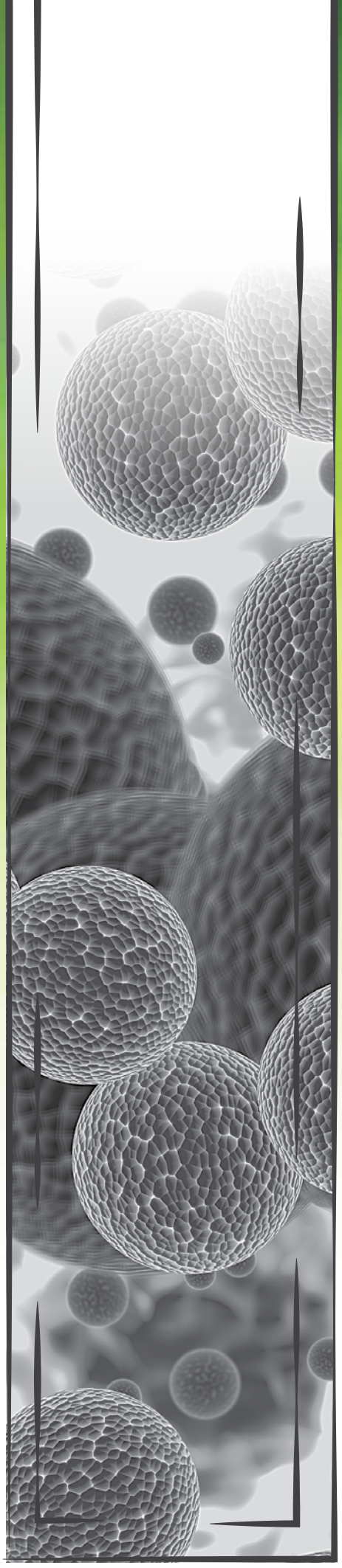
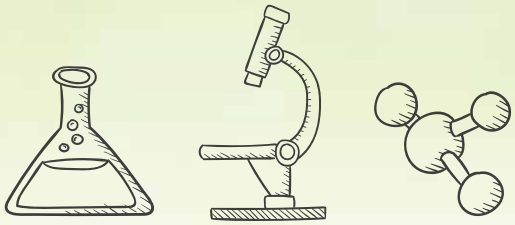




National Institute for Communicable Diseases Annual Overview

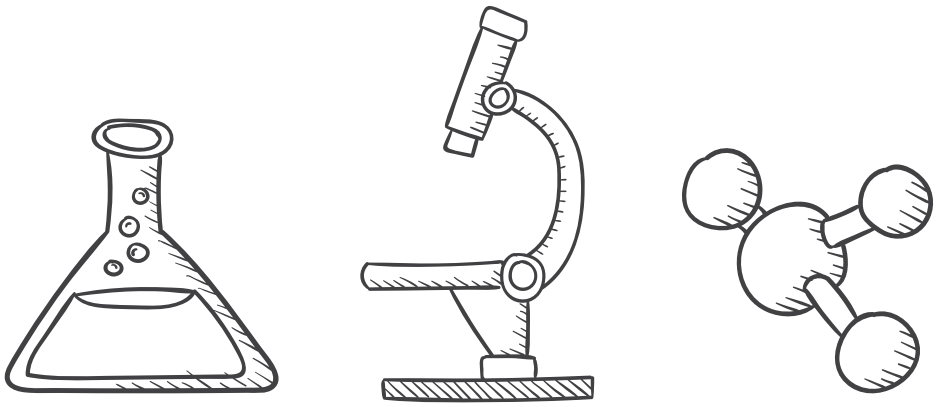
2014/15

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Division of the National Health Laboratory Service

National Institute for Communicable Diseases (NICD)

The National Institute for Communicable Diseases (NICD) is responsible for surveillance of communicable diseases and is a vital resource of knowledge and expertise in communicable diseases intelligence in South Africa.



National Institute for Communicable Diseases Annual Overview

2014/15

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Division of the National Health Laboratory Service

Contents

List of **Abbreviations**

AF	Attributable Fraction
AFI	Acute Febrile Illness
AMR	Antimicrobial Resistance
AMRRL	Antimicrobial Resistance Reference Laboratory
ANISE	African Network for Influenza Surveillance and Epidemiology
ART	Antiretroviral Treatment
ARV	Anti-retroviral
AS-PCR	Allele-specific Polymerase Chain Reaction
BIGS	Bacterial Isolate Genome Sequence
BV	Bacterial Vaginosis
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CDC	Centres for Disease Control and Prevention
CDR	Complementarity-determining Region
CDW	Corporate Data Warehouse
CED	Centre for Enteric Diseases
CEZD	Centre for Emerging and Zoonotic Diseases
CGE	Centre for Genomic Epidemiology
CI	Confidence Interval
cnl	Capsule Null Locus
CM	Cryptococcal Meningitis
CRDM	Centre for Respiratory Diseases and Meningitis
CrAg	Cryptoccal Antigen
CRS	Congenital Rubella Syndrome
CTB	Centre for Tuberculosis
DAFF	Department of Agriculture, Forestry and Fisheries
DGHP	Division of Global Health Protection
DoH	Department of Health
DRC	Democratic Republic of Congo
DRS	Drug Resistant Survey
DST	Department of Science and Technology
DTM&H	Diploma in Tropical Medicine and Hygiene
EC	Elite Controller
EDR	Electronic Drug Resistance Registries
EFV	Efavirenz
EID	Early Infant Diagnosis
EOC	Emergency Operations Centre
EML	Ebola Mobile Laboratory
eMTCT	Elimination of Mother-to-Child Transmission
EPI	Expanded Programme of Immunisation
ESBL	Extended-spectrum Beta-lactamase
ETR	Etravirine
EVD	Ebola Virus Disease
FELTP	Field Epidemiology and Laboratory Training Programme
FIND	Foundation for New and Innovative Diagnostics

GALT	Gut Associated Lymphoid Tissue
GUS	Genital Ulceration Syndrome
HAdV	Human adenovirus
HBoV	Human bocavirus
Hep	Hepatitis
Hib CV	Haemophilus Influenza Serotype B Conjugate Vaccine
HIPSS	HIV Incidence Provincial Surveillance System
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HVTN	HIV Vaccine Trial Network
IAEA	International Atomic Energy Agency
ILI	Influenza-like Illness
IMD	Invasive Meningococcal Disease
IMGT	International Immunogenetics Database
IQC	Internal Quality Control
KNP	Kruger National Park
KZN	KwaZulu-Natal
LARS	Laboratory-based Antimicrobial Resistance Surveillance
LRTI	Lower Respiratory Tract Infection
MARV	Marburg Virus
MDR	Multi-drug Resistant
MG	Mass Gatherings
MIC	Minimum Inhibitory Concentration
MIRU	Mycobacterial Interspersed Repetitive Unit
MLST	Multi-locus Sequence Typing
MLVA	Multi-locus Variable Tandem Repeat Analysis
MNORT	Multisectoral National Outbreak Response Team
mPTB	Microbiologically Confirmed Pulmonary Tuberculosis
MSM	Men-who-have-sex-with-men
MUS	Male Urethritis Syndrome
NATHOC	National Health Operations Centre
NCC	Null Capsule Clade
NEC	Necrotising Enterocolitis
Necsa	National Energy Commission of South Africa
NHLS	National Health Laboratory Service
NIC	National Influenza Centre of the WHO
NICD	National Institute for Communicable Diseases
NICU	Neonatal Intensive Care Unit
NNRTI	Nonnucleoside Reverse Transcriptase Inhibitor
NRF	National Research Foundation
NTBRL	National TB Reference Laboratory
NTP	National TB Control Programme
NTPn	Non-typable
NVP	Nevirapine
OR	Odds Ratio
ORU	Outbreak Response Unit
PCP	Pneumocystis Jirovecii Pnuemonia

PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccines
PEPFAR	President's Emergency Plan for AIDS Relief
PET	Provincial Epidemiology Team
PHASA	Public Health Association of South Africa
PHC	Primary Health Care
PMTCT	Prevention of Mother-to-Child Transmission
PTBr	Pulmonary TB
RAPIDD	Research and Policy for Infectious Disease Dynamics
RCCH	Red Cross War Memorial Children's Hospital
RFLP	Restriction Fragment Length Polymorphism
RITA	Recent Infection Testing Algorithm
RMPRU	Respiratory and Meningeal Pathogens Research Unit
RR	Rifampicin Resistant
RPV	Rilpvirine
RSV	Respiratory Syncytial Virus
RTD	Rapid Test Device
SABA	South African Biorisk Association
SACIDS	Southern African Centre for Infectious Disease
SADC	Southern African Development Community
SAFETP	South African Field Epidemiology Training Programme
SAMEC	South African Malaria Elimination Committee
SANAS	South African National Accreditation System
SaNTHNeT	South African National Travel Health Network
SAR	Secondary Attack Rate
SARGDDC	South African Regional Global Disease Detection Centre
SASTM	South African Society of Travel Medicine
SARI	Severe Acute Respiratory Infections/Illness
s.c.	Subcutaneous
ST	Sequence Type
SIT	Sterile Insect Technique
STI	Sexually Transmitted Infection
TAC	Taqman® Array Card
TB	Tuberculosis
TBF	Tick Bite Fever
TDR	Transmitted HIV Drug Resistance
TRI	Tests for Recent Infections
UCL	University College London
VDPV	Vaccine-Derived Poliovirus
VDS	Vaginal Discharge Unit
VIB	Viral Inclusion Body
VNTR	Variable Number Tandem Repeats
VP-IBD	Vaccine-Preventable Invasive Bacterial Diseases
WASAVA	World Small Animal Veterinary Association
WHO	World Health Organization
WGS	Whole Genome Sequencing
WPV1	Wild Poliovirus Type 1
XDR	Extensively Drug-Resistant

NICD
Director's Overview

Executive Director: Prof. Shabir A Madhi

> The public health-oriented and surveillance undertaken by the NICD continues to inform policy and measure the investment being made in health in South Africa

The year 2014/15 witnessed one of the most severe outbreaks of Ebola virus haemorrhagic fever ever recorded. In addition to the human toll which was exacted in the three most affected west African countries, the economies of these countries and whatever healthcare services had existed were negatively affected. A major lesson from this outbreak, which many governments in low–middle income countries have ignored at their own peril, is the need for functional healthcare systems, adequate laboratory infrastructure and robust surveillance structures. Albeit, somewhat delayed, the mobilisation of resources by the global community eventually saw the Ebola outbreak brought under control. A key intervention in controlling the epidemic was the establishment of laboratory infrastructure to timeously detect cases to inform patient management and contact-tracing.

The National Institute for Communicable Diseases (NICD) Centre for Emerging and Zoonotic Diseases was among the first of any groups which deployed laboratory teams and laboratory equipment to assist in the control of the epidemic in Sierra Leone. This was achievable, largely because of the investment made in South Africa, despite it being at low risk for large outbreaks of viral haemorrhagic fever, in establishing adequate laboratory infrastructure, including the only fixed structure Biosafety Level 4 laboratory facility in Africa. Notably, the funding of the expensive laboratory capabilities in South Africa is independent of donor funding, hence ensuring its sustainability. The mission of the NICD in Sierra Leone also included capacity development and training of local staff, which eventually culminated in the handover of the laboratory facility established by the NICD to the people of Sierra Leone for their ongoing benefit.

The contribution of the NICD team to the people of Sierra Leone was acknowledged by the many visitors, including government officials in the country, World Health Organization (WHO) representatives and the South African parliament itself. It is at times such as these that the selflessness and dedication of the staff at the NICD is truly appreciated and deserves the recognition bestowed on them. Their efforts have further elevated the standing of the NICD as an important public health resource in South Africa and in support of other African countries.

The year also saw a number of other positive developments at the NICD. Included among these was the announcement by the Minister of Finance and the Minister of Health that, effective from 2015/16, the NICD will be funded directly by the Department of Health, albeit remaining under the legal framework of the National Health Laboratory Service (NHLS). Included in this funding is a clear mandate for the NICD to take on a greater role in contributing and safeguarding the health of South Africans. To this effect, the NICD was tasked with developing the first Emergency Operation Centre hub in South Africa, which in future will serve as a focal point for the management of large and dangerous communicable disease outbreaks in South Africa. The secured funding from government also provides an opportunity for the NICD to continue evolving its surveillance activities and to be more pro-active in engaging and supporting the Provincial Centres for Disease Control structures.

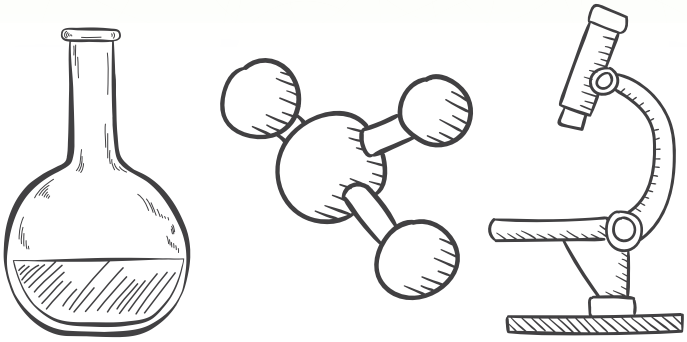
The public health-orientated research and surveillance undertaken by the NICD continues to inform policy and measure the investment being made in health in South Africa. This work by NICD staff was once again profiled in the highest ranking medical journals globally. Included among these was a feature in the journal *Nature*, which highlighted the NICD's surveillance of pneumococcal disease in South Africa and how it has contributed to evaluating the effect of childhood pneumococcal conjugate vaccine immunisation against pneumococcal disease, including reducing the burden of antibiotic-resistant strains. This was followed by the results of this surveillance being published in *The New England Journal of Medicine*, which reported on pneumococcal conjugate vaccine immunisation of young South African children conferring direct protection to them, as well as indirectly protecting unvaccinated individuals against pneumococcal disease (a leading cause of death in children and adults). The surveillance activities at the NICD, reported in *Lancet Infectious Diseases*, showed reductions in all-cause diarrhoea hospitalisation (the second most common killer of children in the 1–59 months age group globally), since having introduced the rotavirus vaccine into the public immunisation programme. This work of the NICD in measuring and informing public health interventions was highlighted in the annual budget speech of the Minister of Health, Dr Aaron Motsoaledi, in parliament. In addition to the above, there continues to be a 10–15% year-on-year increase in publications in international peer-reviewed journals from NICD staff. Many of these are in the leading journals in the field of infectious disease globally, attesting to the quality of surveillance and research undertaken at the NICD.

The NICD continues evolving its mission to contribute to surveillance and the control of communicable diseases in South Africa. This success, however, is very much dependent on the goodwill of the many partners in the different provincial governments being able to leverage upon the NHLS infrastructure and the collaboration of other healthcare workers in the public and private sector. The NICD looks forward to strengthening this relationship during the current year, as it expands its footprint from a core facility based in Gauteng, to having an ever-increasing presence in each of the provinces to assist their Provincial Departments of Health in safeguarding the health of South Africans against communicable diseases.

Centre for Enteric Diseases

Centre Co-Head: Dr Karen Keddy

Centre Co-Head: Dr Nicola Page



The Centre for Enteric Diseases (CED) of the NICD provides information for the Primary Health Care (PHC) Services Programme, Communicable Disease Control Sub-programme on the surveillance of infectious agents that contribute to enteric diseases in South Africa in children under five years of age. The centre contributes to efforts to reduce the under-five mortality rate by focusing on providing data for improved decision-making to combat the number of deaths due to diarrhoea in children under five years of age. The CED also provides information on food and waterborne outbreaks and provides the expertise to strengthen outbreak preparedness and response to public health emergencies in line with international health regulations. The centre focuses on the surveillance of pathogens associated with diarrhoea and enteric fevers, including typhoid fever, and the timeous identification of the possible causes of outbreaks due to these pathogens. Centre staff provide policy advice and technical support to government and contribute to the training of medical professionals, including medical scientists, medical technologists, epidemiologists, public health workers, nurses and registrars.

Surveillance/Diagnostic Services

The centre expanded the diarrhoeal sentinel surveillance network to include sites in the Northern Cape, Limpopo and Free State provinces.

The centre has evaluated rapid new diagnostic methods for the detection of enteric pathogens, including the Taqman® Array Cards (TACs), which are capable of simultaneously detecting 19 different enteric pathogens and molecular serotyping of *Salmonella enterica* serovars Enteritidis and Typhimurium.

Research

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

Intussusception is a rare intestinal blockage associated with a human-simian rotavirus reassortant vaccine formulation. While current rotavirus vaccines have not demonstrated an increased risk of intussusception during large-scale vaccine trials, recent studies have indicated a low-level risk of intussusception after vaccine administration. There are currently no data on intussusception risk in African settings. Active surveillance for intussusception cases has been implemented in seven South African cities. The study will continue for the next two years.

Collaborators: *Dr M Groome (DST/NRF: Vaccine Preventable Diseases, University of the Witwatersrand Respiratory and Meningeal Pathogens Research Unit (RMPRU))*

Evaluation of Taqman® Array Cards for the detection of multiple enteric pathogens in stool specimens

TAC technology has been adapted to simultaneously screen stool specimens for a variety of viral, bacterial and parasitic enteric pathogens. A total of 200 specimens from South Africa, Zambia, Zimbabwe, Rwanda and Mauritius were screened using TACs to evaluate the potential of this technology for routine surveillance activities within the WHO African Rotavirus Network platform. The card was easy to run, with results available within eight hours. Additional parallel testing may be required, as preliminary results indicated that RNA viruses may be missed using TACs.

Collaborator: *Dr E Houpt (University of Virginia)*

Detection and characterisation of human bocavirus and adenovirus species and types associated with diarrhoeal disease in specimens from children <5 years of age from six sentinel sites in South Africa

The study investigated the prevalence and strain variation of human adenoviruses (HAdV) and human bocaviruses (HBoV) associated with gastroenteritis in children under five years of age in South Africa. Between 2009 and 2014, HAdV was detected in 17.4% (1 107/6 357) of stool samples and 496 were characterised by sequencing the hexon gene. Adenoviruses circulating amongst hospitalised children included species A (14.9%), B (27.2%), C (33.5%), D (12.5%), E (0.8%) and F (65.5%). Co-infection with other enteric viruses was observed in 50.2% (556/1107) of HAdV cases. Human BoV was detected in 6.0% (381/6 357) of samples. Co-infection of HBoV with other enteric viruses was common (65.9%: 251/381). A total of 306 HBoVs were genotyped, including 77.8% (238/306) HBoV-1, 15.0% (46/306) HBoV-3, 5.9% (18/306) HBoV-2, and 1.3 % (4/306) HBoV-4.

Comparative characterisation of *Vibrio cholerae* O1 from five sub-Saharan African countries using various phenotypic and genotypic techniques

We used standardised methodologies to characterise *Vibrio cholerae* O1 isolates from Guinea, the Democratic Republic of Congo (DRC), Togo, Côte d'Ivoire and Mozambique. We investigated 257 human isolates collected between 2010 and

2013. The DRC isolates serotyped O1 Inaba, while isolates from other countries serotyped O1 Ogawa. All isolates were biotype El Tor and were positive for cholera toxin. All isolates showed multi-drug resistance but lacked ciprofloxacin resistance. Antimicrobial susceptibility profiles of isolates varied between countries. In particular, the susceptibility profile of isolates from Mozambique (east Africa) included resistance to the extended-spectrum cephalosporins, and was different to the susceptibility profiles from countries located in west and central Africa. Subtyping of isolates using pulsed-field gel electrophoresis analysis showed a complex relationship among isolates. Some PFGE patterns were unique to particular countries and clustered by country; other PFGE patterns were shared by isolates from several countries. Our data added to a better understanding of cholera epidemiology in Africa.

Collaborators: *MA Mengel, B-M Njanpop-Lafourcade (AMP, France), Africhol collaborators*

Rapid multi-locus sequence typing of *Salmonella enterica* via automated analysis of whole-genome sequence data at an online portal

We investigated the use of whole genome sequencing (WGS) of *Salmonella enterica* and automated analysis of WGS data at an online analysis portal as an alternative approach to traditional multi-locus sequence typing (MLST) methodology. Six strains of *S. enterica* were investigated. Genomic DNA was isolated and sequenced using IlluminaMiSeq next-generation sequencing technology. Data were uploaded onto the MLST analysis server at the Centre for Genomic Epidemiology (CGE) of the Technical University of Denmark. At the CGE, automated analysis of data and automated assigning of MLST sequence types were completed within ten minutes. WGS is a single, rapid and cost-effective approach to identify and characterise *S. enterica*. Online analysis portals with automated WGS analysis tools greatly assist in the analysis of data. WGS data can be interrogated to provide vast amounts of information concerning bacterial pathogens. This information has huge benefits for public health, including epidemiological and outbreak investigations, evolutionary studies and identification of antimicrobial resistance determinants and virulence determinants.

Azithromycin susceptibility in recent antimicrobial-resistant *Vibrio cholerae* O1 El Tor isolates in South Africa

The aim of this study was to investigate antimicrobial susceptibility (by E-test and agar dilution methods) to azithromycin, as well as to investigate the presence of seven macrolide resistance determinants among 100 selected South African antimicrobial-resistant *Vibrio cholerae* O1 El Tor variant isolates. All 100 isolates, irrespective of the test method, were susceptible to azithromycin, provided that the tentative breakpoint of ≤16 µg/ml was applied (the EUCAST value for wild-type isolates of *Salmonella enterica* and *Shigella* species). In addition, all isolates were PCR-negative for the seven macrolide resistance determinants. Statistical comparison of the results showed agreement of minimum inhibitory concentration (MIC) values based on the nearest similar dilution factor at 97% ($p > 0.05$; Mann-Whitney) and MIC correlation at 99% ($p < 0.01$; Spearman correlation coefficient).The agreement between the two azithromycin susceptibility testing methods and the significant correlation of the MICs is evidence of the consistency of the two susceptibility testing methods.

Development and evaluation of a multiple-locus, variable-number tandem-repeats analysis assay for subtyping *Salmonella* Typhi strains from sub-Saharan Africa

The aim of our study was to develop and evaluate a relevant and highly reproducible multi-locus, variable-number tandem-repeats analysis (MLVA) assay consisting of five variable number tandem repeats (VNTR) markers to analyse representative *Salmonella* Typhi strains from sub-Saharan Africa. Thirteen previously published polymorphic VNTR loci were evaluated using 50 *Salmonella* Typhi strains from humans selected from the culture collection at the CED. Six of these VNTR loci showed good allele variation and were found to be suitable for use in multi-locus VNTR analysis (MLVA) of *Salmonella* Typhi strains. These were narrowed down to five loci and were combined in a single multiplex PCR assay. This five-loci MLVA assay is used in the CED to analyse *Salmonella* Typhi strains from sub-Saharan Africa.

Characterisation of *Campylobacter* isolates from a South African population

The molecular epidemiology of *Campylobacter* infections was investigated in South Africa. For the years 2014 to date, *Campylobacter* was identified in 416/466 (89%) of specimens submitted to the CED. *Campylobacter jejuni* accounted for the majority (80%) of identified cases of *Campylobacter* infections, followed by *Campylobacter coli* at 11%. There was a preponderance of males (53%) among infected persons. Detection rates of *Campylobacter* infection were highest in children up to four years of age (32%) and were relatively constant across all other ages. Multi-locus sequence typing showed that the predominant subtype of *C. jejuni* strains was ST475.

Molecular epidemiology of *Salmonella* Enteritidis from human isolates in South Africa

A newly described MLVA method was used to subtype *Salmonella* Enteritidis isolates for the years 2013–2014 from Gauteng and the Western Cape. Four-hundred-and-forty isolates were subtyped. MLVA profile numbers were created based on the different MLVA patterns obtained from subtyping. Two MLVA profiles predominated and accounted for 60% of all the isolates. The largest MLVA profile (profile number 28) was represented by 183/440 (42%) isolates, which was also most prevalent among Gauteng isolates (138/183; 75%). Similarly, the second largest profile (profile number 7) (82/440; 19%) was predominant among isolates from the Western Cape (56/84; 67%). Isolates showed a relatively low prevalence of resistance to ampicillin, ciprofloxacin and ceftriaxone; however, 428/440 (97%) showed intermediate resistance to tetracycline and 131/440 (30%) showed full resistance to sulphamethoxazole.

Teaching and Training

Postgraduate level

The CED trained registrars as part of the NICD registrars training course in the identification and epidemiology of enteric bacteria and viruses. Dr KH Keddy lectured on travellers' diarrhoea to the Travel Medicine course, and lectured to MSc students in Epidemiology at Wits University on surveillance for enteric disease.

Professional Development

Postgraduate candidates enrolled at the CED: five PhD, three MSc, one MPH.

Honours

Anthony Smith was appointed as Associate Editor of the *Journal of Infection in Developing Countries* in August 2014.

Research Output

Journal articles

Groome MJ, Page N, Cortese MM, Moyes J, Zar HJ, Kapongo CN, Mulligan C, Diedericks R, Cohen C, Fleming JA, Seheri M, Mphahlele J, Walaza S, Kahn K, Chhagan M, Steele AD, Parashar UD, Zell ER, Madhi SA. Effectiveness of monovalent human rotavirus vaccine against admission to hospital for acute rotavirus diarrhoea in South African children: a case-control study. *Lancet Infect Dis.* 2014; **14**: 1096–104. Erratum in: *Lancet Infect Dis.* 2014; **14**: 1040.

Mans J, Van Zyl WB, Taylor MB, Page NA, Sobsey MD, Barnard TG, Potgieter N. Applicability of Bio-wipes for the collection of human faecal specimens for detection and characterisation of enteric viruses. *Trop Med Int Health.* 2014; **19**: 293–300.

Seheri LM, Mwenda JM, Page N. Report of the 7th African Rotavirus Symposium, Cape Town, South Africa, 8 November 2012. *Vaccine.* 2014; **32**: 6.336–41.

Smith AM, Ismail H, Henton MM, Keddy KH. Probable common source for *Salmonella* Enteritidis strains isolated from humans with gastroenteritis and from captive wild animals in South Africa. *J Infect Dev Countries.* 2014; 13.

Smith AM, Mthanti MA, Haumann C, Tyalisi N, Boon GP, Sooka A, Keddy KH; GERMS-SA Surveillance Network. Nosocomial outbreak of *Salmonella enterica* serovar Typhimurium primarily affecting a paediatric ward in South Africa in 2012. *J Clin Microbiol.* 2014; **52**: 627–31.

Tau N, Smith AM, Keddy KH. Development and evaluation of a multiple-locus variable-number tandem-repeats analysis assay for subtyping *Salmonella* Typhi strains from sub-Saharan Africa. *International Journal of Infectious Diseases.* 2014; **21**: 139–140.

Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever. *Lancet* 2015; **385**: 1 136–45.

Conference Presentations

International congresses: six

National congresses: three

Local congresses, e.g. university academic days: two

Centre for Emerging and Zoonotic Diseases

Centre Head: Prof. Janusz Paweska

An interconnected world, global climate change, encroachment of previously unspoilt lands and forests – these are some of the factors that contribute to the accelerated emergence of infectious disease in human and animal populations around the world. Director-General of the World Health Organization (WHO), Dr Margaret Chan, ascribed the cause of the emergence of, and inability to rapidly control the outbreak of the Ebola virus disease in west Africa with one word: 'poverty'. In 2014, the world was faced with what would become the largest outbreak of Ebola virus disease (and haemorrhagic fever) in recorded history, causing more than 10 000 deaths in the affected West African countries. The outbreak tested the world's capacity to diagnose, monitor and contain haemorrhagic fever outbreaks and has highlighted deficiencies but also abilities in this respect.

The Ebola virus disease outbreak has brought to the fore what has been the mission of the Centre for Emerging and Zoonotic Diseases (CEZD) at the NICD for more than 30 years, namely to ensure that it has the capacity for laboratory detection and response to such outbreaks. The CEZD aims to provide knowledge and laboratory expertise in the field of highly dangerous zoonotic pathogens, many of which are classified as emerging. These include biohazard level 4 agents, such as Ebola, Marburg, Crimean-Congo haemorrhagic fever, Lassa fever and Lujo fever. The CEZD is also concerned with arthropod-borne viruses such as Dengue, chikungunya, Sindbis, Rift Valley fever and West Nile fever. In South Africa, as in many developing countries, many patients still succumb to the most lethal infection known to mankind, namely rabies. The CEZD provides a comprehensive diagnostic service for ante-mortem and post-mortem verification of such cases. Apart from investigating disease associated with these viral aetiologies, the CEZD also specialises in the laboratory investigation of anthrax, plague, botulism, leptospirosis and other important but underestimated bacterial pathogens such as *Bartonella*. The CEZD is a reference laboratory for the diseases caused by these agents, and for the most part represents the sole capacity of South Africa to diagnose them. Apart from being a unique national facility, the CEZD plays a major role internationally in providing diagnostic support, not only to the Southern African Development Community (SADC), but also to the rest of the African continent.

The CEZD operates the only biosafety level 4 facility on the continent, which places it both strategically and critically in a position to assist in emerging and zoonotic disease detection and diagnostic responses on the continent. The CEZD prides itself on its 'Africans for African solutions' approach. It performs research in the field to answer critical questions regarding emerging and zoonotic diseases in Africa. Furthermore, the CEZD contributes extensively to the training of medical professionals, scientists and other allied professions, both nationally and internationally. The CEZD aims at using a 'One Health' approach in its surveillance and research activities, and supports activities nationally towards such an integrated approach in disease surveillance. The CEZD contributed directly to national initiatives for adhering to the WHO's International Health Regulations and to the Global Health Security Agenda.

Surveillance and Diagnostics

CEZD laboratories provide the capacity to investigate viral haemorrhagic fevers, arboviral (arthropod-borne viruses) diseases, human rabies and rabies-related infections of public health relevance in Africa. The centre is accredited for a range of diagnostic tests with the South African National Accreditation System (SANAS). To provide diagnostics of, and to perform research on BSL3 and BSL4 viral and bacterial pathogens, the CEZD manages the operation of high and maximum biocontainment facilities. The centre's BSL4 facility is the only maximum biocontainment suit laboratory on the African continent and provides an invaluable and strategic resource for the investigation, handling and storage of the most deadly pathogens known to science.

During 2014 nearly 200 cases were tested for aetiologies presenting as haemorrhagic fevers in South Africa. A total of six cases of Crimean-Congo haemorrhagic fever were confirmed by laboratory testing. Three of these cases had a fatal outcome. Furthermore, a total of 37 cases were presented to the CEZD for follow-up for Ebola virus disease. Eight of these cases were referred from other African countries, including Zimbabwe (n=2), Namibia (n=4), Angola and Ethiopia. In 2014, the National Department of Health pledged the services of NICD CEZD to provide laboratory support for suspected Ebola cases to SADC.

More than 500 cases of suspected arboviral disease were also investigated by the CEZD. The CEZD provides the only comprehensive laboratory follow-up of arboviruses relevant to public health in South Africa. Cases of Dengue fever and chikungunya in returning travellers are commonly diagnosed by the laboratory. West Nile and Sindbis fevers are endemic to South Africa, and cases are frequently diagnosed. The CEZD also specialises in the diagnosis of human rabies cases. In 2014, of six cases were confirmed in the Limpopo (n=1), North West (n=1) and Eastern Cape (n=3) provinces. An additional case was confirmed in a patient who contracted the disease in Angola.

In addition, the CEZD is tasked with the laboratory confirmation and investigation of anthrax, plague, leptospirosis, cat scratch disease (*Bartonellosis*) and botulism. Work on these agents is carried out in a BSL3 facility accredited with the DAFF and SANAS. The CEZD drives a regional surveillance project for plague (previously the RATZOOMAN project), and is recognised as the anthrax and plague reference laboratory for human diagnostics in South Africa. The CEZD recently expanded its surveillance activities to include other zoonotic pathogens, such as the bacteria that cause brucellosis and Q fever.

The CEZD also operates a transmission electron microscope, providing a versatile and useful tool in its diagnostic arsenal. The Electron Microscope Laboratory progressed towards becoming a core service facility for other NICD centres, in addition to playing a vital role in the CEZD programme of virus discovery (see Figure 1a). Integral to transmission electron microscopy for identifying a variety of pathogens, hosts and vectors, is the development of appropriate processing protocols. The two most valuable 'new' protocols performed this year were the 'pop-off' method for microsporidial diagnostics in biopsied histological sections (see Figure 1b), and a method developed for demonstrating the presence of capsules in pathogenic bacteria (see Figure 1c).

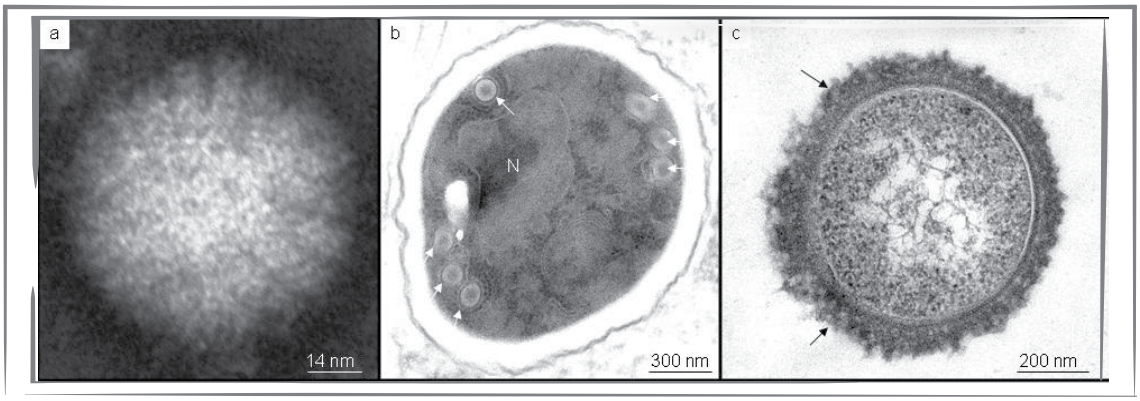


Figure 1: Transmission electron microscopy of (a) a newly-discovered virus assigned to the Reoviridae isolated from the ectoparasites of fruit bats; (b) microsporidial sporoblast identified in a renal biopsy wax section. Arrows indicate gyres of the polar filament, N = nucleus; (c) encapsulated *Streptococcus pneumoniae* cell processed with ruthenium red and L lysine acetate. Arrows indicate the capsular layer

Research and Special Projects

NICD Ebola Mobile Laboratory in Sierra Leone – the largest response to a public health emergency on foreign soil in the history of the institute

On 17 August 2014 the NICD deployed a team of CEZD staff members to Freetown, Sierra Leone. The WHO, through the Global Outbreak Alert and Response Network, requested it to set up and run an Ebola Mobile Laboratory (EML) in the fight against Ebola virus disease. Within a week of arriving in west Africa, the first team under the leadership of Prof. Janusz Paweska set up the EML and started testing its first specimens from suspected cases. The EML became an integral point of reference for diagnosis during the outbreak. It received more specimens during the peak of the outbreak than its small teams could process in good time. The EML occasionally processed and tested double its specimen capacity, often yielding close to 100% positivity on certain days, although this fluctuated and reduced dramatically when the government of Sierra Leone introduced buccal swabbing of all corpses in an attempt to detect previously unidentified transmission chains. From the second week of the establishment of the EML, the CEZD provided training to Sierra Leonean scientists and technicians in its operation and EVD testing. On 24 March 2015, the CEZD handed over the EML to Sierra Leonean authorities, a process which involved signing off various documents, including a full operations and safety manual and staff competency records. The EML was to be operated by the nationals who had been trained for a period of seven months. During this period, eight teams of between three and five NICD staff members each were deployed for periods ranging from four to six weeks. More than 7 000 suspected Ebola cases were tested by the NICD's EML, representing a third of the samples from the whole country, and providing an invaluable and highly appreciated contribution to the fight against Ebola in Sierra Leone. The CEZD continues to facilitate the functioning of the EML, despite the absence of

NICD staff on site. It is expected that the EML, run by Sierra Leoneans and capacitated by CEZD/NICD, will operate until the outbreak is declared over.

Collaborators: *WHO, Centres for Disease Control and Prevention, USA, International Atomic Energy Agency (IATA), Department of Health of South Africa, Ministry of Health and Sanitation of Sierra Leone, University of Pretoria*

Figure 2: Prof. Janusz Paweska and Dr Petrus Jansen van Vuren processing specimens from suspected Ebola virus disease cases in Sierra Leone

Pathobiology of Marburg virus in *Rousettus aegypticus* model

The biology of a reservoir-filovirus system is notoriously poorly understood. The Egyptian fruit bat (*Rousettus aegyptiacus*) is highly suspected of being a reservoir host for Marburg virus (MARV), but transmission mechanisms in this species, and thus the potential modes of spill-over to humans and non-human primates, remain unknown. This study reports on clinical, virological, immunological, gross pathological, histopathological and immunohistochemical results in *R. aegyptiacus* infected by subcutaneous (s.c.) route with low-passage MARV, in-contact exposed susceptible bats, and immunologically primed and s.c. re-challenged bats. This is the first attempted horizontal transmission of MARV in *R. aegyptiacus*, which further contributes towards the establishment of an experimental bat model of sub-clinical filovirus infection. Our findings demonstrate that close physical contact and respiratory infection are not the major routes of MARV transmission in *R. aegyptiacus*, and that this species develops a strong protective immunity after s.c. infection with MARV. The development of a relatively long-lasting viraemia and the replication of the virus in salivary glands after s.c. inoculation suggest that ectoparasites, including blood-sucking arthropods, and/or aggressive behaviour resulting in biting, may play a role in the natural transmission cycle of MARV in *R. aegyptiacus*. While the biology of the *R. aegyptiacus*-MARV association requires further investigation in order to determine the exact mechanisms of natural transmission, our findings in blood, tissues, mucosal swabs and urine confirm that entering *R. aegyptiacus* roosting sites and hunting these bats for food carries a danger of infection to humans.

Collaborators: *Dr TW Geisbert (Galveston National Laboratory, USA); Prof. W Markotter (University of Pretoria)*

Figure 3: A group of six *Roussetus aegyptiacus* (Egyptian fruit bats) from the CEZD experimental colony housed in specially designed cages

Surveillance for zoonotic pathogens in South African bats

Novel pathogens and pathogens closely related to those of public health importance are increasingly being isolated from various bat species, or their sequences are being detected by molecular biology techniques. It is postulated that ancestral viruses of some of the current important zoonotic pathogens originated in bats. The CEZD is conducting an intensive long-term surveillance study in South African bats, with a focus on the Egyptian fruit bat due to the overlap of its distribution with that of various tropical diseases in Africa. Monthly sampling at a cave in Limpopo continued in the past year to expand data on the prevalence and transmission of filoviruses, paramyxo viruses, lyssa viruses and corona viruses already previously detected in this study. Surveillance was also extended to a bat cave on Table Mountain which yielded similar seropositivity rates to the agents detected in the Limpopo cave, further strengthening the distribution overlap independent of geographical location, likely due to the migration of animals. The detection of antibodies against MARV in bats from both caves, and the detection of MARV RNA in the Limpopo cave is particularly intriguing. Novel viruses isolated from ectoparasites of the Egyptian fruit bat have now been characterised by full genome sequencing. Characterisation of two separate isolates of the same virus was the identification of the first bat-associated *Orthoreo* virus in Africa and also the first evidence that some *Orthoreo* viruses might be arthropod borne, an already known fact for other genera in the Reoviridae family. A second new virus, of which 11 separate isolates were made and which belong to the *Orthobunya* virus genus in the Bunyaviridae family, was also isolated from these ectoparasites and the genome characterised, confirming its novelty and distant relatedness to viruses isolated from bats in East Asia and South America. Although both viruses were isolated from arthropods collected from bats, and no evidence of human infection has yet been shown, the currently known closest relatives of these new viruses have been shown to infect and cause disease in humans.

Collaborator: *Prof. W Markotter and postgraduate students of her research group (University of Pretoria)*

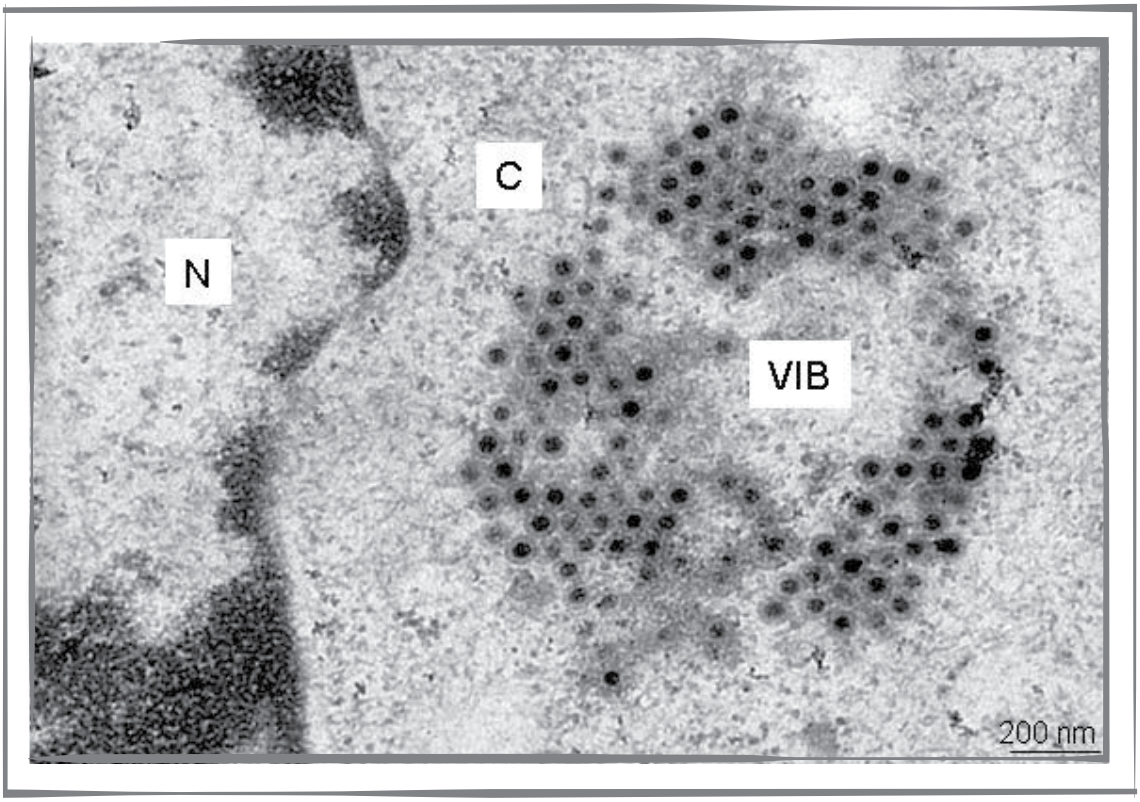


Figure 4: Electron micrograph of newly described *Orthoreovirus* isolated from ectoparasites of the Egyptian fruit bat. RNA-containing viruses are typically formed in the cytoplasm (C) within a differentiated area known as the viral inclusion body (VIB). The bi-layered nature of the developing *Orthoreovirus* virion is well illustrated (N = nucleus)

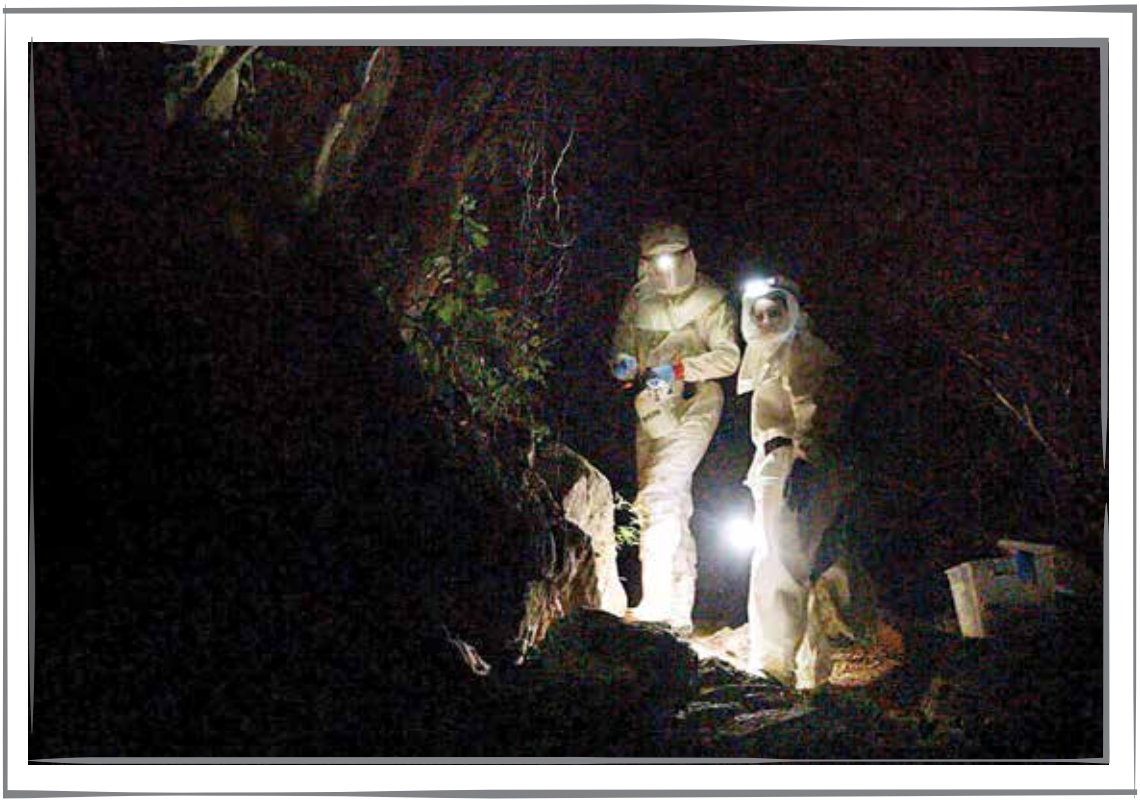


Figure 5: CEZD scientists donning protective equipment, preparing to capture bats at a cave in Limpopo Province (Photo credit: Frank Kraljic)

Teaching and Training

In addition to extensive training of staff and national and international research fellows in laboratory techniques and introducing them to working in BSL3 and BSL4 biocontainment facilities, the CEZD was actively involved in supporting postgraduate studies in the fields of medical microbiology, medical virology and public health through collaborative projects with South African and international universities. The centre is also involved in the training of microbiology and clinical pathology registrars, intern scientists and technologists on an ongoing basis.

The CEZD co-ordinates a number of formal training programmes and is often requested to co-ordinate specialist diagnostic workshops. In October 2014, it hosted a group of scientists from the Public Health Institute of Ethiopia, which included the Executive Director, Dr Ahmed Kebede. The CEZD provided specialist training in the molecular diagnosis of Ebola virus disease and the biosafety aspects involved in these procedures. In doing so, the centre supported the institute in the setting up of its own capacity in response to the 2014 Ebola virus disease outbreak.

During its deployment in Sierra Leone, the NICD team also transferred skills to Sierra Leonean scientists, enabling them to provide laboratory testing in response to the Ebola virus disease outbreak. The NICD was the only organisation that transferred such skills to local scientists. The NICD EML was handed over to these scientists for daily operations in March 2015.

The CEZD provides routine training in support of its plague surveillance programme. This includes training of environmental health officers from the City of Johannesburg (Gauteng province) on the dissection and storage of rodent organs for plague surveillance purposes. In December 2014, three such sessions were held, reaching a total of 27 environmental officers. In November 2014, several CEZD staff members were involved in co-hosting IATA courses on dangerous goods transport, including a train-the-trainer module, in collaboration with the Defense Threat Reduction Agency (USA) and Sandia Laboratories (USA).

Professional Development

CEZD staff members are intimately involved in the postgraduate training of students in virology and related fields. During the reporting period, six MSc and eleven PhD students were co-supervised or supervised by CEZD staff. This included two CEZD staff members who are currently enrolled for PhD programmes with the University of Pretoria and the University of the Witwatersrand. Three post-doctoral fellows are also supported in their research through the Southern African Centre for Infectious Disease Surveillance (SACIDS).

Honours and Awards

In 2014, Prof. Janusz Paweska was appointed as the lead of the Global Health Security Agenda on Zoonotic Diseases, South Africa. He was also recognised as head of the WHO Collaborating Centre for Reference and Research on Viral Haemorrhagic Fevers and Arboviruses. This status of the CEZD was again acknowledged by the WHO in 2014.

The James S Porterfield prize for international virology was awarded to a PhD student and staff member of the CEZD, Ms Nadia Storm. This award is made annually by the William James Laboratory, Oxford University, in recognition of academic promise.

Dr Jacqueline Weyer was appointed as Steering Committee Member to the National One Health Forum and elected as President of the Southern African Biorisk Association (SABA).

Dr Petrus Jansen van Vuren was appointed as Extraordinary Lecturer to the Department of Microbiology and Plant Pathology, University of Pretoria.

Research Output

In the reporting period, the CEZD contributed to 11 peer-reviewed publications. In addition, CEZD staff members authored or co-authored six book chapters.

Papers published in peer-reviewed journals

Goedhals D, **Paweska JT**, Burt FJ. Identification of human linear B-cell epitope sites on the envelope glycoproteins of Crimean-Congo haemorrhagic fever virus. *Epidemiology and Infection.* 2015; **143**: 1451–1456.

Goedhals D, Bester PA, **Paweska JT**, Swanepoel R, Burt FJ. Comparative analysis of the L, M, and S RNA segments of Crimean-Congo haemorrhagic fever virus isolates from southern Africa. *Journal Medical Virology*. 2015; **87** (5): 717–724, doi:10.1002/jmv.24079.

Goedhals D, Bester PA, **Paweska JT**, Swanepoel R, Burt FJ. Next-generation sequencing of southern African Crimean-Congo haemorrhagic fever virus isolates reveals a high frequency of M segment reassortment. *Epidemiology and Infection*. 2014; **142**: 1952–1962.

Markotter W, Coertse J, Le Roux K, Peens J, **Weyer J**, Blumberg L, Nel LH. Utility of forensic detection of rabies virus in decomposed exhumed dog carcasses. *J SA Vet Assoc*. 2015; 86 (1): Art #1220. http://dx/doi/org/10.4102/jsava.v86i1.1120).

Ladapo TA, Nourse P, Pillay K, Frean J, **Birkhead M**, Poonsamy B, Gajjar P. Microsporidiosis in pediatric renal transplant patients in Cape Town, South Africa: Two case reports. *Pediatr. Transplant*. 2014; 00: 1–7, doi:10.1111/petr.12327.

Njenga MK, Njagi L, Thumbi SM, Kahariri S, Githinji J, Omondi E, Baden A, **Paweska JT**, Ithondeka PM, Ngeiwa KJ, Dungu B, Donadeu M, Munyua PM. Randomized controlled field trial to assess the immunogenicity and safety of Rift Valley fever Clone 13 vaccine in livestock. *PLOS Negl Trop Dis*. 2015; **9** (3): e0003550, doi:10.1371/journal.pntd.0003550.

Paweska JT, **Jansen van Vuren P**, Fenton KA, Graves K, **Grobbelaar AA**, **Moola N**, **Leman P**, **Weyer J**, **Storm N**, McCulloch SD, Scott TP, Markotter W, Odendaal L, Clift SJ, Geisbert T W, Hale MJ, Kemp A. Lack of Marburg virus transmission from experimentally infected to susceptible in-contact Egyptian fruit bats. *Journal of Infectious Diseases*. 2015; doi: 10.1093/infdis/jiv13.

Venter M, Zaayman D, Van Niekerk S, Stivaktas V, Goolab S, **Weyer J**, **Paweska JT**, Swanepoel R. Macroarray assay for differential diagnosis of meningoencephalitis in southern Africa. *J Clin Virol*. 2014; **60**: 50–56.

Weyer J, Blumberg L. Ebola virus disease in West Africa – South African perspectives. *SAMJ*. 2014; **104** (11): 754–755.

Weyer J, Blumberg L, **Paweska JT**. The Ebola Virus Disease Outbreak in West Africa – an unprecedented outbreak. *SAMJ*. 2014; **104** (8): 555–556.

Weyer J, **Grobbelaar AA**, Blumberg LH. Ebola virus disease: History, outbreaks, epidemiology. *Current Infectious Diseases Reports*. 2015; **17**: 21, doi 10.1007/s11908-015-0480-y.

Chapters in books

Nel LH, **Weyer J**. Animal viruses pathogenic for humans. *In: Encyclopedia of the Life Sciences*. United Kingdom: John Wiley & Sons, Ltd. 2014: www.els.net, doi: 10.1002/9780470015902.a0001079.pub3.

Paweska JT, **Jansen van Vuren P**. Rift Valley fever virus: a virus with potential for global emergence. *In:* Johnson N, ed. *The role of animals in emerging viral diseases*. Elsevier, Academic Press. 2014: 169–200.

Paweska JT. Rift Valley fever. *In*: Ergönul Ő, Can F, Akova M, Madoff L, eds. *Clinical Case Study of Emerging Infectious Diseases*. Elsevier, Academic Press. 2014: 73–93.

