in the South African context. Baseline data analysis is in progress.

Bacterial and fungal AMR surveillance

Collaborators: *GERMS-SA network, SA Society for Clinical Microbiology and the NICD SIMU*

Surveillance is a key component of the strategy to combat AMR. Senior members of the centre represent the NICD on the Ministerial Advisory Committee for AMR and the WHO Strategic and Technical Advisory Group for AMR. The centre also leads the national effort to conduct surveillance for AMR infections through establishment of a national pathology laboratory surveillance network. Several approaches are currently used for AMR surveillance:

- National or sentinel isolate-based surveys: bacterial and fungal isolates, cultured from patients who meet the surveillance case definitions, are submitted to the centre's reference laboratories for identification, antimicrobial susceptibility testing and genotyping. During the reporting period, the centre conducted surveillance for BSIs caused by *Staphylococcus aureus* (2012-2017), carbapenem resistant Enterobacteriaceae (2015-), *Acinetobacter baumannii* (2017-) and *Candida* species (2016-2017);
- Enhanced laboratory surveillance: detailed clinical information is collected from patients admitted to sentinel hospitals who meet the surveillance case definitions. During the reporting period, the centre conducted enhanced surveillance for BSIs caused by *Staphylococcus aureus*, carbapenem-resistant Enterobacteriaceae and *Candida* species; and

- Electronic laboratory surveillance: annual data was compiled on BSIs caused by the *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species* (ESKAPE) pathogens in 2016 and 2017. 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 national AMR maps by geographic location, pathogen, antibiotic and health sector. AMR data for the public sector are now available at facility level.

Surveillance for mycoses

Collaborators: *GERMS-SA network*

In 2017-2018, the centre reinitiated continuous enhanced surveillance for microbiologically-confirmed cryptococcal disease. The aim of this surveillance was to assess the impact of national reflex cryptococcal antigen screening. Passive laboratory-based surveillance for rarer invasive mycoses continued.

OUTBREAKS

The centre has led or participated in the investigation of several community and healthcare-associated outbreaks during the year. Most recently, these include an outbreak of *Candida auris* candidaemia in a neonatal unit, an environmental survey of *C. auris* in private-sector hospitals, an outbreak of carbapenem-resistant *A. baumannii* in a neonatal unit and an outbreak of methicillin-susceptible *S. aureus* skin infections in a gold mine in Gauteng Province.

Reference laboratory diagnostic services

The centre offers a specialised bacteriology and mycology reference service to diagnostic pathology laboratories which includes:

- Phenotypic, mass spectrometric and sequence-based identification of bacteria and unusual or difficult-to-identify fungi;
- Antibiotic susceptibility testing of bacteria and antifungal susceptibility testing of yeasts, moulds and dimorphic fungi;
- Genotyping of bacteria and fungi; and
- Identification of molecular mechanisms of antimicrobial resistance.

The National Biological Sample Collection maintains characterised bacterial and fungal pathogens of national importance, as a resource for scientists and quality controls for routine laboratory tests.

RESEARCH

National reflex cryptococcal antigen (CrAg) screening at NHLS laboratories

Collaborators: *NHLS NPP unit, NHLS Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) microbiology/ CD4 laboratories, NICD SIMU, NHLS CDW*

A CrAg screening dashboard (integrated into NHLS HIV dashboard) was developed by the centre and CrAg screening data are now available at national, provincial, district and facility level. RfA reports were developed and are distributed to registered, approved clinicians and facility managers with 311 subscribers approved across 292 healthcare facilities in 47 districts.
The centre provided technical assistance for an NHLS CrAg lateral flow assay (LFA) proficiency testing scheme (PTS) at CD4 labs and monitored CrAg discrepancies through inter-laboratory quality assessment.

A pilot CrAg titre project commenced in November 2017 at the CMJAH microbiology laboratory. The centre has begun validation studies of several new assays, including the IMMY semi-quantitative CrAg LFA and IMMY Clarus CrAg EIA.

CAST-NET

Collaborators: *University of Minnesota, US CDC and the Foundation for Professional Development (FPD)*

The centre is evaluating the effectiveness of the CrAg screen and treat intervention to reduce mortality, supported by an NIH R01 grant. In 2017, the NICD partnered with FPD in Tshwane district to roll out the project. Currently, the data collection is 82% complete for CrAg+ patients across 21 sites.

Antimicrobial resistance prevalence and transmission between animal feed and humans

Collaborators: *M van Vuuren, (UP) and D Petty, (private veterinary practitioner*)

Given that AMR is a major global health concern, and that South Africa has high-density industrial farming of food animals, including cattle, poultry and pigs, the routine use of antibiotics for therapeutic, prophylactic and growth promotion on these farms is concerning. Antibiotics in food animals have been linked to increases in clinical resistance in human medicine.

There has been little regulation of antibiotics administered to animals, with overlapping classes of antibiotics used for farming and human therapy. AMR pathogens have been detected on farms; however, the extent of resistance and spill-over in the country remain largely unknown.

This ongoing project aims to describe the antibiotic resistance genes present in food animals and livestock workers, reservoirs from which spill-over may occur into the community and/or hospital environments.

Impact of appropriate antimicrobial therapy on outcome of adult patients with *Staphylococcus aureus* bacteraemia in South Africa, 2013 to 2016

Collaborators: *GERMS-SA network*

The objective of this study was to compare outcomes in adult patients with *S. aureus* bacteraemia who received inappropriate antimicrobial therapy - with those who received appropriate antimicrobial therapy, and to describe the risk factors associated with mortality from five public sector hospitals in South Africa, over a five-year period, from 2013 to 2016.

Invasive fungal infections among hospitalised patients with advanced HIV disease in a large academic hospital in South Africa, 2015-2016

Collaborators: *K Roberg, A Karstaedt, F Sahid, C Menezes, M Tsitsi, J Nkehli, A Motau, J Wadula, S Seetharam and E van den Berg*

Despite increasing access to ART in South Africa, many people living with HIV are still hospitalised with advanced immunosuppression, owing to late presentation to care, disengagement from care or treatment failure. Invasive fungal infections (IFIs) may manifest as AIDS-defining opportunistic infections among patients with advanced HIV disease and are under-diagnosed.

This cross sectional study aimed to determine the prevalence of laboratory-confirmed IFIs among hospitalised patients with advanced HIV disease in a large urban academic hospital. Among 5280 HIV-seropositive patients who were screened for eligibility, 651 (12.3%) had a recent CD4+ T-lymphocyte count <100 cells/µl and 189 patients were enrolled. Seventy-two patients were ART-experienced. The prevalence of IFI was estimated at 11% (21/189); and the majority (11/21, 52%) of these cases had confirmed cryptococcosis.

Factors associated with fluconazole-resistant *Candida parapsilosis* among patients with candidaemia in South Africa, 2012-2016

Collaborators: *GERMS-SA network*

This study aimed to describe the epidemiology of *Candida parapsilosis* in private- and public sector hospitals and to determine risk factors associated with fluconazole resistance. Preliminary analyses showed that >70% of *C. parapsilosis* isolates were resistant to fluconazole. We found that risk factors were those related to healthcare delivery, such as surgery and ventilation, but not prior exposure to antifungal agents. This suggests that infection prevention and control in hospitals remains key in preventing infections with antifungal-resistant *Candida* species.

Independent risk factors associated with *Candida auris candidaemia* in South Africa – an analysis of national surveillance data, 2016-2017

Collaborators: *GERMS-SA network*

Candida auris is a globally-emerging, multi-drug-resistant invasive fungal pathogen. We aimed to determine risk factors for candidaemia caused by *C. auris* versus other *Candida* species. Cases were detected through national laboratory-based surveillance and data from patients admitted to 22 public sector and three private sector enhanced surveillance sites were analysed.

Among 2414 cases of candidaemia, 262 (11%) were caused by *C. auris*. *C. auris* cases predominantly occurred in Gauteng Province (145/262, 94%). Older patients (aOR 1.01 for every year; 95%CI: 1.01-1.03) with prolonged hospitalisation (aOR 1.01 for every day admitted; 95% CI: 1.01-1.03) and admission to private sector facilities (aOR 4.1, 95% CI 1.8-8.7) had an increased odds of *C. auris* candidaemia, possibly owing to exposure to multiple invasive devices and prior antimicrobial therapy.

TEACHING AND TRAINING

Undergraduate

The centre provided training to medical students from UP.

Postgraduate

The centre provided training to postgraduates as follows:

- NICD short course for registrars and fellows;
- Mycology workshop for registrars and fellows;
- DTM&H, Wits; and
- PhD, MSc, MPH and MMed supervision.

Other

Other training activities by the centre included:

- CrAg dashboard and RfA report master training in May 2017 (44 attendees);
- Monthly mycology bench/ clinical rounds; and
- Fungus of the week quizzes.

Professional development

Six postgraduate candidates were enrolled; five for PhDs and one for an MSc. Two postgraduate students graduated with a MPH during the year.

Honours

- Prof Nelesh Govender was awarded the MRC's Silver Scientific Achievement Award/Medal in recognition of the excellence of his body of research;
- Prof Olga Perovic was designated Head of the WHO CC for AMR that is hosted by the centre; and
- Dr Erika van Schalkwyk was selected as an International Ambassador for the Society for Healthcare Epidemiology of America (SHEA) International Ambassadors' Programme.

RESEARCH OUTPUT

Scientific publications

1. Cole DC, Govender NP, Chakrabarti A, Sacarlal J, Denning DW. Improving fungal disease identification and management - combined health systems and public health approaches are needed. Lancet Infect Dis 2017; pii: S1473-3099(17)30308-0.
2. Rajasingham R, Smith R, Park BJ, Jarvis JN, Govender NP, Chiller TM, Denning DW, Loyse A, Boulware DR. Global burden of disease of HIV-associated cryptococcal meningitis: An updated analysis. Lancet Infect Dis. 2017; 17(8):873-881.
3. Osler M, Hilderbrand K, Goemaere E, Ford N, Smith M, Meintjes G, Kruger J, Govender NP, Boulle A. The continuing burden of advanced HIV disease over ten years of increasing antiretroviral therapy coverage in South Africa. Clin Infect Dis 2018;66(suppl_2): S118-S125.
4. Ford N, Meintjes G, Calmy A, Bygrave H, Migone C, Vitoria M, Penazzato M, Vojnov L, Doherty M; Guideline Development Group for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy. Managing Advanced HIV Disease in a Public Health Approach. Clin Infect Dis. 2018;66(suppl_2): S106-SS110.
5. Schwartz IS, Lerm B, Hoving JC, Kenyon C, Horsnell WG, Basson WJ, Otieno-Odhiambo P, Govender NP, Colebunders R, Botha A. Emergomyces africanus in soil, South Africa. Emerg Infect Dis. 2018 Feb;24(2):377-380.
6. Wake RM, Britz E, Sriruttan C, Rukasha I, Omar T, Spencer DC, Nel JS, Mashamaite S, Adelekan A, Chiller TM, Jarvis JN, Harrison TS, Govender NP. High Cryptococcal Antigen Titers in Blood are Predictive of Subclinical Cryptococcal Meningitis Among HIV Infected Patients. Clin Infect Dis 2018 Feb 10;66(5):686-692.
7. Chen Y, Farrer RA, Giamberardino C, Sakthikumar S, Jones A, Yang T, Tenor JL, Wagih O, Van Wyk M, Govender NP, Mitchell TG, Litvintseva AP, Cuomo CA, Perfect JR. Microevolution of Serial Clinical Isolates of Cryptococcus neoformans var. grubii and C. gattii. mBio. 2017 Mar 7;8(2). pii: e00166-17.
8. Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender NP, Colombo AL, Calvo B, Cuomo CA, Desjardins CA, Berkow EL, Castanheira M, Magobo RE, Jabeen K, Asghar RJ, Meis JF, Jackson B, Chiller T, Litvintseva AP. Simultaneous emergence of multidrug resistant Candida auris on three continents confirmed by whole genome sequencing and epidemiological analyses. Clin Infect Dis. 2017;64(2):134-140.
9. Crombie K, Spengane Z, Locketz M, Dlamini S, Lehloenya R, Wasserman S, Maphanga TG, Govender NP, Kenyon C, Schwartz IS. Paradoxical worsening of Emergomyces africanus infection in an HIV-infected male on itraconazole and antiretroviral therapy. PLoS Negl Trop Dis 2018 Mar 8;12(3): e0006173.
10. Cronjé N, Schwartz IS, Retief L, Bastos ADS, Matthee S, Preiser W, Bennett NC, Maphanga T, Govender NP, Colebunders R, Kenyon C. Attempted molecular detection of the thermally dimorphic human fungal pathogen Emergomyces africanus in terrestrial small mammals in South Africa. Med Mycol 2017.
11. Schwartz IS, Kenyon C, Lehloenya R, Claasens S, Spengane Z, Prozesky H, Burton R, Parker A, Wasserman S, Meintjes G, Mendelson M, Taljaard J, Schneider JW, Beylis N, Maloba B, Govender NP, Colebunders R, Dlamini S. AIDS-related endemic mycoses in Western Cape, South Africa and clinical mimics: a cross-sectional study of adults with advanced HIV and recent-onset, widespread skin lesions. Open Forum Infect Dis 2017. 2017 Aug 25;4(4): ofx186.
12. Lerm B, Kenyon C Schwartz I, Kroukamp H, de Witt R, Govender N, de Hoog S, Botha A. First report of urease activity in the novel systemic fungal pathogen Emergomyces africanus: a comparison with the neurotrope Cryptococcus neoformans. FEMS Yeast Research 2017. 2017 Nov 1;17(7).
13. Perovic O, Singh-Moodley A, Govender NP, Kularatne R, Whitelaw A, Chibabhai V, Naicker P, Mbelle N, Lekalakala R, Quan V, Samuel C, van Schalkwyk E for GERMS-SA. Small proportion of community-associated methicillin-resistant Staphylococcus aureus bacteraemia, as compared to healthcare-associated cases, in two South African provinces. Eur J Clin Microbiol Infect Dis 2017. 36(12):2519-2532.
14. Espinel-Ingroff A, Abreu D, Almeida-Paes R, Brilhante R, Chakrabarti A, Chowdhary A, Hagen F, Córdoba S, González G, Govender N, Guarro J, Johnson E, Kidd S, Pereira S, Rodrigues A, Rozental S, M Szeszs, Raquel Ballesté Alaniz, Alexandro Bonifaz, L Bonfietti, Luana Borba-Santos, Javier Capilla, A Colombo, Maribel Dolande, M Isla, Marcia Melhem, A Mesa-Arango, Manoel M. Evangelista de Oliveira, Maria Panizo, Zoilo Pires de Camargo, Rosely Zancope-Oliveira, Jacques Meis, and John Turnidge. Multicenter and international study of MIC/MEC distributions for definition of epidemiological cutoff values (ECVs) for species of Sporothrix identified by molecular methods. Antimicrob Agent Chemother 2017; 61(10). pii: e01057-17.
15. Molloy SF, Chiller T, Greene G, Govender NP, Kanyama C, Mfinanga S, Boulware D, Bury J, Dromer F, Denning D, Day J, Mapoure YN, Stone N, Bicanic T, Jarvis J, Lortholary O, Harrison T, Jaffar S, Loyse A. Cryptococcal meningitis: a neglected NTD? PLoS Negl Trop Dis. 2017;11(6): e0005575.
16. Maphanga TG, Britz E, Zulu TG, Mpembe RS, Naicker SD, Schwartz IS, Govender NP. In vitro antifungal susceptibility of the yeast- and mould-phases of the dimorphic fungal pathogen, Emergomyces africanus (formerly Emmonsia species), from HIV-infected South

African patients. J Clin Microbiol. 2017;55(6):1812-1820.
17. Dukik K, Muñoz JF, Jiang Y, Feng P, Sigler L, Stielow JB, Freeke J, Jamalian A, van den Ende BG, McEwen JG, Clay OK, Schwartz ISS, Govender NP, Maphanga TG, Cuomo CA, Moreno L, Kenyon C, Borman AM, de Hoog S. Novel taxa of thermally dimorphic systemic pathogens in the Ajellomycetaceae (Onygenales). Mycoses. 2017;60(5):296-309.
18. Magobo RE, Naicker SD, Wadula J, Nchabaleng M, Coovadia Y, Hoosen A, Lockhart SR and Govender NP for the TRAC-South Africa group. Detection of neonatal unit clusters of Candida parapsilosis fungaemia by microsatellite genotyping: Results from laboratory based sentinel surveillance, South Africa, 2009-2010. Mycoses. 2017;60(5):320-327.
19. Greene GS, Sriruttan C, Le T, Chiller T and Govender NP. Looking for Fungi in All the Right Places: Screening for Cryptococcal Disease and Other AIDS-Related Mycoses Before Antiretroviral Treatment Initiation. Curr Opin HIV AIDS. 2017;12(2):139-147.
20. Shuping LL, Kuonza L, Musekiwa A, Iyaloo S, Perovic O. Hospital-associated methicillin-resistant Staphylococcus aureus: A cross sectional analysis of risk factors in South African tertiary public hospitals. PLoS One 2017;12(11): e0188216.
21. Schellack N, Benjamin D, Brink A, Duse A, Faure K, Goff D, Mendelson M, Meyer J, Miot J, Perovic O, Pople T, Suleman F, van Vuuren M, Essack S. A situational analysis of current antimicrobial governance, regulation, and utilization in South Africa. Int J Infect Dis. 2017;64:100-106.
22. Singh-Moodley A, Perovic O, Mtshali S, Ismail A, Allam M. Draft Genome Sequence of a Multidrug-Resistant Serratia marcescens Strain, Isolated from a Patient with Peritoneal Cancer in South Africa. Genome Announc. 2017;5(26). pii: e00580-17.

Technical reports/guidelines

1. World Health Organization Guideline. Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-infected Adults, Adolescents and Children. WHO 2018.
2. World Health Organization Guideline. Management of Persons with Advanced HIV Disease and Rapid Initiation of Antiretroviral Treatment. WHO 2017.

Conference presentations

- International conference presentations: 6
- National conference presentations: 13

Centre for Tuberculosis

Prof Nazir Ismail

BACKGROUND

During the year under review, the Centre for Tuberculosis (CTB) continued to make notable progress in its capacity to conduct laboratory-based public health surveillance of TB, as well as serving both as the National TB Reference Laboratory (NTBRL) for South Africa and as a WHO Supranational TB Reference Laboratory globally.

The progress of the CTB is closely aligned with the strategic vision of the planned NAPHISA, which, in the near future, will incorporate the NICD. Involvement in 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, on an ongoing basis.

South Africa developed a new National TB Strategic Plan for the period 2017-2021, which places great emphasis on a data-driven approach to TB management and control efforts in the country. The CTB will co-lead this stream that forms part of the new five-year plan. Major initiatives for example include a TB prevalence survey coupled to inventory studies which aim to better define the magnitude of the problem.

Additional work aimed at facility level hotspots provided valuable new insights into the epidemic. The expanded use of BDQ is accomplishing encouraging results, but at the same time, the emergence of the first few cases of resistance to this new drug is concerning.

The implementation of new rapid diagnostic tools refined patient triaging towards effective and patient-friendly regimens, while strain characterisation by next generation WGS technologies revolutionised our understanding of what TB transmission means in a high endemic setting. The year under review has no doubt been exciting for TB management in South Africa and also for the CTB at the NICD.