Paweska JT. Lujo haemorrhagic fever. *In:* Ergönul Ő, Can F, Akova M, Madoff L, eds. *Clinical Case Study of Emerging Infectious Diseases*. Elsevier, Academic Press. 2014: 95–110.

Weyer J, Blumberg B. Rabies prevention and management. *In:* Blumberg L, ed. MIMS, *Handbook of Infectious Diseases*. Times Media Pty Ltd: 247–256.

Weyer J, Nel LH. Poxviral vectored vaccines for rabies. *In:* Rupprecht C, Najaran T eds. *Current Laboratory Techniques in Rabies Diagnosis*. Academic Press. 2014: 245–254.

Conference Presentations

International: 13

National: five

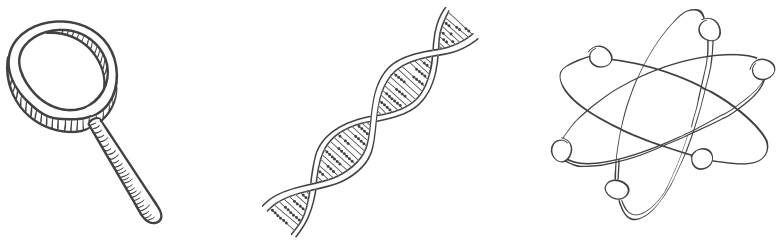
Local: on

Centre for HIV and Sexually Transmitted Infections

Centre Head: Prof. Adrian Puren

Centre Co-Head: Prof. Caroline Tiemessen

Centre Co-Head: Prof. Lynn Morris



The Department of Health's (DoH) National Strategic Plan 2014–2019, as it specifically relates to HIV and sexually transmitted infections (STIs), focuses on the prevention of new infections, reduction of the high burden of disease and the decrease of maternal and infant morbidity and mortality. The centre has played its part in addressing the Strategic Plan in diverse ways. HIV surveillance activities included exploring, with key organisations, how the co-ordination of surveillance and monitoring of various data can be triangulated to inform the surveillance landscape and how to address key questions such as HIV incidence. Data for action, in the form HIV PCR data reports for early infant diagnosis for facilities to follow up on, continued. The centre's laboratories continued to support testing for various surveys that inform HIV surveillance, and the introduction of new methods/platforms played a pivotal role in producing results. HIV testing to access care and treatment is essential. It is estimated that 8 million HIV rapid tests were performed in the reporting year. The centre assisted the DoH in the development of plans, materials, test kit monitoring and training, to respond to this challenge.

The centre released the first national transmitted drug surveillance data to address the concerns of drug resistance in the context of 2.1 million individuals reportedly being on antiretroviral therapy. STI surveillance expanded over the year, and better described the aetiological burden of infections and also assessed for microbial resistance, a growing concern with limited treatment options.

The introduction of the HPV vaccine in South Africa in 2014 was an important step towards reducing the burden of cervical cancer, and the results of baseline HPV molecular surveillance in expanded sites is informative for future planning and monitoring.

The centre maintained its high research profile with a range of exciting projects that provided an understanding of HIV viral pathogenesis, the role of broadly neutralising antibodies in HIV vaccine development and the search for an HIV-1 'functional' cure. With the number of HIV vaccine trials increasing, the centre continued to conduct various endpoint antibody and endpoint diagnostic studies. The activities in the centre entailed close collaborations, both nationally and internationally, which were consolidated and increased in number and scope during the year. Substantial funding was attracted from both national and international organisations. Teaching and training of a wide array of professionals and students and the supervision of postgraduate students continued apace. Staff and students in the centre benefited from various short- and long-term training opportunities at national and international institutions. The productivity and quality of the work of the centre is reflected in the honours awarded and the number of publications produced.

Surveillance and Monitoring

HIV Surveillance and Monitoring

The DoH, in partnership with the NICD, and in close collaboration with Public Health England and UNAIDS, organised the National Consultation on HIV Surveillance and Estimates in Pretoria, South Africa, in April 2014. The purpose of the meeting was two-fold – firstly to establishing a National Surveillance Steering Group, and secondly to find consensus on South African HIV prevalence and incidence estimates. The main objectives were to (1) establish a National HIV Surveillance Steering Group; (2) review available data and data sources in South Africa that can contribute to a better understanding of the HIV epidemic in the country; (3) review methods for obtaining HIV incidence estimates from laboratory-based assays, epidemiological models, and cohort studies; (4) critically review HIV incidence estimation from the LAg assays; and (5) compare assumptions and outputs of existing epidemiological models in South Africa and work towards consensus on HIV Estimates for South Africa. Several key organisations, including government, academic institutions and development partners, participated in the meeting.

Laboratory support for various surveillance activities continued, including co-ordination with NHLS laboratories on the 34th Annual Antenatal HIV Prevalence and Incidence Survey and the Male Circumcision Study part D; and studies focusing on HIV incidence at a district/sub-district level including the HIV Incidence Provincial Surveillance System (HIPPS) Study led by CAPRISA. An external quality assurance programme was developed for HIV-1 RNA viral load measurements from dried blood spots using a reference panel and field-collected specimens. An additional focus for the centre is the collaboration with the HSRC and UCSF, centred on surveillance in 'key populations' including sex workers, truck drivers (Truck Driver and Commercial Sex Worker (KPN3) Study in KZN) and men-who-have-sex-with-men.

Various laboratory-based protocols for surveillance, including HIV prevalence and incidence, were approved for implementation in the first quarter of 2015/16. The first and second surveys to assess the effectiveness of the Prevention of Mother-to-Child Transmission (PMTCT) studies, led by the MRC, demonstrated declines in transmission at the 4–8 week post-partum stage. The third survey, including follow-up testing of HIV-exposed infants up to the age of 18 months, was completed. An important data source for the PMTCT Programme is the NHLS Corporate Data Warehouse (CDW). Monthly distribution of Early Infant

Diagnosis (EID) HIV PCR Reports were provided to ±200 stakeholders for monitoring PMTCT. Birth testing studies are conducted at Rahima Moosa Mother and Child and Kalafong Hospitals, in collaboration with the Empilweni Research and Service Unit, MRC, Kalafong Paediatrics Department and the DoH. The use of cellphone technology to close PMTCT cascade gaps for the elimination of mother-to-child transmission (eMTCT) is being investigated with UNICEF.

HIV transmitted drug resistance surveillance

The centre's HIV drug resistance laboratory is the designated centre for national surveillance activities and also serves as a WHO regional HIV drug resistance laboratory. Surveillance for transmitted HIV drug resistance (TDR) among individuals assumed to be recently infected, was undertaken using specimens collected as part of the 2012 annual antenatal survey conducted by the DoH. Remnant serum specimens were obtained from primigravid women under 21 years of age, and genotyping performed on HIV-infected specimens by sequencing the protease and reverse transcriptase genes. A total of 770 available specimens that met eligibility criteria were selected for analysis, from which 532 (69%) were successfully amplified and genotyped. Weighted national TDR point prevalence was estimated at 5.3% (3.7–7.5%) for the NNRTI drug class, 1.1% (0.5–2.4%) for NRTI and 0.6% (0.1–1.6%) for PI. Four provinces had NNRTI point prevalence estimates >5%, although some of these analyses were limited by small sample sizes. The predominant mutations detected were K103N (57%), V106M (23%) and K101E (11%), whereas M184V/I was the predominant NRTI mutation (9%). Two specimens had dual NNRTI and NRTI class resistance. This analysis provides the first national TDR estimates for South Africa, and indicates that levels of TDR are >5% for the NNRTI drug class, but remain low (<5%) for NRTI and PI classes.

STI clinical syndrome, aetiological and gonococcal antimicrobial resistance surveillance

The Gauteng STI Surveillance Project, run by the centre in collaboration with the Gauteng DoH, continued to collect STI syndrome data from public clinics throughout the review period. In 2014/15, in collaboration with the DoH, Alexandra Health Centre, Ethekwini Municipal Clinic and Inkosi Albert Luthuli NHLS Laboratory, the centre undertook aetiological surveillance of three major STI syndromes (male urethritis syndrome (MUS), vaginal discharge syndrome (VDS), and genital ulceration syndrome (GUS). Surveillance of gonococcal antimicrobial resistance was also undertaken in Gauteng (Johannesburg) and KwaZulu-Natal (Durban). Thus, all nine provinces have had at least one STI national microbiological survey performed in the period 2006–2015. Following the approval of the new protocol by the funder and collaborator, Centers for Disease Control and Prevention (CDC), for national STI aetiological surveillance, training of primary healthcare nurses took place in each of South Africa's nine provinces in March 2014. Specimen collection started in April 2014 in 36 clinics (four per province) across the country and was completed by September 2015. During this reporting period, STI surveillance was introduced in the GERMS platform to allow for continuous STI surveillance in nine sentinel clinics (one in each province). The centre continued to monitor gonococcal resistance patterns in the MSM population in collaboration with ANOVA Health Institute in Cape Town and further sites are being initiated in Johannesburg and Durban. The new STI guidelines were introduced in South Africa following review of surveillance data with recommended changes for the treatment of STI syndromes.

Sentinel surveillance of STI syndrome aetiologies and HPV genotypes among patients attending public health facilities in South Africa (2013–current)

STIs, including HIV infection, continue to be highly prevalent among individuals of reproductive age within South Africa. As STIs may increase both the acquisition and transmission of HIV infection, a national STI surveillance programme is a critical tool, not only to monitor trends in STIs themselves, but also to indirectly track changes in sexual behaviour. HPV genotyping was performed on cervical samples from 201 young women, aged 18–20 years old, attending 36 family planning clinics (four clinics per province). HPV prevalence was found to be 77% (155/201) among young women engaged in family planning. They were more likely to have infections with multiple HPV types (75%, 116/155) than with a single HPV type (25%, 39/155). A high burden of HPV was observed among women attending family planning clinics in South Africa.

HIV-1 rapid testing quality assurance and post-marketing surveillance of HIV rapid test devices

The National Department of Health embarked on an ambitious programme to ensure that each citizen in South Africa is tested for HIV. South Africa has the largest antiretroviral programme, with an estimated 2.4 million of the 6.5 million infected individuals on therapy. Testing for HIV using HIV rapid test devices (RTDs) at facility level, is the entry point to enrolling HIV-infected individuals into care and treatment and supporting tested HIV-negative persons. Performance of the rapid tests in public health facilities is challenging, as it is performed by non-laboratory trained individuals with varying experience, including nurses, doctors and counsellors.

To strengthen the effectiveness of the HIV response system at the national, provincial, district and facility levels, the NICD continued to support the implementation of a quality assurance programme for the HIV testing service provided within the National HIV Counselling and Testing Programmes. Following a joint review of the National HIV and TB Programmes by the DoH, WHO and other stakeholders in late 2012, one of the recommendations made was to immediately implement quality assurance for HIV rapid testing.

In response to the recommendation, a quality assurance and quality improvement (QA-QI) programme was developed in collaboration with the CDC. The programme is aligned with the National Quality Assurance Guidelines for HIV rapid testing. The QA-QI Plan was adopted by the DoH. The centre participated in the review of the current National HCT Policy and HCT Register with a view to including quality assurance and continuous improvement. Training materials from a current WHO-based training manual for a HIV rapid testing quality system were used as the basis for a draft manual, and an external agent that specialises in training was identified to develop an easy to use manual and tools to assist in the implementation of quality assurance activities at facility level. Training of major stakeholders and master trainers to support the national roll-out of training to all provinces was provided. In total, 232 HCT counsellors were trained on the HIV Rapid Testing Manual and 12 NGO HCT Programme officers were trained on the WHO QMS Programme. In addition, 1 000 healthcare workers were trained on the QA/QI Programme, and 150 support visits were conducted among the 360 facilities trained on the QA Programme and 291 baseline assessment site visits were conducted to assess conformance to stated quality assurance. The DoH estimates that 8.7 million tests were performed during the reporting period.

The assuring of HIV rapid test performance and quality assurance of HIV rapid testing is a major activity for the centre. A revised protocol for HIV rapid test evaluations, following the example of the WHO and UNAIDS/CDC, led to a successful outcome with the selection of two HIV rapid test kits and the awarding of the DoH tender in 2014 for Abon HIV 1/2/0 Triline HIV Rapid and the Advanced Quality Rapid anti-HIV (1&2). A key follow-on activity undertaken by the centre was the post-marketing surveillance of the lots/batches of devices prior to release in testing sites and 25 Advanced Quality batches and 39 Abon batches were tested. Quality assurance implementation at a testing facility level is a major undertaking. A serum-based internal quality control (IQC) was distributed to various facilities in various provinces, including Limpopo, Free State, Mpumulanga and the Northern Cape, as well as NGOs that support HIV rapid testing in the public sector. The purpose of the IQC is to provide testers with a key control step prior to testing and also an early warning indicator of test kit performance.

Support for HIV vaccine trials

The centre continued to provide results from validated end-point humoral antibody and molecular HIV assays for the HIV Vaccine Trial Network (HVTN). A major activity was the HVTN 097 safety trial, which is a repeat of the RV144 trial in the South African population. This regimen, which makes use of a poxvirus vector followed by a gp120 protein boost, provided the first indication that protection by an HIV vaccine may be possible with an efficacy of 31%. Subsequent analysis showed that V2 binding antibodies correlated with protection. The binding and neutralising antibody responses in HVTN 097 were similar to RV144 suggesting that these products, designed for use in Asia, were immunogenic in the South African population. This has paved the way for HVTN 100, in which vaccines have been redesigned to target viruses that circulate in South Africa. The NICD will be involved in evaluating the immune responses elicited by these HIV subtype C vaccines, that are based on those used in RV144 and HVTN 097. The current protocols for end-point testing (HIV Infection) included HVTN 802, 404, 910, 097, 915 and 100 using revised testing algorithms in line with current diagnostic approaches.

Current Research Projects

The HIV Incidence Provincial Surveillance Systems

This project was initiated to establish a population-level HIV incidence Provincial Surveillance System (HIPSS) platform in a household-based representative sample of men and women, in order to monitor changes in HIV incidence in association with the up-scaling of prevention efforts in a 'real world', non-trial setting. The study is designed to be cross-sectional with two embedded cohorts. Baseline and follow-up measurements will be undertaken using a structured questionnaire and biological specimens. The sequential cohorts of HIV uninfected individuals (15–35 years of age), selected from a representative sample of households, will be followed up at month 12 and assessed for HIV infection. Population level changes in HIV incidence will be measured. HIPSS will further provide an opportunity to evaluate laboratory tests for recent infections (TRIs) for estimating population level HIV incidence using the recent infection testing algorithm (RITA). Secondary endpoints include the prevalence and incidence of pulmonary tuberculosis (TB), STIs and hepatitis (Hep) B and C infection.

Key collaborator: *Dr A Kharsany (CAPRISA)*

STIs in men-who-have-sex-with-men (MSM) (2011–2015)

The centre, in collaboration with the ANOVA Health Institute, previously determined the prevalence of gonococcal and chlamydial infections at urethral, rectal and pharyngeal sites in 200 symptomatic and asymptomatic MSM attending the Ivan Toms Centre for Men's Health in Cape Town. During 2014/15, the DNA extracts were additionally tested for HPV infection and any HPV-positive samples were genotyped and analysed. There was a high prevalence of HPV infection, particularly in ano-rectal specimens. Overall, 600 specimens (a urine, a pharyngeal swab and an ano-rectal swab from each of the 200 patients) were analysed for the presence of HPV genotypes. An overall HPV prevalence of 79% (158/200) was observed for all patients, irrespective of the site of HPV positivity. Ongoing studies will include assessing behavioural risk factors that are associated with HPV prevalence in this population.

Key collaborator: *Dr K Rebe (Ivan Toms Centre for Men's Health, ANOVA Health Institute)*

Detection of HPV types not detected by commercial kits in penile samples from South African men (2013–2015)

The aim of the study was to investigate HPV types that were not detected by the commercial Roche linear array HPV genotyping assay. HPV prevalence in penile samples was investigated in 337 men using the FAP PCR method. Of the 337 penile samples, 74% (249/337) were HPV positive. HIV-positive men had significantly higher HPV prevalence compared to HIV-negative men (89%, 124/140, and 63%, 125/197 respectively, P<0.001). Among 218 FAP PCR positive samples that were randomly selected for HPV genotyping by NGS, 174 different HPV types/isolates were detected in a total of 978 incidences of infection. The majority of the identified HPV types/isolates occurred only once in the population (35.6%, 62/174). HIV-positive men were more likely to have multiple HPV types than HIV-negative men. There were 15 possible new HPV types/isolates detected. The burden of HPV types is high in both HIV-positive and HIV-negative men, but it is further increased in HIV-positive men. The possible new HPV types will be cloned and full sequence will be performed.

Collaborators: *A/Prof. D Coetzee (UCT), Dr T Meiring (UCT)*

Women Initiative in Sexual Health (2013–current)

HPV prevalence was found to be 68% (102/149) at baseline visit in young women from Masiphumelele, Cape Town. Infection with multiple HPV types was found to be significantly higher than single HPV infection (77%, 79/102 and 33%, 23/102 respectively, P=0.001). Of the HPV types targeted by the HPV vaccines, 12.1% (18/149) were infected with HPV-16, 7.4% (11/149) with HPV-6, 4.7% (7/149) with HPV-18 and 4.0% (6/149) with HPV-11. In the follow-up visit (approximately four months after baseline) HPV prevalence was found to be 72% (64/89). In women from Soweto, Johannesburg, HPV prevalence was found to be 65% (63/97). Multiple HPV infection was not found to be significantly higher than single infection (59%, 37/63 and 41%, 26/63 respectively, P=0.06). In the Johannesburg cohort, 11.3% (11/97) were infected with HPV-16, 6.2% (6/97) with HPV-6, 5.2% (5/97) with HPV-18 and 1.0% (1/97) with HPV-11. The overall HPV prevalence was found to be similar in the Cape Town and Johannesburg cohorts (68% vs. 65%). This is a particularly high prevalence taking into consideration that the women were all HIV-negative. The high prevalence of quadrivalent HPV types indicates that South African women will greatly benefit from a HPV vaccine.

Collaborator: *A/Prof. J-A Passmore (UCT/NHLS)*

High prevalence of HIV-1 drug resistance mutations in subtype C transmitting mothers detected using 454 ultra-deep sequencing

In 2010, PMTCT guidelines recommended that pregnant women with a CD4 count of less than 350 cells/ml receive HAART (Option B), and women with a CD4 count above 350 cells/ml receive antenatal and intrapartum prophylaxis (Option A). In this study we performed 454 ultra-deep pyrosequencing to determine the prevalence of maternal drug resistance variants in HIV-1-transmitting mothers. The FInHDER Study, conducted in five clinics and hospitals in Johannesburg in 2011, set out to recruit treatment-naive HIV-infected infants and children under two years of age presenting at routine PMTCT follow-up clinics and in-patient services. In this study, 201 maternal plasma samples were collected and sequenced for HIV drug resistance mutations using pyrosequencing technology and 454 prototype plates containing lyophilised MID tagged primers. Sequence reads were analysed using 454 AVA software and Seq2Res pipeline. Of the 201 women, 115 had received PMTCT, 65 had received no PMTCT, 15 were receiving cART, and six had unknown exposure. Ultra-deep sequencing by 454 was successful in 200 (98%) specimens. A total of 80 specimens (40%) had HIV-1 drug resistance detected. NNRTI mutations were detected in 68 (34%) specimens, NRTI mutations in 17 (9%) and dual-class resistance

in 13 (7%). Single PI mutations were identified in 12 specimens. When stratified by age of child, NNRTI mutations were present in 17.2% (11.4–25.1%) of women in the exposed group whose time since childbirth was under six months versus 6.1% (2.4–14.6%) in the unexposed group. Lower rates of NNRTI mutation were present between six months and one year [3.4% (1.3–8.5%)] and up to two years [2.6% (0.9–7.3%)] post-exposure in the exposed group. However, in the unexposed group, the NNRTI mutation rate remained constant [4.5% (1.6–12.5%)]. NNRTI resistance was driven by the K103N (n= 28, 24.3%) and Y181C (n=11, 9.5%) mutations in the exposed group, and by K103N (n=4, 5.4%) in the unexposed group. These data highlight the value of deep sequencing to reveal the presence of resistance mutations in transmitting mothers, suggesting poor compliance and/or regimen failure during PMTCT exposure.

Collaborators: *Dr L Kuhn (CU), Prof. S Travers (SANBI), Dr K Technau (Wits)*

Impact of drug resistance-associated amino acid changes in HIV-1, subtype C on susceptibility to newer nonnucleoside reverse transcriptase inhibitors

The objective of this study was to assess the phenotypic susceptibility of HIV-1 subtype C isolates, with nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated amino acid changes, to newer NNRTIs. A panel of 52 site-directed mutants and 38 clinically derived HIV-1 subtype C clones was created, and the isolates were assessed for phenotypic susceptibility to etravirine (ETR), rilpivirine (RPV), efavirenz (EFV), and nevirapine (NVP) in an *in vitro* single-cycle phenotypic assay. The amino acid substitutions E138Q/R, Y181I/V, and M230L conferred high-level resistance to ETR, while K101P and Y181I/V conferred high-level resistance to RPV. Y181C, a major NNRTI resistance-associated amino acid substitution, caused decreased susceptibility to ETR and, to a lesser extent, RPV when combined with other mutations. These included N348I and T369I, amino acid changes in the connection domain that are not generally assessed during resistance testing. However, the prevalence of these genotypes among subtype C sequences was, in most cases, less than 1%. The more common EFV/NVP resistance-associated substitutions, such as K103N, V106M, and G190A, had no major impact on ETR or RPV susceptibility. The low-level resistance to RPV and ETR conferred by E138K was not significantly enhanced in the presence of M184V/I, unlike for EFV and NVP. Among patient samples, 97% were resistant to EFV and/or NVP, while only 24% and 16% were resistant to ETR and RPV respectively. Overall, only a few, relatively rare NNRTI resistance-associated amino acid substitutions caused resistance to ETR and/or RPV in an HIV-1 subtype C background, suggesting that these newer NNRTIs would be effective in NVP/EFV-experienced HIV-1 subtype C-infected patients.

Collaborators: *SY Rhee (Stanford), CM Parry (HPA, MRC/UCL, MRC/UVRI), S Charalambous (Aurum Institute), T De Oliveira (UKZN), D Pillay (HPA, MRC/UCL), C Hoffmann (Aurum Institute, Johns Hopkins), D Katzenstein (Stanford), RW Shafer (Stanford)*

South African HIV-1 subtype C-transmitted variants with a specific V2 motif show higher dependence on α4β7 for replication

The integrin α4β7 mediates the trafficking of immune cells to the gut associated lymphoid tissue (GALT) and is an attachment factor for the HIV gp120 envelope glycoprotein. We developed a viral replication inhibition assay to more clearly evaluate the role of α4β7 in HIV infection and the contribution of viral and host factors. Replication of all 60 HIV-1 subtype C viruses collected over time from 11 individuals in the CAPRISA cohort were partially inhibited by antibodies targeting α4β7. However, dependence on α4β7 for replication varied substantially among viral isolates from different individuals as well as over time in some individuals. Among eight transmitted/founder (T/F) viruses, α4β7 reactivity was highest for viruses having P/SDI/V tri-peptide binding motifs. Mutation of T/F viruses that had LDI/L motifs to P/SDI/V resulted in greater infectivity, whereas mutating P/SDI/V to LDI/L motifs was associated with reduced replicative capacity. P/SDI/V motifs were more common among South African HIV subtype C viruses (35%), compared to subtype C viruses from other Africa regions (<8%) and to other subtypes, due in part to a founder effect. In addition, individuals with bacterial vaginosis (BV) and who had higher concentrations of IL-7, IL-8 and IL-1α in the genital tract had T/F viruses with higher α4β7-dependence for replication, suggesting that viruses with P/SDI/V motifs may be preferentially transmitted in the presence of BV in this population. Collectively, these data suggest a role for α4β7 in HIV infection that is influenced by both viral and host factors, including the sequence of the α4β7 binding motif, the cytokine milieu and BV in the genital tract. The higher frequency of P/SDI/V sequences among South African HIV-1 subtype C viruses may have particular significance for the role of α4β7 in HIV infection in this geographical region.

Collaborators: *Dr L Masson (UCT), Dr L Werner (CAPRISA), Dr N Garrett (CAPRISA), Prof. SS Abdool Karim (CAPRISA), Prof. Q Abdool Karim (CAPRISA), Prof. C Williamson (UCT), Dr JS Passmore (UCT)*

Ability to develop broadly neutralising HIV-1a antibodies is not restricted by the germline Ig Gene repertoire

The human immunoglobulin (Ig) repertoire is vast, producing billions of unique antibodies (Abs) from a limited number of germline Ig. The IgHV region (IGHV) is central to antigen binding and consists of 48 functional genes. In this study, we analysed whether HIV-1-infected individuals who develop broadly neutralising Abs show a distinctive germline IGHV profile. Using both 454 and Illumina technologies, we sequenced the IGHV repertoire of 28 HIV-infected South African women from the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 002 and 004 cohorts, 13 of whom developed broadly neutralising Abs. Of the 259 IGHV alleles identified in this study, approximately half were not found in the International Immunogenetics Database (IMGT). This included 85 entirely novel alleles and 38 alleles that matched rearranged sequences in non-IMGT databases. Analysis of the rearranged H chain V region genes of mAbs isolated from seven of these women, as well as previously isolated, broadly neutralising Abs from other donors, provided evidence that at least eight novel or non-IMGT alleles contributed to functional Abs. Importantly, we found that, despite a wide range in the number of IGHV alleles in each individual, including alleles used by known broadly neutralising Abs, there were no significant differences in germline IGHV repertoires between individuals who do and do not develop broadly neutralising Abs. This study reports novel IGHV repertoires and highlights the importance of a fully comprehensive Ig database for germline gene usage prediction. Furthermore, these data suggest a lack of genetic bias in broadly neutralising Ab development in HIV-1 infection, with positive implications for HIV vaccine design.

Collaborators: *Dr N Garrett (CAPRISA), Prof. SS Abdool Karim (CAPRISA), Prof. Q Abdool Karim (CAPRISA), Dr S Travers (SANBI)*

Studies on HIV-1 functional cure – paediatric and adults (2014–2018)

There is widespread consensus that an HIV cure is required and is feasible. The ideal of controlling HIV-1 in the absence of antiretroviral treatment (ART) ('functional cure' or remission) or eradicating HIV-1 ('eradicating cure') will have enormous individual and public health benefits. The natural control of HIV-1 infection, where disease course ranges from very rapid progression on the one hand, to the opposite extreme that occurs in a very rare group of individuals called elite controllers (ECs), which provide the ideal model for the study of functional cure (suppress viral load to <50 RNA copies/ml in the absence of ART). Recently funded studies have commenced with the following research aims: (i) to identify viral and host targets that can be developed for functional cure strategies in our populations by exploring mechanisms of suppressive control in South African elite controllers and other phenotypes of HIV-1 control; and (ii) to explore early ART as a modality to reduce viral reservoir size in HIV-1-infected infants identified at birth in order to address the possibility of functional cure in some infants and identify predictive markers, and to understand success or failure to inform future strategies.

Collaborators: *Prof. L Kuhn (Columbia University, NY), Dr A Coovadia (ESRU, RMMCH), Dr K Technau (ESRU), Dr N Martinson, (PHRU), Dr D Spencer (Right to Care), Dr P Ive (CHRU), Prof. M Ramsay (SBIMB), Dr P Kiepiela (MRC HIV Prevention Unit), M Vermeulen (SANBS)*

Teaching and Training

The centre provided a diverse array of teaching and training. This included specialist registrar training on topics such as surveillance of HIV and STIs, including drug resistance; current topics on diagnostics for HIV and STIs; and HIV vaccine developments. Training support was also provided to the FETP Programme. Four intern scientists were trained during the reporting period, and the centre provided training for one national and four international postgraduate students in the HIV vaccine field as part of its collaborative commitments. Technical training and support was provided for SADC countries, including implementation of quality assurance for HIV at the National Reference Laboratory in Lesotho and HIV drug resistance training for the National Reference Laboratory of Zimbabwe. International scholarships, such as the Bill and Melinda Gates Foundation inaugural CAVD Science Exchange Fellowship and the Columbia University-Southern African Fogarty AITRP Traineeship Awards, provided opportunities for postgraduate students and staff to acquire the necessary expertise to further several of the vaccine-related research efforts. Thirteen PhD, six MSc and two BSc (Hons) students were supervised at the centre.

Grant Funding

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

The National Agency for AIDS Research, France (ANRS)

Bill and Melinda Gates Foundation

Canadian HIV Vaccine Initiative's CANSSA HIV/AIDS Network Pilot Grant

Department of Science and Technology/National Research Foundation Chair of HIV Vaccine Translational Research

National Health Laboratory Research Trust

National Research Foundation Professional Development Programme and Incentive Funding for Rated Researchers

National Institute of Allergy and Infectious Diseases, NIH (U01, R01, HVTN, CHAVI, HIVRAD)

Poliomyelitis Research Foundation

President's Emergency Plan for AIDS Relief (PEPFAR)

South African Medical Research Council

Wellcome Trust

Honours and Awards

Kurt Wibmer was awarded the 2013 Faculty Research Prize in April 2014.

Jinal Bhiman was selected as one of five New Investigator Award recipients at the HIV Research for Prevention 2014: AIDS Vaccine, Microbicide and ARV-based Prevention Science (HIV R4P Conference), the first global scientific conference focused exclusively on HIV prevention research, held from 28–31 October in Cape Town, South Africa.

Jinal Bhiman received a 2014 DST South African Women in Science Doctoral Award.

Prof. Lynn Morris received the University of the Witwatersrand's 2014 Vice-Chancellor's Research Award. This is the university's most prestigious award.

Simone Richardson received a 2014 Duke CHAVI-ID Pre-Doctoral Award. The Duke CHAVI-ID Scientific Leadership Group presents these awards every year to recognise the accomplishments of dedicated and talented investigators and laboratory staff whose contributions have been outstanding and essential to the success of Duke CHAVI-ID programmes and initiatives.

Prof. Penny Moore received a B3 rating from the NRF.

Prof. Caroline T Tiemessen was promoted to Research Professor.

A third prize was awarded to the HIV Rapid Testing QA team at the ASLM Conference 2014, for their poster presentation on the Quality of HIV rapid testing.

Research Output

The centre published 37 peer-reviewed publications. Staff participated in various national and international conferences, where conference presentations included 11 oral presentations, 13 poster presentations, four invited talks and two plenary sessions.

The following publications present work that has advanced public health and/or laboratory science within South Africa:

Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, Ernandes MJ, Georgiev IS, Kim HJ, Pancera M, Staupe RP, Altae-Tran HR, Bailer RT, Crooks ET, Cupo A, Druz A, Garrett NJ, Hoi KH, Kong R, Louder MK, Longo NS, McKee K, Nonyane M, O'Dell S, Roark RS, Rudicell RS, Schmidt SD, Sheward DJ, Soto C, Wibmer CK, Yang Y, Zhang Z, NISC Comparative Sequencing Program, Mullikin JC, Binley JM, Sanders RW, Wilson IA, Moore JP, Ward AB, Georgiou G, Williamson C, Karim SSA, Morris L, Kwong PD, Shapiro L, and Mascola JR. Developmental pathway for potent V1V2- directed HIV-neutralising antibodies. *Nature*. 2014; May 1; 509 (7498): 55–62.

Synopsis: Antibodies capable of neutralising HIV-1 often target variable regions 1 and 2 (V1V2) of the HIV-1 envelope, but the mechanism of their elicitation has been unclear. Here we define the developmental pathway by which such antibodies are generated and acquire the requisite molecular characteristics for neutralisation. Twelve somatically-related neutralising antibodies (CAP256-VRC26.01–12) were isolated from donor CAP256 (from CAPRISA); each antibody contained the protruding tyrosine-sulphated, anionic antigen-binding loop (complementarity-determining region (CDR) H3) characteristic of this

category of antibodies. Their unmutated ancestor emerged between weeks 30–38 post-infection with a 35-residue CDR H3, and neutralised the virus that superinfected this individual 15 weeks after initial infection. Improved neutralisation breadth and potency occurred by week 59 with modest affinity maturation, and was preceded by extensive diversification of the virus population. HIV-1 V1V2-directed neutralising antibodies can thus develop relatively rapidly through initial selection of B cells with a long CDR H3, and limited subsequent somatic hypermutation. These data provide important insights relevant to HIV-1 vaccine development.

Loubser S, Paximadis M, Gentle N, Puren A, Gray CM and Tiemessen CT. Frequencies of immune hypersensitivity reaction-associated HLA class I alleles in healthy South African Indian and mixed ancestry populations determined by a novel real-time assay. *Tissue Antigens.* 2014; **84**: 389–397.

Synopsis: This study describes the development and optimisation of a novel real-time allele-specific polymerase chain reaction (AS-PCR) assay to detect human leukocyte antigen (HLA) class I alleles that have previously been shown to be associated with hypersensitivity reactions to abacavir (B*57:01) and nevirapine (B*35:05; C*04 and C*08) in antiretroviral drug-treated HIV-1-infected individuals. This assay was applied to determine the frequencies of these specific alleles in the less studied mixed ancestry and Indian South African populations, where there are no HLA class I published data. The representations within each group determined for these alleles, together with South African demographic data, suggested that a substantial number of individuals would benefit from such assays where these drugs may be administered for patient care.

Publications

Basson AE, Rhee S-Y, Parry CM, El-Khatib Z, Charalambous S, De Oliveira T, Pillay D, Hoffmann C, Katzenstein D, Shafer RW and Morris L. Impact of Drug Resistance-Associated Amino Acid Changes in HIV-1 Subtype C on Susceptibility to Newer Nonnucleoside Reverse Transcriptase Inhibitors. *Antimicrobial Agents and Chemotherapy*. 2015; **59**: 960–971.

Bharuthram A, Paximadis M, Picton AC and Tiemessen CT. Comparison of a quantitative real-time PCR assay and droplet digital PCR for copy number analysis of CCL4L genes. *Infection Genetics and Evolution.* 2014; **25**: 28–35.

Derdeyn CA, Moore PL, Morris L. Development of broadly neutralizing antibodies from autologous neutralizing antibody responses in HIV infection. *Curr Opin HIV AIDS.* 2014; **9**: 210–6.

Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, Ernandes MJ, Georgiev IS, Kim HJ, Pancera M, Staupe RP, Altae-Tran HR, Bailer RT, Crooks ET, Cupo A, Druz A, Garrett NJ, Hoi KH, Kong R, Louder MK, Longo NS, McKee K, Nonyane M, O'Dell S, Roark RS, Rudicell RS, Schmidt SD, Sheward DJ, Soto C, Wibmer CK, Yang Y, Zhang Z, NISC Comparative Sequencing, Mullikin JC, Binley JM, Sanders RW, Wilson IA, Moore JP, Ward AB, Georgiou G, Williamson C, Abdool Karim SS, Morris L, Kwong PD, Shapiro L, Mascola JR. Developmental pathway for potent VIV2-directed HIV-neutralizing antibodies. *Nature.* 2014; **509**: 55–62.

Garrett N, Werner L, Naicker N, Naranbhai, V, Sibeko S, Samsunder N, Gray CM, Williamson C, Morris L, Abdool Karim QA, Abdool Karim SS. HIV Disease Progression in Seroconvertors from the CAPRISA 004 Tenofovir Gel Pre-exposure Prophylaxis Trial. *J Acquir Immune Defic Syndr.* 2015; **68**: 55–61.

Goga A, Dinh T, Jackson D, Lombard C, Delaney K, Puren A, Sherman G, Woldesenbet S, Ramokolo V, Crowley S, Doherty T, Chopra M, Shaffer N, Pillay Y (for the South Africa PMTCT Evaluation (SAPMCTE) team). First Population-level Effectiveness Evaluation of a National Programme to Prevent HIV Transmission from Mother to Child, South Africa. *J Epidemiol Community Health.* 2014; **0**: 1–9,doi:10.1136/jech-2014-204535.

Hunt G, Morris L, Moorthy A, Coovadia A, Abrams EJ, Strehlau R, Kuhn L and Persaud D. Concordance between allele-specific PCR and ultra-deep pyrosequencing for the detection of HIV-1 non-nucleoside reverse transcriptase inhibitor resistance mutations. *Journal of Virological Method.* 2014; **207**: 182–187.

Hong HA, Paximadis M, Gray GE, Kuhn L and Tiemessen CT. Maternal human leukocyte antigen-G (HLA-G) genetic variants associate with in utero mother-to-child transmission of HIV-1 in Black South Africans. *Infection, Genetics and Evolution.* 2014; **30**: 147–158.

Jemmott JB III, Jemmott LS, O'Leary A, Heeren A, Ngwane Z, Lewis DA, Bellamy SL, Larry D, Icard CG, Heerden A, Tayler JC, Makiwane MB, Teitelman A. Associations Between Psychosocial Factors and Incidence of Sexually Transmitted Disease Among South African Adolescents. *Sex Trans Dis.* 2015; **42**: 135–139.

Jemmott JB III, Jemmott LS, O'Leary A, Ngwane Z, Lewis DA, Bellamy SL, Icard LD, Carty CG, Heeren A, Tyler JC, Makiwane MB, and Teitelman A. HIV/STI Risk-Reduction Intervention Efficacy With South African Adolescents Over 54 Months. *Health Psychology.* 2014; 1. http://dx.doi.org/10.1037/hea0000140

Kepler TB, Liao H-X, Alam SM, Bhaskarabhatla R, Zhang R, Stewart S, Anasti K, Kelsoe G, Parks R, Lloyd KE, Stolarchuk C, Pritchett J, Solomon E, Friberg E, Morris L, Abdool Karim SS, Walter EM, Moody A, Wu X, Altae-Tran HR, Georgiev IS, Kwong PD, Boyd SD, Fire AZ, Mascola JR, Haynes BF. Immunoglobulin gene insertions and deletions in the affinity maturation of HIV-1 broadly reactive neutralising antibodies. *Host Cell & Microbe*. 2014; **16**: 304–13.

Kuhn L, Hunt G, Technau K-G, Coovadia A, Ledwaba J, Pickerill S, Penazzato M, Bertagnolio S, Mellins CA, Black V,Morris L, Abrams EJ. Drug resistance among newly-diagnosed HIV-infected children in the era of more efficacious antiretroviral prophylaxis. *AIDS*. 2014; **28**: 1673–1678.

Kuhn L, Schramm DB, Shiau S, Strehlau R, Pinillos F, Technau K, Coovadia A, Abrams EJ, Puren A, and Tiemessen CT. Young age at start of antiretroviral therapy negative HIV antibody results in HIV-infected children when suppressed. *AIDS*. 2015. In press.

Lai RPJ, Hock M, Radzimanowski J, Tonks P, Hulsik DL, Effantin G, Seilly DJ, Dreja H, Kliche A, Wagner R, Barnett SW, Tumba N, Morris L, LaBranche CC, Montefiori DC, Seaman MS, Heeney JL, Weissenhorn W. A fusion intermediate gp41 immunogen elicits neutralizing antibodies to HIV-1. *J Biol Chem*. 2014; **289**: 29912–26.

Lewis DA. Epidemiology, clinical features, diagnosis and treatment of *Haemophilusducreyi* – a disappearing pathogen Expert Rev. *Anti Infect Ther.* 2014.

Lilian RR, Johnson LF, Moolla H, Sherman GG. A mathematical model evaluating the timing of early diagnostic testing in HIV-exposed infants in South Africa. *J Acquir Immune Def Syndr*. 2014; **67**: 341–348.

Lopes de Campos WRL, Chirwa N, London GM, Rotherham LS, Morris L, Mayosi BM, Khati M. HIV-1 Subtype C unproductively infects Human Cardiomyocytes *in vitro* and induces Apoptosis mitigated by an anti-gp120 aptamer. *PLOS ONE*. 9 (10): e110930.

Loubser S, Paximadis M, Gentle N, Puren A, Gray CM and Tiemessen CT. Frequencies of immune hypersensitivity reaction-associated HLA class I alleles in healthy South African Indian and mixed ancestry populations determined by a novel real-time assay. *Tissue Antigens*. 2014; **84**: 389–397.

Mao C, FirnhaberLu LS, Faesen M, Lewis DA, Goeiema BJ, Swarts AJ, Pam M, Michelow S, Williams JS. Evaluation of a Cervicography-Based Program toEnsure Quality of Visual Inspection of the Cervix in HIV-Infected Women in Johannesburg, South Africa. American Society for Colposcopy and Cervical Pathology. *Journal of Lower Genital Tract Disease*. 2015; **19**: 7–11.

Mcleod K, Omar T, Tiemessen CT, Tshabangu N, and Martinson N. Prevalence of premalignant cervical lesions in women with a long-term non-progressor or HIV controller phenotype. *J AIDS*. 2014; **65**: 29–32.

Mitchell HD, Lewis DA, March K, Hughes MG. Distribution and risk factors of Trichomonas vaginalis infection in England: an epidemiological study using electronic health records from sexually transmitted infection clinics, 2009–2011. *Epidemiol Infect*. 2014; **142**: 1678–1687.

Mlisana K, Werner L, Garrett NJ, McKinnon LR, Van Loggerenberg F, Passmore JS, Gray CM, Morris L, Williamson C, Abdool Karim SS and the CAPRISA 002 Study Team. Rapid disease progression in HIV-1 subtype C infected South African women. *Clinical Infectious Diseases*. 2014; **59**: 1322–31.

Moore PL, Williamson C, Morris L. Virological features associated with the development of broadly neutralizing antibodies to HIV-1. *Trends in Microbiology*. 2015; **23**: 204–211.

Mosha F, Ledwaba J, Ndugulile F, Ng'ang'a Z, Nsubuga P, Morris L, Kasubi M, Swai A, Vercauteren J, Vandamme AM. Clinical and virological response to antiretroviral drugs among HIV patients on first-line treatment in Dar es Salaam, Tanzania. *J Infect Dev Ctries*. 2014; **8**: 845–52.

Müller R, Mulani I, Basson A, Pribut N, Hassam M, Morris L, Van Otterlo W and Pelly S. Novel indole based NNRTIs with improved potency against wild type and resistant HIV. *Bioorg Med Chem Lett*. 2014; **24**: 4376–4380.

Napierala MS, Müller EE, Lewis DA, Chipato T, Morrison C, Weiss HA. Mycoplasmagenitaliumis associated with increased genital HIV-1 RNA in Zimbabwean women. *J Infect Dis*. 2015; **211**: 1388–1398.

Pancera M, Zhou T, Druz A, Georgiev I, Soto C, Acharya P, Gorman J, Stewart-Jones G, Yang Y, Zhang B, Ofek G, Stuckey J, Munro J, Blanchard S, Mothes W, Bailer R, Chuang G-Y, Joyce MG, Louder M, Mascola J, Cohen M, Morris L, Tumba N, Haynes B, Burton D, Koff W, Huang J, Connors M, Kwong P. Structure and immune recognition of trimeric prefusion HIV-1 Env. *Nature*. 2014; **514**: 455–61.

Polonsky JA, Singh B, Masiku C, Langendorf C, Kagoli M, Hurtado N, Berthelote M, Heinzelmanne A, Puren AF, Graisa R. Exploring HIV infection and susceptibility to measles among older children and adults in Malawi: a facility-based study. *International Journal of Infectious Diseases*.

Prach LM, Puren A, Lippman SA, Carmona S, Stephenson S, Cutler E, Barnhart S, Liegler T. Design and implementation of an external quality assessment program for HIV viral load measurements using dried blood spots. *J Clin Microbiol*. 2015; **53**: 964–6.

Radebe F, Gumede L, Ricketts C, Vezi A, Maseko V, Lewis DA. The Evaluation and comparison of two transport media for the growth, holding and transport of Neisseria gonorrhoeae. *Inter J Med & Bio Sci*. 2014; **2**: 39-45.

Remco CPH, Peters JH, van der Eem LD, Verweij SP, Myrte LA, Ouburg BS, Lewis DA, Struthers H, McIntyre JA, and Morré SA. Cross-Sectional Study of Genital, Rectal, and Pharyngeal Chlamydia and Gonorrhea in Women in Rural South. *Sex Trans Dis*. 2014; **41**: 564–569.

Trama AM, Moody MA, Alam SM, Jaeger FH, Lockwood B, Parks R, Lloyd KE, Stolarchuk C, Scearce Foulger RA, Marshall D, Whitesides JF, Jeffries TL Jr, Wiehe K, Morris L, Lambson B, Soderberg K, Hwang K-K, Tomaras GD, Vandergrift N, Jackson KJ, Roskin KM, Boyd SD, Kepler TB, Liao H-X, and Haynes BF. HIV-1 envelope gp41 antibodies can originate from terminal Ileum cells that share cross-reactivity with commensal bacteria. *Cell Host and Microbe*. 2014; **16**: 215–226.

Wei X, Hunt G, Abdool Karim SS, Naranbhai V, Sibeko S, Abdool Karim Q, Li J-F, Kashuba ADM, Werner L, Passmore JS, Morris L, Heneine W, Johnson JA. Sensitive Tenofovir resistance screening of HIV-1 from the genital and blood compartments of women with breakthrough infections in the CAPRISA 004 Tenofovir gel trial. *J Infect Dis*. 2014; **209**: 1916–20.

Wiehe K, Easterhoff D, Luo K, Nicely N, Bradley T, Jaeger FH, Dennison SM, Zhang R¬, Lloyd KE, Stolarchuk C, Parks R, Sutherland LL, Scearce RM, Morris L, Kaewkungwal J, Nitayaphan S, Pitisuttithum P, Rerks-Ngarm S, Michael M, Kim J, Kelsoe G, Montefiori DC, Tomaras G, Bonsignori M, Santra S, Kepler TB, Alam SM, Moody MA, Liao H-X, and Haynes BF. Phylogenetic conservation of light chain-restricted recognition of the site of immune pressure in an HIV-1 vaccine trial. *Immunity*. 2014; **41**: 909–18.

Woldesenbet SA, Jackson D, Goga AE, Crowley S, Doherty T, Mogashoa MM, Dinh TH, Sherman GG. Missed opportunities for Early Infant HIV Diagnosis: Results of a National Study in South Africa. *J Acquir Immune Defic Syndr*. 2015; **68**: e26–32, doi: 10.1097/QAI.0000000000000460.

Centre for Opportunistic, Tropical and Hospital Infections

Centre Head: Prof. John Frean

Centre Co-Head: Dr Nelesh Govender

Centre Co-Head: Dr Basil Brooke

Centre Co-Head: Prof. Olga Perovic

The surveillance, reference and research thrusts of the Centre include opportunistic infections, particularly those that are related to HIV/AIDS; tropical infections, especially malaria and its vectors; and nosocomial infections, concentrating on antimicrobial resistance, molecular epidemiology and outbreak investigations in the hospital setting. A satellite Molecular Epidemiology Unit, based at Groote Schuur Hospital in Cape Town, focuses on nosocomial infections and antimicrobial resistance.

Surveillance, Diagnostic and Reference Services

In the Antimicrobial Resistance Reference Laboratory (AMRRL), phenotypic and genotypic characterisation of mechanisms of bacterial resistance was aimed at ESKAPE organisms (*Enterococcus, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas* and ESBL (*Enterobacter* and *E. coli*)), with special focus on *Staphylococcus aureus, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. A reference service was offered for all multidrug-resistant organisms, such as the emerging carbapenem-resistant Enterobacteriaceae, at the NICD and its satellite unit at the University of Cape Town. Other specialised diagnostic services offered by the Parasitology and Mycology Reference Laboratories are in the fields of opportunistic or unusual parasitic and fungal infections. Surveillance functions encompassed national and regional monitoring of cryptococcal meningitis, candidaemia, pneumocystosis, protozoal diarrhoea, and antibiotic-resistant hospital infections.

The Centre provides an identification service for medically important arthropods for entomologists, medical practitioners and environmental health officers. Malaria vector mosquitoes were routinely identified and insecticide-resistance studies were carried out by the Vector Control Reference Laboratory for Mpumalanga's Malaria Control Programme and the WHO Pesticide Evaluation Scheme. Malaria parasite infection surveillance has been expanded to support the Department of Health's plans to halt malaria transmission in South Africa. These activities include antimalarial drug resistance, submicroscopic and gametocyte infection detection, malaria serology and rapid diagnostic test quality assessment. Advice and expertise were provided to the Department of Health, both at national and provincial levels, with participation on the SA Malaria Elimination Committee.

Quality assessment (QA) services provided by the Centre contributed to assessing diagnostic laboratory proficiency in South Africa and other African countries in malaria, bacteriology, mycology and tuberculosis. The Centre has played an active role in reporting on laboratory capacity in the WHO African region for the past 12 years, and has supported QA for laboratories for international malaria vaccine trials. 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.

The Centre was also involved in outbreak investigations and responses during 2014/15. These included cases of malaria affecting Gauteng residents without recent travel history, that is, odyssean malaria, which has increased substantially (including some deaths) over the past few years. Entomological investigations revealed no evidence of local breeding of vector anophelines. The Centre led the investigation of outbreaks of neonatal candidaemia at a Gauteng hospital and carbapenem-resistant Enterobacteriaceae in private health facilities.

Current Research and Surveillance

Insecticide resistance in malaria vectors

Anopheles arabiensis is a major malaria vector in much of sub-Saharan Africa, including South Africa. Resistance to insecticides in populations of this species is widespread, necesitating ongoing research into the mechanisms conferring resistance. Recent investigations showed that pyrethroid and DDT resistance in *An. arabiensis* in Sudan is based on target site mutations as well as detoxification mechanisms. It was also demonstrated that infection with the entomopathogenic fungus *Beauveria bassiana* does not affect the expression of the metabolic resistance genes in South African and Sudanese *An. arabiensis*, supporting the hypothesis that fungal pathogens are suitable candidates in the search for novel malaria vector control strategies. Research on *An. arabiensis* also showed that multiple blood feeding confers a competitive advantage on insecticide-resistant females by increasing their longevity and maintaining the expression of insecticide resistance with age. *Anopheles funestus* is also a major malaria vector in sub-Saharan Africa. Material recently collected from Zambia and Zimbabwe showed resistance to pyrethroid and carbamate insecticides. These collections also included the first record of *An. funestus* mtDNA clade II in Zambia. In addition, experimental work on laboratory-reared strains of *An. funestus* showed that monooxygenase-based pyrethroid resistance in southern African populations of this species is primarily expressed in the adult stage, suggesting that these resistance factors can only be selected at the adult stage. In general, the incidence of insecticide resistance in malaria vector populations is increasing at an alarming rate and has

necessitated the development of online mapping tools such as the IR Mapper database, which was recently launched. This tool will enable investigations into temporal and spatial trends in insecticide resistance distribution.

Collaborators: *Dr T Knox (World Health Organization), Prof. H Ranson (Liverpool School of Tropical Medicine), Dr S Blanford (Penn State University)*

Malaria vector control and transmission dynamics

Understanding the biology of malaria vector mosquitoes is critical for disease epidemiology and vector control. This is especially important in terms of how climate change is likely to affect malaria transmission. It was shown that tolerance to desiccation in the African malaria vectors *An. funestus* and *An. arabiensis* is based on a reduced water loss rate. It was also shown that *An. funestus* is substantially less tolerant to increasing salinity in larval breeding sites than the closely related species, *An. rivulorum*. These data are likely to prove important in the development of population dynamic models of these vectors. Understanding male mosquito biology is an important component in the development of novel vector control strategies, such as the sterile insect technique (SIT). It was shown that temperature affects male genital rotation, which affects the rate at which they become sexually mature. In terms of developing the SIT as a potential malaria vector control intervention in South Africa, a recent survey of *Anopheles* mosquito fauna in the northern Kruger National Park (KNP) was completed. This survey shows that several anopheline species occur in the KNP, including perennial populations of *An. arabiensis*. The major malaria vector species, *An. gambiae,* is closely related to *An. arabiensis*. It was shown that the phenomenon of delayed time-to-hatch in *An. gambiae* eggs is based on a diapause state causing some eggs to hatch later. Delayed hatching is likely an adaptation to maximise reproductive output, despite the increased risk of desiccation in an unstable aquatic environment.

Collaborators: *Dr C Lyons (University of Stellenbosch), Dr SChown (Monash University, Australia), Prof. F Duncan (University of the Witwatersrand), Dr D Govender (South African National Parks (SANParks)), Mr A Mabuza (Department of Health, Mpumalanga)*

Laboratory-based antimicrobial resistance surveillance for nosocomial bacteria (LARS)

Laboratory surveillance for antimicrobial resistance (AMR) provides the platform for future co-ordination, with the generation of reliable data on the occurrence of AMR in different geographical regions. A limited number of nosocomial bacterial pathogens such as *Staphylococcus aureus*, *Klebsiella pneumoniae* (2010–2012), and *Pseudomonas aeruginosa* (from 2014) were chosen to monitor trends in resistance at sentinel sites at the NHLS over the reporting period.