SURVEILLANCE AND DIAGNOSTIC SERVICES

Integration of public health surveillance and reference laboratory functions are now well established to provide enhanced and strategic information to guide TB control activities for South Africa. National surveillance covers various types of laboratory-confirmed TB cases, including pulmonary and extra-pulmonary, as well as the following new drug-resistant TB cases identified by NHLS laboratories:

- Rifampicin-resistant (RR);
- Multidrug-resistant (MDR); and
- Extensively drug- resistant (XDR) cases.

Surveillance findings continue to be regularly analysed and reported to the national and provincial TB programmes and are now made publically available through an online TB surveillance dashboard. Additional work involving mapping cases at a facility level made good progress, while weekly alerts of emerging RR/multi-drug resistant tuberculosis linked to a treatment initiation indicator are being sent out on a continuous basis. 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 CTB played a pivotal role in the introduction of the line-probe assay (LPA) for the identification of second-line drug resistance and specifically for the rapid detection of resistance to fluoroquinolones and injectable agents, which are both core groups of drugs for the treatment of drug resistant TB.

A revised algorithm was developed with the NDoH, integrating laboratory results and triaging patients for the most appropriate and effective treatment regimens. The CTB also expanded its use of specialised molecular techniques for detection and strain characterisation of *Mycobacterium tuberculosis* using next generation sequencing (NGS), to study drug resistance, in particular to new and re-purposed agents, as well as identify transmission patterns.

We published a seminal paper on drug resistance to BDQ, both phenotypic and genotypic, and established interpretive criteria which were accepted by the WHO for policy formulation. The reporting year has also been important in modernising our approach to molecular epidemiological tracking of TB transmission, with development of in-house tools and capacity building.

TB prevalence survey – South Africa

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

The survey is conducted according to the international recommendations of the WHO Global Task Force on TB Impact Measurement, Sub-group on Prevalence Surveys, as detailed in the "Lime Book." The survey is undertaken using a nationally representative sample of approximately 55 000 adults (≥15 years), from 110 population clusters/enumeration areas, across all nine provinces of South Africa.

Cases of TB disease will be detected through initial screening for TB symptoms and chest X-rays (CXRs) of all eligible individuals, and a subsequent bacteriological examination of two sputum samples per individual for those individuals with symptoms suggestive of TB and/or an abnormal CXR. All sputum samples will be examined by GeneXpert Ultra and cultured for the detection of *M. tuberculosis*. In addition to the testing for TB, voluntary testing for HIV will be performed. This will be important to determine if there is a differential by HIV status compared to those represented in the routine data.

The survey, which is a collaborative activity between the NDoH, NICD, HSRC and MRC, was piloted early in the year and enrolments officially commenced in August 2017. Three provinces, namely KZN, EC and NC are completed, and rollout is expanding to other provinces. More than 12000 participants have been enrolled thus far. The field work is targeted to be completed before the end of 2018. The aim is to provide a more accurate estimate of the TB burden and the magnitude of missing TB cases. This is a key barrier to the ultimate global goal of ending TB by 2035, and will be addressed in the coming years.

Online TB surveillance dashboard

A TB surveillance dashboard was launched with the Minister of Health on 24 March 2017, and is available online at www.nicd.ac.za, as an open access tool that allows tracking of the TB epidemic over a 11-year period, and to the level of sub-district.

The dashboard was updated to include data from the new year, which has continued to show a year-on-year decline in mPTB incidence relative to the previous one. The age-gender pyramids reflect a male dominated epidemic, with high incidence rates occurring in the 25 -to 45-year age groups. The map view section on the dashboard makes it possible to drill down to hotspots, enabling quick and easy visualisation of the areas of greatest concern.

The public access dashboard was enhanced with a restricted access version (Figure 1 below), which is aimed at providing greater detail to the NTCP managers, to assist them with programme planning and prioritisation. This new version does not only provide rates of microbiologically confirmed pulmonary TB (mPTB) incidence, but it also gives the absolute number of cases which are plotted on trend lines and are geospatially mapped.

In addition, resistance rates for RR-, MDR and XDR-TB are provided and are also graphically displayed by age, gender, geography and trend. The dashboard also includes the functionality to export and download aggregated data. Mirroring the work of the HIV EID programme, all the relevant staff has access to this self-help portal and are able to use it for multiple applications. These new enhancements should make a significant contribution towards strengthening the data-driven approach, which is a cornerstone of the NTP strategy.

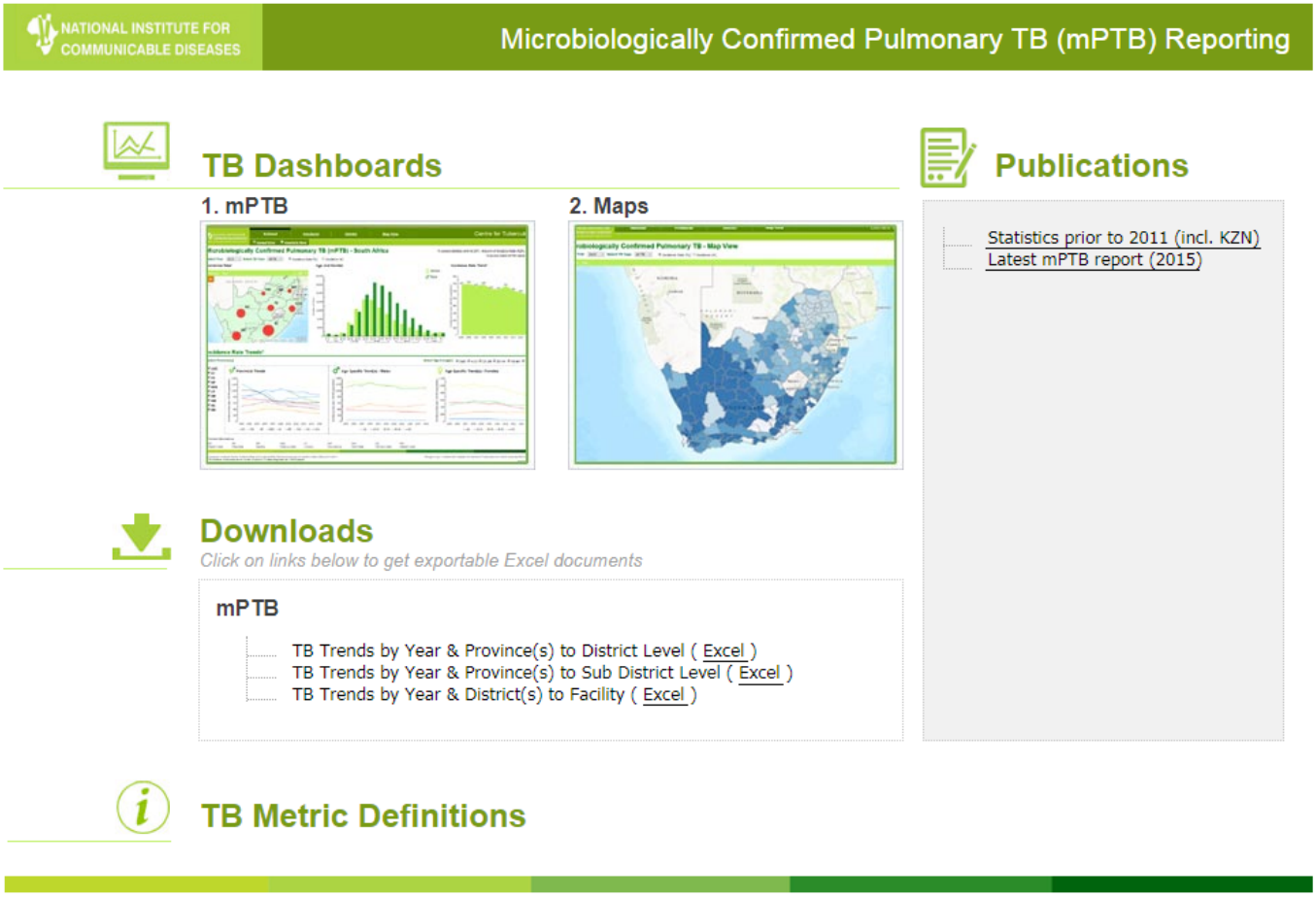

Figure 1. Advanced online TB Surveillance dashboard landing page (www.nicd.ac.za)

Geospatial surveillance of microbiologically confirmed TB in South Africa

The geospatial distribution of mPTB has previously shown to be highly heterogeneous at sub-district level. The administrative boundaries are however often arbitrary, and thus not optimal for designing geographically targeted interventions. Clustering of individuals with mPTB was furthermore widely reported.

An improved method of describing the mPTB epidemic was investigated, aiming to take it to a facility level, which would be much more relevant for public health action. The initial approach was based on incident cases of mPTB reported in 2015. Thiessen polygons were used to estimate catchment populations and calculate facility-level mPTB incidence rates. District hospitals and clinics were analysed separately. Discrete Poisson models were used to identify clusters with high and low mPTB incidence rates (SaTScan 9.4). Empirical Bayesian Kriging (EBK) was used to interpolate incidence rates.

Clinic-level mPTB caseload hotspots were predominantly located in the large metropolitan municipalities and clinic-level clusters of high mPTB incidence rates were identified in less populated regions of the Western Cape, Eastern Cape, Northern Cape and Free State provinces. EBK interpolation of clinic-level mPTB, demonstrated the highest incidence rates in the Eastern and Northern Cape provinces. EBK interpolation of hospital-level mPTB identified high incidence rates in KZN. Additional granular assessment within municipalities showed geographically concentrated areas in the City of Cape Town as a hotspot, while for the City of Tshwane, it correlated with a transport route.

The heterogeneity observed highlights the need for a targeted response, to achieve the greatest impact with the limited budgets available. Additional work is still required to evaluate the "cold spots" to confirm if these are true or a result of poor case detection.

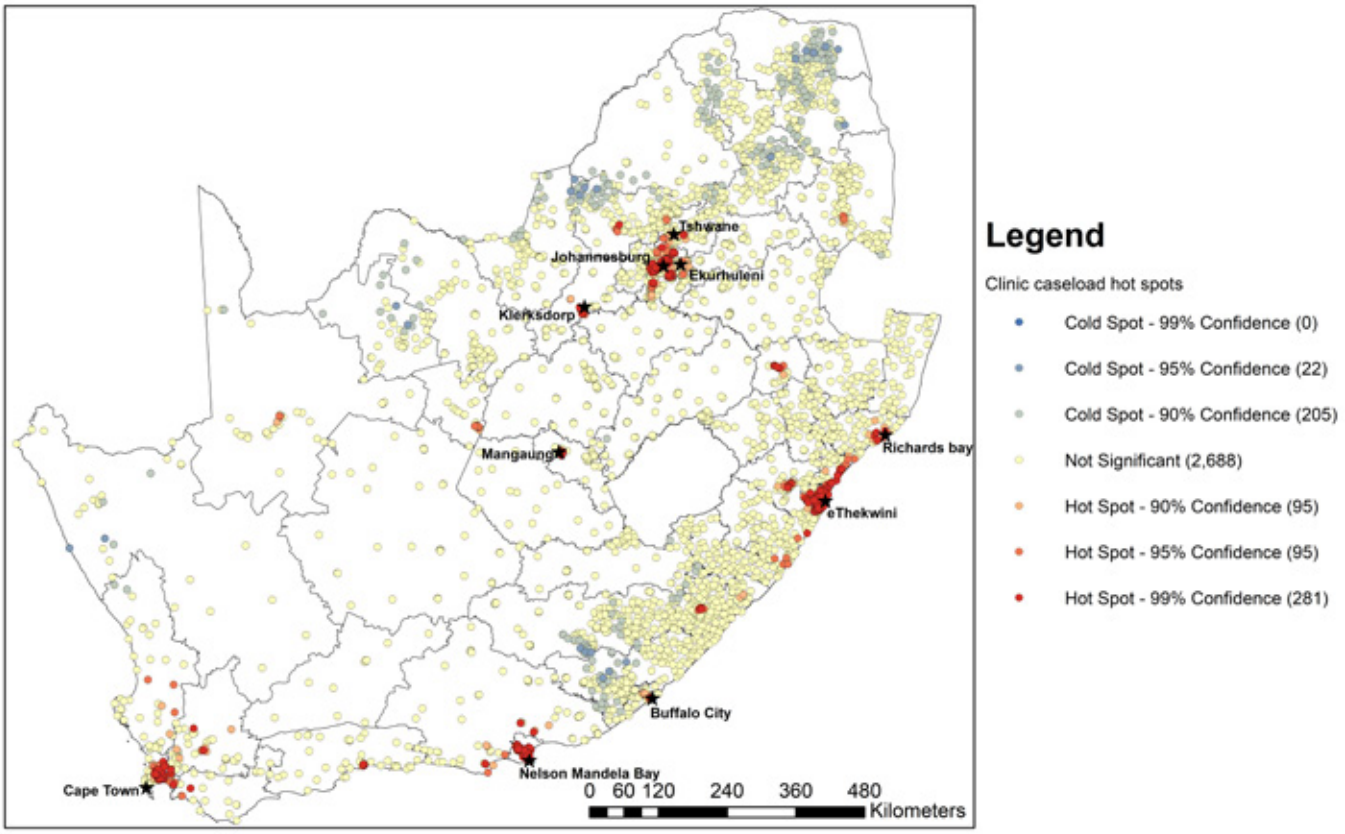

Figure 2. Clinic hotspots of TB burden (unadjusted), South Africa: 2015

Provincial- and district-wide alerts for public health action

The National TB Strategic Plan 2017-2021 identified initial loss to follow-up for TB treatment as a major concern and an important area that requires attention. These are cases diagnosed with active TB that have not commenced with treatment, resulting in increased risk of mortality and further transmission.

To address this concern, weekly alerts providing a line listing of cases diagnosed with RR-TB were introduced for each province, that are emailed to the nine provincial and 52 district managers in each province for public health action. This exercise is now being conducted on an ongoing basis, and has proven to be a meaningful tool for case management in the health system. It also supports the patient tracing initiatives by the respective teams in the field.

The RR-TB treatment initiation rate indicator proved to be a vital measure, while the alerts provide actionable data that can be monitored for progress. The success achieved with the drug resistance alert warranted expansion to include drug susceptible TB. These alerts were developed and will be integrated into the quality improvement programme that is in place, to strengthen response at a facility level.

Alignment with the revised and enacted legislation on NMCs is also planned, and alerts will be engineered into the NMC mobile application, to ensure that the information reaches health workers directly and that an appropriate public health response to these active and infectious cases can be initiated.

Surveillance for BDQ resistance

BDQ is a diarylquinoline antimycobacterial 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.

Surveillance for early detection of BDQ resistance is advised by the WHO and is incorporated into the South African policy framework. The framework determines that all patients starting BDQ treatment will have samples tested at baseline, at week 8 and at week 24, using BDQ minimal inhibitory concentration (MIC) determination.

To date, approximately 6 800 samples from patients initiating treatment with or on BDQ, have been received. Resistance to BDQ was identified in a small number of these patients who were assessed. A cohort of 13 patients were fully analysed clinically and their isolates were characterised both phenotypically and by genotype (EBioMedicine 28 (2018) 136–142). Although no mutations were found in the atpE target gene, resistance development to BDQ was associated with mutations in the efflux pump regulator and occurred when there were >/= two active drugs in the background regimen.

Additional BDQ-resistant (BDQ-R) clinical isolates (BDQ MIC ≥0.5 µmg/mL) from BDQ-experienced patients were identified at the NICD, and, of these, ~34% belonged to the XDR-TB resistance subtype. A full investigation of these isolates is currently in progress.

Supporting NTBRLs and surveys in Africa – Supra-National TB Reference Laboratory

The reference laboratory experienced a busy year in supporting the introduction of the new LPA (GenoType MTBDRsl), that provides rapid identification of resistance to fluoroquinolones and second line injectable drugs. This included validation of the method and ensuring that the selected regional centres were proficient in the methodology.

In addition, we have been actively working with the NDoH and the MDR advisory committee in introducing a new diagnostic algorithm for RR-TB, ensuring that there is good synergy between the respective diagnostic and clinical services. We are also assisting the NHLS TB Laboratories with the second line phenotypic DST, by performing all the linezolid testing on all pre-XDR and XDR patients. The CTB furthermore assists with determining treatment regimens for failing MDR and XDR patients, by testing additional drugs that are not routinely tested by NHLS laboratories (e.g., linezolid, bedaquiline, clofazimine and delamanid).

On the regional front, we successfully completed the fourth round of external quality assessments of the 16 high burden countries in Africa, through WHO AFRO. Findings showed consistent improvements in performance across many countries, reflecting the positive impact of QA activities in the region.

We are now also key role players in the newly formed GLI-AFRO consortium that will oversee laboratory improvement initiatives in Africa. Lastly, the CTB continued to provide support to the reference laboratory in Namibia and supported training staff from the Swaziland reference laboratory on an ad hoc basis.

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

The previously reported outbreaks in South Africa were characteristically identified late and were often accompanied by high mortality rates. For this reason, it is critical to have early warning systems to detect clusters of transmission, particularly for drug resistant TB.

In 2014, a molecular-based epidemiological surveillance programme was introduced at district level, which aims to identify areas of high-risk transmission of RR-TB cases. At least one district per high burden province is targeted, with additional districts purposely selected. Genetically identical RR-TB cases by spoligotyping and MIRU-24-loci typing are investigated to identify epidemiological links.

To date, this surveillance programme has been implemented in seven of the nine provinces, and a total of 223 clusters has been identified, over the three-year period. When analysed by district, the cluster sizes ranged between two - 89 cases, with a detailed breakdown as follows:

- 60 clusters from Nelson Mandela Metro (two – 89 cases per cluster);
- 50 from Ehlanzeni (two – 38 cases per cluster);
- 41 from Dr Kenneth Kaunda (two – nine cases per cluster);
- 27 from UMgungundlovu (two –12 cases per cluster);
- 13 from the City of Johannesburg (D) (two –nine cases per cluster);
- Seven from Frances Baard (two – three cases per cluster); and
- Five from Mangaung (two – four cases per cluster).

The overall proportion of cases estimated to be due to transmission was 29%. This proportion varied from site to site, with the highest estimated rate of transmission in Nelson Mandela Metro (47%) and the lowest in Mangaung (10%).

The surveillance data showed that one third of RR-TB is due to transmission, emphasising the need for improved control measures through careful monitoring of trends, transmission routes, and the provision of effective therapy. In addition, the varied size of clusters highlights the need for tailored interventions, suggesting that close contact is likely to be the most vulnerable in most areas. In selected districts however, a more widespread pattern is observable, that will require broader campaigns to detect cases.

RESEARCH PROJECTS

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

Investigating the usefulness of the new QuantiFERON-TB Plus assay in diagnosing latent TB infection and progression to active TB disease among healthcare workers in high-incidence settings

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

TB continues to have a significant health impact worldwide with an estimated one third of the world's population infected with latent TB (LTBI) and annually more than 9 million new cases of active TB are occurring.

In addition, it poses a significant occupational health problem and 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) is a new fourth generation QFT technology developed by Qiagen Company in 2015 to detect LTBI. It has increased sensitivity with improved performance in high risk populations such as HIV positive patients. It also incorporates a marker that is able to potentially predict active TB cases which has important value in detecting high risk exposures early.

This project, which is a collaboration with the TB South Africa Project and the NDoH, is designed to understand and provide a baseline of the prevalence of LTBI, as well as the progression from latent to active TB among HCWs. Additionally, it will seek to assess the feasibility of using QFT-Plus amongst HCWs in a routine healthcare setting in the country.