Collaborators: *A Whitelaw, A Duse, A Hoosen, C Samuel, C Bamford, M Nicol, J Wadula, P Naicker, R Kularatne, S Seetharam, T Nana, N Bosman, N Mbelle, R Lekalakala, H Dawood, S Haffejee, K Mlisana, Y Coovadia, K SweSwe Han, P Ramjathan, P Bohla*

Carbapenemase screening and characterisation

Carbapenem non-susceptible isolates obtained from eight provinces during routine diagnostic testing at the NHLS were confirmed at the NICD, and isolates from Western Cape Laboratories (Groote Schuur Hospital, Tygerberg Hospital and George Hospital) were submitted to the NICD Satellite Unit for carbapenemase gene characterisation.

Collaborators: *L Robberts and D Rip (University of Cape Town)*

Molecular epidemiology of *Clostridium difficile*

Specimens found to be positive for *C. difficile* from patients admitted to Groote Schuur Hospital are characterised using molecular fingerprinting and results are communicated to Infection Control to assist with infection prevention and control activities. Environmental sampling to identify hospital sources of infection are performed via characterisation using multi-locus variable tandem repeat analysis (MLVA), ribotyping, and antimicrobial drug susceptibility testing.

Collaborators: *Dr B Kullin and Prof. S Reid, Dept. of Molecular and Cell Biology, University of Cape Town*

Pneumocystis jirovecii pneumonia (PCP) in hospitalised patients with severe acute respiratory infections (SARI) using an existing surveillance network in South Africa

Surveillance is being done for PCP in adults and children at sentinel sites in North West and KwaZulu-Natal provinces. The relative contribution of PCP to the burden of severe acute respiratory infections is being determined together with the Centre for Respiratory Diseases and Meningitis, NICD.

Sentinel surveillance for parasitic causes of diarrhoea in hospitalised children

Five sentinel sites provide stool samples from children under the age of five with diarrhoea as part of a rotavirus surveillance programme. Residual samples are screened for bacterial and parasitic pathogens. About 13% of samples contain pathogenic parasites, but the vast majority (>95%) are *Cryptosporidium* species. Genotyping has previously shown that these are predominantly *C. hominis*. This human-specific species is therefore emerging as an important cause of childhood diarrhoea in South Africa.

Malaria parasite infection surveillance

The NICD is re-establishing the country's only molecular antimalarial drug resistance surveillance programme, as well as initiating surveillance for submicroscopic malaria infections, gametocyte carriage, and will undertake malaria serosurveys. The rate of false results of malaria rapid diagnostic tests will also be investigated. These efforts are all in support of the National Department of Health's plans to eliminate transmission of malaria in South Africa by 2018.

Collaborators: *Provincial Malaria Control Programmes of Limpopo, Mpumalanga and KwaZulu-Natal provinces; Prof. I Kleinschmidt, London School of Hygiene and Tropical Medicine*

Monitoring and evaluation of a public health intervention: screen-and-treat for cryptococcal disease

Cryptococcal meningitis (CM), a common AIDS-defining fungal opportunistic infection, has a fatal outcome in more than half of cases in routine care in South Africa. In 2013, 6 273 new cases of laboratory-confirmed CM were detected by the NICD. In two multi-site, randomised clinical trials, cryptococcal antigen (CrAg) screening of HIV-infected persons with a CD4 count <100 cells µL at the time of their initial CD4 count and pre-emptive oral fluconazole resulted in a ~30% relative reduction in 6–12 month mortality on ART. Two laboratory-based approaches have been tested in South Africa to date. Reflex laboratory CrAg testing was implemented at three NHLS laboratories serving 199 healthcare facilities in four districts of Gauteng and the Free State. This was paired with healthcare worker training and intensive monitoring and evaluation. From September 2012 through to April 2015, 34 848 people were screened, 1 160 (3%) of whom tested CrAg-positive. In parallel, clinician-initiated CrAg screening was implemented at all ART facilities in five Western Cape districts, with no clinical training. Only 20% of eligible patients were screened, 2.4% of whom screened CrAg-positive. Detailed clinical guidance for the screen-and-treat intervention was included in the 2015 national consolidated guidelines for HIV and will spur implementation across the country. If properly implemented, this intervention has the potential to directly reduce deaths associated with CM.

Programme partners: *Department of Health, USAID, CDC, PEPFAR partners*

A description of clinical cases of disseminated emmonsiosis

We have recently described the geographic distribution, clinical characteristics and management of patients with disease caused by *Emmonsia* sp., a novel dimorphic fungal pathogen recently described in South Africa. We performed a multicentre, retrospective chart review of laboratory-confirmed cases of emmonsiosis diagnosed across South Africa from January 2008 through to February 2015. Fifty-four patients were diagnosed in five provinces. Fifty-one patients (94%) were HIV co-infected (median CD4 count 16 cells/µL). All patients had disseminated disease, most commonly involving the skin and lung. Twenty-four of 34 patients (71%) treated with amphotericin B deoxycholate survived, vs. 4/12 (33%) treated with a triazole alone (P=0.04). Twenty-six patients (48%) died, including eight who did not receive antifungals. Continuing work on this fungal pathogen and disease is focused on the development of an accurate diagnostic assay (antigen and/or molecular assays), whole genome sequencing and exploration of its ecological niche.

Collaborators: *Prof. C Kenyon (University of Cape Town), Dr I Schwartz (University of Antwerp)*

Clinical epidemiology of candidaemia at sentinel hospitals in seven provinces, including a large outbreak investigation

Patients with candidaemia were identified through active laboratory-based surveillance at sentinel hospitals in seven provinces (except Gauteng and the Western Cape, where surveillance was conducted in previous years) in 2014/15. An incident case of candidaemia was defined as the isolation of *Candida* species from the first submitted blood culture. Detailed clinical information was collected, including underlying diseases and in-hospital mortality. Identification of isolates and antifungal susceptibility testing was performed at the Centre. From August 2014 onwards, we conducted an investigation of a large outbreak of candidaemia at a sentinel hospital. During 2014, 80/118 (68%) cases of candidaemia (all *Candida* species), occurred in the neonatal intensive care unit (NICU) of this sentinel hospital; 48 neonatal cases of *Candida krusei* were detected from

July through to October of 589 admissions to the NICU (attack rate 8.1%). Overlapping collection dates for the first positive specimen suggested a propagated outbreak. Risk factors, which were significantly associated with *C. krusei* candidaemia, included necrotising enterocolitis (NEC), birth weight <1 500 g and being admitted during the months of July and August. Neonates weighing 1 000–1 500 g at birth were seven times more likely to develop candidaemia than those with a body weight of over 2 500 g. At the time of audit, the patient census was 12% above the ward's bed capacity and staff compliance with hand-washing protocols was 76%. *C. krusei* was not isolated from the environment.

Collaborators: *Dr S Mahlangu, Dr B Maloba, Dr G Ntlemo, Dr K Sanyane, Prof. D Mawela (Medunsa)*

Research Funding

Centers for Disease Control and Prevention through NHLS/CDC Co-operative Agreement

German Academic Exchange Service (DAAD)

Gates Grand Challenges Explorations

Global Disease Detection, Centers for Disease Control and Prevention

Hillel Friedland Fellowship

Innovative Vector Control Consortium

International Atomic Energy Agency (IAEA)

London School of Hygiene and Tropical Medicine

Medical Research Council of South Africa

NHLS Research Trust

National Institutes of Health

National Institutes of Health (ICEMR – Johns Hopkins Malaria Institute)

National Research Foundation (SARChI, NRF Incentive, DST-NRF Centre of Excellence for Invasion Biology and DST/NRF Research Chair awards)

Pennsylvania Department of Health (Tobacco Settlement Funds)

Research and Policy for Infectious Disease Dynamics (RAPIDD) Programme

Sir Ratanji Dalal Research Scholarship

South African Nuclear Energy Corporation (Necsa)

Stellenbosch University Hope Project

Carnegie-Wits Alumni Diaspora Programme

Teaching and Training

Teaching and training in various aspects of bacteriology, parasitology, mycology, entomology and communicable diseases were provided to students at postgraduate level (MSc, PhD), medical students, technicians, medical technologists, intern medical scientists, pathology registrars, SASTM travel medicine course participants as well as doctors enrolled in a postgraduate Diploma in Tropical Medicine and Hygiene (DTM&H). The Centre assisted the Department of Health with the development of laboratory and clinical training materials for the relevant disease programmes.

Professional Development

Postgraduate students enrolled: 17 (ten MSc, seven PhD)

Postgraduate students graduated: five (four MSc, one PhD)

Honours

Dr NP Govender was nominated by the University College London (UCL) Board of Examiners for the Dean's Research Prize for his dissertation for his Master of Science degree in Medical Mycology.

Dr NP Govender was awarded first prize in the oral abstract category at the Southern African HIV Clinicians' Society conference in 2014 for an abstract titled *Cryptococcal screening in Gauteng Province, South Africa: update from the first two years of implementation,* 2012–2014.

Prof. Maureen Coetzee was awarded the Elsdon Dew Medal for contributions to parasitology by the Parasitological Society of South Africa.

Research Output

Top five publications from the Centre

Munhenga G, Brooke BD, Spillings BL, Essop L, Hunt RH, Midzi S, Govender D, Braack L, Koekemoer LL. Field study site selection, species abundance and monthly distribution of anopheline mosquitoes in the northern Kruger National Park, South Africa. *Malaria Journal*. 2014; **13**: 27.

Synopsis: This manuscript details a survey of *Anopheles* fauna in the northern Kruger National Park and shows that there is a perennial presence of the major malaria vector *Anopheles arabiensis* at the Malahlapanga thermal spring, which may be a suitable locality for conducting a pilot study of the feasibility of using the sterile insect technique for malaria vector control.

Govender NP, Roy M, Mendes JF, Zulu TG, Chiller TM and Karstaedt AS. Evaluation of screening and treatment of cryptococcal antigenaemia among HIV-infected persons in Soweto, South Africa. *HIV Medicine*. 2015. Published online 17 Feb 2015, doi: 10.1111/hiv.12245.

Synopsis: After screening and pre-emptive treatment for cryptococcal disease was implemented at an HIV clinic in Soweto, we retrospectively determined the operational barriers to setting up this intervention in a real-world setting.

Magobo RE, Corcoran C, Seetharam S, Govender NP. *Candida auris*-associated candidemia, South Africa. *Emerging Infectious Diseases*. 2014; **20**: 1250–1251.

Synopsis: We described the emergence of candidaemia caused by *Candida auris*, an unusual and azole-resistant fungal pathogen, in South Africa.

Moodley K, Govind CN, Peer AKC, Van der Westhuizen M, Parbhoo D, Ming Sun L, Du Plessis DC, Frean JA. First detection of human dirofilariasis in South Africa. *Infectious Disease Reports*. 2015; **7**: 5 726.

Synopsis: We describe two patients with dirofilariasis, an accidental zoonotic infection of humans acquired via a mosquito vector, with companion dogs and cats as the main reservoir hosts. Although endemic in Europe and North America, the infection has never previously been described in humans in southern Africa.

Perovic O, Singh-Moodley A, Duse A, Bamford C, Elliott G, Han KS, Kularatne R, Lowman W, Whitelaw A, Nana T, Wadula J, Lekalakala R, Saif A, Fortuin De-Smit M, Marais E. National sentinel site surveillance for antimicrobial resistance in *Klebsiella pneumoniae* isolates in South Africa, 2010–2012. *South African Medical Journal* 2014; **104**: 563–568.

Synopsis: The increasing rates of antimicrobial resistance observed in the nosocomial pathogen *Klebsiella pneumonia* are of major public health concern worldwide. We described the antibiotic susceptibility profiles of *K. pneumonia* isolates from bacteraemic patients submitted by sentinel laboratories in five regions of South Africa from mid-2010 to mid-2012. Molecular methods were used to detect the most commonly found extended-spectrum beta-lactamase (ESBL) and carbapenemase-resistant genes.

Other Publications

Abdalla H, Wilding CS, Nardini L, Pignatelli P, Koekemoer LL, Ranson H, Coetzee, M. Insecticide resistance in *An. arabiensis* in Sudan: temporal trends and underlying mechanisms. *Parasites & Vectors*. 2014; **7**: 213.

Bengis R, Frean J. Anthrax as an example of the 'One Health' concept. *OIE Scientific and Technical Review.* 2014; **33**: 593–604.

Blumberg L, Frean J, Moonasar D and the SA Malaria Elimination Committee. Successfully controlling malaria in South Africa. *South African Medical Journal.* 2014; **104S**: S224–S227.

Choi KS, Christian R, Nardini L, Wood OR, Agubuzo E, Muleba M, Munyati S, Makuwaza A, Koekemoer LL, Brooke BD, Hunt R H, Coetzee M. Insecticide resistance and role in malaria transmission of *Anopheles funestus* populations from Zambia and Zimbabwe. *Parasites & Vectors.* 2014; **7**: 464.

Coetzee M. How important are Dipteran vectors of disease in Africa? *Transactions of the Royal Society of Tropical Medicine & Hygiene*. 2014; **108**: 179–180.

Dahan YL, Koekemoer LL. Analysis of the genitalia rotation in the male *Anopheles funestus* (Diptera: Culicidae). *Acta Tropica.* 2014; **132S**: S20–S25.

Fortuin-de Smidt MC, Singh-Moodley A, Badat R, Quan V, Kularatne R, Nana T, Lekalakala R, Govender NP, Perovic O, for GERMS-SA. *Staphylococcus aureus* bacteraemia in Gauteng academic hospitals, South Africa. *International Journal of Infectious Diseases*. 2015; **30**: e41–e48.

Frean J, Brooke B, Thomas J, Blumberg L. Odyssean malaria outbreaks in Gauteng Province, 2007–2013. *South African Medical Journal.* 2014; **104**: 335–338.

Govender NP, Magobo RE, Zulu TG, Du Plooy M, Corcoran C. Disseminated fatal *Talaromyces (Pencillium) marneffei* infection in a returning HIV-infected traveller. *Southern African Journal of HIV Medicine.* 2014; **15**: 154–155.

Govender NP, Meintjes G, Banoo S. Access to flucytosine for HIV-infected patients with cryptococcal meningitis: an urgent need. *South African Medical Journal.* 2014; **104**: 594–595.

Govender NP, Dlamini S. Management of HIV-associated cryptococcal disease in South Africa. *South African Medical Journal.* 2014; **104**: 896.

Jarvis JN, Bicanic T, Loyse A, Meintjes G, Hogan L, Roberts CH, Shoham S, Perfect JR, Govender NP, Harrison T S. Very low levels of 25-hydroxyvitamin D are not associated with immunologic changes or clinical outcome in South African patients with HIV-associated cryptococcal meningitis. *Clinical Infectious Diseases.* 2014; **59**: 493–500.

Kaiser ML, Duncan FD, Brooke BD. Embryonic development and rates of metabolic activity in early and late hatching eggs of the major malaria vector *Anopheles gambiae*. *PLOS ONE* 2014; 9: e114381.

Knox TB, Juma EO, Ochomo EO, Jamet HP, Ndungo L, Chege P, Bayoh MN, N'guessan R, Christian RN, Hunt RH, Coetzee M. An online tool for mapping insecticide resistance in major *Anopheles* vectors of human malaria parasites and review of resistance status for the Afrotropical region. *Parasites & Vectors.* 2014; **7**: 76.

Koekemoer LL, Waniwa K, Brooke BD, Nkosi G, Mabuza A. Larval salinity tolerance of two members of the *Anopheles funestus* group. *Medical and Veterinary Entomology.* 2014; **28**: 187–192.

Ladapo TA, Nourse P, Pillay K, Frean J, Birkhead M, Poonsamy B, Gajjar P. Microsporidiosis in pediatric renal transplant patients in Cape Town, South Africa: Two case reports. *Pediatric Transplantation.* 2014; **18**: e220–e226.

Lees RS, Knols B, Bellini R, Benedict MQ, Bheecarry A, Bossin HC, Chadee DD, Charlwood J, Dabire RK, Djogbenou L, Egyir-Yawson A, Gato R, Gouagna LC, Hassan MM, Khan SA, Koekemoer LL, Lemperiere G, Manoukis NC, Mozuraitis R, Pitts RJ, Simard F, Gilles J. Review: Improving our knowledge of male mosquito biology in relation to genetic control programmes. *Acta Tropica.* 2014; **132S**: S2–S11.

Lyons CL, Coetzee M, Terblanche JS, Chown SL. Desiccation tolerance as a function of age, sex, humidity and temperature in adults of the African malaria vectors *Anopheles arabiensis* and *Anopheles funestus*. *Journal of Experimental Biology*. 2014; **217**: 3823–3833.

Nardini L, Blanford S, Coetzee M, Koekemoer LL. Effect of *Beauveria bassiana* infection on detoxification enzyme transcription in pyrethroid resistant *Anopheles arabiensis*: a preliminary study. *Transactions of the Royal Society of Tropical Medicine & Hygiene.* 2014; **108**: 221–227.

Oliver SV, Brooke BD. The effect of multiple blood-feeding on the longevity and insecticide resistant phenotype in the major malaria vector *Anopheles arabiensis* (Diptera: Culicidae). *Parasites & Vectors.* 2014; **7**: 390.

Roberts DR, Maharaj R, Coetzee M, Hunt RH, Govere J, Tren R, Urbach J, Attaran A, Blumberg L. Response to Bouwman H, *et al*. Halogenated pollutants in terrestrial and aquatic bird eggs: Converging patterns of pollutant profiles, and impacts and risks from higher levels. *Environmental Research.* 2014; **132**: 457–458.

Strydom KA, Ismail F, Frean J. *Plasmodium ovale* malaria: a case of not-so-benign tertian malaria. *Malaria Journal.* 2014; **13**: 85.

Van Hougenhouck-Tulleken WG, Papavarnavas NS, Nel JS, Blackburn LY, Govender NP, Spencer DC, Lippincott CK. HIV-associated disseminated emmonsiosis, Johannesburg, South Africa. *Emerging Infectious Diseases.* 2014; **20**: 2164–2166.

Wood OR, Spillings BL, Hunt RH, Koekemoer LL, Coetzee M, Brooke BD. Sub-lethal pyrethroid exposure at the larval or adult life stage and selection for resistance in the major African malaria vector *Anopheles funestus* (Diptera: Culicidae). *African Entomology.* 2014; **22**: 636–642.

Yamada H, Vreysen MJB, Gilles JRL, Munhenga G, Damiens DD. The effects of genetic manipulation, dieldrin treatment and irradiation on the mating competitiveness of male *Anopheles arabiensis* in field cages. *Malaria Journal.* 2014; **13**: 318.

Book Chapters

Frean J. Animal bites. *In*: Blumberg L (ed.). *MIMS Handbook of Infectious Diseases.* Johannesburg: MIMS, 2014: 216–220.

Frean J. Intestinal worms. *In*: Blumberg L (ed.). *MIMS Handbook of Infectious Diseases.* Johannesburg: MIMS, 2014: 203–207.

Frean J. Schistosomiasis. *In*: Blumberg L (ed.). *MIMS Handbook of Infectious Diseases.* Johannesburg: MIMS, 2014: 198–202.

Govender NP. Fungal infections in general practice. *In*: Blumberg L (ed.). *MIMS Handbook of Infectious Diseases.* Johannesburg: MIMS, 2014: 95–102.

Perovic O. Understanding antibiotics. *In*: Blumberg L (ed.). *MIMS Handbook of Infectious Diseases.* Johannesburg: MIMS, 2014: 208–215.

Stein CM, Parry C, Frean J, Warrell D, Suputtamongkol Y, Griffith K, *et al.* Multi-system diseases and infections. *In*: Davidson R, Brent A, Seale A (eds). *Oxford Handbook of Tropical Medicine*, 4th edition. Oxford: Oxford University Press. 2014: 729–822.

Conference Presentations

International: 12

National: 12

Local: several

Centre for Respiratory Diseases and Meningitis (CRDM)

Centre Co-Head: Associate Prof. Cheryl Cohen

Centre Co-Head: Dr Florette Treurnicht
(acting head March 2014)

Centre Co-Head: Associate Prof. Anne von Gottberg

During 2014/15, the centre continued to perform its core functions of syndromic surveillance for pneumonia and influenza-like illness (ILI) at sentinel sites within South Africa and laboratory-based surveillance for important bacterial causes of invasive bacterial disease and meningitis throughout the country through the GERMS-SA platform. Using these surveillance programmes, the centre identified key seasonal and epidemiological variations of viral and bacterial pathogens. This year the centre published important data documenting the reductions in invasive pneumococcal disease in South Africa and estimates of vaccine effectiveness following the introduction of the pneumococcal conjugate vaccine into the expanded programme on immunisation in 2009. In addition, detailed data on burden and risk groups for important respiratory pathogens such as influenza were generated. These data are essential to implement and monitor the impact of ongoing interventions, and to plan for future interventions to reduce the burden of severe disease and death due to pneumonia and meningitis.

The centre expanded its capacity to use new diagnostic technologies such as the Taqman® Array Card (TAC, Life Technologies) to assist with surveillance. The centre continues to provide polymerase chain reaction (PCR) testing of samples as the WHO/ Regional Office for Africa (AFRO) Regional Reference Laboratory for vaccine-preventable invasive bacterial diseases (VP-IBD) for the southern and east African region. This function includes site visits and ongoing training to improve surveillance systems in these countries. The CRDM continues to function as a WHO National Influenza Centre (NIC), and with a newly established biosafety level 3 laboratory, the CRDM/NIC will expand work to support the diagnosis of known and emerging causes of respiratory diseases and meningitis in South Africa and the region.

Current Surveillance Programmes

Pneumonia surveillance

A protocol for pneumonia surveillance was developed to replace the Severe Acute Respiratory Illness (SARI) Programme, including surveillance for severe respiratory illness, irrespective of duration of symptoms and testing for core pathogens of public health importance. Ethical approval was obtained for this surveillance and the programme was started in April 2015. In the year under review, the SARI Programme ascribed the contribution of influenza, other respiratory viruses and pneumococcus to the SARI syndrome at all surveillance sites. At two of the surveillance sites surveillance was enhanced to describe the pathogens associated with more chronic respiratory illness, and includes collection and testing of specimens for atypical bacterial causes of pneumonia, *Pneumocystis jirovecii*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Bordetella pertussis*, *Haemophilus influenzae* and atypical bacterial causes of pneumonia (*Legionella* species, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*). Surveillance for ILI is ongoing in outpatient clinics at two sites.

Ongoing influenza surveillance

In 2014, influenza A(H3N2) dominated the influenza season and we had a 67% (50/75) success rate for isolating these strains in cell cultures. Most H3N2 viruses were similar to viruses in the genetic lineage 3C.3. They include the sublineage 3C.3a, in which is the vaccine strain recommended for the 2015 influenza vaccine groups. Influenza A(H1N1)pdm09 and influenza B were circulating at frequencies of 12% and 16% respectively. Influenza A(H1N1) viruses belonged to the subgroup 6B and reacted well to the vaccine strain antisera. Influenza B strains mainly grouped with the 2014 vaccine strain, B/Massachusetts/2/2012 in the clade 2 of the B/Yamagata lineage. No reduction in susceptibility to oseltamivir was observed.

Laboratory-based surveillance

The CRDM continues to contribute to the evaluation of the impact of both the pneumococcal conjugate vaccines (PCV) and the *Haemophilus influenzae* serotype b conjugate vaccine (Hib CV) through national, laboratory and population-based, active surveillance for invasive pneumococcal and Hib disease and case-control and other epidemiologic studies. The CRDM also contributes data on numbers and serogroups of *Neisseria meningitidis* and supports diagnostic testing and outbreak response for suspected cases of meningococcal meningitis.

Specific/Selected Projects

Pneumonia and Influenza-like Illness Surveillance

Influenza vaccine effectiveness, 2014

The effectiveness of the trivalent seasonal influenza vaccine was assessed using a test-negative case-control study design including 472 cases and 362 controls. The overall vaccine effectiveness estimate, adjusted for age and underlying conditions,

was 43.1% (95% CI: -26.8%–74.5%). In 2014, influenza A(H3N2) dominated the season and was mainly in sub-lineage 3C.3 with amino acid mutations that were different to those of the vaccine strain in the 2014 vaccine strain of sublineage 3C.1.

Household transmission of influenza in HIV-infected and HIV-uninfected individuals

The overall secondary attack rate (SAR) for influenza was 27%. The SAR from the HIV-infected index cases was 19% and 32% from the HIV-uninfected cases (odds ratio (OR): 0.5; 95% confidence interval (CI): 0.3–0.9). The SAR stratified by age group of index cases: under 5 years old (SAR: 42%; OR: 2.4, 95% CI: 1.3–4.2) and >=5 years (SAR: 23%). On multivariable analysis, adjusting for age of the index case, number of people and crowding in the household, the odds of a household contact being infected with influenza from a HIV-infected index case was 0.4 (95% CI: 0.2–1.1). HIV-infected index cases appeared to be less likely to transmit influenza to household contacts.

Risk factors for influenza in individuals aged ≥5 years

Adults in specific risk groups are recommended to receive annual influenza vaccinations. On multivariable analysis, factors independently associated with increased risk of influenza-associated SARI hospitalisation were: (i) ≥65 years of age compared to 5–24 years (aOR: 34.9; 95% CI: 5.7–215.1); (ii) underlying medical conditions (aOR: 5.1; 95% CI: 1.7–14.8); (iii) working in mines (aOR: 16.5; 95% CI: 2.9–93.3); and (iv) HIV infection (aOR: 3.9; 95% CI: 1.4–11.2). Among women of childbearing age on multivariable analysis, adjusting for confounders, pregnancy remained significantly associated with increased risk of influenza-associated SARI hospitalisation (aOR: 21.5; 95% CI: 2.5–185.9).

The attributable fraction of influenza and other respiratory virus infections among patients with SARI and ILI

We enrolled 1 739 patients with SARI, 3 538 outpatient cases with ILI and 1 440 controls. In children under 5 years of age, influenza virus (attributable fraction (AF): 90.5; 95% CI: 75.7–96.3), RSV (AF: 91.0; 95% CI: 85.0–94.6), hMPV (AF: 90.8; 95% CI: 69.6–97.2) and to a lesser extent rhinovirus (AF: 38.8; 95% CI: 20.5–52.8) infections were associated with severe disease. Influenza had the highest AF-adjusted prevalence (AF: 94.7%; prevalence of illness: 14.0%) among children under five years of age with ILI. Influenza, RSV and hMPV can be considered likely pathogens if detected in patients with ILI and SARI, while rhinovirus in comparison may cause a proportion of clinical disease that manifests either as ILI or SARI.

Influenza mortality in pregnant women

We used Poisson regression modelling of vital statistics data to estimate mortality in pregnant women. Among women of childbearing age, the majority of seasonal influenza-associated deaths occurred among HIV-infected individuals. Pregnant women had an increased risk of death associated with seasonal A(H1N1)pdm09 influenza infection, compared to non-pregnant women. During 1999–2009 the mean annual seasonal influenza-associated mortality rates were 13 (123 deaths) and seven (914 deaths) among pregnant and non-pregnant women respectively. Among pregnant women, the mean annual seasonal influenza-associated mortality rates were 75 (109 deaths) among HIV-infected women and two (14 deaths) among HIV-uninfected individuals. Among non-pregnant women the mean annual seasonal influenza-associated mortality rate was 41 (824 deaths) in HIV-infected and one (90 deaths) among HIV-uninfected individuals. Pregnant women experienced an increased risk of seasonal influenza-associated mortality compared to non-pregnant women (relative risk [RR]: 2.8; 95% confidence intervals [CI]: 2.1–3.7). In 2009 the influenza A(H1N1)pdm09-associated mortality rates were 19.3 (181 deaths) and 9.4 (1189 deaths) among pregnant and non-pregnant women respectively (RR: 3.2; 95% CI: 2.3–4.1).

Laboratory-based Surveillance

Molecular epidemiology of invasive serogroup A meningococcus in South Africa, 2003–2012

Two pandemic serogroup A (MenA) clones (ST1 and ST5/ST7) have been circulating in South Africa since 1968 and 1996 respectively. Endemic MenA, collected through the invasive meningococcal disease (IMD) surveillance from 1999–2002, was predominantly ST-1 with a small proportion of ST7. Of the samples collected, 34 randomly selected MenA isolates were characterised from 2003–2012 using whole genome analysis. A total of 4 535 IMD cases were reported and 63% (n=2 865) had viable isolates. MenA, B, C, W and Y represented 6% (179), 22% (628), 9% (252), 51% (1 457) and 11.5% (330) respectively, with an average annual incidence of 1/100 000 population. MenA disease declined from a 0.2 to 0/100 000 population ($p<0.0001$) with no MenA cases reported in 2011 or 2012. Sequence types were ST1 (n=30), ST7 (n=3) and ST6709 (n=1). Compared to available ST1 genomes from Africa and Asia, our ST-1 isolates clustered separately, forming three phylogenetic groups, stratified by time.

Molecular characterisation of two capsule null locus meningococci causing invasive disease in South Africa

Encapsulation is an important virulence determinant for invasive meningococcal disease. Capsule null locus (cnl) isolates do not express a capsule and are common among distinct lineages of colonising *N. meningitidis*, but are rare among invasive isolates. Through IMD surveillance, two cnl isolates were identified. One with genotype NG:P1.7-2,30:F1-2:ST-53, was cultured in 2006 from a 46-year-old male who had diabetes mellitus. The second with genotype NG:P1.18-11,42-2:F-ND:ST-192, was isolated in 2010 from a 15-year-old male. Both patients recovered. ST-53 is associated with carriage and has not been described in invasive disease, whereas ST-192 has previously been described in IMD in Burkina Faso, although with a different cnl-3 allele. Phylogenetic analysis showed clustering by country and time period – the South African isolates were distinct from ST-53 or ST-192 from other countries.

Molecular characterisation of non-typeable *S. pneumoniae*-causing invasive disease in South Africa, 2003–2013

Almost all invasive pneumococci express a capsule, an important virulence factor and target for current vaccines. Some invasive isolates show no serological evidence of capsule expression and are defined as non-typeable (NTPn). Forty (0.1%, 40/46 485) NTPn were identified through national surveillance. Twenty-three (58%) had partial cps genes (group I) and 17 (42%) had a cps locus replaced by other genes (Group II or null capsule clade (NCC)). Group I comprised a mixture of unrelated sequence types of which two were associated with vaccine serotypes. In addition, ST217 clonal complex and ST53 isolates, usually associated with vaccine serotype 1 and non-vaccine serotype 8 respectively, were also present. Group II was a mixture of genotypes. Consistent with other studies globally, NTPn represented <1% of our invasive isolates. In contrast, a significant proportion (42%) of our isolates were NCC NTPn, compared to <10% described in other studies. NCC genotypes were mostly novel, although ST344 has been previously associated with conjunctivitis outbreaks.

A decade of invasive meningococcal disease surveillance in South Africa: 2003–2012

Currently invasive meningococcal disease (IMD) is at a nadir, which should alert us to the possibility of an increase in the disease over the next few years. Of the 4 537 sporadic IMD cases, 66% (3 461) were from the CSF, 23% (1 052) from blood and 1% (24) from other specimen types. The average annual population incidence was 0.9/100 000. Incidence peaked at 1.4/100 000 in 2006 and decreased to 0.5/100 000 in 2012 ($p<0.001$). Incidence was highest in infants (8/100 000), decreasing with increased age. IMD was more common in males (55%, 2 423/4 409). In 2003, serogroup A was predominant (0.2/100 000), but numbers declined steadily with no cases reported since 2010. From 2004–2012, serogroup W emerged as the predominant serogroup (0.7/100 000). Serogroup B disease was consistently the second most common serogroup (0.13/100 000). The average case-fatality ratio was 17% (269/1 565); however, 30% (52/175) of patients with bacteraemia died, versus 16% (217/1 380) with meningitis ($p<0.001$). HIV prevalence among IMD patients was 39% (range 25–48%) – 3.4 times the HIV prevalence (11%) among the general population during 2003–2012 (range 10–12%).

Population snapshot of *S. pneumoniae*-causing invasive disease in South Africa prior to the introduction of pneumococcal conjugate vaccines (PCV)

This study determined the sequence types of invasive pneumococci prior to the introduction of PCV in South Africa. PCV13 + 6C isolates collected in 2007 (n=1 461) from patients of all ages were characterised by multi-locus sequence typing. Non-PCV isolates from children under two years of age were also characterised (n=134). Similar sequence types (ST) circulated among adults and children. Globally disseminated clones were common among serotype 1 (ST217, 98%) and 14 (ST230, 43%), whereas serotypes 3 and 19A were of rarer sequence types (ST458, 60% and ST2062, 83% respectively). In children, serotypes 15B and 8 were most common among non-PCV serotypes, of which ST7052 and ST53 accounted for 58% (7/12) and 64% (9/14) respectively. Penicillin resistance was highest in serotypes 19F, 14, 19A and 15B. Rare genotypes among our PCV isolates highlight the importance of these data as these genotypes may emerge following PCV introduction.

Legionnaires' disease in South Africa, 2012–2014

The prevalence of *Legionellae* as a cause of community-acquired pneumonia in South Africa is unknown. Syndromic surveillance for patients hospitalised with lower respiratory tract infection (LRTI) was conducted from June 2012 through to September 2014. Sputum specimens were tested for *Legionella* spp. by real-time polymerase chain reaction. Demographic and clinical information was collected, and a retrospective epidemiological case investigation was conducted. Sputum was collected from 1 805/4 525 (40%) LRTI cases, and *Legionella* spp. were detected in 21 (1%) of 1 805. All cases occurred in adults aged 19–59 years, with 75% (15/20) HIV infected and 43% (9/21) positive for tuberculosis. A previous history of

TB was reported for 82% (14/17) of cases. Only one case received *Legionella*-specific treatment. Legionnaires' disease in South Africa occurs predominantly in chronically ill adults with HIV and/or tuberculosis, and the majority of cases are not diagnosed and appropriately treated.

Phylogenetic exploration of nosocomial transmission chains of influenza A(H1N1)pdm09 transmission at the Red Cross War Memorial Children's Hospital, Cape Town, South Africa

This study demonstrates how viral sequence data enrich more traditional observational epidemiological investigations to unravel transmission. Influenza A(H1N1)pdm09 hemagglutinin (HA) sequence phylogenies were used to investigate suspected nosocomial transmissions of influenza A over four months at the Red Cross War Memorial Children's Hospital (RCCH), Cape Town. Transmission chains were determined through a combination of patient admission data, maximum likelihood and time-scaled Bayesian phylogenetic analyses. Putative HA transmission clusters were inferred if two or more sequences clustered with greater than 0.75 posterior probability support and if dates of the root nodes suggested that they represented hospital acquired infections. Based on this criterion, four transmission clusters were identified.

Zoonotic transmission of human influenza A viruses to swine populations in South Africa observed through serological and molecular surveillance in 2013

This study investigated the frequency of zoonotic transmissions from humans to pigs in South Africa. A total of 551 upper respiratory tract samples were collected from pigs in Gauteng and the Western Cape, of which 3% (n=16) were positive for influenza A. Influenza A positives were obtained from five farms in Gauteng, showing that about 5% (16/308) of pigs in Gauteng were infected with influenza A. Swine-origin influenza A viruses represented 75% (12/16) of positives, of which 67% (8/12) were influenza A(H1N1)pdm09. Serological investigation of pig samples from the national serosurvey conducted in 2013 showed that 32% (118/364) reacted with titres ≥40 against the human influenza A(H1N1)pdm09 antigen, and 4% (13/364) reacted with titres ≥40 against the human influenza A(H3N2) antigen. However, only 5% (19/364) of sera reacted with titres ≥40 against swH1N1/Italy antigen and only 1/364 (0.3%) reacted with titre ≥40 against the swH3N2/Italy antigen. Here we showed that swine populations in South Africa are at risk for infection with human influenza A viruses, especially the influenza A(H1N1)pdm09 strain.

Enterovirus (EV) D68 and other enterovirus genotypes identified in South African patients hospitalised with SARI, 2009–2011

EV-D68 may be a concern for SARI in South Africa, and should be tested for in cases of non-poliovirus-associated acute flaccid paralysis, especially following a respiratory illness episode. From 2009 through to 2011, EV was detected in 7% (648/10 260) of enrolled SARI cases, and 29% (200/648) were selected for genotyping, of which only 22% (45/200) could be genotyped. Of these, 16% (7/45) were EV-A, 44% (20/45) were EV-B, 18% (8/45) were EV-C and 22% (10/45) were EV-D. Seventeen distinct EV genotypes were identified, of which EV-D68 (22%, 10/45) and Echovirus 3 (11%, 5/45) were the most prevalent. EV-A to EV-D were detected throughout 2009–2011, with no evident trend by season or year. The majority of identified EV-D68 strains (90%, 9/10) clustered in clade B or sub-lineage 1.2. All ten patients with EV-D68 infection were children under five years of age and eight presented with fever. No history of flaccid paralysis was reported in South African patients infected with EV-D68 in this study.

Collaborators: *The SARI Surveillance Programme investigators; The Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA) investigators; AL Cohen, S Tempia, J Duque, C Whitney, J Winchell, M McMarrow (The United States Centres for Disease Control and Prevention); N Martinson (Perinatal HIV Research Unit, University of the Witwatersrand); S Velaphi and E Variava (University of the Witwatersrand); KP Klugman (Director: Pneumonia, the Bill and Melinda Gates Foundation); MCJ Maiden, KA Jolley, HB Bratcher, E Watkins (Department of Zoology, University of Oxford); SD Bentley, J Parkhill, R. Gladstone (Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus); R Heyderman, D Everett, G Mapurisa (Malawi Liverpool-Wellcome Trust, Blantyre, Malawi); G Milne (University of Western Australia, Perth); R Breiman (Emory University, Atlanta, Georgia, USA); L McGee (Centers for Disease Control and Prevention, Atlanta, Georgia USA)*

Honours

Anne von Gottberg won the Prestigious Postgraduate Degree (PhD) Award for 2013 from the Faculty of Health Sciences. Prize-Giving Ceremony: 3 April 2014, held at the Charlotte Maxeke Johannesburg Academic Hospital Auditorium.

Anne von Gottberg was promoted to Associate Professor at the University of the Witwatersrand.

Cardia Fourie was named best student in Molecular Biology for 2014 by the Society of Medical Laboratory Technology of South Africa.

Teaching and Training

CRDM staff lecture at the Universities of the Witwatersrand and Pretoria and are involved in registrar training and ongoing postgraduate supervision of students.

The South Africa 2014 influenza season report was submitted to the WHO on 10 September 2014.

The CRDM hosted the 4th African Network for Influenza Surveillance and Epidemiology (ANISE) meeting and a pre-meeting workshop on the Burden of Disease, 4–6 December 2014, in Cape Town, South Africa.

CRDM staff travelled to Antananarivo, Madagascar, to attend the International Advanced Influenza workshop on 26–30 January 2015.

CRDM staff attended an Emergency Operations Centre Training workshop from 17–19 March 2015 at the Genesis Conference Suites, presented by the SA Regional and Global Disease Detection Centre and the US Defence Threat Reduction Agency.

Ellie Watkins from the Department of Zoology, Oxford University, UK, visited the Bacteriology Unit on 31 March 2015 to assist with bacterial whole genome analyses using the Bacterial Isolate Genome Sequence (BIGS) platform.

Professional Development

Number of postgraduate students who graduated: two

Cheryl Cohen was awarded her Doctor of Philosophy degree on 11 December 2014. The title of her thesis is Influenza-associated morbidity and mortality in South Africa.

Nireshni Naidoo received her MSc (Epidemiology and Biostatistics) from the School of Public Health on July 2014 (research report awarded with distinction). The title of her thesis is *Streptococcus pneumoniae* serotypes and mortality in adults in South Africa: analysis of national surveillance data (2003–2008).

Research Output

Top publications

Von Gottberg A, De Gouveia L, Tempia S, Quan V, Meiring S, Von Mollendorf C, Madhi SA, Zell ER, Verani JR, O'Brien KL, Whitney CG, Klugman KP, Cohen C, GERMS-SA investigators. Effects of vaccination on invasive pneumococcal disease in South Africa. *N Engl J Med.* 2014 13; 371(20): 1889–1899.

Synopis: Surveillance identified 35 192 cases of invasive pneumococcal disease. The rates among children younger than two years of age declined from 54.8 to 17.0 cases per 100 000 person-years from the baseline period to 2012, including a decline from 32.1 to 3.4 cases per 100 000 person-years in disease caused by PCV7 serotypes (-89%; 95% confidence interval [CI]: -92 to -86). Among children not infected with HIV, the estimated incidence of invasive pneumococcal disease caused by PCV7 serotypes decreased by 85% (95% CI: -89 to -79), whereas disease caused by non-vaccine serotypes increased by 33% (95% CI: 15 to 48). Among adults 25–44 years of age, the rate of PCV7 serotype disease declined by 57% (95% CI: -63 to -50), from 3.7 to 1.6 cases per 100 000 person-years. Rates of invasive pneumococcal disease among children in South Africa fell substantially by 2012. Reductions in the rates of disease caused by PCV7 serotypes among both children and adults most likely reflect the direct and indirect effects of vaccination.

Tempia S, Walaza S, Viboud C, Cohen AL, Madhi SA, Venter M, McAnerney JM, Cohen C. Mortality associated with influenza and respiratory syncytial virus among children less than five years of age in a high HIV-prevalence setting – South Africa, 1998–2009. *Clinical Infect Dis.* 2014 (online ahead of print).

Synopsis: A Poisson regression mode was used to estimate deaths attributable to influenza and respiratory syncytial virus (RSV) among persons under five years of age in South Africa during 1998–2009. We applied regression models to monthly deaths and laboratory surveillance data. Rates were expressed per 100 000 person-years. The mean annual number of seasonal influenza-associated deaths was 9 093 (rate 21.6). Persons over 65 years of age and HIV-positive persons accounted for 50% (n = 4 552) and 28% (n = 2 564) of overall seasonal influenza-associated deaths, respectively. In 2009, an estimated 4 113 (rate 9.2) influenza A(H1N1)pdm09-associated deaths occurred. The mean of annual RSV-associated deaths during the study period was 511 (rate 1.2). No RSV-associated deaths were estimated in persons over 45 years of age. This study supports the recommendation for influenza vaccination of older persons and HIV-positive persons.

Cohen C, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, Hellferscee O, Dawood H, Haffejee S, Variava E, Kahn K, Tshangela A, von Gottberg A, Wolteer N, Cohen A L, Kgokong B, Venter M, Madhi SA. Epidemiology of severe acute respiratory illness (SARI) among adults and children aged ≥ 5 years in a high HIV-prevalence setting, 2009–2012. *PLOS ONE*. 23 February 2015: 1–16, doi:10.1371/journal.pone.

Synopsis: Of a total of 7 193 individuals with SARI, 9% (621/7 067) tested positive for influenza and 9% (600/6 519) for pneumococcus. HIV prevalence was 74% (4 663/6 334). The annual SARI hospitalisation incidence ranged from 325–617/100 000 population. HIV-infected individuals experienced a 13–19 times greater SARI incidence than HIV-uninfected individuals (p<0.001). On multivariable analysis, compared to HIV-uninfected individuals, HIV-infected individuals were more likely to be receiving tuberculosis treatment (odds ratio (OR): 1.7; 95% CI:1.1–2.7), to have pneumococcal infection (OR: 2.4; 95% CI:1.7–3.3) to be hospitalised for more that seven days rather than less that two days (OR: 1.7; 95% CI:1.2–2.2) and to have a higher case-fatality ratio (8% vs. 5%; OR: 1.7; 95% CI:1.2–2.3), but were less likely to be infected with influenza (OR 0.6; 95% CI: 0.5–0.8). On multivariable analysis, independent risk indicators associated with death included HIV infection (OR: 1.8; 95% CI:1.3–2.4), increasing age group, receiving mechanical ventilation (OR: 6.5; 95% CI:1.3–32.0) and receiving supplemental oxygen therapy (OR: 2.6; 95% CI: 2.1–3.2). HIV-infected individuals are the most important risk group for SARI hospitalisation and mortality in this setting.

Cohen C, Von Mollendorf C, De Gouveia L, Naidoo N, Meiring S, Quan V, Nokeri V, Fortuin-de Smit M, Malope-Kgokong B, Moore D, Ruebenson G, Moshe M, Madhi SA, Eley B, Hallbauer U, Kularatne R, Conklin L, O'Brien K, Zell ER, Klugman K, Whitney CG, Von Gottberg A, for the South African Invasive Pneumococcal Disease Case-Control Study Group. Effectiveness of 7-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in HIV-infected and uninfected children in South Africa: a matched case-control study. *Clinical Infectious Diseases*. 2014, **59 (6)**: 808–818.

Synopsis: From March 2010 through to November 2012, we enrolled 187 HIV-uninfected (48 [26%] vaccine serotype) and 109 HIV-infected (43 [39%] vaccine serotype) cases and 752 HIV-uninfected and 347 HIV-infected controls aged ≥16 weeks. Effectiveness of ≥2 PCV7 doses against vaccine-serotype IPD was 74% (95% CI: 25%–91%) among HIV-uninfected and -12% (95% CI: -449%–77%) among HIV-infected children. Effectiveness of ≥3 doses against vaccine-serotype IPD was 90% (95% CI: 14%–99%) among HIV-uninfected and 57% (95% CI: -371%–96%) among HIV-infected children. Among HIV-exposed but uninfected children, the effectiveness of ≥2 doses was 92% (95% CI: 47%–99%) against vaccine-serotype IPD. Effectiveness of ≥2 doses against all-serotype multidrug-resistant IPD was 96% (95% CI: 62%–100%) among HIV-uninfected children. A 2+1 PCV7 schedule was effective in preventing vaccine-serotype IPD in HIV-uninfected and HIV-exposed but uninfected children. This finding supports the WHO's recommendation for this schedule as an alternative to a 3-dose primary series among HIV-uninfected individuals.

Wolter N, Tempia S, Cohen C, Madhi SA, Venter M, Moyes J, Walaza S, Malope-Kgokong B, Groome M, Du Plessis M, Magomani V, Pretorius M, Hellferscee O, Dawood H, Kahn K, Variava E, Klugman KP, Von Gottberg A. High nasopharyngeal pneumococcal density, increased by viral coinfection, is associated with invasive pneumococcal pneumonia. *J Infect Dis*. 2014; **210**: 1649–1657.

Synopsis: Pneumococcal colonisation was detected in 55% of cases (534 of 969). On multivariable analysis that controlled for age and tuberculosis treatment, infection with influenza virus (adjusted odds ratio [OR]: 2.2, 95% confidence interval [CI]: 1.1–4.5), adenovirus (adjusted OR: 1.7; 95% CI: 1.1–2.7), rhinovirus (adjusted OR, 1.6; 95% CI, 1.1–2.3), and HIV (adjusted OR: 1.6; 95% CI: 1.1–2.4) were associated with pneumococcal colonisation. High colonisation density was associated with respiratory virus co-infection (adjusted OR: 1.7; 95% CI: 1.1–2.6) and invasive pneumococcal pneumonia (adjusted OR: 2.3; 95% CI: 1.3–4.0) after adjustment for age and sex. In 7% (52 of 749) pneumococci were detected in the blood. On multivariable analysis among colonised cases, invasive pneumococcal pneumonia was associated with HIV (adjusted OR: 3.2; 95% CI: 1.4–7.5), influenza virus (adjusted OR: 8.2; 95% CI: 2.7–25.0), high colonisation density (adjusted OR, 18.7; 95% CI: 2.3–155.1), and ≥5 days of hospitalisation (adjusted OR: 3.7; 95% CI:1.7–8.2). Respiratory virus infection was associated with elevated colonisation density and, in turn, invasive pneumococcal pneumonia.

Publications

Budgell E, Cohen AL, McAnerney J, Walaza S, Madhi SA, Blumberg L, Dawood H, Kahn K, Tempia S, Venter M, Cohen C. Evaluation of two influenza surveillance systems in South Africa. *PLOS ONE*. 2015 Mar 30; 10 (3): e0120226.

Cohen AL, Hellferscee O, Pretorius M, Treurnicht F, Walaza S, Madhi S, Groome M, Dawood H, Variava E, Kahn K, Wolter N, Von Gottberg A, Tempia S, Venter M, Cohen C. Epidemiology of influenza virus types and subtypes in South Africa, 2009–2012. *Emerg Infect Dis*. 2014 Jul; 20 (7): 1 162–1 169.

Cohen C, Moyes J, Tempia S, Groome M, Walaza S, Pretorius M, Dawood H, Chhagan M, Haffejee S, Variava E, Kahn K, Von Gottberg A, Wolter N, Cohen AL, Malope-Kgokong B, Venter M, Madhi SA. Mortality amongst patients with influenza-associated severe acute respiratory illness, South Africa, 2009–2013.*PLOS ONE*. 2015 Mar; 10 (3): e0118884.

Cohen C, Von Mollendorf C, De Gouveia L, Naidoo N, Meiring S, Quan V, Nokeri V, Fortuin-de Smit M, Malope-Kgokong B, Moore D, Ruebenson G, Moshe M, Madhi S A, Eley B, Hallbauer U, Kularatne R, Conklin L, O'Brien K, Zell E R, Klugman K, Whitney CG, Von Gottberg A, for the South African Invasive Pneumococcal Disease Case-Control Study Group. Effectiveness of 7-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in HIV-infected and uninfected children in South Africa: a matched case-control study. *Clin Infect Dis*. 2014 Sep 15; 59 (6): 808–818.

Cohen C, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, Hellferscee O, Dawood H, Chhagan M, Naby F, Haffejee S, Variava E, Kahn K, Nzenze S, Tshangela A, Von Gottberg A, Wolter N, Cohen AL, Kgokong B, Venter M, Madhi SA. Epidemiology of viral-associated acute lower respiratory tract infection among children <5 years of age in a high HIV-prevalence setting, South Africa, 2009–2012. *Pediatr Infect Dis.* 2014; Aug 4.

Cohen C, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, Hellferscee O, Dawood H, Haffejee S, Variava E, Kahn K, Tshangela A, Von Gottberg A, Wolter N, Cohen AL, Kgokong B, Venter M, Madhi SA. Epidemiology of severe acute respiratory illness (SARI) among adults and children aged ≥5 years in a high HIV-prevalence setting, 2009–2012. *PLOS ONE*. Feb 23; 10 (2): e0117716.

Dangor Z, Izu A, Moore DP, Nunes MC, Solomon F, Beylis N, Von Gottberg A, McAnerney JM, Madhi SA. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. *PLOS ONE*. 2014; Mar 11; 9 (3): e91464.

Du Plessis M, Wolter N, Crowther-Gibson P, Hamstra HJ, Schipper K, Moodley C, Cohen C, Van de Beek D, Van der Ley P, Von Gottberg A, Van der Ende A. Meningococcal serogroup Y lpxL1 variants from South Africa are associated with clonal complex 23 among young adults. *J Infect*. 2014; **68**: 455–461.

Groome MJ, Page N, Cortese MM, Moyes J, Zar HJ, Kapongo CN, Mulligan C, Diedericks R, Cohen C, Fleming JA, Seheri M, Mphahlele J, Walaza S, Khan K, Chhagan M, Steele D, Parashar UD, Zell ER, Madhi SA. Effectiveness of monovalent human rotavirus vaccine against admission to hospital for acute rotavirus diarrhoea in South African children: a case-control study. *Lancet Infectious Diseases.* 2014 Nov; 14 (11): 1096–1104.

Kyeyagalire R, Tempia S, Cohen AL, Smith AD, McAnerney JM, Dermaux-Msimang V, Cohen C. Hospitalizations associated with influenza and respiratory syncytial virus among patients attending a network of private hospitals in South Africa, 2007–2012. *BMC Infect Dis.* 2014 Dec 16; **14**: 694.

Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, Adrian PV, Van Niekerk N, Treurnicht F, Ortiz JR, Venter M, Violari A, Neuzil KM, Simões EA, Klugman KP, Nunes MC, the Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med.* 2014 Sep 4; 371 (10): 918–931.

Magomani V, Wolter N, Tempia S, Du Plessis M, De Gouveia L and Von Gottberg A. Challenges of using molecular serotyping for surveillance of pneumococcal disease. *J. Clin. Microbiol.* 2014; 52 (9): 3 271.

McMorrow ML, Wemakoy EO, Tshilobo JK, Emukule GO, Mott JA, Njuguna H, Waiboci L, Heraud JM, Rajatonirina S, Razanajatovo NH, Chilombe M, Everett D, Heyderman RS, Barakat A, Nyatanyi T, Rukelibuga J, Cohen AL, Cohen C, Tempia S, Thomas J, Venter M, Mwakapeje E, Mponela M, Lutwama J, Duque J, Lafond K, Nzussouo NT, Williams T, Widdowson MA. Severe acute respiratory illness deaths in Sub-Saharan Africa and the role of influenza: a case series from 8 countries. *J Infect Dis.* 2015 Feb 23; Pii:piv [epub ahead of print].

Ndlangisa M, Du Plessis M, Wolter N, De Gouveia L, Klugman KP, Von Gottberg A for GERMS-SA. Population snapshot of *Streptococcus pneumoniae* causing invasive disease in South Africa prior to introduction of pneumococcal conjugate vaccines. *PLOS ONE*. 2014 Sep 18; 9 (9): e107666.