The project will be conducted at three different hospitals in three provinces (Eastern Cape, Free State and Gauteng provinces). Provisional ethics permission to conduct the project has already been granted, pending hospital approvals. The study is a cohort study design and will follow through on the HCWs enrolled for the total period of thee years.

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

Collaborators: *I Abubakar (University College London, UK) and S Moyo (HSRC South Africa)*

South Africa has one of the highest incidence rates of TB globally and despite the widespread use of new diagnostics that can rapidly detect TB and drug resistant TB, a large proportion of diagnosed cases do not initiate treatment and are referred to as pre-treatment loss to follow up (PTLFU).

A recent transmission model concluded that reducing PTLFU by 50% (from 16% to 8%) could have a potent impact on TB incidence in South Africa. Published literature indicates that the proportion of patients with microbiologically confirmed PTB (mPTB) in South Africa who do not initiate TB treatment ranges between 11% and 25%. The patients with mPTB are highly infectious and contribute to ongoing transmission, which is a major obstacle to achieving population level TB control

The study will assess the effectiveness of a combination of interventions aimed at decreasing PTLFU among adults (>18 years) who are subjected to Xpert testing or smear microscopy for pulmonary TB. It will consist 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.

The design applied is a randomised complete stepped-wedge study of the combination of interventions and is conducted in 14 clinics in Gauteng Province. The order in which clinics will cross over from non-intervention to intervention phases, will be randomised.

The study also includes a health economics analysis, to determine the cost-effectiveness of the interventions. The pilot phase of the study commenced and the baseline determination of PTLFU was also completed. This exercise highlighted important health system issues such as poor data quality that impact on PTLFU.

Inventory study measuring the level of under-reporting and estimating incidence for TB 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 disease is essential to successful programme planning. National TB programmes (NTPs) should use data collected through routine surveillance, to directly measure TB incidence and track progress against global TB targets. Most high TB burden and resource-limited countries, however, lack TB national surveillance systems that have the sufficient robustness to accomplish this.

An estimated three million TB cases are undetected by national TB programmes globally each year, but the level of under-reporting in high TB burden settings is largely unknown. The South African NDoH, in collaboration with the NICD and WHO, will undertake an inventory study to:

- Estimate the level of under-reporting of TB cases to the national TB surveillance system nationally; and
- Conduct a capture-recapture analysis to estimate TB incidence in South Africa, using published WHO guidelines.

Retrospective analysis of all TB records from the NTP (ETR.Net & EDRweb), the NHLS and private laboratories will be matched, using specialised algorithms, as well as a manual review process. The proportion of case overlap among sectors will be used to estimate TB incidence and estimate the under reporting of TB notification for South Africa.

Risk factor analysis will be conducted in relation to under reporting with exploratory analysis on clinical diagnosed cases and test practices included. Outcomes of this work will help strengthen private sector engagement in TB control, as well as the national TB surveillance system in South Africa. This work will also be important in facilitating the integration of systems prospectively, which is a target of the NDoH five-year strategic plan.

The individulised M(X) drug-resistant TB treatment strategy study

Collaborator: *N Padayachi (CAPRISA, SA)*

The individualised M(X) (InDEX) drug-resistant TB treatment strategy study is a collaboration between the CTB and CAPRISA. This is a randomised controlled clinical trial and the primary objective of the study is to determine whether gene-derived (Xpert MDRTB /RIF) individualied treatment approach in patients with drug-resistant TB, will improve treatment success. This is based on the hypothesis that a gene-derived individualised treatment approach for drug resistant TB has a higher success rate.

Patients who have a RR-TB result and are ≥18 years, will be eligible for the study. Three hundred participants will be enrolled; 200 MDR (100 per arm) and 100 XDR (50 per arm). Participants in the intervention arm will have WGS performed on their isolates. All patients will be followed up for the full duration of the treatment. The study outcome will be determined by time to culture conversion, defined as: two negative cultures taken 30 days apart for MDR-TB, and three negative cultures taken 30 days apart for XDR-TB.

Enrolment began in June 2017, with more than 40 participants enrolled. WGS is being evaluated in a randomised control trial, to assess its impact on patient-relevant outcomes for drug resistant TB. This study will provide robust information on this next generation technology in the fight against the most challenging form of TB.

Phenotypic and genotypic investigation of in vitro generated mutants to BDQ, clofazimine (CFZ) and linezolid (LZD)

Collaborator: *R Peters (ANOVA Health)*

We compared in vitro approaches for generation of *M. tuberculosis* mutants encoding resistance to BDQ, CFZ and LZD to further investigate associated genetic variants. We investigated the genetic basis used by the most prevalent strain types circulating in South

Africa for acquisition of drug resistance to these drugs, in vitro. BDQ, CFZ and LZD are important drugs in the treatment of drug-resistant TB. Mutants resistant to these drugs, provide important insights into resistance acquisition mechanisms.

In the pilot phase, we used American Type Culture Collection (ATCC) reference strains with varying mono-resistance profiles to determine mutation rates. Both approaches successfully led to in vitro mutants with novel resistance-associated variants (RAVs), being described in atpE and rv0678 genes. It was observed that pre-existing resistance, as seen with the pyrazinamide (PZA) resistant strain, can influence mutant phenotypic and genotypic characteristics and warrants further attention.

In addition, we found that Rv0678 mutants display cross-resistance between BDQ and CFZ, irrespective of the method or drug used for mutant generation. The study is currently investigating the genetic bases for resistance acquisition, using clinical isolates with varying resistance profiles and strain types that are representative of South Africa.

Using mHealth to improve TB case identification in South Africa: results from a pilot study

Collaborators: *V Chihota (Aurum Institute) and K McCarthy (Aurum Institute and NICD)*

TB incidence in South Africa is among the highest globally. Initial loss to follow-up (ILFU) defined as not starting on TB treatment within 28 days of testing positive, is undermining control efforts, despite the introduction of advanced TB diagnostics. The use of mobile technologies in health (mHealth), is a useful tool that is widely available and accessible and that provides an avenue for information exchange in near real-time. It could also support health programmes to ensure that newly diagnosed patients are placed on treatment, quicker and more effectively. There is however limited data on the feasibility and acceptability of an mHealth application, as well as its potential for addressing ILFU.

The study team developed an mHealth application that was purposefully designed to:

1. Include all data traditionally written in paper TB identification registers;
2. Automatically retrieve data from the laboratory service;
3. Notify providers and patients when results are available; and
4. Track individual progress through the TB care continuum.

This was implemented in two PHCs in the inner city of Johannesburg. In the pre-implementation phase, we only used data from paper-based registers. In the post-implementation phase, we utilised the mHealth application in conjunction with standard of care paper-based TB programme tools.

Feasibility and effectiveness of the two methods were compared by assessing the number of patients who obtained results within 48 hours through each method, as well as the number of patients who commenced with TB treatment within 28 days of testing TB positive. Findings from the study demonstrated that the mHealth APP made results to the clinic available much faster, and that the number of patients on treatment was higher, even though not to a statistically significant degree. The patients who tested positive, conveniently received their results via SMS, which decreased waiting time to commence treatment.

The mHealth application was thus feasible to implement, is acceptable to health care providers and patients, and has the potential to reduce the time to TB treatment initiation in a PHC setting.

TEACHING AND TRAINING

The centre provided on-site experiential and didactic learning to Malawi's second and newly established TB Reference Laboratory. In addition, the CTB provided instruction in a train-the-trainer course for NTP/National Reference Laboratory managers with participants from SADC countries.

Training was also provided on both reference mycobacteriology testing and public health aspects of TB, to rotating registrars from university-based medical microbiology departments in South Africa, as well as for intern scientists in the country.
The CTB also mentored a Field Epidemiology and Laboratory Training Programme (FELTP) student, further expanding capacity in epidemiology in South Africa. Training on Xpert MTB/RIF, LPA and WGS was conducted at an international skills building workshop, with participants from Africa, Europe and Asia.

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

Postgraduate candidates

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

Medical scientists

Two candidates were enrolled and two graduated.

Honours

Prof Nazir Ahmed Ismail received a C2 NRF rating.

RESEARCH OUTPUT

Scientific publications

NA Ismail, SV Omar, L Joseph, N Govender, L Blows, F Ismail, H Koornhof, AW Dreyer, K Kaniga, N Ndjeka
Defining Bedaquiline Susceptibility, Resistance, Cross-Resistance and Associated Genetic Determinants: A Retrospective Cohort Study
EBioMedicine 01/2018; DOI:10.1016/j.ebiom.2018.01.005

Background: BDQ is a novel agent approved for use in combination treatment of MDR-TB. We sought to determine BDQ epidemiological cut-off values (ECVs), define and assess interpretive criteria against putative resistance associated variants (RAVs), microbiological outcomes and cross resistance with CFZ.

Methods: A retrospective cohort study was conducted. MICs to BDQ were determined using 7H9 broth microdilution (BMD) and MGIT960. RAVs were genetically characterised using WGS. BDQ ECVs were determined using ECOFFinder and were compared with six-month culture conversion status and CFZ MICs.

Findings: A total of 391 isolates were analysed. Susceptible and intermediate categories were determined to have MICs of 0.125 µg/ml and 0.25 µg/ml, using BMD and 1 µg/ml and 2 µg/ml using MGIT960 respectively. Microbiological failures occurred among BDQ exposed patients with a non-susceptible BDQ MIC, an Rv0678 mutation and >/=2 active drug classes. The Rv0678 RAVs were not the dominant mechanism of CFZ resistance and cross resistance was limited to isolates with an Rv0678 mutation.

Interpretation: Criteria for BDQ susceptibility are defined and will facilitate improved early detection of resistance. Cross- resistance between BDQ and CFZ is an emerging concern, but in this study it was primarily observed among those with an Rv0678 mutation.

NA Ismail, L Mvusi, A Nanoo, A Dreyer, SV Omar, S Babatunde, T Molebatsi, M van der Walt, A Adelekan, V Deyde, C Ihekweazu, SA Madhi
National and sub-national cross sectional survey of drug resistant tuberculosis prevalence and imputed burden in South Africa
The Lancet Infectious Diseases. 2018; (in press)

Background: Globally, per capita, South Africa reports a disproportionately high number of M/XDR-TB. We sought to estimate the prevalence of resistance provincially and nationally to TB drugs in newly diagnosed and retreated TB patients, and compared these to the 2001-2 estimates.

Methods: A cross sectional survey (2012-2014) was conducted, through the use of population proportionate randomised cluster samples. Consenting participants (≥18years), completed a questionnaire and had a sputum sample tested for resistance to first- and second-line drugs. Logistic regression with robust standard errors and inverse probability weighted against routine data was performed, and estimates were derived, using a random effects model.

Results: A total of 101 422 participants were tested. Nationally, MDR-TB prevalence was 2·1% (95% confidence interval:1·5%-2·7%) in new cases and 4·6% (3·2%-6·0%) in retreatment cases. The overall provincial point prevalence of MDR-TB ranged between 1·6% (0·9%-2·9%) to 5·1% (3.7%-7.0%). Overall, RR-TB prevalence (4.6%) was higher than MDR-TB prevalence (2.8%; p=0.01). Isoniazid mono-resistance(IMR)-TB was above 5% in all provinces.

The prevalence of ethionamide and PZA resistance among MDR-TB, was 44·7% (25·9%-63·6%) and 59·1% (49·0%-69·1%) respectively. Prevalence of XDR-TB was 4·9% (1·0%-8·8%). Nationally, the estimated number of cases of RR-TB, MDR-TB and IMR-TB for 2014 was 13551, 8249, and 17970, respectively.

Conclusion: The overall MDR-TB prevalence in South Africa in 2014 (2·8%) was similar to that of 2001-2 (2·9%). Prevalence of RR-TB however almost doubled among new cases (3·4% compared to 1.8%). The high prevalence of IMR-TB, not routinely screened for, and resistance to second line drugs, furthermore has implications for empiric management.

M Zignol, AM Cabibbe, AS Dean, D Cirillo, C Gilpin, R Hasan, S Hoffner, NA Ismail, L Rigouts, S Niemann, K Weyer, N Alikhanova, C Ama, S Andres, A Barbova, A Borbe-Reyes, A Dreyer, M Driesen, Z Hasan, A Hussain, A Jurilio, M Kamal, FM Khanzada, TA Kohl, M Mansjö, P Miotto, SV Omar, I Sela, M Seyfaddinova, G Skenders, A Skrahina, S Tahseen, P Glaziou, MC Raviglione
Genetic sequencing for surveillance of drug resistance in tuberculosis in highly endemic countries: a multi-country population-based study
The Lancet Infectious Diseases. 2018 Mar 21. pii: S1473-3099(18)30073-2. doi: 10.1016/S1473-3099(18)30073-2. [Epub ahead of print]

Background: In many countries, regular monitoring of the emergence of resistance to anti-TB drugs is hampered by limitations of phenotypic drug susceptibility testing.

Methods: Population-based surveys were conducted in seven countries to investigate the use of genetic sequencing to estimate levels of resistance of mycobacterium TB isolates to rifampicin, isoniazid, ofloxacin, moxifloxacin, PZA, kanamycin, amikacin and capreomycin. For each drug, the accuracy of genetic sequencing was assessed and the adjusted prevalence of resistance as measured by genetic sequencing was compared to the prevalence of resistance determined by phenotypic testing.

Findings: A total of 7,094 patients were enrolled in the study. Overall, pooled sensitivity values for predicting resistance by genetic sequencing among all TB cases were 91% (95% confidence interval - CI: 87-94%) for rpoB (rifampicin), 86% (95%CI: 74-93%) for katG, inhA and fabG promoter combined (isoniazid), 54% for pncA (pyrazinamide), 85% (95%CI: 77-91%) for gyrA and gyrB combined (ofloxacin) and 88% (95%CI: 81-92%) for gyrA and gyrB combined (moxifloxacin). For nearly all drugs and in most settings, there was a large overlap in the prevalence of drug resistance estimated by genetic sequencing, compared with prevalence by phenotypic testing.

Interpretation: Genetic sequencing can be a valuable tool for surveillance of drug resistance, providing new opportunities for the monitoring of drug resistance in TB in resource-limited countries. Before its widespread adoption for surveillance purposes, there is a need to standardise DNA extraction methods, recording and reporting nomenclature, and data interpretation.

S Ferrian, C Manca, S Lubbe, F Conradie, NA Ismail, G Kaplan, CM Gray, D Fallows
A combination of baseline plasma immune markers can predict therapeutic response in multidrug resistant tuberculosis
PLoS ONE 05/2017; 12(5)., DOI:10.1371/journal.pone.0176660

Objective: To identify plasma markers predictive of therapeutic response in patients with MDR-TB.

Methods: 50 HIV-negative patients with active pulmonary MDR-TB were analysed for six soluble analytes in plasma at the time of initiating treatment (baseline) and over six months thereafter. Patients were identified as sputum culture positive or negative at baseline. Culture positive patients were further stratified by the median time to sputum culture conversion (SCC) as fast responders (< 76 days) or slow responders (>= 76 days). Chest X-ray scores, body mass index, and sputum smear microscopy results were obtained at baseline.

Results: Unsupervised hierarchical clustering revealed that baseline plasma levels of IP-10/CXCL10, VEGF-A, SAA and CRP could distinguish sputum culture and cavitation status of patients. Among patients who were culture positive at baseline, there were significant positive correlations between plasma levels of CRP, SAA, VEGF-A, sIL-2Ra/CD40, and IP-10 and delayed SCC.

Using linear discriminant analysis (LDA) and receiver operating curves (ROC), we demonstrated that a combination of MCP-1/CCL2, IP-10, sIL-2Ra, SAA, CRP and AFB smear, could distinguish fast from slow responders and were predictive of delayed SCC with high sensitivity and specificity.

Conclusion: Plasma levels of specific chemokines and inflammatory markers measured before MDR-TB treatment are candidate predictive markers of delayed SCC. These findings require validation in a larger study.

SV Omar, M Allam, L Joseph, S Mtshali, NA Ismail, A Ismail
Draft Genome Sequence of Mycobacterium peregrinum Isolated from an HIV-Positive Patient in South Africa
Genome Announcements. 2017;5(31):e00759-17. doi:10.1128/genomeA.00759-17

Background: *Mycobacterium peregrinum* is a nontuberculous mycobacterium that belongs to the *Mycobacterium fortuitum* complex. Although the complex members are not usually pathogenic for humans, they are opportunistic in that they can cause disease in people with disadvantageous conditions or who are immunocompromised.

Methods: A specimen was obtained from a 42-year-old female with a history of HIV, diagnosed clinically as a new TB case. Molecular identification of the species using the GenoType *Mycobacterium* CM version 2.0 (Hain Lifescience GmbH, Nehren, Germany) identified the strain as *M. peregrinum*. We performed WGS to confirm the presence of *M. peregrinum*. Genomic DNA was extracted from three independent liquid cultures using the NucliSENS easyMAG (bioMérieux, France).

Paired-end libraries were prepared followed by two × 300-bp sequencing on an Illumina MiSeq (Illumina, San Diego, CA, USA). The paired-end reads were quality trimmed and de novo assembled using Qiagen CLC Genomics Workbench version 10 (Qiagen, The Netherlands). The assembly contains 216 contig sequences of longer than 500 bp and covers 6,931,852 bp, with a G+C content of 66.2% and an N50 of 124,779 bp. All contigs were then submitted to GenBank, where gene annotation was implemented using the NCBI Prokaryotic Genome Annotation Pipeline (PGAP).

Results: The total number of 6,808 genes predicted by PGAP includes 6,582 protein-coding genes, 145 pseudogenes, and 81 RNA genes (75 tRNAs and 3 6RNAs). The annotation was further uploaded to Rapid Annotation using Subsystems Technology (RAST) for subsystems-based annotation. The RAST annotation assigned these genes into 436 subsystems, with a maximum number of genes associated with amino acids and derivative metabolism (15.99%).

Conference presentations

- International: 5 posters
- National: 7 oral and 5 posters

Centre for Respiratory Diseases and Meningitis

Prof Cheryl Cohen

BACKGROUND

In the financial year under review, the centre maintained ongoing syndromic surveillance for pneumonia and influenza-like illness (ILI) at sentinel sites within South Africa and expanded ILI surveillance to include an additional rural site in Mpumalanga. Laboratory-based national surveillance for important causes of invasive bacterial disease and meningitis through the GERMS-SA platform also continued.

We furthermore published new guidelines for pertussis diagnosis, management and public health response and recommendations for the use of meningococcal vaccination. Outbreak investigations were conducted for avian influenza (H5N8), Group A streptococcus, pertussis, diphtheria and *Listeria monocytogenes*. Finally, the PHIRST study completed its second year of follow up in 2017.

SURVEILLANCE PROGRAMMES

Pneumonia surveillance

The National Pneumonia Surveillance Programme (NPSP) is fully operational in five provinces. The protocol includes surveillance for severe respiratory illness (SRI), irrespective of duration of symptoms, as well as testing for core pathogens of public health importance, namely, influenza, respirotary syncytial virus (RSV) and *Bordetella pertussis*.

In addition, surveillance for *Streptococcus pneumoniae* continued at three of the surveillance sites. The case definition was expanded to include a broader case definition for RSV, allowing for cases without fever to be included.

The 2017 influenza season started in week 24, peaked in week 27 and continued through week 39. It was predominated by influenza A(H3N2) (114/201, 57%) with co-circulation of influenza B (63/201, 31%) and A(H1N1) pdm09 (23/201,11%). Influenza B predominated in the last weeks of the season. Influenza B/Yamagata lineage strains dominated all influenza B virus detections.