Nunes MC, Jones SA, Groome MJ, Kuwanda L, Van Niekerk N, Von Gottberg A, De Gouveia L, Adrian PV, Madhi SA. Acquisition of *Streptococcus pneumoniae* in South African children vaccinated with 7-valent pneumococcal conjugate vaccine at 6, 14 and 40 weeks of age. *Vaccine.* 2015 29 January; 33 (5): 628–634.

Nzenze SA, Shiri T, Nunes MC, Klugman KP, Kahn K, Twine R, De Gouveia L, Von Gottberg A, Madhi SA. Temporal association of infant immunisation with pneumococcal conjugate vaccine on the ecology of *Streptococcus pneumoniae*, *Haemophilus*

influenzae and *Staphylococcus aureus* nasopharyngeal colonisation in a rural South African community. *Vaccine.* 2014 Sep 22; 32 (42): 5520–5530.

Nzenze SA, Von Gottberg A, Shiri T, Van Niekerk N, De Gouveia L, Violari A, Nunes MC, Madhi SA. Temporal changes in pneumococcal colonization in HIV-infected and HIV-uninfected mother-child pairs following transitioning from 7-valent to 13-valent pneumococcal conjugate vaccine, Soweto, South Africa. *J Infect Dis.* 2015 Mar 17; Pii:jiv167 [epub ahead of print].

Pretorius MA, Tempia S, Treurnicht FK, Walaza S, Cohen AL, Moyes J, Hellferscee O, Variava E, Dawood H, Chhagan M, Haffjee S, Madhi SA, Cohen C, Venter M. Genetic diversity and molecular epidemiology of human rhinoviruses in South Africa. *Influenza Other Respir Viruses.* 2014 Sep; 8 (5): 567–573.

Tempia S, Walaza S, Viboud C, Cohen AL, Madhi SA, Venter M, McAnerney JM, Cohen C. Mortality associated with influenza and respiratory syncytial virus among children less than 5 years of age in a high HIV-prevalence setting – South Africa, 1998–2009. *Clinical Infect Dis.* 2014 May; 58 (9): 1241–1249.

Tempia S, Walaza S, Viboud C, Cohen AL, Madhi SA, Venter M, Von Mollendorf C, Moyes J, McAnerney JM, Cohen C. Deaths associated with respiratory syncytial and influenza viruses among persons ≥5 years of age in HIV-prevalent area, South Africa, 1998–2009(1). *Emerg Infect Dis.* 2015 Apr; 21 (4): 600–608.

Van Tonder AJ, Mistry S, Bray J E, Hill D M, Cody AJ, Farmer CL, Klugman KP, Von Gottberg A, Bentley SD, Parkhill J, Jolley KA, Maiden MC, Brueggemann AB. Defining the estimated core genome of bacterial populations using a Bayesian decision model. *PLOS Comput Biol.* 2014 Aug 21; 10 (8): e1003788.

Von Gottberg A, De Gouveia L, Tempia S, Quan V, Meiring S, Von Mollendorf C, Madhi SA, Zell ER, Verani JR, O'Brien KL, Whitney CG, Klugman KP, Cohen C. GERMS-SA investigators. Effects of vaccination on invasive pneumococcal disease in South Africa. *N Engl J Med.* 2014 Nov 13; 371 (20): 1889–1899.

Von Mollendorf C, Cohen C, De Gouveia L, Naidoo N, Meiring S, Quan V, Lindani S, Moore DP, Reubenson G, Moshe M, Eley B, Hallbauer UM, Finlayson H, Madhi SA, Conklin L, Zell ER, Klugman KP, Whitney CG, Von Gottberg A for the South African IPD Case-Control Study Group. Risk factors for invasive pneumococcal disease among children less than 5 years of age in a high HIV-prevalence setting, South Africa, 2010–2012. *Pediatr Infect Dis J.* 2015 Jan; 34 (1): 27–34.

Von Mollendorf C, Cohen C, De Gouveia L, Quan V, Meiring S, Feldman C, Klugman KP, Von Gottberg A. Factors associated with ceftriaxone nonsusceptibility of *Streptococcus pneumoniae*: Analysis of South African National Surveillance Data, 2003–2010. *Antimicrol Agents Chemother.* 2014 June; 59 (6): 3 293–305.

Walaza S, Cohen C. Recommendations pertaining to the use of viral vaccines: Influenza 2014. *S Afr Med J.* 2015 February; 105 (2): 90–91.

Walaza S, Tempia S, Dawood H, Variava E, Moyes J, Cohen AL, Wolter N, Groome M, Von Mollendorf C, Kahn K, Pretorius M, Venter M, Madhi SA, Cohen C. Influenza virus infection is associated with increased risk of death amongst patients hospitalised with confirmed pulmonary tuberculosis in South Africa, 2010–2011. *BMC Infect Dis.* 2015 Jan 27; 15 (1): 26.

Wolter N, Cohen C, von Gottberg A. Causes of fever in Tanzanian children. (Letter to) *N Engl J Med.* 2014 Jun 5; 370 (23): 2 243.

Wolter N, Tempia S, Cohen C, Madhi SA, Venter M, Moyes J, Walaza S, Malope-Kgokong B, Groome M, Du Plessis M, Magomani V, Pretorius M, Hellferscee O, Dawood H, Kahn K, Variava E, Klugman KP, Von Gottberg A. High nasopharyngeal pneumococcal density, increased by viral coinfection, is associated with invasive pneumococcal pneumonia. *J Infect Dis.* 2014 Nov 15; 210 (10): 1 649–1 655.

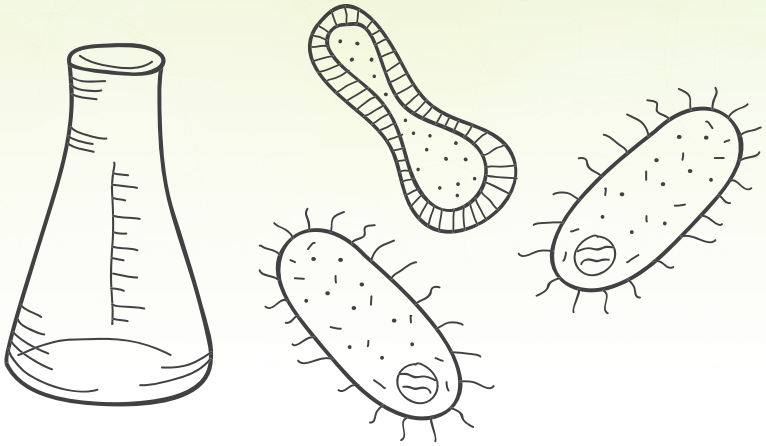
Conference Presentations

International: 38

Local and national: 21

Centre for Tuberculosis

Centre Head: Dr Nazir Ismail



In line with the national mandate of the NICD, the Centre for Tuberculosis (CTB) conducts ongoing laboratory-based public health surveillance of TB in South Africa, serves as a national TB reference laboratory (NTBRL) and participates in microbiology and epidemiology-oriented training programmes. The CTB also initiates applied public health research related to the National TB Control Programme (NTP). It furthermore advises and works closely with the Department of Health (DoH) on strategic planning and assists with the formulation of policy and guidelines concerning the diagnosis and treatment of TB in South Africa. Global policies and guidelines are formulated through the World Health Organization (WHO), which has included representation from CTB for expert group meetings.

Surveillance and Diagnostic Services

The CTB uses an integrated approach, combining public health surveillance and reference laboratory functions to provide enhanced and strategic information to guide TB control activities for South Africa. Continued support to the NTP has been provided by conducting national surveillance of new cases of laboratory-confirmed TB as well as new drug-resistant TB; including rifampicin-resistant (RR), multi-drug-resistant (MDR) and extensively drug resistant (XDR) cases identified by NHLS laboratories, which serve over 80% of the population. Information on the prevalence of drug resistance determined through a national survey will also advise on the performance of the NTP in pursuit of the Millennium Development Goals, allowing guidance on directing human and financial resources to be provided to areas of need.

New specialised molecular techniques for *Mycobacterium tuberculosis* have been integrated into the surveillance system to better define drug resistance mutation profiles and clonal strains using next-generation sequencing, restriction fragment length polymorphism (RFLP) types, spoligotypes and mycobacterial interspersed repetitive unit (MIRU) types. In addition, the centre is also involved in the development and application of methods of drug resistance determination to new anti-mycobacterial agents.

Surveillance of microbiologically confirmed TB in South Africa

Trend analysis of the incidence of pulmonary TB in South Africa between 2004 and 2012, using de-duplicated laboratory-based information and population data has been completed. This analysis assessed changes at national and provincial levels of microbiologically confirmed pulmonary tuberculosis (mPTB), as well as registered cases of pulmonary TB (PTBr) on treatment in the programme, with the former being analysed in relation to HIV prevalence and anti-retroviral (ARV) roll-out over the same period. The mPTB incidence rates for several provinces are above 1 000/100 000 population, which ranks these regions amongst the highest incidence areas globally. In total, 55% of cases were males with an average age of 38 years, whilst among females the average age was 33 years. Thus the pattern is similar to that of the HIV epidemic, with the economically active age group being the most affected. The incidence of mPTB in South Africa declined by 8.7% in 2012 since its peak in 2008. The largest declines occurred approximately four years after the largest rates of increase in ART coverage. The declines have varied temporally by province, with KwaZulu-Natal (KZN) being the last province to show a decline starting in 2011. The highest incidence recorded was in males between the ages of 25 and 44 years with an incidence of 1 517/100 000 people in 2008, declining to 1 256/100 000 in 2012. Although these declines are evidence of a turn-around, the overall incidence rates are still exceedingly high. Additionally, the gap between those diagnosed and treated needs to be closed. In 2011, this gap was 16% nationally, with six of the nine provinces showing a gap above 20%. Thus much more needs to be done to strengthen health systems, but more importantly, to maximise the surveillance data being generated to assist in targeting interventions at hotspots and areas with identified weaknesses.

Maximising on the electronic reporting system in the NHLS, weekly alerts providing a line listing of cases diagnosed with RR TB by the Xpert MTB/Rif assay are e-mailed to the nine provincial and 52 district managers for public health action. This was initiated in collaboration with the national DoH's TB cluster, with the aim of reducing the gap between diagnosis and treatment. This has provided an important tool for case management in the health system and to support continued efforts with patient tracing initiatives by the respective teams in the field. Additional work is underway to perform a surveillance assessment of the system looking at accuracy, completeness, timeliness and other qualitative aspects. Once this is completed, extension of the programme to include other test methods and patient groups can be included.

Survey of drug resistance in TB – South Africa

The drug resistant survey (DRS) of TB cases in South Africa, which was initiated in the second half of 2012, is one of the largest of its kind globally, with patients recruited from over 400 facilities for a one-year period. The unique design of this survey is the recruitment of TB suspects rather than cases, allowing assessment of the drug resistance burden in both smear-positive and smear-negative patients – an important issue for high HIV/AIDS burdened settings like South Africa. An additional difference is the testing of all culture-confirmed cases for a full range of drugs, including second-line agents. This is crucial as the generated data are essential to inform the applicability of new regimens that combine the improved agents with existing anti-TB drugs. The levels of resistance to the latter are critical factors that will influence the success or

failure of these new interventions. Enrolments in the provinces were staggered, resulting in an implementation phase of approximately one year and a completion phase of approximately one year, in addition to the concurrent enrolment phase to complete the survey. All enrolments for the survey were completed in June 2014. All the primary laboratory testing has been completed and final performance of outstanding tasks is underway. The report is expected to be released in 2015.

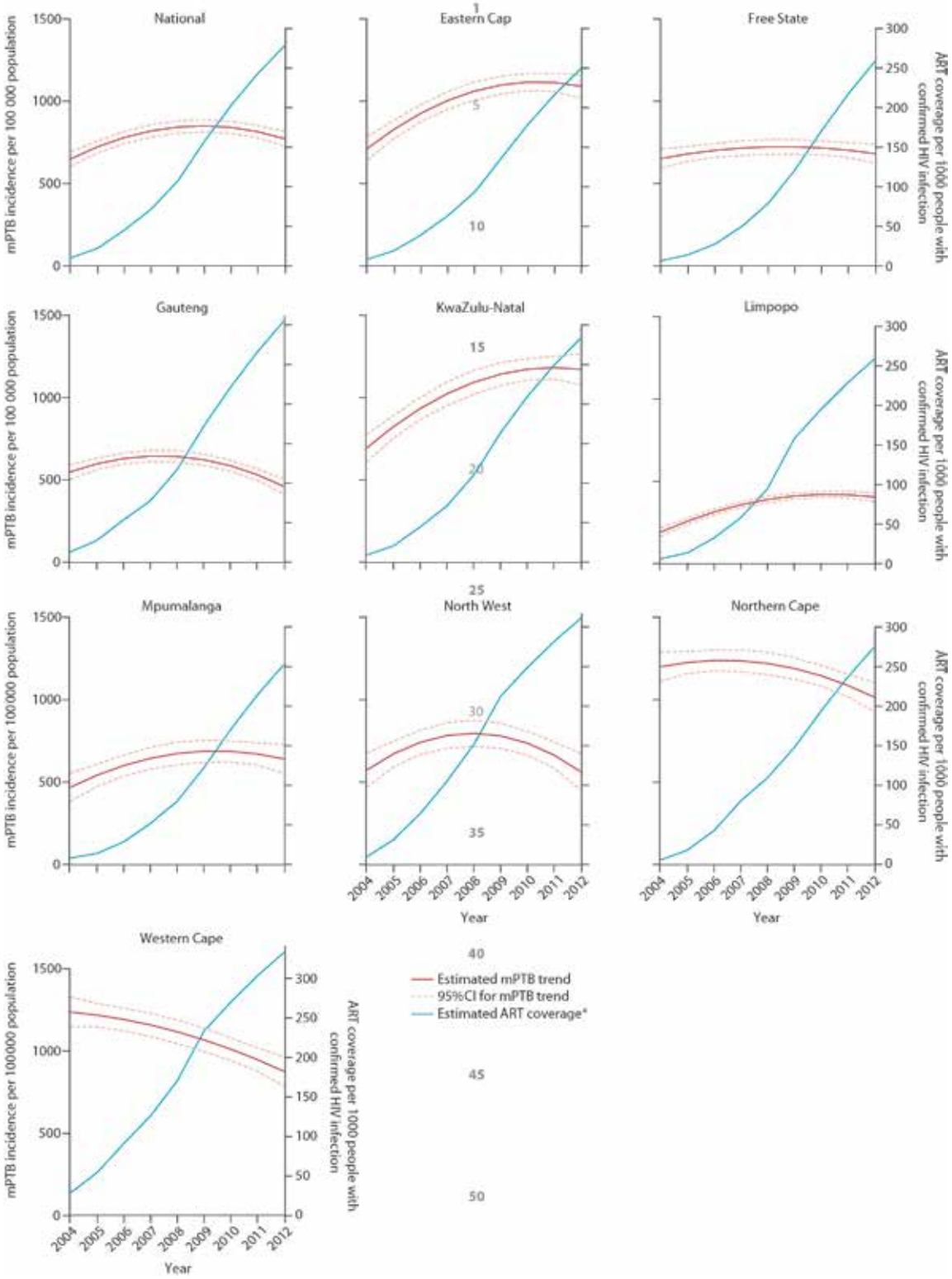


Figure 6: Nanoo A, Izu A, Ismail NA, Ihekweazu C, Abubakar I, Mametja D, Madhi SA. Nationwide and regional incidence of microbiologically confirmed pulmonary tuberculosis in South Africa, 2004-12: a time series analysis. Lancet Infect Dis 2015; published online June 23. http://dx.doi.org/10.1016/S1473-3099(15)00147-4.

Population-based whole genome sequencing to inform new drug regimens for South Africa

As as extension of the survey, whole genome sequencing (WGS) of all *M. tuberculosis* isolates from the DRS for two provinces, Gauteng and KwaZulu-Natal, has been included. This was initiated as part of a multi-country WHO-co-ordinated effort to determine baseline resistance to fluoroquinolones and pyrazanimide as these drugs are planned for inclusion in the new regimens currently under investigation. The use of sequencing will also inform future testing and screening of these drugs using molecular technology. The CTB has successfully established WGS as a method for use in surveillance, and is one of the very few TB reference laboratories globally to have done this. Early findings have shown relatively low levels of fluoroquinolone and pyrazanimide resistance in new cases of TB. In addition, the performance of WGS is closely comparable to phenotypic testing to determine the prevalence of resistance. This work is currently in the process of being finalised.

Surveillance for bedaquiline resistance

Medicines Control Council of South Africa has recently approved the use of bedaquiline, a new anti-TB drug. This has been a breakthrough after decades without any new options for TB treatment. A large scale-up is planned aimed at improving the current poor treatment success in MDR cases, which is below 50%. However, surveillance to monitor the emergence of drug resistance to this new drug has been identified as an important need and has now been incorporated into the national policy framework for new drugs. The centre has been proactive and has participated in developing a quality standard phenotypic test for bedaquiline as part of a global FDA-approved multi-country project – a key first step for robust surveillance. This has been successfully completed with over 95% consistency observed within a very tight minimum inhibitory concentration (MIC) range across multiple testing sites. Testing of this drug is now established at the NTBRL. Thus testing during the early phase will be performed at the NTBRL, initially to monitor the MIC of baseline isolates and at two subsequent time points from enrolled patients receiving bedaquiline treatment.

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

The CTB has been appointed as a candidate Supra-National Reference Laboratory by the WHO. As part of this function it supports two national reference laboratories in Africa, as part of the Malawi and Namibia. Missions to improve quality management systems for laboratory testing. It is also involved in programme initiatives for TB surveillance activities which have been progressively implemented in these countries. The CTB also provided reference laboratory support to the Malawi prevalence survey and the Namibia drug-resistant survey for both quality assurance and second-line drug susceptibility testing. A broader project, aiming to test the proficiency of nine of the 22 reference laboratories until the highest burden of TB in Africa on culture identification and susceptibility testing, was recently initiated through WHO-AFRO. With completion of the first round, significant problems which have been identified, will be further investigated.

Figure 7: SRLN map May 2015

Prospective sentinel surveillance of RR TB, TB/HIV integration and hospitalised TB in South Africa

Complementing the broad surveillance using routine data, an enhanced surveillance programme has been introduced to provide additional quality-assured data on demographics, clinical presentation and risk factors. In addition, a surveillance specimen was collected and was used to generate complementary microbiological data. The first surveillance for TB was established for RR TB, and this has now been implemented in seven of South Africa's nine provinces. Early findings

have shown high HIV co-infection rates ranging between 70–90% depending on region. More than 50% of these RR cases have not had previous TB infection, suggesting that RR TB has developed through primary transmission. Further investigations are being conducted to stratify the analysis comparing rifampicin mono-resistance and MDR TB cases and to test for associations.

A second surveillance system monitoring severe acute respiratory infections has provided early data indicating that almost one in six new pulmonary TB cases are hospitalised. Co-infection with other pathogens, notably *S. pneumoniae*, has also been frequently observed, highlighting the need to investigate for TB in patients presenting with acute respiratory infections. The most recent surveillance introduced is clinic-based rather than laboratory-based, and will monitor TB and HIV programmatically to assess trends and relative risk factors. Monitoring of drug resistance has also been incorporated. Since both TB and HIV use empiric regimens for treatment without primary resistance testing, except for rifampicin in TB, this surveillance is critical and will allow monitoring of baseline resistance to Isoniazid and other first-line drugs as well as baseline HIV resistance in those starting treatment. Both these are important and are lacking in the routine system, notably for TB, where Isoniazid mono-resistance is expected at >5%, but is not detected by the widely implemented Xpert MTB/Rif assay.

Molecular epidemiology-based surveillance for early detection of RR clusters in selected districts

Several outbreaks of drug-resistant TB have been reported in South Africa; however, these have been identified late and when high mortality has been observed. There is thus an urgent need for early detection of transmission clusters to initiate appropriate interventions. Strain typing methodologies, including RFLP analysis (automated and manual), MIRU-VNTR 24 loci and spoligotyping are now fully established and operational at CTB centre. Evaluation of the most suited typing methodology for South Africa has been completed using a cohort of patients from Gauteng. The data indicate the use of MIRU-VNTR 24 loci typing to be the best suited with the highest discriminatory power for our setting, followed by IS6110-RFLP and spoligotyping.

Surveillance activities using molecular typing have been implemented in four high-burden districts in South Africa and these will be expanded. All RR TB patients within these districts, detected by the Xpert MTB/RIF assay, are targeted for enrolment, and specimens are sent to the centre for phenotypic susceptibility testing and strain typing. Early finding of strains from the Kenneth Kaunda district in North West have shown important differences in strain diversity compared with data published from other regions (KwaZulu-Natal and Western Cape), suggesting that we may be dealing with multiple smaller epidemics rather than a large generalised epidemic.

Research Projects

Evaluation of the TBDx automated computer-aided smear microscopy system for diagnosis and use as a cost-effective screening tool

Microbiological diagnosis of TB has improved dramatically with the introduction of the Xpert MTB/RIF assay, an automated molecular test. However, the use of GXP is limited in high-burden countries because of its cost, meaning that TB diagnosis still relies on conventional smear microscopy, which may miss half of all cases. The TBDx automated microscopy system is a novel TB test that relies on high-throughput digital evaluation of microscopy images with no requirement for a skilled microscopist. The use of TBDx to screen specimens prior to using GXP could allow the detection of 90% of patients with GXP-positive TB, while reducing the number of GXP tests required by 73%. Using the TBDx system as a stand-alone tool can deliver performance equivalent to two highly skilled microscopists, which would eliminate the need to hire these personnel.

Collaborators: *D Dowdy (Guardian Technologies), G Churchyard (Aurum)*

Treatment initiation and clinical outcomes among MDR TB patients in KwaZulu-Natal, South Africa

This was a public health field investigation initiated in collaboration with the KwaZulu-Natal (KZN) Provincial Department of Health and KZN district offices. The primary objective of the study is to ascertain the number of people diagnosed with pulmonary MDR TB in 2011 and the final disposition or clinical outcome two years after initial diagnosis. All cases diagnosed through the laboratory and recorded on the NHLS corporate data warehouse were extracted and merged with the Electronic Drug Resistance (EDR) registries from the DoH. A stratified sample of matched and unmatched records were selected for field investigation. This study provided important information on the estimated cases diagnosed and the estimated number of cases on treatment. The findings provided valuable information on outcomes, including initial defaulter rates.

Collaborator: *J Ngozo, KwaZulu-Natal Department of Health, Pietermaritzburg, South Africa*

Assessment of treatment practices for paediatric drug-resistant TB in three provinces of South Africa

Paediatric TB is a significant portion of the global TB burden; however, DR TB has been poorly studied in children. The study aimed to assess the effectiveness of individual drugs and regimens used to treat DR TB in children. We showed that children with DR TB who received an effective second-line injectable, an effective fluoroquinolone, or at least four effective drugs, had greater odds of treatment success (>4-fold increase). Thus susceptibility to first and second-line drugs should be determined quickly for children at risk for DR TB in order to develop a regimen containing at least four effective drugs.

Collaborator: *B Moore, Centers for Disease Control and Prevention, USA*

Novel methods for diagnosis of paediatric tuberculosis

Diagnosis of paediatric tuberculosis is challenging due to paucibacillary disease and difficulty in collecting sputum. Hospital studies have demonstrated the use of alternative sampling strategies, such as nasopharyngeal aspirate, and new diagnostics, such as GXP assay. We aimed to determine the optimal sampling strategy and diagnostics at primary care, where children present with less severe disease. The study was conducted for approximately one year, and we showed that alternative sampling strategies proved feasible at primary healthcare level, but resulted in a low diagnostic yield with available tools. Extensive efforts to diagnose children bacteriologically did not contribute to clinical management, as almost all children started treatment based on clinical findings.

Collaborator: *A Van Rie, University of North Carolina Gillings School of Global Public Health, Chapel Hill, USA*

Whole genome sequencing predicts *M. tuberculosis* drug resistance – a machine learning algorithm

The centre has implemented and optimised whole genome sequencing for use in drug resistance surveillance and research on TB. A simple, user-friendly bioinformatics pipeline has been developed, allowing resistance information to be easily extracted and analysed, and a new beta-phase dashboard is being evaluated. The centre is collaborating with the WHO New Diagnostic Working Group, which was established to create a global network to standardise and improve on the prediction capability of WGS, and with Oxford and Cambridge Universities. This now includes machine learning algorithms that improve the power of prediction as new genomes are added, and is an important new approach to deciphering the resistance potential of rare mutations.

HIV Incidence Provincial Surveillance System: A longitudinal sub-study to monitor TB prevalence and incidence trends in the uMgungundlovu district, KwaZulu-Natal, South Africa

Despite improvements in HIV-related morbidity and mortality, the rate of new HIV infections remains unacceptably high. In response to the provincial and national priorities to better monitor HIV incidence in high-prevalence areas, the HIV Incidence Provincial Surveillance System (HIPSS) was successfully established in two sub-districts in KwaZulu-Natal. The cohort is a household-based representative sample of men and women in the sub-districts of Vulindlela and Greater Edendale in the uMgungundlovu municipality of KwaZulu-Natal. For the sub-study, the prevalence and incidence of TB, sexually transmitted infections (STIs) and hepatitis B and C infections are measured at baseline and at follow-up. Following project initiation, it was found that yields of cases with TB have been low and challenging, therefore this combined strategy is being reviewed.

Collaborator: *A Kharsany, KwaZulu-Natal Research Institute for Tuberculosis and HIV*

Transmission of HIV-associated XDR-TB in South Africa (TRAX study)

Following the disastrous Tugela Ferry outbreak of XDR-TB in KwaZulu-Natal in 2006, the present study was designed to prospectively investigate transmission of XDR-TB in the province. The study aims to determine the proportion of new XDR-TB cases with primary drug resistance; identify risk factors associated with such transmission through epidemiological and social network analysis; and to demonstrate, using molecular genotyping and more recently WGS, transmission patterns involving persons and locations associated with XDR-TB transmission.

Recent work completed using WGS on strains over a five-year period and previously clustered as the original Tugella Ferry outbreak strain, has shown that more than 80% of these strains were identical on WGS, which is strong evidence that these infections are due to recent direct transmission. In the remaining set of strains, micro-clusters were observed, which suggests that the strain may still be undergoing evolutionary change over time. Furthermore, an important finding

from the assessment of other genetic markers from these strains is increased mutations in genes associated with lipid metabolism, which may play a role in transmission and host immune response, warranting further research.