RSV was detected in 15% (688/4324) of individuals hospitalised with pneumonia. The RSV season preceded the influenza season, starting in week seven, peaking in week 16 and ending in week 32. The prevalence of *B. pertussis* was 2% (86/4206) in pneumonia surveillance patients. There was no obvious seasonality for *B. pertussis* and *S. pneumoniae*. An increase in pertussis cases from Western Cape sites was reported in the last three months of 2017, prompting an alert to clinicians.

ILI surveillance

Influenza A(H3N2) viruses predominated in ILI surveillance, comprising 72% (488/682) identified influenza strains in the Viral Watch programme (ILI in private practitioners) and 63% (174/278) in the systematic surveillance for ILI at public health clinics. Regional differences were observed in the circulation of influenza A(H1N1) pdm09, which was only detected in four of the nine provinces, namely Western Cape, North West, Gauteng and Eastern Cape. Surveillance for ILI is ongoing at outpatient clinics at three sites, including a new site which was initiated in Mpumalanga, early in 2017.

Influenza virus characterisation

Cell culture-derived influenza virus isolates were obtained with a 63% (66/105) success rate. All influenza A(H1N1) pdm09 viruses were in the 6B.1 genetic lineage and continued drift was observed. All influenza A(H3N2) viruses were in the 3C.2a genetic lineage of which 84% (60/71) were in the 3C.2a1 subclade.

No genetic mutations associated with reduced susceptibility to oseltamivir were observed in the neuraminidases of influenza A and B viruses. Influenza virus isolates and/or original clinical specimens from 74 surveillance programme participants were shared with WHO CCs. In addition, specimens were sent to US-CDC to confirm influenza B lineage type.

Laboratory-based surveillance for *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae* (GERMS)

CRDM continued national laboratory-based, population-based active surveillance for invasive diseases caused by *S. pneumoniae, H. influenzae* and *N. meningitidis*. Enhanced surveillance was continued at 26 hospital sites (at least one in every South African province) where additional clinical data were collected from each patient with invasive disease.

Surveillance data contribute to the evaluation and understanding of the impact of both the pneumococcal conjugate vaccine (PCV) and the *H. influenzae* serotype b conjugate vaccine (Hib CV). The CRDM also contributed data on numbers and serogroups of *N. meningitidis* and supported diagnostic testing and outbreak responses for suspected cases of meningococcal meningitis. The data allow for descriptive epidemiology of invasive diseases and emergence of resistance in these three pathogens.

WHO/AFRO supported surveillance for the invasive bacterial vaccine-preventable disease (IB-VPD) surveillance network

CRDM continued to serve as a Regional Reference Laboratory for the WHO Global Invasive Bacterial Vaccine-Preventable Disease network (IB-VPD). Cerebrospinal fluid (CSF) samples were received from 12 countries (mostly SADC) for molecular detection and serotyping/grouping of *S. pneumoniae, H. influenzae* and *N. meningitidis*. Data were reported back to countries and WHO AFRO. Assistance (training and site assessments) was also provided to improve surveillance capacity in these 12 countries.

WHO RSV pilot

CRDM participated in the WHO RSV surveillance pilot project to conduct RSV surveillance through the influenza surveillance platform. The centre played a key role in the epidemiology of the pilot design and in analysing the interim data which were presented at the WHO RSV surveillance meeting in Washington DC in December 2017. The National Influenza Centre within CRDM served as a regional reference laboratory for this programme.

RESEARCH PROJECTS

Published

Attributable fraction of influenza virus detection to mild and severe respiratory illnesses in HIV-infected and HIV-uninfected patients, South Africa, 2012-2016

S Tempia, S Walaza, J Moyes, AL Cohen, C von Mollendorf, ML McMorrow, FK Treurnicht, M Venter, M Pretorius, O Hellferscee, N Wolter, A von Gottberg, A Nguweneza, JM McAnerney, H Dawood, E Variava, SA Madhi and C Cohen
Emerging Infectious Diseases Journal 2017 23 (7): 1124-1132

This study estimates the rates of ILI, severe acute severe acute respiratory infections (SARI)-10, or chronic respiratory illness (SCRI-10) to estimate the influenza adjusted rates (per 100 000) and relative risk (RR) in HIV-infected and HIV–uninfected populations. HIV-infected individuals are at a 2.3 (95% CI: 2.2-2.4)-, 9.7 (95% CI: 8.0-11.8)-, and 10.0 (95% CI: 7.9-12.7)-fold increased risk of influenza-associated illness in ILI, SARI-10, and SCRI-10, respectively.

Overall, 34% of patients who were hospitalised for influenza-associated infections, experienced symptom duration of >10 days. The increased risk of hospitalisation in HIV-infected individuals supports influenza vaccination in this group. A cut-off of ≤10 days for symptom duration will underestimate influenza burden estimates.

Respiratory syncytial virus in adults with severe acute respiratory illness (SARI) in a high HIV prevalence setting, 2009-2013

J Moyes, S Walaza, M Pretorius, M Groome, A von Gottberg, N Wolter, S Haffejee, E Variava, AL Cohen, S Tempia, K Kahn, H Dawood, M Venter, C Cohen and SA Madhi
Journal of Infection 2017 75 (4): 346-355

There are limited data on the epidemiology of RSV illness in HIV-infected adults or the elderly in Africa. When compared to HIV-uninfected individuals, HIV-infected individuals with RSV-associated SARI, had greater odds of being in the age groups of between 18-44 and 45-64

years (adjusted odd ratios (aOR) 26.3; 95% confidence interval (CI) 6.2-112.1 and aOR 11.4; 95% CI 2.6-50.0, as compared with those ≥65 years) and being female (OR 2.7; 95% CI 1.4-5.4).

Incidence of hospitalisation was higher in the ≥65-year age group across all three years in both the HIV-infected and -uninfected adults. The relative risk of hospitalisation with RSV-associated SARI was 12-18 times higher in HIV-infected individuals in age adjusted data over five years. These data supports the introduction of a vaccine in risk groups, as soon as a vaccine is available.

The burden and clinical presentation of pulmonary tuberculosis in adults with severe respiratory illness in a high human immunodeficiency virus prevalence setting, 2012-2014

S Walaza, S Tempia, A Dreyer A, H Dawood, E Variava, NA Martinson, J Moyes, AL Cohen, N Wolter, C von Mollendorf, A von Gottberg, S Haffejee, FK Treurnicht, O Hellferscee, N Ismail and C Cohen
Open Forum Infectious Diseases 2017 7;4(3): ofx116

The tuberculosis detection rate was higher in those with symptom duration >14 days (34% compared to 18%). Tuberculosis-confirmed cases with acute presentations were less likely to present with cough (adjusted odds ratio [aOR] 0.2, 95% confidence interval [CI] 0.1-0.5), night sweats (aOR 0.4, 95% CI 0.3-0.7), or be started on tuberculosis treatment on admission (aOR 0.4, 95% CI 0.3-0.7), but they were more likely to be coinfected with pneumococcus (13% [16 of 124] vs 6% [26 of 411]; aOR 2.3, 95% CI 1.3-5.3).

The annual incidence rate of acute and chronic tuberculosis-associated severe respiratory infection per 100,000 population was 28 (95% CI = 22-39) and 116 (95% CI = 104-128), respectively. Tuberculosis should be considered in the differential diagnosis of patients admitted with acute respiratory infection in South Africa.

In-and out-of-hospital mortality associated with seasonal and pandemic influenza and RSV in South Africa, 2009-2013

C Cohen, S Walaza, FK Treurnicht, ML McMorrow, SA Madhi, JM McAnerney and S Tempia
Clinical Infectious Diseases 2017 66(1): 95-103

Seasonal influenza and RSV all-cause mortality rates were estimated as 23.0 (95% CI 11.0-30.6) and 13.2 (95% CI 6.4-33.8) per 100 000 population annually (2.3% [95%CI 2.3%-2.4%], and 1.3% [95% CI 1.2%-1.4%] of all deaths respectively). Influenza deaths peaked in the elderly ≥75 years (386.0; 95% CI 176.5-466.3) and RSV deaths peaked in infants (143.4; 95% CI 0-194.8).

For influenza A(H1N1) pdm09, the mortality rate was 6.7 (95% CI 6.4-33.8) in the first wave in 2009, 20.9 (95% CI 6.4-33.8) in the second wave in 2011, and 30% (95% CI 29%-32%) of A(H1N1) pdm09-associated deaths in 2009 occurred out of hospital.

Molecular characterisation of Corynebacterium diphtheriae outbreak isolates from South Africa, March – June 2015

M du Plessis, N Wolter, M Allam, L de Gouveia, F Moosa, G Ntshoe, L Blumberg, C Cohen, M Smith, P Mutevedzi, J Thomas, V Horne, P Moodley, M Archary, Y Mahabeer, S Mahomed, W Kuhn, K Mlisana, K McCarthy and A von Gottberg
Emerging Infectious Diseases 2017 23(8): 1309-1315

In 2015, a cluster of respiratory diphtheria cases was reported from KwaZulu-Natal. Using whole-genome analysis, we characterised 21 *Corynebacterium diphtheriae* isolates collected from 20 patients and contacts during the outbreak (one patient was infected with two variants of *C. diphtheriae*). In addition, one cutaneous isolate, two endocarditis isolates, and two archived clinical isolates (ca. 1980) were included for comparison.

Two novel lineages were identified: toxigenic sequence type (ST) ST-378 (n=17) and nontoxigenic ST-395 (n=3). The absence of pre-existing molecular sequence data limits drawing conclusions pertaining to the origin of these strains. These findings however provide baseline genotypic data for future cases and outbreaks. Neither ST has been reported in any other country and appear to be endemic in South Africa only.

Enterovirus genotypes among patients with severe acute respiratory illness, influenza-like illness, and asymptomatic individuals in South Africa, 2012-2014

O Hellferscee, S Tempia, S Walaza, E Variava, H Dawood, N Wolter, SA Madhi, M du Plessis, C Cohen and FK Treurnicht
Journal of Medical Virology 2017 89(10):1759-1767

Enteroviruses can cause outbreaks of severe acute respiratory illness. We characterised and determined the prevalence of enterovirus genotypes among patients with respiratory illness and controls from June 2012 to July 2014. Among the 101/236 (42.8%) enterovirus-positive specimens that could be genotyped from respiratory specimens, there was a high diversity of circulating enterovirus genotypes from all four human enterovirus species, with high prevalence of enterovirus-B (60.4%; 61/101).

Of the enterovirus genotypes identified, echovirus 30 (9.9%, 10/101), coxsackie virus B5 (7.9%, 8/101) and enterovirus-D68 (6.9%, 7/101) were most prevalent. There was a high number of enterovirus genotypes in patients with respiratory illness and in controls with no disease association of enterovirus species with disease severity.

Epidemiology of influenza B/Yamagata and B/Victoria lineages in South Africa, 2005-2014

M Seleka, FK Treurnicht, S Tempia S, O Hellferscee, S Mtshali, AL Cohen, A Buys, JM McAnerney, TG Besselaar, M Pretorius, A von Gottberg, S Walaza, C Cohen, SA Madhi and M Venter
PLoS One 2017 12(5): e0177655

A prospective study was conducted to describe the circulation of influenza B/Victoria and B/Yamagata lineages among patients of all ages, through three respiratory illness surveillance platforms. Influenza viruses were detected in 22% (8,706/39,804) of specimens from patients with ILI or SARI during 2005-2014, of which 24% (2,087) were positive for influenza B. B/Victoria predominated prior to 2011 (except 2008), whereas B/Yamagata predominated thereafter (except 2012). Hospitalised SARI cases display differential susceptibility for the two influenza B lineages, with B/Victoria being more prevalent among children and HIV-infected persons.

Invasive disease caused simultaneously by dual serotypes of *Streptococcus pneumoniae*

K Ndlangisa, M du Plessis, M Allam, N Wolter, L de Gouveia, KP Klugman, C Cohen, RA Gladstone and A von Gottberg
Journal of Clinical Microbiology 2018; 56(1): e01149-17

Invasive pneumococcal disease (IPD), is usually caused by a single serotype whereas dual serotype IPD is rare. Factors associated with dual serotype IPD were assessed and patient information from laboratory-based IPD surveillance from 2005-2014 was reviewed. Isolate genomes from co-infected individuals were genetically characterised. For 30/33 (91%) patients with dual serotypes, one or both isolates were a pneumococcal conjugate vaccine serotype.

Dual serotype IPD was associated with children aged <5 years [adjusted odds ratio (aOR), 4.7, 95% CI, 1.8-11.7], underlying illness (other than HIV) (aOR, 2.8; 95% CI, 1.1-6.6) and death (aOR, 2.5; 95% CI, 1.08-6.09). Isolates were genotypically unrelated and genotypes were common among isolates of the same serotype in South Africa. The association of dual serotypes with death warrants increased awareness of IPD co-infection.

The cost-effectiveness of trivalent and quadrivalent influenza vaccination in communities in South Africa, Vietnam and Australia

PT de Boer, JK Kelso, N Halder, TP Nguyen, J Moyes, C Cohen, IG Barr, MJ Postma and GJ Milne
Vaccine 2018 36(7): 997-1007

Individual-based dynamic simulation models were developed to estimate the cost-effectiveness of vaccinating 15% of the population with quadrivalent influenza vaccines (QIVs) or trivalent influenza vaccines (TIVs) in three communities, in three different countries. Vaccination was prioritised for HIV-infected individuals, elderly aged 65+ years and children <5 years.

Published data were used for influenza strain circulation, clinical outcomes and costs. Outcomes were expressed in international $ (I$) per quality-adjusted life-year (QALY) gained. The QIV (compared to TIV) model described a greater reduction in influenza-related morbidity in South Africa and Vietnam, as compared with Australia. The incremental cost-effectiveness ratio of QIV versus TIV was estimated to be lower in South Africa and Vietnam (I$4183/QALY and I$1505/QALY respectively), as compared to Australia (I$80,966/QALY).

Epidemiology and molecular identification and characterization of *Mycoplasma pneumoniae* in South Africa, 2012-2015

M Carrim, N Wolter, AJ Benitez, S Tempia, M du Plessis, S Walaza, F Moosa, MH Diaz, BJ Wolff, FK Treurnicht, O Hellferscee, H Dawood, E Variava, C Cohen, JM Winchell and A von Gottberg
Emerging Infectious Diseases 2018 24(3): 506-513

Respiratory specimens from patients with SRI, ILI and controls were tested by real-time PCR for *Mycoplasma pneumoniae*, with culture and molecular characterisation of positive samples. *M. pneumoniae* prevalence was 1.6%, 0.7% and 0.2% among SRI, ILI and control subjects, respectively (p<0.001). Age <5 years (aOR 7.1; 95% CI 1.7–28.7) and HIV infection (aOR 23.8; 95% CI 4.1–138.2) among *M. pneumoniae*–positive persons were associated with severe disease.

The detection rate attributable to illness was 93.9% (95% CI 74.4%–98.5%) in SRI patients and 80.7% (95% CI 16.7%–95.6%) in ILI patients. The hospitalisation rate was 28 cases/100,000 population. All isolates had a macrolide-susceptible genotype.

RESEARCH PROJECTS (ONGOING/UNPUBLISHED)

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

C Cohen, A Tshangela, P Iyengar, C von Mollendorf, Z Valley-Omar, S Walaza, O Hellferscee, M Venter, N Martinson, G Mahlase, ML McMorrow, B Cowling, AL Cohen and S Tempia

The secondary infection rate (SIR) and mean serial interval (SI) were 17% (19/113) and 1.2 days (range 1-5) from HIV-infected (27 cases) vs 29% (64/220) and 2.5 days (1-6) from HIV-uninfected (57 cases) index cases. On multivariable analysis, HIV-infected index cases were less likely to transmit influenza to household contacts (odds ratio (OR) 0.3 95% CI 0.1-0.8). Factors associated with increased SIR were index age group 1-4 years (OR 3.0 95%CI 1.3-6.9), and 25-44 years (OR 4.3 95%CI 1.4-13.1) and contact age group 1-4 years (OR 3.4 95%CI 1.2-9.2) compared to 5-14 years, sleeping with index (OR 2.6 95%CI 1.4-4.8), cycle threshold value <30 in index (OR 2.2 95%CI 1.1-4.7) and household size >7 people (OR 3.8 95%CI 1.5-9.8). HIV-infection was not associated with SI.

Combining case-based and ecological studies to improve estimates of influenza-associated illness: a case study from South Africa, 2013-2015

S Tempia, S Walaza, J Moyes, AL Cohen, ML McMorrow, FK Treurnicht, O Hellferscee, N Wolter, A von Gottberg, A Nguweneza, JM McAnerney, H Dawood, E Variava, SA Madhi and C Cohen

The estimated mean annual number of influenza-associated illness episodes was 10,737,847 (19.8% of 54,096,705 inhabitants). Of these episodes, 10,598,138 (98.7%), 128,173 (1.2%) and 11,536 (0.1%) were mild, severe-non-fatal and fatal, respectively. 2,718,140 (25.6%) mild, 56,226 (43.9%) severe-non-fatal and 4,945 (42.8%) fatal episodes were medically-attended.

Influenza-associated respiratory illness accounted for 99.2% (10,576,146), 65.5% (83,941) and 33.7% (3,893) of any mild, severe-non-fatal and fatal illness, respectively. The estimated case fatality rate among individuals with influenza-associated severe illness (fatal and non-fatal) was 8.3% (11,536/139,709) overall; 4.4% (3893/87,834), 18.6% (3,138/16,831) and 12.9% (4,505/35,044) among individuals with influenza-associated respiratory, circulatory and non-respiratory/non-circulatory severe (fatal and non-fatal) illness, respectively.

Framework to guide influenza vaccination policy in resource limited settings – a case study from South Africa

ML McMorrow, S Tempia, S Walaza, FK Treurnicht, W Ramkrishna, E Azziz-Baumgartner, SA Madhi and C Cohen

Due to competing health priorities, low- and middle-income countries (LMIC) may need to prioritise different influenza vaccine risk groups. Risk group prioritisation may differ in LMIC, based upon country-specific prevalence of risk conditions and influenza-associated morbidity and mortality.

Pregnant women (228.5), HIV-infected adults (190.9), and adults and children with tuberculosis (162.0), had among the highest estimates of hospitalisations averted per 100,000 vaccinated and adults ≥65 years old (96.6), had the highest estimated deaths averted per 100,000 vaccinated. However, when assessing both the cost per hospital day averted (range: USD148-1,458) and the cost per year of life saved (range: USD112-1,230); adults and children with TB, HIV-infected adults and pregnant women had the lowest cost per outcome averted.

Molecular epidemiology of *Legionella pneumophila* in South African hospitals, 2015 – 2016

M Carrim, N Wolter, M du Plessis, R Stewart, L de Gouveia and A von Gottberg

Healthcare facilities globally are often identified as sources of Legionnaires' disease (LD). Globally, serogroup (SG) 1, sequence type (ST) 1 is the most common strain identified by sequenced-based typing (SBT). *Legionella* spp. was isolated from samples collected from 17 private and public hospitals, representing four of the nine provinces (Eastern Cape, Western Cape, Gauteng and Mpumalanga). 42/77 (55%) isolates were *L. pneumophila* SG1, 31 (40%) were *L. pneumophila* SG2-14 and 4 (5%) were other *Legionella* spp.

For *L. pneumophila*, we identified genotypes ST1 (59%; 43/73), ST421 (21%; 15/73), ST87 (1%;1/73) and ST242 (1%;1/73) and several novel STs. SG1 predominantly comprised ST1 (91%;30/33), while SG2-14 predominantly comprised ST1 (50%;13/26) and ST421 (42%;11/26). SG1 ST1 was the most common strain detected in the water systems of hospitals.

Meningococcal carriage amongst first-year students entering university: is there a need in South Africa for meningococcal prevention strategies?

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

To determine *Neisseria meningitidis* carriage prevalence and risk factors amongst first-year university students, oropharyngeal swabs and data were collected from students during registration week at two universities, in Western Cape and Gauteng, in 2017. 2121 students participated. 41% (876) were male and 0.8% (16/1985) were HIV infected. 66 students (3%, 95% CI 2.5% - 3.9%) were carriers, of which 52% (34/66, p=0.09) were male and all were HIV uninfected.

When adjusting for recent smoke exposure, party, nightclub or pub attendance, the results were as follows: Eastern Cape adjusted OR 3.1, CI1.1-8.8, p=0.004, KZN adjusted OR3.7, CI1.7-8.3, p=0.001; Western Cape adjusted OR2.6, CI1.4-5.0, p=0.004 and Gauteng adjusted OR2.9, CI1.3-6.7, p=0.01. Intimate kissing partners (aOR2.7, CI1.5-4.8, p=0.001) remained significant risk factors for carriage.

The fraction of rhinovirus detections attributable to mild and severe respiratory illness in a high HIV-prevalence setting, South Africa, 2013-2015

O Hellferscee, FK Treurnicht, S Walaza, M du Plessis, A von Gottberg, N Wolter, J Moyes, H Dawood, E Variava, M Pretorius, M Venter, C Cohen, S Tempia

The association of rhinovirus (RV) detection with illness is poorly understood. The RV prevalence among ILI or SRI cases was compared to those of controls, stratified by HIV-serostatus. RV was detected in 17.4% (368/2120), 26.8% (979/3654) and 23.0% (1003/4360) of controls, ILI and SRI cases, respectively.

The RV attributable fraction higher among <5y AND >5y and then HV-infected AND HIV-uninfected. Although RVs were commonly detected among controls, they were also responsible for a substantial proportion of clinical illness across age groups, irrespective of HIV status.

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

Z Valley-Omar, A Cloete, R Pieterse, S Walaza, Y Salie-Bassier, M Smith, N Govender, M Seleka, O Hellferscee, S Mtshali, M Ali, A Ismail, T Anthony, M Romito, L Rotherham, A van Schalkwyk, M Seutloali, K McCarthy, L van Helden, C Cohen and FK Treurnicht

The avian influenza A(H5N8) risk of transmission and laboratory preparedness during the 2017 outbreak was assessed. Active and passive surveillance identified 74 symptomatic individuals, but none tested positive for avian influenza. Variance in the efficiency of commercial assays in identifying A(H5N8) in avian-derived samples was shown. NICD-validated assays identified 94-100% of the known-positive samples compared to 6% for an alternative assay.

Next generation sequencing of these samples demonstrated limited genomic sequence diversity, suggesting entry of a single viral variant into this region during this period. All samples were shown to contain the known NS (P42S) and PB2 (L89V) mammalian-adaptive

mutations, also identified in phylogenetically-related A(H5N8) isolates from Egypt in 2016, suggesting a possible phylogeographic association.

Acknowledgements and collaborators

1. The Pneumonia Surveillance Programme investigators;
2. GERMS-SA investigators;
3. Drs S Tempia, J Duque, C Whitney, J Winchell, M McMorrow, L McGee, X Wang and L Tondella: CDC, Atlanta, USA;
4. Prof KP Klugman: Director, Pneumonia, The Bill and Melinda Gates Foundation, Seattle, USA;
5. Drs MCJ Maiden, KA Jolley and O Harrison: Department of Zoology, University of Oxford, UK;
6. Drs SD Bentley, R Gladstone and S Lo: Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, UK;
7. Drs R Breiman and J Vidal: Emory University, Atlanta, USA;
8. Mr R Stewart: Infection Control, CMJAH, NHLS;
9. PHIRST study teams, Peri- Natal HIV Research Unit, Klerksdorp (Dr N Martinson), MRC/Wits-Agincourt Rural Public Health and Health Transitions Research Unit (Prof K Kahn), University of the North West (Prof Stuart Piketh) and Environment & Health Research Unit, MRC, UJ;
10. Dr L Hathaway and A Mueller, University of Bern, Switzerland;
11. Prof Ben Cowling, University of Hong Kong;
12. Dr Cecile Viboud, Fogarty Institute, USA;
13. Dr Ciro Cuttata, ISI Foundation, Italy; and
14. Dr James Nokes, University of Warwick, Wellcome Trust and Kenya Medical Research Institute.

TEACHING AND TRAINING

The CRDM staff lecture at the Universities of Witwatersrand and Pretoria and are involved in registrar training, medical scientist intern training and technical training for other healthcare professionals.

Prof Cohen coordinated the Infectious Diseases Epidemiology 1-week module at Wits, School of Public Health for the MSc Epidemiology. Our senior staff are also involved in the teaching of undergraduate and postgraduate students from various schools at Wits.

PROFESSIONAL DEVELOPMENT

Postgraduate training

Karistha Ganesh graduated with an MSc.

Additional students registered

The following candidates were enrolled for PhDs: Orienka Hellferscee; Kedibone Ndlangisa; Lorens Maake; Susan Meiring; Jocelyn Moyes; Annelies Mueller and Sibongile Walaza.

MSc

The following candidates were enrolled for an MSc: Mvuyo Makhasi; Thabo Mohale and Zothile Skosana.

MMed

Krishnee Moodley was registered for an MMed.

RESEARCH OUTPUTS (PUBLICATIONS)

NICD publications

1. NICD Influenza recommendations for diagnosis, prevention , management and public health response guidelines were published on the NICD website on the 25 May 2017 http://www.nicd.ac.za/wp-content/uploads/2017/03/Influenza-guidelines final_24_05_2017.pdf.
2. Epidemiology of respiratory pathogens from influenza-like illness and pneumonia surveillance programmes, South Africa, 2016, NICD Communicable Diseases bulletin on the 29 May 2017. http://www.nicd.ac.za/wp-content/uploads/2017/03 CommDisBullMay2017.pdf.
3. GERMS-SA annual surveillance report for laboratory confirmed invasive meningococcal, pneumococcal and *Haemophilus influenzae* disease, South Africa, 2016http://www.nicd.ac.za/wp-content/uploads/2017/09/NICD-Newsletter-2nd-Bulletin-Edition_V07.pdf.
4. Pertussis – NICD recommendations for diagnosis, management and public health response published on the NICD website in December 2017. http://www.nicd.ac.za/wp-content/uploads/2017/03/Guidelines_pertussis_v1_20-December-2017_Final.pdf.

Peer-reviewed publications

1. Carrim M, Wolter N, Benitez AJ, Tempia S, du Plessis M, Walaza S, Moosa F, Diaz MH, Wolff BJ, Treurnicht FK, Hellferscee O, Dawood H, Variava E, Cohen C, Winchell JM, von Gottberg A. Epidemiology and molecular identification and characterization of *Mycoplasma pneumoniae*, South Africa, 2012-2015. *Emerging Infectious Diseases* 2018; 24(3): 506-513. doi: 10.3201/eid2403.162052.
2. Lee VJ, Ho ZJM, Goh EH, Campbell H, Cohen C, Cozza V, Fitzner J, Jara J, Krishnan A, Bresee J; WHO Working Group on Influenza Burden of Disease. Advances in measuring influenza burden of disease. *Influenza and Other Respiratory Viruses* 2018; 12(1)**:** 3-9. doi: 10.1111/irv.12533.
3. de Boer PT, Kelso JK, Halder N, Nguyen TP, Moyes J, Cohen C, Barr IG, Postma MJ, Milne GJ. The cost-effectiveness of trivalent and quadrivalent influenza vaccination in communities in South Africa, Vietnam and Australia. *Vaccine* 2018; 36(7): 997-1007. doi:10.1016/ j.vaccine.2017.12.073.
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Conferences

- International conference presentations: 16
- National conference presentations: 5

Funding

- US CDC;
- Bill and Melinda Gates Foundation;
- WHO;
- NRF;
- Sanofi Pasteur; and
- The NHLS Research Trust

Centre for Vaccines and Immunology

Dr Melinda Suchard

BACKGROUND

The Centre for Vaccines and Immunology (CVI) comprises the national and WHO regional reference laboratories for AFP, as well as measles and rubella surveillance. In addition, the centre conducts projects on viral hepatitis, TB and other vaccine preventable diseases.

A biosafety level three laboratory and environmental surveillance laboratory support the endgame of the GPEI. The centre provides epidemiological, virological and immunological support to the NDoH for vaccine preventable diseases.

SURVEILLANCE/DIAGNOSTIC SERVICES

Polio surveillance

The Poliovirus Isolation Laboratory, within the Centre for Vaccines and Immunology serves as a national reference laboratory for AFP surveillance as part of the GPEI. The laboratory serves seven countries within the Southern African region in this capacity, namely; Angola, Botswana, Lesotho, Mozambique, Namibia, Swaziland and South Africa. The centre serves the broader African region as a Regional Reference Laboratory.

For any AFP case, stool samples are inoculated into cell cultures, and any sample with suggestive poliovirus cytopathic effects, is subjected to molecular typing and characterisation to confirm poliovirus serotype and differentiate poliovirus subtype. During the reporting period, 2698 South African samples were processed for poliovirus isolation. Results showed 22 suspected polioviruses and 392 non-polio enteroviruses. The case-based non-polio AFP detection rate for 2017 was 2.3/100 000 children under 15 years.

The Centre for Vaccines and Immunology is the only polio sequencing laboratory in the region. In January 2017, 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 arena. 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 due to inherited primary 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; and were all negative. The index case was treated with intravenous immunoglobulin (IVIG) and responded well. Stool samples from the case will be tested monthly, until there are two consecutive negative results.

As the regional reference laboratory, the Centre for Vaccines and Immunology also processes samples from other countries. For this reason, we identified one case of VDPV serotype 1, as well as four cases and one contact of VDPV serotype 2 in samples from the Democratic Republic of Congo (DRC). The VDPV type 1 was classified as ambiguous, as there were no other detections of related viruses.

The VDPV type 2 viruses were circulating viruses and formed part of the initial detection of the outbreak in the DRC. Sabin polioviruses type 2 were detected in 33 other samples, all from countries that use monovalent oral polio vaccine type 2 to halt VDPV type 2 transmission, namely Cameroon, Chad, Mozambique and Niger. One VDPV type 1 was also identified in the DRC, but no other related viruses have been detected ever since.

The NICD applied to the NDoH to host a Polio Essential Facility (PEF), which will be one of a handful globally. This PEF will enable the NICD to work with poliovirus type 2 under high containment, following global certification of eradication. Operations in the proposed PEF already commenced in 2016, and the application was approved by the NDoH in March 2017. The National Authority for Containment was formed late in 2017, and will facilitate review of the application.

Measles

The Centre for Vaccines and Immunology is the national reference laboratory for measles surveillance. In support of the regional measles elimination initiative, which has a measles elimination goal of 2020, the centre provides serological and molecular testing for the measles virus.

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 6118 South African samples were tested during the reporting period and 188 tested positive for measles Ig M.

In late 2017, the centre confirmed an outbreak of measles in eThekwini, KZN, South Africa. The centre supported provincial and national departments of health with weekly situation reports for the duration of the outbreak, ensuring that decisionmakers have rapid, real-time information to plan localised vaccination responses.

There were 42 cases in eThekwini, with 21 cases detected in six other districts of KZN, equating to a total of 63 cases. The outbreak, which occurred largely in vaccine hesitant communities, was declared over on 20 February 2018.

Gauteng and Western Cape provinces also experienced similar measles outbreaks in 2017, with 96 cases in Gauteng and 36 in the Western Cape during the year. South Africa is in pre-elimination phase for measles and supports the WHO AFRO elimination target of 2020.

Measles is a major driver of ≤5 year old mortality rates, and is one of the most highly transmissible infectious diseases. Control of any measles outbreak is therefore of relevance to the country and the region. The pre-elimination target is less than five cases per million population. Due to the three outbreaks, the national measles incidence rate per million population in 2017 was 3.7 per million. In Gauteng, the provincial incidence rate was 7.0 per million.

There were 2679 rubella IgM positive cases identified in the review period via febrile rash surveillance. We detected 10 laboratory-confirmed congenital rubella syndrome cases, via sentinel site surveillance, which includes 28 study sites in all nine provinces of South Africa.

Rubella vaccine is not yet included in the South African Expanded Programme on Immunisation. Such data is required to inform timelines and targeted age groups for future introduction.

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, Swaziland, Zambia and Zimbabwe. A total of 393 samples were tested. There was good concordance for measles IgM results (90-100%), with slightly poorer concordance for rubella IgM results (80-100%).

Hepatitis

The Centre for Vaccines and Immunology, together with the NDoH, is committed to reach the 2030 viral hepatitis elimination goals. To provide accurate data on hepatitis B and C, data was mined from the NHLS corporate data warehouse.

Of the patients captured on the database from January to December 2017, 43554 were positive for hepatitis B viral (HBV). The number of acute cases (defined by anti-HBcIgM) was 3496. This analysis allowed hepatitis B data to be reported via the joint reporting form to the WHO, for the first time.

For hepatitis C, of the 10276 patients tested in 2017, 3024 (29%) tested positive for anti hepatitis C virus (HCV). Laboratory tests are unable to distinguish acute- from chronic hepatitis C.

RESEARCH AND / OR SPECIAL PROJECTS

Immunological biomarkers for TB detection

South Africa bears a huge burden of TB, particularly in HIV infected individuals. New TB biomarkers that can detect TB in HIV infected individuals more effectively, could improve overall detection rates and aid the prediction of the onset of active disease or the monitoring of response to treatment. We evaluated a little known biomarker called indoleamine 2,3 dioxygenase for diagnosis of TB in HIV infection from patient plasma. A biomarker which can utilise blood as a sample of choice, will improve diagnosis in many patients.

The exercise demonstrated excellent results through the use of mass spectrometry (sensitivity of 97%, specificity of 99%, positive predictive value of 89% and negative predictive value of 100%) for diagnosis of active TB (Adu-Gyamfi et al, CID 2017).

We are further evaluating the tool using enzyme-linked immunosorbent assay (ELISA), which is a lower cost, higher throughput method.

Hepatitis A virus (HAV) seroprevalence in South Africa - estimates using routine laboratory data, 2005-2015

A Mazanderani, NV Motaze and MS Suchard

Hepatitis A serology results (IgM, IgG and total antibody) from 2005-2015 were extracted from South Africa's NHLS' CDW. Anti-HAV total antibody testing within the South African public health sector demonstrates that seroprevalence rates reach levels of >90% only in adulthood, which suggests that South Africa could be in transition from high- to intermediate endemicity. (Mazanderani et al, manuscript submitted). Such data is important to inform vaccination policies. Hepatitis A vaccination is not part of the Expanded Programme on Immunization but is available, should evidence support its introduction.

Environmental Polio Surveillance

S Moonsamy, MF Modiko, H Du Plessis and W Howard

This is an ongoing project at eight sites in Angola, four sites in Mozambique and four sites in the Republic of South Sudan, in support of GPEI. In the reporting period, 93 samples were received from Angola, 57 from Mozambique and 77 from the Republic of South Sudan.

There were a total of five suspected polioviruses and 127 non-polio enteroviruses. In addition, 86 samples were referred to the NICD from other environmental laboratories. Of these, 43 were non-polio enterovirus and 40 were poliovirus positive for Sabin vaccine strains, the latter of which were from Niger, Cameroon, Senegal and Madagascar.

TEACHING AND TRAINING

The centre 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 centre hosted cell culture and poliovirus isolation training for the AFRO region from 11-23 September 2017. We also hosted PCR workshops on intratypic differentiation of polioviruses at the Francophone African Polio Lab Heads; from 13-17 November 2017, and at the Anglophone African Polio Lab Heads; from 27 November - 1 December 2017.

From 5-16 March 2018, polio laboratory training (cell culture, virus isolation and intratypic differentiation) was provided to two WHO staff members from the Zambia Polio Reference Laboratory. Onsite training on measles serology was also provided to staff from Mozambique, from 7-11 August 2017.

The centre furthermore facilitated a Vaccinology Congress for stakeholders from national and provincial departments of health, as well as the private sector and academia in Magaliesburg, from 1-3 October 2017.

Our staff also facilitated a training workshop on Systematic Reviews and Evidence-Based Healthcare to senior managers from the NDoH in Pretoria, South Africa, from 28-30 November 2017.

Professional development

In 2017, the centre enrolled three candidates for an MSc, one from the FETP for an MPH, two for an MMed and two for PhDs. One student graduated with a BSc Hons and one with a MSc.

Honours

- Dr MS Suchard received a ministerial appointment as a member of the National Advisory Group on Immunization (NAGI), and the National Technical Advisory Group on Immunization (NITAG); and
- Dr NV Motaze was appointed as a member of the Global Measles/Rubella WHO Strategic Advisory Group of Experts (SAGE) working group.

RESEARCH OUTPUT

Journal articles:

1. Adu-Gyamfi C, Snyman T, Hoffmann CJ, Martinson NA, Chaisson RE, George JA and Suchard MS. Plasma indoleamine 2,3-dioxygenase, a biomarker for Tuberculosis in HIV infected patients. *Clinical Infectious Diseases* 2017; 65: 1356-63.
2. 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.
3. Fernandez-Garcia MD, Majumdar M, Kebe O, Fall AD, Kone M, Kande M, Dabo M, Sylla MS, Sompare D, Howard W, Faye O, Martin J, Ndiaye K. Emergence of Vaccine-Derived Polioviruses during Ebola Virus Disease Outbreak, Guinea, 2014-2015. *Emerging Infectious Diseases* 2018; 24: 65-74.
4. Gerloff N, Sun H, Mandelbaum M, Maher C, Nix WA, Zaidi S, Shaukat S, Seakamela L, Nalavade UP, Sharma DK, Oberste MS, Vega E. Diagnostic Assay Development for Poliovirus Eradication. *Journal of Clinical Microbiology* 2017; 56: e01624-17.
5. Jallow S, Cutland CL, Masbou AK, Adrian P, Madhi SA. Maternal HIV infection associated with reduced transplacental transfer of measles antibodies and increased susceptibility to disease. ***J**ournal of Clinical Virology* 2017; 94: 50–56.
6. Jallow S, Madhi SA, Madimabe MR, van Niekerk N, Parbhoo K, Moosa F, Thandrayen K, Sipambo N, Violari A, Kala U, Petersen K, Naidoo S, Verwey C, Moore DP, Nunes MC. Immunogenicity of 13-valent pneumococcal conjugate vaccine among children with underlying medical conditions. *Vaccines* 2017; 35: 4321-4329.
7. Jallow S, Madhi SA. Pneumococcal conjugate vaccine in HIV-infected and HIV-exposed, uninfected children. *Expert Rev Vaccines* 2017; 16: 453-465.
8. Johansen M, Rada G, Rosenbaum S, Paulsen E, Motaze NV, Opiyo N, Wiysonge CS, Ding Y, Mukinda FK and Oxman AD. A comparative evaluation of PDQ-Evidence. *Health Research Policy and system**s*** 2018; 16: 27-41.

Conference presentations

- International congresses: 3
- National congresses: 7

WHO Cell Culture and Poliovirus Isolation Workshop for the AFRO Region, NICD, 11-23 September 2017

South African Regional Global Disease Detection Centre

Dr Natalie Mayet

BACKGROUND

The South African Global Regional Global Disease Detection Centre (SARGDDC) established in 2011 in the year under review focussed primarily on the close-out of various projects in the Research- and Non-Research Co-operative Agreements. The strengthening and support of the re-engineering of the NMC Surveillance System, in collaboration with the NDoH, were key priorities during the year.

Since the inception of the SARGDDC, the budget allocated to both types of co-operative agreements totalled $15 823 968. This facilitated the employment of 22 staff members at the NICD and the integration of five staff members at the NDoH.

The Non-Research Co-operative Agreement was streamlined into the following six projects:

1. Analysing the South African Notifiable Disease Surveillance System;
2. PulseNet Africa;
3. Fever surveillance with laboratory testing for emerging pathogens;
4. Capacity building for field epidemiology in South Africa;
5. Support for the establishment of the NAPHISA; and
6. Partnering with the NDoH to address the import and export of biological agents.

The Research Co-operative Agreement was concluded in September 2017 with seven projects as follows:

1. Investigation of the influenza burden, interaction with other pathogens and nosocomial transmission at sentinel surveillance sites;
2. Household transmission of influenza amongst HIV-infected and -uninfected individuals;
3. Healthcare utilisation survey in Johannesburg and Cape Town;
4. Effectiveness of trivalent inactivated influenza maternal vaccination and evaluation of the vaccination programme among pregnant women and their new-borns;
5. Additional Methods for Controlling Malaria;
6. Harbouring of Viral Zoonotic Agents by the Southern African Bat population; and
7. Investigating the contribution of Swine and/or Avian Influenza A Viruses to ILI and pneumonia.

The collective output of this agreement was 57 publications, 84 policy documents and report inputs, 35 presentations at local and international conferences and 22 training outputs, including two PhDs. The specific objectives and highlights of these projects are covered under the respective centres in the annual report.

SPECIAL PROJECTS

The SARGDDC continues to support the development of business case for the establishment of the NAPHISA, following the passing of the NAPHISA Bill by Cabinet in March 2017.

As the Chair of the International Association of National Public Health Institutes (IANPHI)- Africa, with the secretariat based at the NICD, 22 communications were distributed to the network and leadership training was facilitated for IANPHI representatives from 19 African countries.

The Co-Director was part of the IANPHI peer review panel for the review of Public Health England (PHE), at the end of June 2017. The IANPHI-Africa network is engaging with Africa CDC to develop a framework for the establishment of the public health institutes and is part of the health informatics and field epidemiology workforce development task team.

As an Advisory Board member on the Gates-funded Child Health and Mortality Prevention Surveillance (CHAMPS) project, there are ongoing discussions on how this data can be used to improve surveillance.

Dr Mayet, in her capacity as Chairperson of the SAMEC Health Promotional Sub-committee, has been engaging with the NDoH, as well as both public and private sector healthcare professionals on increasing malaria awareness.

The year under review saw the Co-Director relinquish the role as the Acting NICD HR manager to the new NICD HR manager, Ms Azia Nxumalo, who will continue to work on the unresolved HR issues related to the NHLS Proficiency process.

Dr Mayet facilitated a pre-conference workshop titled "Field Epidemiology Capacity Building for Strengthening Public Health Institutes" at the Training Program in Epidemiology and Public Health Intervention (TEPHINET) conference, in Thailand, which was attended by 23 participants from 15 countries. Outcomes from the workshop were shared with TEPHINET and IANPHI and will inform workforce strategy development for public health institutes.

Collaborators

1. **Private Sector:** Board of Healthcare Funders of Southern Africa; Council for Medical Schemes; the National Pathology Group; AMPATH Laboratories; Alliance of South African Independent Practitioners Association and KZN Doctors Healthcare Coalition;
2. **Associations:** Health Professions Council of South Africa (HPSCA); the Hospital Association of South Africa (HASA); South African Medical Association (SAMA) and the South African Nursing Council (SANC);
3. **Universities:** Schools of Public Health as partners in delivering MPH and MSc degrees; and the University of South Africa (UNISA) Institute for Social and Health Sciences (ISHS) as a Board member;
4. **Regional:** The Regional Collaborating Centre of Africa CDC in Zambia; and
5. **International:** The African CDC; IANPHI network and China CDC.

In 2017, the South African Field Epidemiology Training Programme (SAFETP) had an intake cohort of seven first-year and seven second-year students. Eight residents from the 2015 cohort graduated with an MPH conferred by UP during the year. To date, the programme has trained more than 80 health professionals, 88% of whom remain in public service in South Africa. The graduation attainment rate was 87% from a baseline of 51% in 2011.

The team continues to work with the NDoH in having epidemiology recognised as a professional discipline in the Human Resource for Health Strategy and are defining the epidemiology core competencies required for existing health staff in the health service. Pursuant to building epidemiology capacity at grass root level, we also developed an Applied Epidemiology e-learning course with I-Tech, which is being rolled out in 2018.

In September, the team facilitated and presented a preconference workshop at the Public Health Association of South Africa (PHASA), conference titled: "International Health Regulations and Requirements to Build Epidemiology Capacity in South Africa." The outcomes of the workshop were shared with the NDoH, with the aim to help build the epidemiology requirements for the International Health Regulations.

In the year under review, residents participated in 25 outbreak investigations, conducted seven large data base analyses and produced the following dissertations as part of their core learning activities:

1. Brucellosis Knowledge, Attitudes, and Practices of cattle keepers in a rural community in the Eastern Cape, South Africa, 2017;
2. Estimating the impact of the pneumococcal conjugate vaccine using pneumococcal meningitis surveillance data in South Africa from 2005-2015;
3. Drug Resistant Tuberculosis (DR-TB) Treatment Outcomes in Limpopo Province, South Africa, 2012-2016;
4. Cross-sectional Analysis of New Drug Resistant Tuberculosis in the North West Province, South Africa, 2013-2015;
5. Estimating vaccine timeliness and coverage among children using secondary data collected through the rotavirus and severe acute respiratory infections (SARI) surveillance programmes, South Africa, 2009-2015;
6. Relative prevalence and associated factors of persistent sexually transmitted infections syndromes in surveillance sentinels, South Africa, Jan 2015 - Jun 2016; and
7. A retrospective analysis of the causes of maternal mortalities (obstetric and non-obstetric) in the Nelson Mandela Metropolitan Health District, Eastern Cape, 2011 to 2015.

Dr Reddy, in his capacity as the Chair of the TEPHINET, presented at the Food and Agriculture Organization meeting titled "Global Epidemiology Coordination and Development Workshop on Field Epidemiology Training Programs for Veterinarians" in Italy and he played an active role in the development of the TEPHINET Strategic Plan for 2017-2020. As a member of the TEPHIConnect Steering Committee he also oversaw the establishment of TEPHIConnect – an online and mobile networking platform for FETP alumni worldwide, with more than 1000 registered users.

Dr Kuonza, in his role as an Advisory Board member at UJ, is working on the curriculum for trainee environmental health practitioners and is enrolled for his PhD.

TEACHING AND TRAINING

The SARGDDC provided the resources to train 276 public and private healthcare professionals in the NMC Surveillance System and facilitated the training of 36 staff members from the NICD, NIOH and NDoH in Advanced Biological Risk Mitigation.

During the year, the SAFETP staff delivered training courses for a total of 93 health professionals as follows:

- Basic Applied Epidemiology in East London;
- The Principles of Outbreak Investigations for the provincial DoH in Randfontein;
- Outbreak investigation training for Environmental Health Practitioners at the City of Johannesburg; and
- A short course in basic epidemiology for GERMS field project coordinators.

The SAFETP staff also co-facilitated a Supervisor's training workshop at the NICD to orientate new field supervisors on SAFETP guidelines for supervision of trainees.

Professional Development

Hetani Ngobeni attended a non-communicable disease short course at the WITS School of Public Health and she and Ms Pinky Manana attended the "Introduction to R-management, exploration, and communication of data" course at Stellenbosch University.

Honours

Ms Jackie Kleynhans, a 2nd year resident, received an award in the category for "Best Poster Presentation" at the TEPHINET conference for her poster on the Outbreak of influenza A(H3N2) among students at a boarding school in Eastern Cape Province, South Africa, July 2016.

Ms Natasha Abraham, a 1st year resident, won the "Best Oral Presentation" Award at the PHASA conference for her poster on Leading cancers among men and women: South Africa, 2002-2012.

RESEARCH OUTPUT

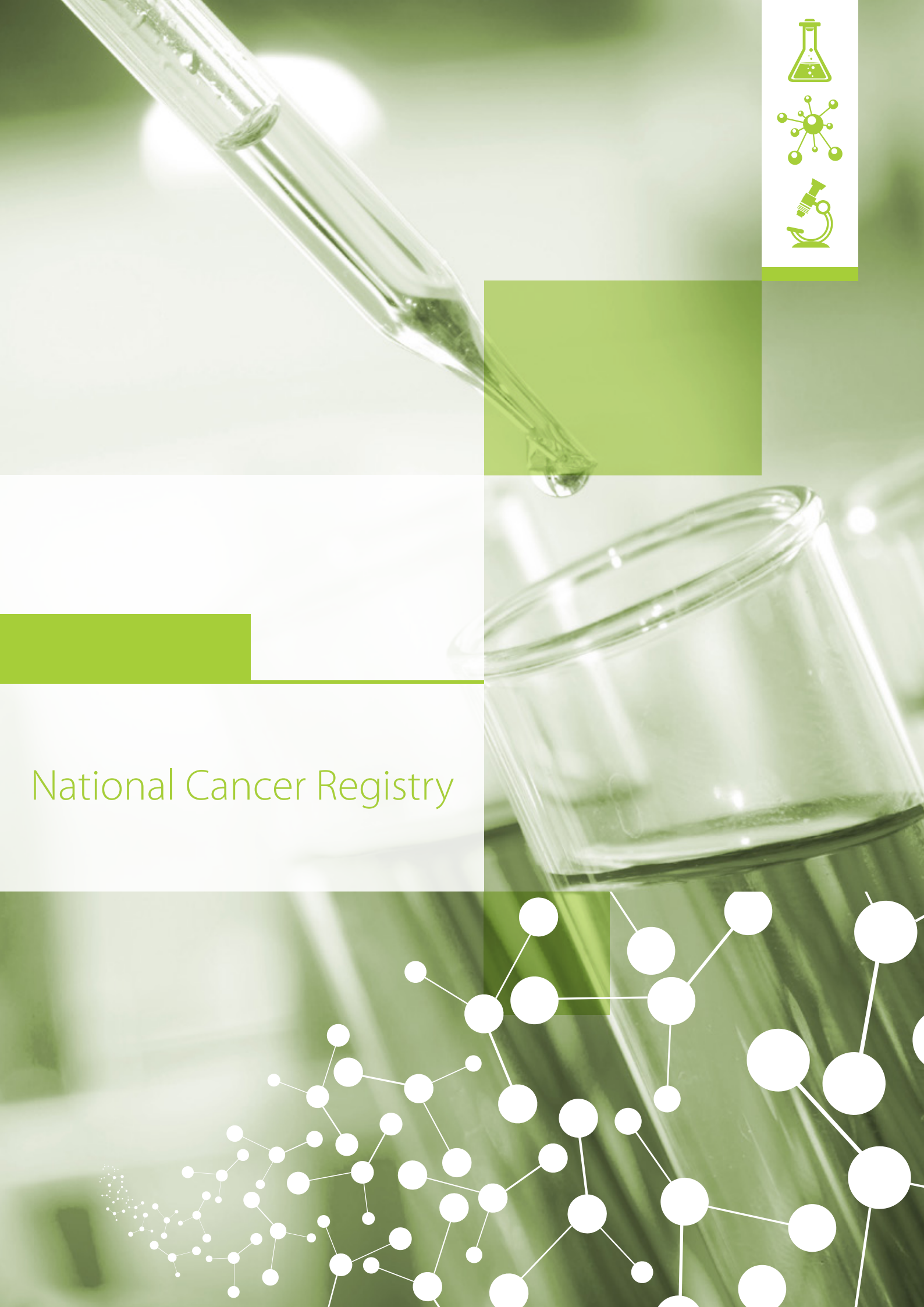
1. Pinky N Manana; Lazarus Kuonza; Alfred Musekiwa; Hluphi D Mpangane and Lizette L Koekemoer. Knowledge, attitudes and practices on malaria transmission in Mamfene, KwaZulu-Natal Province, South Africa 2015. *BMC Public Health 2017;18(1):41*; and
2. Shuping LL, Kuonza L, Musekiwa A, Iyaloo S, Perovic O (2017). Hospital-associated methicillin-resistant *Staphylococcus aureus:* A cross-sectional analysis of risk factors in South African tertiary public hospitals. *PLoS ONE 12(11).*

Presentations

- International conferences: 11
- National conferences: 11

Advanced Biological Risk Mitigation Training Programme with Mr Sean Kaufman Practical training on mitigating risks associated with BSL3 laboratories

Residents who successfully completed the 2-year Field Epidemiology Training Programme



National Cancer Registry

Dr Elvira Singh

BACKGROUND

The primary roles of the National Cancer Registry (NCR), are national pathology-based cancer surveillance and implementation of population-based cancer registration. In the year under review, the NCR made further strides in reducing the cancer incidence reporting backlog of previous years, with 2013 and 2014 data published.

A new NCR application was developed by the NICD IT division, which allowed efficient coding and real-time tracking of coding targets. Two NCR coders who were previously employed on grants were employed permanently, and one additional coder was appointed. Nine surveillance officers were placed at private and public hospitals in Ekurhuleni District, who collected and captured population-based cancer data for the 2017 year.

A RedCap database was created, tested and implemented in the Ekurhuleni population-based cancer registry (EPBCR), enabling simultaneous offsite data entry by all surveillance officers. This system is significantly more advanced and efficient in capturing data, than the previous CanReg system. In addition, the EPBCR data was cleaned and ready for analysis at the end of the financial year.

In the 2017/2018 financial year, the NCR published key research that illustrates the positive impact of implementing relevant health policies on cancer control in the country. Our studies amongst other, demonstrated that the expansion of the national ART roll-out has reduced incidence and improved survival of HIV-associated Kaposi sarcoma (KS), in recent years.

The introduction and expansion of pap-based cervical cancer screening at a Johannesburg HIV clinic, led to significant reductions in cervical cancer incidence in HIV-positive women on ART. The NCR also co-authored a review article on global epidemiology of HIV-associated malignancies in children. The NCR work was presented at two international conferences (AORTIC 2017, Kigali, Rwanda and CROI 2018, in Boston, Massachusetts, USA) as oral, poster and themed discussion presentations.

The NCR furthermore continued to build cancer epidemiology capacity, by conducting lectures at local universities and providing supervision and mentorship of nine Masters and three PhD students. One of our researchers was awarded a Thuthuka research grant by the NRF.

SURVEILLANCE PROGRAMMES

Pathology-based cancer registry

In the year under review, the pathology-based cancer registry data for the years 2013 and 2014 was cleaned and analysed. The main challenges were data extraction errors from the CDW and incompatibility of the old NCR application with the new Windows 2016 operating system.

This was counteracted through the development of a new NCR application by the NICD IT, that allows efficient coding and real-time tracking of coding targets. The NICD IT division was able to load the outstanding 2015 data in the last quarter of the financial year and coding is underway. Two NCR coders who were previously employed on grants were permanently employed, and one additional coder was appointed.

EPBCR

Nine surveillance officers were placed at private and public hospitals in Ekurhuleni district and collected and captured population-based cancer data for the year 2017. A RedCap database was created, tested and implemented in the EPBCR, allowing for simultaneous offsite entry of data by all surveillance officers.

All NCR staff members were trained on how to use the RedCap software, which is significantly more advanced and efficient than the previous CanReg system. The EPBCR data was furthermore cleaned and ready for analysis at the end of the financial year.

Funding for year three of the EPBCR was secured from the SAMRC. There is, however, a need for surveillance officers to be funded from the NCR operational budget, as population-based cancer registration is a core function and mandate of the NCR.

RESEARCH PROJECTS

South African HIV cancer match study (SAM)

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

Within the SAM study, we are concurrently using and testing three different methods of record linkage, namely:

1. Supervised machine learning techniques that are executed by Mr Victor Olago (MSc Health Informatics Epidemiology fellow);
2. Probabilistic record linkage (PRL) by Dr Lina Bartels (ISPM Bern); and
3. Machine learning, through the use of Dedupe software by Mr Wenlong Chen.

Mr Victor Olago and Mr Wenlong Chen traveled to Switzerland for training on PRL and handling missing data. The Bern team also traveled to Johannesburg to work with the NCR linkage team. Mr Victor Olago completed pre-processing the HIV dataset for the entire country. He is currently applying supervised machine learning techniques on the data to identify records belonging to the same person.

Dr Lina Bartels is using bloom-filtered (encrypted to preserve privacy) HIV data for Gauteng Province, which will be linked to the NCR data through PRL. Mr Wenlong Chen completed de-duplicating of the entire HIV dataset within and across provinces for the whole country, using Dedupe software. He also completed linking of the entire HIV dataset to the NCR, and the data is now ready for post-processing.

Burden of cancers attributable to HIV (2004-2014) (BCAH)

The BCAH 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 and the additional cancer risk of HIV-positive people compared to HIV negative people in the era of ART.

This study is funded under the Beginner Investigator Grant for catalytic research in cancer, awarded to Dr Mazvita Sengayi. In July 2017, we recruited an MSc Cancer Epidemiology fellow, Ms Tafadzwa Dhokotera who received ethical approval to proceed with the study in November 2017. She has since completed the data cleaning and analysis and is currently preparing a manuscript for publication.

Johannesburg Cancer Case-control Study (JCS)

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

Data collection, data entry and cancer coding for the JCS was completed in 2016. Data cleaning of the JCS database and blood sample mapping of all JCS blood samples was completed in 2017. Several genetic and epidemiological studies are currently using JCS samples and data.

ERICA-SA project (breast, esophageal and cervical cancer)

The main objective of this collaborative study is to identify genetic variants which are associated with susceptibility to breast, cervical and oesophageal cancer in African cancer patients. The first shipment of DNA samples for genotyping arrived safely at Kings College London (KCL). Genotyping arrays were ordered and genotyping of the oesophageal samples is anticipated to be completed in June 2018. DNA extraction from blood samples for other cancers under study, is in progress at the SBIMB.

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, with over 300 controls and 400 cases recruited. SBIMB extracted all new DNA samples. Mr Wenlong Chen was given access to the Prostate RedCap database and will commence with data cleaning and analysis for a cohort description paper.

Genetic aetiology of inherited breast cancer in black South African women

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. The DNA samples that were sent to Mary-Claire King Lab were sequenced. Dr Fiona Baine obtained the result set and she is currently preparing a manuscript.

Genetic aetiology of eesphageal squamous cell carcinoma (OSCC)

Mr Wenlong Chen, a medical scientist at the NCR, is conducting this study for his PhD. The aim of this project is to test the hypothesis that genetic variation in the South African black population contributes significantly to the risk of OSCC. Tumour sample collection is ongoing.

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. SAFETP resident, Ms Natasha Abrahams, is conducting this study for her MPH and received ethical approval to continue in February 2018.

Breast cancer CYP loci and tamoxifen

A grant application was submitted for a new project to investigate drug metabolism of tamoxifen treatment in breast cancer.

Ovarian cancer research project

This study is a collaboration with the UCT and aims to investigate the genetic profile of ovarian cancer patients with African heritage, compared to those of European or mixed heritage. The material transfer agreement (MTA) was signed and the list of samples is being developed for analysis.

Hepatocellular carcinoma HBV miRNA

This is a collaboration with the University of KZN to explore the feasibility of circulating miRNA as a diagnostic tool for hepatocellular carcinoma in South Africa.

Pancreatic cancer research project

The NCR is collaborating with Prof Jonathan Blackburn at the UCT to investigate the "Analysis of expression profile and antigenicity of cancer-testis antigens in pancreatic adenocarcinoma." Serum samples were shared with Prof Blackburn's laboratory for analysis.

Colorectal cancer research project

This is a collaborative research project with MRC/Wits Common Epithelial Cell Cancer Research Centre, 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. Dr Mazvita Sengayi completed the data analyses and Dr Brendon Bebbington is preparing the first draft of the manuscript.

The uranium health study: an epidemiological study of uranium mineworkers

This is a collaboration between a Uranium Mine in Namibia, the University of Manchester UK, the Namibian Cancer Registry and the South African NCR. The main objective is to determine retrospectively whether there have been excess work-related specific cancer risks in the uranium mineworkers employed at a selected mine.

A specific concern in this Namibian mine arises from an unpublished cohort study report by Sitas et al (2001) indicating a possible excess cancer mortality amongst the workforce of this mine, with a possible higher incidence of brain cancer. The NCR competed the PRL between the Uranium workers' data and the NCR, and the data was shared with the University of Manchester for analysis of excess risk.

Anatomical distribution of colorectal cancer in South Africa

This is a study being conducted by an MMed surgery student, Dr Akrem Amer, at the Department of General Surgery at UCT. Historically, two-thirds of colorectal malignancies are located in the left colon and rectum. Recent studies, however, suggest a trend towards an increase of right-sided tumours. The main objective of this study is to describe the anatomic location of colorectal cancer in South Africa from 2006-2010. Ethical approval was obtained from the UCT HREC and NCR data shared with Dr Amer.

HPV-related cancers and HIV

Dr Admire Chikandiwa, a PhD student at the Wits School of Public Health is studying HPV-related cancer trends (anogenital, head and neck cancers) in the context of the HIV epidemic in South Africa. A mature draft of this manuscript is ready for submission to a selected journal.

Hepatocellular carcinoma (HCC) and hepatitis viruses

Mr Daniel Mak, a PhD student at the Hepatitis Virus Diversity Research Unit, Wits School of Clinical Medicine, studied the relationship between the hepatitis viruses and HCC in the context of HIV and other environmental factors. He also studied the national liver cancer incidence and mortality trends in the context of the increasing HIV prevalence and the introduction of hepatitis B vaccination in 1995. Both manuscripts were submitted to peer-reviewed journals and are under review.

Cervical cancer incidence and mortality in South Africa

Dr Gbenga Oluronfemi completed his Masters project on "Trends and Determinants of Incidence and Mortality of cervical Cancer in South Africa." The manuscript was reviewed by the International Journal of Cancer and was resubmitted with revisions.

Acknowledgements and collaborators

1. Prof Matthias Egger, Dr Julia Bohlius and Dr Adrian Spoerri. Institute of Social and Preventive Medicine, University of Bern, Switzerland;
2. Prof Tim Rebbeck, Harvard TH Chan School of Public Health, Harvard University, Boston, USA;
3. Prof Chris Mathew, Department of Medical & Molecular Genetics, Guy's Hospital, KCL, UK;
4. Prof Debbie Bradshaw, MRC;
5. Prof Amanda Krause and Dr Fiona Baine, Division of Human Genetics, Wits;
6. Dr Kathryn Chu and Dr Akrem Amer, Department of General Surgery, UCT;
7. Prof Raymond Agius, Prof Roseanne McNamee and Prof Richard Wakeford, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, UK;
8. Dr G von Oertzen, Rossing Uranium Limited;
9. Prof Anna Kramvis and Mr Daniel Mak, Hepatitis Virus Diversity Research Unit, Department of Internal Medicine, Wits;
10. Dr Pedro Pisa and Dr Admire Chikandiwa, Reproductive Health Institute, Wits;
11. Prof Paul Ruff and Dr Brendan Bebbington, MRC/Wits Common Epithelial Cell Carcinoma Research Centre; and
12. Dr Maureen Joffe, Developmental Pathways to Health, Wits and Wits Health Consortium.

TEACHING AND TRAINING

- Dr Elvira Singh and Dr Mazvita Sengayi continued to teach undergraduate, MPH and MSc Epidemiology students at the Wits School of Public Health;
- Ms Lactatia Motsuku gave lectures to SAFETP students on cancer surveillance and on introduction to programming with R software; and
- Ms Tafadzwa Dhokotera (cancer epidemiology MSc fellow) provided epidemiological support to the SA Expanded Programme Review on Immunization (a DoH and WHO collaborative initiative) for a week as part of the NICD team. She attended training in Pretoria before being assigned to the Western Cape for the EPI review field work in October 2017.

Professional development

- Dr Mazvita Sengayi and Dr Elvira Singh attended a workshop organised by IARC Environmental Health Unit to discuss the work that was performed on cancer and uranium contamination in South Africa in April 2017;

- Dr Mazvita Sengayi attended the Cancer Survival Methods for Cancer Registries course from 19-23 June 2017 at the International Agency for Research in Cancer (IARC) in Lyon, France;
- Ms Lactatia Motsuku (epidemiologist) joined the Software Carpentry Foundation (https://software-carpentry.org), an international network that teaches researchers analytical skills and data carpentry. Throughout the year, she attended several software carpentry instructor and online training workshops (at UCT and the University of Addis Abba, Ethiopia) and she qualified as a software data carpentry instructor in R programming. She has been using these skills to teach *"Introduction to R programming"* to SAFETP residents and for tutoring Masters students at the Wits School of Mathematical Sciences;
- Ms Lactatia Motsuku and Mr Wenlong Chen attended the QGIS course on mapping offered by the NICD;
- Mr Wenlong Chen (medical scientist) attended the Stevenage GSK Africa Open-lab face-to-face workshop, from 10-15 September 2017;
- Mr Wenlong Chen and Mr Victor Olago attended record linkage training at the University of Bern from 14– 8 August 2017,
- Mr Wenlong Chen was also trained on handling missing data at the Swiss Epidemiology Winter School in January 2018;
- The NCR team attended a Brain Dominance Course at the NICD; and
- Mr Wenlong Chen received a joint-staff appointment with the SBIMB and Wits.

Students supervised and registered during 2017/2018

Three students were registered for PhD degrees (Mr Carl Chen, Mr Daniel Mak and Dr Admire Chikwanda). Nine students registered for MSc/MPH/MMed degrees (Ms Tafadzwa Dhokotera, Mr Victor Olago, Ms Babongile Ndlovu, Dr Gbenga Olorunfemi, Ms Lerato Khoali, Ms Natasha Abraham, Dr Susan Akach, Dr Chuma Makunga and Dr Akrem Amer). Dr Gbenga Olorunfemi graduated in December 2017 with an MSc in Epidemiology (with distinction). One student, Ms Matshidiso Mohlala, was registered for a BSc Hons in Computer Science.

Honours

1. Dr Mazvita Sengayi was awarded the African Cancer Leaders Institute (ACLI) 2017 at the African Organization for Research and Training in Cancer (AORTIC 2017);
2. Dr Mazvita Sengayi was awarded the Top 5 Best Published PhD Article Award by the Swiss School of Public Health (SSPH) for 2016, at the SSPH conference held in Basel in November 2017, for her article titled "Record linkage to correct under-ascertainment of cancers in HIV cohorts: The Sinikithemba HIV clinic linkage project;"
3. Mr Wenlong Chen was awarded an NRF Thuthuka research grant for 2018;
4. Dr Gbenga Olorunfemi (MSc Epidemiology student), was awarded a certificate of excellence for the impact and health policy relevance of his Master's research report titled: "Trends and determinants of incidence and mortality of cervical cancer in South Africa 1994 – 2012" at the Wits Faculty of Health Sciences prizegiving ceremony. He was supervised by Dr Elvira Singh;
5. Ms Natasha Abrahams (SAFETP resident), was awarded the best oral presentation at the PHASA conference for her presentation titled: "Leading Cancers Among Men and Women: South Africa, 2002 – 2012;" and
6. Ms Lactatia Motsuku was awarded a Union for International Cancer Control (UICC) African Cancer Fellowship to visit the Zimbabwean Cancer Registry to receive practical training on population-based cancer registration in March 2018.

RESEARCH OUTPUTS

Top publications

1. ***E Singh, G Naidu, M Davies and J Bohlius***
   HIV-associated malignancies in children
   Curr. Opin. HIV AIDS 2017;12(1):77–83

   This review of current literature on malignancies in children with HIV concluded that ART reduces the risk of developing cancer in HIV infected children. Cancer risk remains increased in children who commence with ART at older ages or more advanced immunosuppression, as compared to children who commence with ART at younger ages and with mild immunosuppression. Commencing with ART before severe immunosuppression develops, is key to prevent cancer in HIV-infected children.

2. ***MM Sengayi, D Kielkowski, M Egger, L Dreosti and J Bohlius***
   Survival of patients with Kaposi's sarcoma in the South African antiretroviral treatment era: A retrospective cohort study
   South African Medical Journal 2017;107(10):871–6

This is a survival study of HIV-positive adults with KS who are receiving oncology care at Steve Biko Academic Hospital. This study showed that mortality was 62.7% lower (adjusted hazard ratio (HR) 0.37, 95% confidence interval (CI) 0.19 - 0.73) in the late (2009 - 2012), than in the early (2004 - 2008) ART period. We concluded that the national ART rollout programme successfully reduced KS-related mortality at an individual patient level. Should ART coverage be extended in the context of test and-treat-all, KS-associated morbidity and mortality are likely to drop even further.

3. ***E Rohner, M Sengayi, B Goeieman, P Michelow, C Firnhaber, M Maskew, & J Bohlius (2017)***
Cervical cancer risk and impact of pap-based screening in HIV-positive women on ART in Johannesburg, South Africa
International Journal of Cancer, 141(3)

This study estimated ICC incidence rates in HIV-positive women who initiated ART at the Themba Lethu Clinic (TLC) in Johannesburg, South Africa, identified risk factors for developing ICC in these women and assessed the effect of the introduction and expansion of a pap smear-based cervical cancer screening programme on ICC incidence rates. The ICC incidence rate was highest (615/100,000 pys) in women who initiated ART before cervical cancer screening became available in 04/2005 and was lowest (260/100,000 pys) in women who initiated ART from 01/2009 onwards, when the cervical cancer screening programme was implemented. ICC incidence substantially decreased after the implementation of the pap-based screening programme. The ICC risk however remained high in women who initiated ART at low CD4 cell counts.

List of publications

1. Bohlius J, IeDEA AICPWG for, EuroCoord C in. Comparison of Kaposi sarcoma risk in HIV-positive adults across five continents: a multiregional multicohort study. Clin. Infect. Dis. 2017;20(October):20.
2. Rohner E, Sengayi M, Goeieman B, Michelow P, Firnhaber C, Maskew M, & Bohlius J. (2017). Cervical cancer risk and impact of Pap-based screening in HIV-positive women on antiretroviral therapy in Johannesburg, South Africa. International Journal of Cancer, 141(3).
3. Sengayi MM, Kielkowski D, Egger M, Dreosti L, Bohlius J. Survival of patients with Kaposi's sarcoma in the South African antiretroviral treatment era: A retrospective cohort study. S Afr Med J 2017;107(10):871–6.
4. Singh E, Naidu G, Davies M, Bohlius J. HIV-associated malignancies in children. Curr. Opin. HIV AIDS 2017;12(1):77–83.
5. York K, Dlova NC, Wright CY, Khumalo NP, Kellett PE, Kassanjee R, et al. Primary cutaneous malignancies in the Northern Cape Province of South Africa: A retrospective histopathological review. S Afr Med J 2017;107(1):83–8.
6. Sartorius k, Sartorius B *et al.* Circulating microRNA's as a diagnostic tool for hepatocellular carcinoma in a hyperendemic HIV setting, Kwa-Zulu Natal, South Africa: a case-control study protocol focusing on viral aetiology. BMC Cancer 2017; 17:894.

Conferences

- International: 7 oral presentations and 4 poster presentations
  Local: 2 oral presentations

Division of Public Health Surveillance and Response

Dr Kerrigan McCarthy

BACKGROUND

The Division of Public Health Surveillance and Response (DPHSR) includes the GERMS-SA surveillance programme, the Epidemiology Support Unit (responsible for provincial epidemiology support and the national NMC) and the Outbreak Response Unit (responsible for the Emergency Operations Centre). Together, these three units contribute significantly to national communicable disease surveillance and response efforts. The activities of these units furthermore support the surveillance and research activities of all the NICD centres.

Signatory countries were requested to host a 'Joint External Evaluation' (JEE) of adherence to requirements of the IHR in November 2017, which included activities to support prevention, detection and response to communicable disease, chemical and radiation events. The NICD contributed through capacity building for communicable disease diagnostics, disease surveillance and technical support for response activities to fulfil and support numerous requirements of the IHR.

The NICD Emergency Operations Centre (EOC) supported by the ORU, is able to coordinate and manage public health events of national and regional concern, through the use of an incident management system and dedicated staff. Because of this capability, the NICD is also a key role-player in national, regional and international responses to public health threats.

The DPHSR collaborates and cooperates with the NDoH, the National Disaster Management Centre, the National Joint Operations Committee in support of the IHR. Disease intelligence emanating from the NICD surveillance activities, is reported regularly through the Multinational Outbreak Response Team (MNORT), and to other government structures as the need arises.

At a national level, the technical expertise of the NICD is made available to provinces and districts within South Africa through multiple arms of the DPHSR, as follows:

- Provincial epidemiologists are based in the provinces and support analysis of routine TB and HIV data, outbreak investigation and interpretation of communicable disease data;
- NMC alerts triggered by the NHLS laboratory information system and clinicians in public sector health facilities, ensure that district and provincial communicable disease staff are timeously informed about the presence of disease;
- The ORU staff provide support for appropriate public health interventions on request and in response to NMC alerts; and
- The 24-hour hotline staffed by NICD pathologists and doctors and coordinated by the DPHSR, provides a forum for rapid alert and notification of disease of public health importance, as well as technical advice for a range of infectious conditions.

The year ending 31 March 2018 was marked by significant strengthening of the DPHSR's contributions in the above areas, notably the NMC surveillance system and the growth in experience and reach of the EOC. The foundational role of the GERMS-SA surveillance programme remains pivotal to the NICD's capacity to provide communicable disease surveillance.

GROUP FOR ENTERIC RESPIRATORY AND MENINGITIS SURVEILLANCE, SOUTH AFRICA (GERMS-SA)

Dr Vanessa Quan

The GERMS-SA surveillance programme is coordinated by a core team within the division and works closely with the NICD centres to implement both laboratory-based and enhanced surveillance systems.

The laboratory surveillance pathogens include: *Candida spp, Salmonella* Typhi, *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus, carbapenem-* resistant *Enterobacteriaceae* (CRE), *Acinetobacter baumannii and Cryptococcus spp.* as well as outbreak-related *Salmonella* non-Typhi, *Shigella spp, Vibrio cholerae, Listeria monocytogenes, Campylobacter spp, enterohaemorrhagic E.coli* and *diarrheoagenic E.coli.*

GERMS-SA is an active surveillance programme and not only relies on participating laboratories to submit isolates, but also makes use of the NHLS CDW to ensure that all cases that meet the case definition are included in the database.

Annually, approximately 250 laboratories (NHLS and private) perform cultures on cerebrospinal fluid and blood send specimens for the NICD centres. These laboratories contribute approximately 18 500 cases of communicable diseases to the GERMS-SA database, that meet the GERMS-SA case definitions. With this network, an enhanced surveillance arm is operational at 25 sentinel public sector sites across the country.

As part of enhanced surveillance, nurse surveillance officers collect clinical information on patients relating to specific pathogens where additional clinical and outcome data are required to support centre outputs. This includes invasive *S. pneumoniae, H. influenzae, N. meningitidis, Salmonella* Typhi*; S. aureus, CREs and Candida spp bacteraemia; Cryptococcus spp***,** rifampicin-resistant- and susceptible TB.

GERMS-SA, together with the NICD centres, continues to use data collected through surveillance, to inform and guide public health policymakers in their decisions. The objectives include:

- Estimating the burden of both community- and hospital-acquired infectious diseases under surveillance;
- Monitoring antimicrobial susceptibility trends;
- Monitoring the impact of treatment on HIV-associated opportunistic infections; and;
- Evaluating the impact of vaccines included in the Expanded Programme on Immunisation (EPI).

GERMS-SA's work is funded through the NICD/DoH.

TB surveillance

In the context of improved diagnostic tests and treatment modalities and new national guidelines, some amendments to TB surveillance were implemented in the first quarter of 2018. Enhanced surveillance for RR TB, that was conducted to monitor the molecular epidemiology of TB in selected districts and detect transmission clusters, was discontinued at the end of 2017. A new isolate-based approach will allow for expansion of the activity to more districts.

Clinic-based rifampicin-susceptible TB surveillance, conducted at a facility in KZN and Gauteng in 2017, will largely be discontinued and replaced by hospital-based surveillance in selected provinces including Gauteng and North West (initiated in 2017), Mpumalanga and KZN (commenced in 2018) and the Eastern Cape. The surveillance will focus on isoniazid mono-resistance and issues around patient health seeking behaviour and household contact tracing.

GERMS-SA clinic-based surveillance (STI and HIV)

In 2017, HIV drug-resistance surveillance in patients initiating ART was conducted in two facilities in KZN and in a facility in Free State and in Mpumalanga. GERMS-SA staff also assisted with a paediatric HIV drug resistance survey conducted by the Centre for STI and HIV.

GERMS-SA continue to support STI surveillance to monitor aetiology of STIs as well as Neisseria gonorrhoea antimicrobial resistance. Surveillance of Human Papilloma Virus among young women attending family planning services, was also included. Surveillance was conducted in KZN, Free State and Western Cape in 2017 and initiated in Northern Cape in 2018.

Acute febrile illness surveillance for zoonoses

The acute febrile illness surveillance project continues at one clinic site in rural Mpumalanga. The Mnisi area is bordered by the Kruger National Park and contact between wildlife, livestock and humans is frequent. This surveillance is a One Health project and takes place in collaboration with veterinary practitioners and researchers from the Veterinary Faculty at UP.

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 perform a malaria test. Laboratory testing includes PCR and serology for brucellosis, Bartonella infections, leptospirosis, Q-fever, tick bite fever, West Nile virus, Sindbis, RVF and chikungunya virus infections. Study data published show a high seroprevalence of tick bite fever, Q-fever and leptospirosis, parallel to significant exposure at the human/animal interface.

EPIDEMIOLOGY AND SURVEILLANCE UNIT

Dr Portia Mutevedzi

Notifiable Medical Conditions Surveillance System (NMCSS)

In keeping with the requirements of the IHR, every signatory country is required to implement a real-time surveillance system for communicable diseases to enable timely implementation of interventions for disease control.

Such national surveillance entails a list of legislated outbreak and/or epidemic prone diseases named "notifiable medical conditions" (NMC), that must be closely monitored and reported to health authorities, the moment it is detected. In December 2017, South Africa updated its regulations governing the surveillance and control of NMC to align it with the National Health Act and the IHR.

Since 2015, the NICD has been responsible for managing the national NMCSS on behalf of the NDoH. Rapid and accurate detection followed by notification of NMC such as tuberculosis, listeriosis, measles, typhoid and malaria create opportunities for timely and effective interventions to prevent local, regional and international disease outbreaks.

Category 1 NMCs must be reported within 24 hours of detecting a case. Recent measles, typhoid and listeriosis outbreaks in South Africa emphasized the need to strengthen the NMC surveillance. To this end, the NICD, in partnership with national and provincial health departments, developed and implemented an integrated and simple NMC national surveillance system that allows for rapid detection and notification of NMC. This new system comprises a mobile and web APP, as well as an improved paper-based notification system for use in areas with no connectivity/network.

Since taking over the national NMC surveillance responsibilities, the NICD has achieved the following:

1. Development and adoption of a national NMC surveillance strategy in close consultation with all relevant stakeholders;
2. Updating of the recently gazetted regulations pertaining to the surveillance and control of NMC;
3. Assessment of the old NMC notification process at facility, district and provincial level; to determine NMC surveillance best practice within the South African context;
4. Development and implementation of new NMC surveillance system (NMCSS) tools and systems for paper-based reporting, including:
    a. A standardised NMC case notification form;
    b. Standardised case definitions, operating procedures, guidelines and flowcharts; and
    c. Integration of laboratory and clinical notification streams.
5. Development and implementation of an electronic real-time reporting NMC APP;
6. Appointment of NMC surveillance trainers who are deployed in each of the nine provinces to provide facility-based, ongoing training on NMC surveillance. To date over 10 000 healthcare and diseases control personnel across approximately 1000 health facilities have been trained on the new NMC surveillance system, processes and procedures; and
7. Extensive stakeholder engagement and creation of awareness in both the public and private health sectors.

The new NMC APP enables real-time notification of NMC at the point of diagnosis, with built-in SMS and email alerts and feedback channels. In practise, this means that nurses and doctors can use the APP to report NMC almost immediately after diagnosis via their mobile gadgets. As soon as the case is logged on the NMC APP, information is transmitted to all relevant disease control personnel at local, provincial and national levels, via SMS and email.

This rapid transmission of information, facilitates timely disease control interventions and provides a platform for communication between and across sectors for a coordinated response. In addition, this new system utilises various data sources, including data from laboratories and medical schemes, to holistically identify and address all NMC.

The APP has a reports dashboard that provides statistics of disease burden and trends. Use of the APP is free of charge and it has an offline mode to enable cases to be logged in areas where there is intermittent connectivity/network. Data is automatically transmitted, as soon as connectivity is restored. The APP was implemented at the end of March 2018 and at the time of reporting, national rollout has commenced, and will be completed over a six- to nine-month period.

A new paper-based notification system was furthermore launched in August 2017 to strengthen notifications in regions where there is no connectivity to utilise the electronic platform. Comprehensive standard operating procedures and case definitions were developed to assist nurses and doctors to notify correctly and in a uniform manner.

From the date of launch of this new system until the end of March 2018, 4 905 notifications have been received. The top ten notifications include malaria, TB (pulmonary and extra-pulmonary), measles, hepatitis A and B, listeriosis, foodborne illness outbreaks, bilharzia and pertussis.

Evidence shows that the new NMC system has enabled more rapid notification of outbreak prone diseases by both the public and private sector. This has in turn enabled us to detect public health risks sooner and implement effective interventions for disease control timeously. For more information about the system, visit www.nicd.ac.za (NMC page).

Provincial epidemiology team (PET)

Epidemiologists play a key role in the assessment of disease burden and health needs of a population, designing interventions to improve the health of that population and evaluating the effectiveness of interventions to inform future public health practice

A key recommendation from the JEE assessment in South Africa, which was similar to recommendations to other African countries, was to fast-track the development of epidemiology expertise and to define a clear career trajectory within the public service.

Since 2014, the NICD has made significant strides to address this gap, through increasing access to epidemiology expertise across South Africa by placing an epidemiologist in each of the nine provinces of South Africa, with the following objectives:

1. Utilisation of epidemiological methods to support the provinces in meeting their responsibilities of preventing and controlling the spread of infectious diseases in line with IHR requirements;
2. Contributing to the strengthening of public health epidemiology capacity in South Africa to enable better responses to public health challenges. As a way of building and strengthening the epidemiology capacity within the provinces, the provincial epidemiologists identify training needs and provide the required training and mentoring; either directly or via available structures of the NICD such as the SAFETP and centre specific training programmes; and
3. Ensuring that the NICD's core services of surveillance, outbreak response, specialist microbiology and public health research are available to the provincial departments of health in a timely, flexible and locally relevant manner.

During 2017, there were four provincial epidemiologists with an additional three epidemiologists appointed at the beginning of 2018. Recruitment efforts are underway to provide epidemiology support to Northern Cape and Mpumalanga provinces.

To date, provincial epidemiologists together with the NICD Centres, have played a pivotal role in strengthening surveillance of infectious diseases through routine analyses of surveillance data to identify and address any deficiencies in data collection and collation.

Additionally, results from such data analyses are utilised to assist disease programme managers to identify and implement interventions to improve programme performance within the set national, provincial and district strategic plans.

In support of the National Strategic Plan for HIV, TB and STIs 2017-2022, the PET provides epidemiological support for prompt linkage of laboratory diagnosed drug-resistant TB and EID of HIV, using PCR. Results from epidemiological analyses of TB data data identified TB hotspots and high-risk groups in Eastern Cape and KZN.

In the Eastern Cape, the provincial epidemiologist developed a quarterly TB bulletin that highlights TB burden and TB programme performance. In Gauteng, the Genexpert-diagnosed RR TB data was analysed to determine the treatment uptake of patients diagnosed in 2017 and the reasons for non-initiation of treatment.

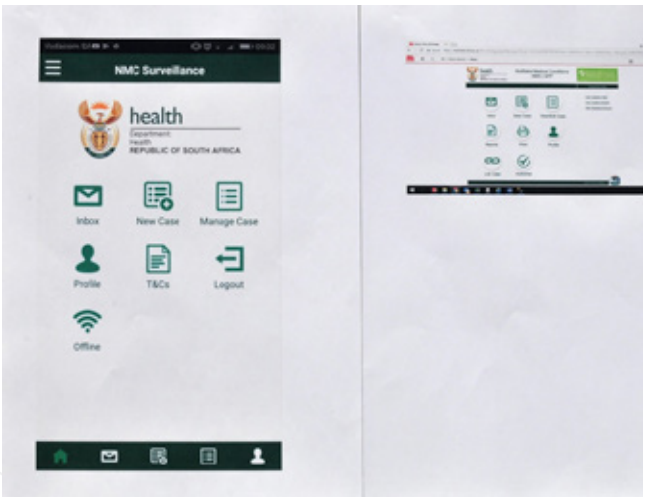
Pertaining to outbreak response, the provincial epidemiologists play a vital role in ensuring thoroughness of case investigations, contact tracing, mapping of cases, data analysis and report writing. The significance of their contributions has been evident in:

- The measles outbreaks in the Western Cape and Gauteng;
- The malaria outbreak in Limpopo;

- The diphtheria cases and typhoid clusters in the Western Cape;
- The human rabies cases in Eastern Cape and Free State;
- The typhoid outbreak in Limpopo;
- Several food-borne outbreaks across all provinces; and
- The ongoing listeria outbreak.

Over the last year, the PET contributed to the following activities and initiatives:

- The PET participated in the WHO-led comprehensive national EPI review, which was integrated with data quality, effective vaccine management and in-depth surveillance across all provinces from 30 October – 10 November 2017;
- The PET assisted with preparations for the extraordinary JEE of the IHR, 2005 by the WHO;
- The PET are members of the provincial specific AMR Stewardship Committees where they fulfil a key role in supporting analysis and interpretation of AMR data;
- The Gauteng epidemiologist conducted a detailed analysis of the epidemiology of malaria over a two-year cycle;
- The epidemiologist in Limpopo assessed trends in measles and rubella; and
- The PET supported the implementation of the new NMC surveillance system across all the provinces.



OUTBREAK RESPONSE UNIT

The ORU provides technical support for all aspects of communicable disease outbreaks and control in South Africa. Through close collaboration with provincial and national DoHs 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 as 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 meeting, and report on surveillance and outbreak investigation activities.

The ORU coordinates 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 healthcare workers who require emergency information pertaining to the post-exposure management of rabies and other infectious diseases;
- Requests and advice for diagnostic tests for suspected epidemic-prone diseases; and
- Technical advice regarding the management of cases of infectious disease.

The ORU continues to publish the monthly Communicable Diseases Communiqué, which reports recent outbreaks and communicable disease cases/issues of relevance. This is distributed to a wide audience, including general practitioners, specialists, infectious diseases and travel medicine societies, and national and provincial public health personnel. In addition, the unit published special urgent advisories and communiqués in response to acute events that required immediate dissemination of information.

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

- A measles outbreak occurred among a cluster of high schools in the Cape Winelands District in the Western Cape Province from January - March 2017. The outbreak was contained through rapid implementation of a school vaccination campaign, followed by district and provincial campaigns targeting children under 15 and under 5 years of age respectively;
- A measles outbreak occurred amongst predominantly vaccine-hesitant persons in the West Rand District in Gauteng Province from April - June 2017. This was managed through a province-wide vaccination campaign amongst children under 5 years of age;
- An upsurge in malaria cases occurred in the Mopani and Vhembe Districts of Limpopo Province in the month of April 2017, soon after the Easter long weekend during which there was increased travel within South Africa and to adjacent malaria-endemic countries;
- The NICD ORU and CRDM conducted screening of persons including farm workers and veterinarians who were exposed to poultry infected with the avian influenza H5N8 virus in July 2017. In addition, the NICD supported the promotion of health and risk communication activities to create awareness on avian influenza among the general public;
- A diphtheria outbreak occurred in the Cape Town Metropolitan District in August 2017 when four laboratory-confirmed cases of diphtheria and one asymptomatic carrier of toxin-producing Corynebacterium diphtheriae were identified. The outbreak was followed by a vaccination campaign targeting six to 12-year old children in the community;
- The listeriosis outbreak was recognised by the NICD ORU in August 2017. The EOC was activated in response;
- The ORU supported the NDoH through activities for plague preparedness during the outbreak of plague in Madagascar from September - December 2017. ORU staff assisted with investigation of a traveller who returned from Madagascar and contracted plague while attending a basketball tournament in Antananarivo;
- An outbreak of *Streptococcus pyogenes* in a long-term residential care facility in Gauteng Province that resulted in three deaths was contained through provision of antibiotic post-exposure, infection control advice, and monitoring of care-workers' carriage status;
- A foodborne illness that affected 94 students at a university residence in Johannesburg over the December 2017 exam period, was investigated. *Salmonella* species was found in the stool of affected students, in food and in the stool of a kitchen worker who developed gastro-enteritis a few days prior to the outbreak. Molecular testing indicated that all *Salmonella* strains were identical, suggesting that the healthcare worker may have been the origin of the outbreak;

- A measles outbreak was declared in KZN from August 2017 - January 2018, which predominantly occurred amongst vaccine hesitant communities in eThekwini and Pietermaritzburg;
- An outbreak of skin abscesses among workers at a mine in Gauteng Province was investigated by CHARM, and it was found to be caused by *Staphylococcus aureus*;
- An increase in pertussis cases in the Western Cape Province was identified through surveillance activities. The CRDM and ORU supported diagnostics, provision of case-report forms and clinical guidelines;
- The ORU and CVI supported the Western Cape Provincial DoH to respond to a case of vaccine-derived polio virus type 3 that occurred in a 3-month old infant with an inherited immunodeficiency. Response activities included obtaining stool samples from community members, a localised vaccine-coverage survey and intensified district surveillance for AFP;
- A single cholera case was reported from Umkhanyakude District in KZN province. The NICD provided supported through case investigations and response that included enhanced district surveillance, health promotion and strengthened laboratory diagnostics;
- A typhoid fever outbreak involving 122 suspected cases and seven laboratory-confirmed cases was reported and investigated in Sekhukhune District in Limpopo Province. The outbreak was found to be associated with contaminated water sourced by the residents in the district from irrigation furrows; and
- A cluster of 17 hepatitis A cases was identified in the Hessequa sub-district in the Western Cape Province. The source of the outbreak is still under investigation.

EMERGENCY OPERATIONS CENTRE

Nevashan Govender

On 27 February 2017, the Emergency Operations Centre (EOC) was activated by the Director-General of the NDoH for a non-public health emergency to facilitate the relocation of former Life Esidimeni mental healthcare users (MHCU) from non-governmental organisations - to appropriate care facilities identified by the GDoH. A project management team, drawn from the NICD EOC, NDoH and GDoH staff, used the EOC IMS to plan and execute the safe, humane and compassionate relocation of 751 MHCUs within 38 working days. This first activation of the EOC provided an opportunity to apply and review the policies and procedures.

On 5 December 2017, the Minister of Health, Dr Aaron Motsoaledi, announced that an outbreak of listeriosis was underway. This followed investigations by the NICD into an increase in laboratory-confirmed cases of listeriosis which was reported in July 2017. Prior to 2017, an average of 60-80 laboratory-confirmed listeriosis cases per year, were reported in South Africa, but listeriosis was not notifiable until 15 December 2017. The EOC was activated on 5 December 2017 to facilitate coordination of multisectoral investigations to establish the source.

Food from the homes of persons with laboratory-confirmed listeriosis was submitted for culture of *Listeria monocytogenes*, and if isolated, sent for WGS at the NICD. The source of the outbreak was identified as ready-to-eat processed meat products manufactured at Enterprise Foods' Polokwane production facility. Following an announcement by the Minister of Health on 5 March 2018, a recall of affected products was initiated.

On 28 March 2018, the WHO regraded the outbreak to grade 2 on account of the risk to South Africa's international trade partners. Subsequently, the WHO commenced with support for activities aimed at controlling and ending the outbreak, and strengthening systems to prevent future outbreaks.

A team of technical experts in the field of risk communication, EOC management, food safety, incident management and epidemiology was seconded to work with the NICD EOC and South African government officials to develop and implement a project plan. The EOC played an active role in submission of responses to the JEE, and in presenting EOC activities to the evaluation team in November 2017.

RESEARCH AND SPECIAL PROJECTS

G Ntshoe, E Webb, K McCarthy and N Page

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

This project entails the development, pilot implementation and evaluation of an mHealth application to track and manage foodborne illness outbreaks. The application will be developed following a comprehensive review of the role of mHealth applications in the context of outbreaks. The application will integrate with the NMC software that is currently being rolled out by the NICD. Feasibility, user-friendliness and acceptability will be assessed by district staff before and after the pilot implementation. A cost-effectiveness evaluation will also be conducted after the piloting of the application.

Representation on committees and advisory groups

Prof Blumberg serves on the:

- WHO Scientific Advisory Group for the Blueprint on Research and Development Preparedness for Emerging Pathogens, which conducted the following activities:
  - Prioritisation of emerging diseases for preparedness planning;
  - Research and development pertaining to vaccines and therapy; and
  - Developing of funding opportunities to support preparedness activities.
- WHO IHR Emergency Committee pertaining to EVD, which was responsible for declaration and rescinding the status of 'Public Health Emergency of International Concern' in respect of the Ebola virus outbreak in West Africa; and
- 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 haemorraghic fevers.

She was also eleted as:

- Chair of the WHO Scientific and Technical Advisory Group on Yellow Fever Risk Mapping; and
- A member of the Strategic Advisory Group of Experts on Immunisation working group on rabies vaccines and immunoglobulins.

Dr Kerrigan McCarthy is a member of:

- The Global Outbreak Alert and Response Network (GOARN) of the WHO;
- The South African National Immunisation Safety Committee (NISEC); and
- The Technical Working Group for Diarrhoeal Diseases.

TRAVEL HEALTH

The Travel Health Unit fulfils the following critical functions:

- Provides a consultative service for health practitioners regarding pre-travel advice for travellers and clinical consultations for returning travellers with suspected infectious diseases;
- Develops guidelines for a number of travel-related diseases and neglected diseases;
- Serves as a point of contact and liaison internationally for infectious diseases acquired in Southern Africa; and
- Assists 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, brought about by the interactions between animal and human health and the environment. The unit was recently accepted as a Geosentinal Programme member. This programme includes 64 global sites that monitor imported infectious diseases in business and leisure travellers, as well as migrants and displaced persons.

South African National Travel Health Network (SaNTHNet) – http://www.santhnet.co.za

SaNTHNet is a travel health network run by the DoH, the NICD and the South African Society of Travel Medicine (SASTM). SaNTHNet provides up-to-date information on health risks for travel in the Southern African region, with a primary South African focus by developing and providing guidelines on communicable diseases and up-to-date information on disease outbreaks.

An informative website was developed, which attracts over 5 000 visits a month, a significant number of which are of international origin. The network will focus on developing further guidelines around travel-related health matters and will serve as a surveillance platform to gather information around imported communicable diseases, e.g. dengue, trypanosomiasis and leishmaniasis, as well as expert advice on diagnosis and management of tropical and travel-related diseases. The unit also manages a supply of essential drugs for a selection of tropical and neglected diseases, e.g., leishmaniasis, trypanosomiasis and severe malaria.

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 has now become part of the WHO Mass Gatherings CC Network, which includes:

- The Disaster Research Centre, Flinders University, Australia;
- The PHE, UK;
- The NICD, South Africa;
- The Institute of Public Health of Vojvodina, Serbia;
- The School of Public Health, University of Washington, USA; and
- The Ministry of Health, Saudi Arabia.

TEACHING AND TRAINING

Staff of the DPHSR delivered lectures for training activities related to communicable diseases for the national and provincial DoHs to under- and postgraduate students of:

- Wits (School of Public Health, Departments of Medicine, Obstetrics and Gynaecology, Community and Family Medicine, Diploma in Tropical Medicine and Hygiene),
- UP, Onderstepoort Veterinary Institute;
- North-West University (School of Pharmacology); and
- University of Stellenbosch (Department of Medicine).

The unit collectively supervised 15 FETP residents and four public health registrars from the Universities of Witwatersrand and Pretoria on rotation through the unit.

Professional development

Dr Kerrigan McCarthy, Joy Ebonwu (Wits School of Public Health), and Genevie Ntshoe (UP) are registered for PhDs.

RESEARCH OUTPUTS

Publications

1. Benson FG, Musekiwa A, Blumberg L, Rispel LC. Comparing laboratory surveillance with the notifiable diseases surveillance system in South Africa. Int J Infect Dis. 2017 Jun; 59:141-147. doi: 10.1016/j.ijid.2017.03.007. Epub 2017 May 19.
2. Book Chapter: Infectious Diseases: A Geographical Guide, Second Edition. Edited by Petersen, Chen and Schlagenhauf. Chapter 11: Southern Africa; Mendelson M, Perovic O and Blumberg L.
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24. Prof Blumberg was appointed as one of the editors for the Oxford Handbook of Tropical Medicine 5e (November 2017).

NICD publications

1. Monthly NICD Communiqué;
2. Quarterly NICD Communicable Diseases Surveillance Bulletin;
3. Surveillance Officer Monthly Communiqué;
4. Monthly NICD Surveillance Report;
5. Monthly MNORT Reports;
6. Quarterly GERMS-SA ESSORs, Provincial Statistics and PEPFAR Report; and
7. Quarterly Pertussis Surveillance Project Progress Report to Sanofi Pasteur.

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RP252/2018
ISBN: 978-0-621-45701-8