Collaborator: *S Shah, Inkosi Albert Luthuli Hospital Laboratory, KZN*

Multi-centre study to assess the non-inferiority of Nipro NTM+MDRTB and HainGenoTypeMTBDR plus V2 line LPA compared to HainGenoTypeMTBDR plus V1

As part of the NTBRL network, we have become a preferred site for the Foundation for New and Innovative Diagnostics (FIND) and conduct novel diagnostic evaluations and validations. We have been part of a multi-centre study to assess the non-inferiority of Nipro NTM+MDRTB and YD Line Probe assays and GenoTypeMTBDR plus V2 line probe assays compared to GenoTypeMTBDR plus V1.

For MTB detection, a high specificity of 100% was achieved by all three assays with sensitivity levels of 99.1% (Nipro), 99.5% (Hain v2) and 99.5% (Hain v1). Indeterminate rates were highest with Nipro, followed by Hain v2 and Hain v1 for both Rifampicin (1.5% vs. 0.6% vs. 0.4%) and INH (1.1% vs. 0.6% vs. 0.6%) respectively. Both Hain v2 and Nipro were non-inferior to Hain v1 for Rifampicin specificity, Isoniazid sensitivity and Isoniazid specificity. For Rifampicin sensitivity, although the confidence intervals for all three assays cross the lower limit of the non-inferiority margins, the performances of the tests were exactly the same and therefore comparable.

Teaching and Training

Training accommodating experiential as well as didactic learning was provided on site in Malawi at their National TB Reference Laboratory. Additionally, CTB participated in developing course material and structure for the train-the-trainer course for SADC countries, which will be implemented through the SADC Secretariat. Training was also provided for both reference mycobacteriology testing and public health aspects of TB, rotating registrars from university-based medical microbiology departments in South Africa, as well as for intern scientists in the country. In addition, CTB mentored a Field Epidemiology and Laboratory Training Programme (FELTP) student, further expanding capacity in epidemiology in South Africa. Lastly, three staff members were supported to attend a specialised TB culture and drug susceptibility course, which they have successfully completed.

Professional Development

Postgraduate candidates

Number of candidates enrolled: four PhDs, one MMed, four MSc

Number of candidates who graduated: nil PhD, one MMed, two MSc, two TB technicians

Honours

Two TB technicians passed the board examination with distinction.

Research Output

Publications

Ajbani K, Lin SY, Rodrigues C, Nguyen D, Arroyo F, Kaping J, Jackson L, Garfein RS, Catanzaro D, Eisenach K, Victor TC, Crudu V, Gler MT, Ismail NA, Desmond E, Catanzaro A, Rodwell TC. Evaluation of pyrosequencing for detecting extensively drug-resistant tuberculosis (XDR-TB) in clinical isolates from four high-burden countries. *Antimicrob Agents Chemother.* 2015 Jan; 59 (1): 414–20, doi: 10.1128/AAC.03614-14. Epub 2014 Nov 3.

Daum LT, Fourie PB, Bhattacharyya S, Ismail NA, Gradus S, Nontuthuko E, Maningi NE, Omar SV, Fischer GW. Next-generation sequencing for identifying pyrazinamide resistance in *Mycobacterium tuberculosis*. *Clin Infect Dis.* 2014; 58 (6): 903–904.

Daum LT, Peters RP, Fourie PB, Jonkman K, Worthy S A, Rodriguez JD, Ismail NA, Omar SV, Fischer GW. Molecular detection of *Mycobacterium tuberculosis* from sputum transported in PrimeStore(R) from rural settings. *Int J Tuberc Lung Dis.* 2015; 19: 552–55710.5588/ijtld.14.0769.

Ismail NA, Omar SV, Lewis JJ, Dowdy DW, Dreyer AW, Van der Meulen H, Nconjana G, Clark DA, Churchyard GJ. Performance of a novel algorithm using automated digital microscopy for diagnosing tuberculosis. *Am J Respir Crit Care Med.* First published online 31 Mar 2015 as doi: 10.1164/rccm.201502-0390OC.

Riou C, Gray CM, Lugongolo M, Gwala T, Kiravu A, Deniso P, Stewart-Isherwood L, Omar SV, Grobusch MP, Coetzee G, Conradie F, Ismail NA, Kaplan G, Fallows D. A subset of circulating blood mycobacteria-specific CD4 T cells can predict the time to *Mycobacterium tuberculosis* sputum culture conversion. *PLOS ONE.* 2014 21; 9 (7): e102178. Epub 2014 Jul 21.

Rodwell TC, Valafar F, Douglas J, Qian L, Garfein RS, Chawla A, Torres J, Zadorozhny V, Soo Kim M, Hoshide M, Catanzaro D, Jackson L, Lin G, Desmond E, Rodrigues C, Eisenach K, Victor TC, Ismail NA, Crudu V, Gle MT, Catanzaro A. Predicting extensively drug-resistant tuberculosis (XDR-TB) phenotypes with genetic mutations. *J Clin Microbiol.* 2014; 52 (3): 781–789.

Conference Presentations

International congresses: one

Outside Africa: five oral, six posters

Regional/Africa: nil

National congresses: four oral; three posters

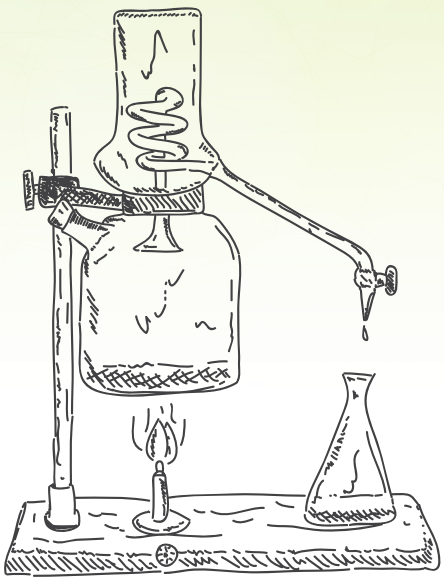
Local congresses: nil

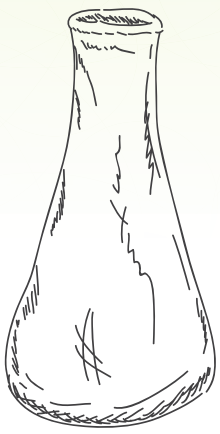
Acknowledgements

The CTB thanks the NICD/NHLS for funding and operational support, and the President's Emergency Plan for AIDS Relief (PEPFAR) through the CDC, under terms of agreement (1U19GH000571); Global Disease Detection (U2GPS001328); and the National Institute of Allergy and Infectious Diseases of the NIH (1R01 AI089349 and AI080737) for funding support.

The South African Regional Global Disease Detection Centre (SARGDDC)

Co-Director: Dr Natalie Mayet





The South African Regional Global Disease Detection Centre (SARGDDC) was established in South Africa in 2010 as the eighth of ten global diseases detection programmes with the purpose of integrating and embedding its core activities with collaborating partners in preventing, detecting and effectively building capacity for responding to infectious disease threats.

The SARGDDC supports 33 staff members through projects in both research and non-research co-operative agreements. The three projects in the research co-operative agreement include the use of new molecular technology in diagnosing neonatal sepsis; investigation of the influenza burden, interaction with other pathogens and nosocomial transmission at sentinel surveillance sites; the effectiveness of trivalent inactivated influenza maternal vaccination and evaluation of the vaccination programme among pregnant women and their newborns in South Africa. The non-research co-operative agreement includes 11 projects with principal investigators located at both the NICD and DoH: public health emergency preparedness and response capacity building in South Africa; strengthening malaria surveillance in South Africa; PulseNet Africa; investigation of vector-borne viruses as the cause of neurological disease of humans; harbouring of viral zoonotic agents by the southern African bat population; emergency funds for VHF outbreaks in Africa – mobile laboratory; analysing the South African Notifiable Disease Surveillance System; surveillance for invasive pneumococcal disease in infants; investigating the contribution of swine and or avian influenza-like illness and pneumonia in South Africa; supporting capacity for field epidemiology in South Africa; and partnering with South Africa to address the Global Health Security Agenda.

Other activities that the SARGDDC has been contributing to include the development of field epidemiologists through the South African Field Epidemiology Training Programme; the development of the Emergency Operations Centre at the NICD; participation in the South African Malaria Elimination Committee; contribution towards various influenza research activities; the formulation of the One Health Strategy for South Africa; the provision of technical support to the DoH Communicable Disease Cluster and support to the NICD as it evolves to become the National Public Health Institute of South Africa.

Dr Rachel Eidex, Co-Director of SARGDDC, took on the position as Director of the Global Health Programme in Tanzania, and Dr Seymour Williams, the Resident Advisor for the South African Field Epidemiology Training Programme, was appointed as Co-Director of the South African Global Disease Detection Centre in February 2015.

Ms Stephanie Griswold was appointed as Deputy Director of SARGDDC in February 2015. She holds an MPH in Epidemiology from Emory University in Atlanta, Georgia, USA, and previously served as the Branch Chief for Partner Management for Mozambique.

Prof. Marietjie Venter, the SARGDDC One Health Programme Director, has also been the acting International Emerging Infections Programme Director since August 2014.

Capacity Building

The SARGDDC hosted the *Effective Communication to Diverse Audiences* workshop in April 2014. The training was conducted by Ms Ruth Cooke-Gibbs, a health communication specialist at the US Centers for Disease Control and Prevention (CDC), Center for Global Health, in the Division of Global Health Protection (DGHP). The workshop was attended by 30 participants from the NICD, DoH, and provincial DoH, and was followed by a talk on Communication in Crises Situations to 60 staff members of the NICD and NHLS.

The SARGDDC supported the first South African Biorisk Association (SABA) symposium held at the NICD in May 2014. The meeting was aimed at increasing the awareness of biosafety and biosecurity and was attended by 34 participants.

In June 2014 the SARGDDC facilitated the Eritrean Study Group visit to the NHLS together with the Office of the CEO. The group of 14 representatives were from various departments in the Eritrean Government, and they expressed interest in the NHLS and its support to the National DoH.

The SARGDDC continues to assist the DoH with the re-engineering of the permit system for the import/export of biological agents, with the assistance of Dr James Blaine and Dr Von McClee from the CDC in the USA. The aim is to move to an electronic system. The backlog of processing of permits has been reduced in the last year from 2 800 to 140 outstanding permits per month.

The SARGDDC participated in the DoH Communicable Disease Cluster's strategic session held in March and April 2015, and opportunities for partnerships in health system strengthening were identified. The SARGDDC co-hosted the DoH

Communicable Disease Cluster meeting on One Health, Neglected Tropical Diseases and International Health Regulations with provinces in August 2014, and specific action plans were developed by the 65 participants in each of the respective areas.

The South African Malaria Elimination Committee (SAMEC) held its meetings in May and November 2014. The SARGDDC was involved in the road shows in the provinces and is currently involved in the development of 24-hour reporting tools, the strengthening and migration of the Malaria Information System, malaria advocacy and the development of a malaria mobile App.

The unprecedented Ebola virus disease outbreak in West Africa necessitated the establishment of an Emergency Operations Centre (EOC) for the DoH. Dr Mayet assumed the role of Acting Incident Manager for the EOC in October 2014. The EOC development included:

- The establishment of EOC operational streams
- The development of interoperable information technology systems
- Preparation of the EOC facility
- The development of the EOC Social Mobilisation Action Plan
- Liaison with the National Health Operations Centre (NATHOC), Port Health and private and public hospitals
- Partnership relationships with stakeholders, e.g. Discovery Health, to assist with the call centre operations of the EOC, MTN, HPCSA, Telkom, the Department of Tourism/Discovery Health and Soul City.

An EOC training workshop was conducted by the Defence Threat Reduction Agency in March 2015. The three-day EOC training was attended by 50 participants who learned the principles of command and control and the co-ordination of critical resources required during an outbreak.

Dr Adam Cohen was deployed to Nigeria from 3–16 September 2014 and Dr Seymour Williams to Liberia from 27 October–25 November 2014, to provide epidemiology capacity and to assist with Ebola contact tracing. Prof. Marietjie Venter was deployed to Congo Brazzaville from 7–24 January 2015.

Teaching and Training

Dr Mayet lectured on Notifiable Diseases Surveillance and Occupational Health Surveillance to South African Field Epidemiology Training Programme (SAFETP) residents, MPH students of the University of Pretoria and MSc students at Wits University.

Mr Alfred Musekiwa, the SARGDDC biostatistician, provided training on advanced epidemiology held at the end August to the first week in September 2014 for the Namibia FETP residents. He also facilitated the Statistics Training for Communicable Diseases held at the DoH in September 2014. The training explored how to apply quantitative techniques to investigate public health problems. The sessions were comprised of highly participatory lectures and practical exercises.

Ms Dorothy Southern, the SARGDDC scientific writer, facilitated a ten-day scientific writing workshop in August 2014 for participants from the Kenyan CDC Influenza Programme, the IEIP and FETP, and participants from the Kenya Medical Research Institute.

South African Field Epidemiology Training Programme

The South African Field Epidemiology Training Programme (SAFETP) was established in 2006 and its primary objective is to develop capacity for field epidemiology competencies that align with and support priority health issues, strategies and goals identified by the DoH.

The programme underwent a name change in 2014 and dropped the laboratory component of the training in line with developments in the CDC in the USA to create a laboratory epidemiology training course.

The programme is hosting a total cohort of 24 residents, 11 first-year students and 13 second-year students. Staff and residents were involved in the South African Ebola preparedness planning while assigned to the Communicable Disease Cluster of the DoH and were involved in assisting with the communications and support of National Health Operations Centre (NATHOC) and Multisectoral National Outbreak Response Team (MNORT).

SAFETP facilitated the establishment of the Public Health Association of South Africa (PHASA) Epidemiology Special Interest Group. This group will focus on building epidemiology skills in the health services and its terms of reference will be finalised at the PHASA Conference in September 2015.

Augusto Lopez and Ken Johnson from CDC in the USA visited South Africa in April 2014 and reviewed the progress of SAFETP since the external review in 2012. The implementation of the three-tiered pyramidal training model for building epidemiology capacity was discussed – basic, intermediate and advanced courses.

SAFETP progress, recruitment, supervision, graduation, placement and programme sustainability was provided to Dr Thomas Frieden, Director of the CDC in the USA in Durban on 21 June 2014 as part of the SA Global Health Protection Division update.

The programme hosted Dr Helen Maguire, Consultant Medical Epidemiologist, Head of Department; Field Epidemiology Services (Victoria), from Public Health England in October 2014. Discussions were aimed at sharing experiences and the training curriculum, and exploring opportunities of working together.

Two Basic Epidemiology short courses were conducted in North West in May and August, and 25 HIV/AIDS, TB and STI programme managers attended.

SAFETP staff participated in a Field Epidemiology Training Global Seminar, an interactive webinar on 21 May 2014.

The SAFETP Supervisors/Mentorship training was conducted by Denise Traicoff and the SAFETP team from 21–23 July 2014. The 21 participants were made up of current supervisors from the NICD, the National and Provincial DoHs. They learnt skills and techniques required to effectively mentor and coach.

A Basic Epidemiology and Surveillance Course was conducted in Nelspruit, Mpumalanga, from 28 July to 1 August 2014, and 29 environmental health practitioners from the malaria-endemic provinces of Mpumalanga, Limpopo and KwaZulu-Natal attended.

Drs Charles Mugero and Carl Reddy were funded by the DTRA to attend the International Epidemiology Course at Emory University, Atlanta, USA, from 19 September to 19 October 2014. The course was attended by 27 participants representing 16 countries in Africa, Asia and Europe. The course strengthened the analytical skills and the knowledge and skills in study designs, data collection, and risk assessment, and provided a networking opportunity for further collaboration with other epidemiologists.

Training on Basic Epi Info for viral haemorrhagic fever was conducted by Dr Patrick Nadol from the CDC South Africa on 26 November 2014. A total of five people were trained (SAFETP staff, residents and alumni).

Ms Ntsieni Ramalwa attended the South African Non-Communicable Diseases Alliance Workshop held on 17–18 November 2014. The meeting was aimed at exploring the strengthening of non-communicable disease control and management in South Africa.

The SAFETP arranged a Dale Carnegie Workshop, which took place as part of the induction of the new residents in January 2015 at the NICD. Eleven residents from the 2015 cohort, three staff members from the SAFETP and two provincial epidemiologists attended.

Five residents of the 2012 cohort received their Masters in Public Health from the University of Pretoria, School Health Systems and Public Health, in April 2014. The MPH graduation rate has increased from 51% in 2011 to the current rate of 76%.

Conference Presentations

National: 14

International: 12

New Staff

Ms Athalia Mathatho, the SAFETP administrator, commenced duty on 1 April 2014, along with Thulisa Mkhencele, an epidemiologist who joined the Outbreak Response Unit (ORU), NICD, on the same date. Thulisa orientates, supervises and teaches SAFETP residents when they rotate through the ORU. Dr Karien Viljoen, a medical epidemiologist, joined the programme on 1 September 2014.

Awards/Prizes

Ms Ntsieni Ramalwa, a SAFETP graduate and staff member, received an invitation from the Golden Key International Honour Society to attend their award ceremony as she was identified by the University of Pretoria as one of its top 15% achievers. The award ceremony was held in September 2014.

Research Output

Two second-year residents from the 2013 cohort, Nomathibane Mangisa and Nontobeko Mtshali, were co-authors of the following publications:

Mangisa N *et al.*, Outbreak Response Unit, SAFETP. Diarrhoeal disease outbreak, Bloemhof, North West province. *NICD-NHLS Communicable Diseases Communiqué*. June 2014; 13 (6): 1–2.

Ntshoe G, Mtshali N, Cengimbo A, Thomas J. Laboratory-confirmed hepatitis A in the South African public health sector, 2011–2013. *NICD-NHLS Communicable Diseases Surveillance Bulletin*. June 2014; 12 (2): 39–43.

Ramalwa N (Alumni, 2012 cohort) was the lead author of the following publications:

Ramalwa N *et al.* Anopheles species composition and insecticide susceptibility status of the major malaria vector *Anopheles arabiensis* at Vlakbult, Mpumalanga, 2012/13. *NICD-NHLS Communicable Diseases Surveillance Bulletin*. June 2014; 12 (2): 52–56.

Ramalwa N, Spillings BL, Misiani E, De Jager T, Oliver SV, Mabuza A, Moonasar DP, Koekemoer LL. Insecticide susceptibility analysis of Anopheles gambiae complex in Vlakbult, Mpumalanga 2012/13. *Epi Bulletin of the NICD*. July 2012; 2 (2).

Ngobeni N, Cohen C, Walaza S, Wolter N, Von Gottenberg N, Cohen A, Tempia S. Press Release: *World Pneumonia Day*, November 2014.

Publications

Peer-reviewed

Archer BN, Thomas J, Weyer J, Cengimbo A, Landoh DE, Jacobs C, Ntuli S, Modise M, Mathonsi M, Mashishi MS, Leman PA, Le Roux C, Jansen van Vuren P, Kemp A, Paweska JT, Blumberg L. Epidemiologic investigations into outbreaks of Rift Valley fever in humans, South Africa, 2008–2011. *Emerg Infect Dis.* 2013 Dec; 19 (12), doi: 10.3201/eid1912.121527.

Blumberg L, Frean J, Moonasar D, South African Malaria Elimination Committee. Successfully controlling malaria in South Africa. *South African Medical Journal*. 2014 Mar; 104 (3 Suppl 1): 224–227.

Blumberg LH, Weyer J. Ebola virus disease in West Africa – South African perspectives. *South African Medical Journal*. 2014; 104 (11): 754–755, doi: 10.7196/SAMJ.9045.

Blumberg LH. Recommendations for the treatment and prevention of malaria: Update for the 2015 season in South Africa. *South African Medical Journal.* 2015 Mar; 105 (3): 175–178.

Cohen C, Von Mollendorf C, De Gouveia L, Naidoo N, Meiring S, Quan V, Nokeri V, Fortuin-de Smit M, Malope-Kgokong B, Moore D, Reubenson G, Moshe M, Madhi S, Eley B, Hallbauer U, Kularatne R, Conklin L, O'Brien K, Zell E, Klugman K, Whitney C, and Von Gottberg A, for the South African Invasive Pneumococcal Disease Case-Control Study Group. Effectiveness of 7-Valent Pneumococcal Conjugate Vaccine against Invasive Pneumococcal Disease in HIV-infected and -Uninfected Children in South Africa: A Matched Case-Control Study. *Clin Infect Dis.* 2014; 59 (6): 808–818, doi:10.1093/cid/ciu431.

Frean J, Brooke B, Thomas J, Blumberg L. Odyssean Malaria Outbreaks in Gauteng Province, South Africa, 2007–2013. *South African Medical Journal.* May 2014; 104 (5): 335–338, doi:10.7196/samj.7684.

Imanishi M, Kweza P, Slayton R, Urayai T, Ziro O, Mushayi W, Chizororo M, Kuonza L, Ayers T, Freeman M, Govore E, Duri C, Chonzi P, Zinyowera S, Manangazira P, Kilmarx P, Mintz E, Lantagne D, the Zimbabwe Typhoid Fever Outbreak Working Group 2011–2012. Household Water Treatment Uptake during a Public Health Response to a Large Typhoid Fever Outbreak in Harare, Zimbabwe. *Am J Trop Med Hyg.* 2014 May; 90 (5): 945–954. doi: 10.4269/ajtmh.13-0497. Epub 2014 Mar 24.

Mantero J, Szegedi E, Payne, Hallstrom L, Lenglet A, Depoortere E, Kaic B, Blumberg L, Linge JP, Coulombier D. Enhanced epidemic intelligence using a web-based screening system during the 2010 FIFA World Cup in South Africa. *Euro Surveill.* 2014 May 8; 19 (18) pii: 20796.

Ntshoe GM, McAnerney JM, Tempia S, Blumberg L, Moyes J, Buys A, Naidoo D, Venter M, Besselaar T, Schoub BD, Harris BN, Cohen C. Influenza epidemiology and vaccine effectiveness among patients with influenza-like illness, viral watch sentinel sites, South Africa, 2005-2009. *PLOS ONE.* 2014 Apr 15; 9 (4): e94681, doi: 10.1371/journal.pone.0094681. eCollection 2014.

Quan V, Hulth A, Kok G and Blumberg L. Timelier notification and action with mobile phones – towards malaria elimination in South Africa. *Malaria Journal.* 2014; **13**: 151, doi:10.1186/1475-2875-13-151. (Impact factor: 3.4).

Raphaely N, Takalani A, Maphosa B, Weyer J, Blumberg L. Prevention of human rabies in South Africa. *Inf Dis Update.* April 2014; 3 (1): 9–11.

Roberts DR, Maharaj R, Coetzee M, Hunt RH, Govere J, Tren R, Urbach J, Attaran A, Blumberg L. Response to: Bouwman, H, *et al.* Hallogenated pollutants in terrestrial and aquatic bird eggs: converging patterns of pollutant profiles, and impacts and risks from higher levels, Environ Res. 2013: http://dx.doi.org/ 10.1016/j.envres.2013.06.003. *Environ Res.* 2014 July; **132**: 457–8, doi: 10.1016/j.envres.2014.01.010. Epub 2014 Apr 28.

Sewlall NH, Richards G, Duse A, Swanepoel R, Paweska J, Blumberg L, Dinh TH, Bausch D. Clinical features and patient management of Lujo haemorrhagic fever. *PLOS Negl Trop Dis.* 2014 Nov 13; 8 (11): e3233, doi: 10.1371/journal.pntd.0003233. eCollection 2014.

Von Gottberg A, De Gouveia L, Tempia S, Quan V, Meiring S, Von Mollendorf C, Madhi S, Zell E, Verani J, O'Brien K, Whitney C, Klugman K and Cohen C, for the GERMS-SA Investigators. Effects of Vaccination on Invasive Pneumococcal Disease in South Africa. *N Engl J Med.* 2014; 371 (20): 1889–1899, doi: 10.1056/NEJMoa1401914. Epub 2014 Nov 11.

Von Mollendorf C, Cohen C, De Gouveia L, Quan V, Meiring S, Feldman C, Klugman KP and Von Gottberg A. Factors associated with ceftriaxone non-susceptibility of *Streptococcus pneumoniae*: Analysis of South African national surveillance data: 2003–2010. *Antimicrob Agents Chemother.* 2014; 58 (6): 3293, doi:10.1128/AAC.02580-13.

Von Mollendorf C, Von Gottberg A, Tempia S, Meiring S, De Gouveia L, Quan V, Lengana S, Avenant T, Du Plessis N, Eley B, Finlayson H, Reubenson G, Moshe M, O'Brien KL, Klugman KP; Whitney C, Cohen C. Increased risk and mortality of invasive pneumococcal disease in HIV-exposed-uninfected infants. *Clinical Infectious Diseases.* 2015; doi: 10.1093/cid/civ059.

Weyer J, Blumberg LH, Paweska JT. Ebola virus disease in West Africa – an unprecedented outbreak. *South African Medical Journal.* 2014; 104 (8): 555–556. doi:10.7196/samj.8672.

Peer-reviewed chapters

Blumberg L, Enria D, Bausch D. *Manson's Tropical Diseases* 23rd Edition. Section 5; Viral Infections; Viral Haemorrhagic Fevers (pp 171–194). Eds. Farrar J, Hotez P, Junghans T, Kang G, Lalloo D, White N.

Blumberg L. *AFEM handbook of acute and emergency care*. Part 4, Infectious diseases. Eds. Wallis L, Reynolds T.

Non-peer reviewed

Monthly NICD Communiqué.

Quarterly NICD Communicable Diseases Surveillance Bulletin.

Surveillance Officer Monthly Communiqué.

Monthly NICD Surveillance Report.

Monthly MNORT Reports.

Quarterly GERMS-SA ESSORs, Provincial Statistics and PEPFAR Report.

Quarterly Pertussis Surveillance Project Progress Report to Sanofi Pasteur.

Pfizer Vaccine Focus for 50+: Article on I*nvasive pneumococcal disease in South African adults: pre- and post-vaccine surveillance data*; Meiring S.

Ntshoe G, Mtshali N, Cengimbo A, Thomas J. Laboratory-confirmed hepatitis A in the South African public health sector, 2011–2013. *NICD-NHLS Communicable Diseases Surveillance Bulletin*. June 2014 issue.

Information documents drafted for healthcare workers or the general public

Brucellosis fact sheet for KZN DoH for purposes of health promotion and community education.

Malaria alert and FAQs drafted and circulated to key role players and posted on NICD website.

Malaria fact sheet updated and posted on website.

Malaria alert and FAQs drafted and circulated to key role players and posted on NICD website.

Malaria factsheet updated and posted on website.

Fact sheet on *Escherichia coli* bacteria that cause diarrhoea (diarrhoeagenic *E. coli*) compiled and posted on website.

EVD draft guidelines.

Suspected Ebola virus disease case definition and risk assessment as well as algorithm for testing.

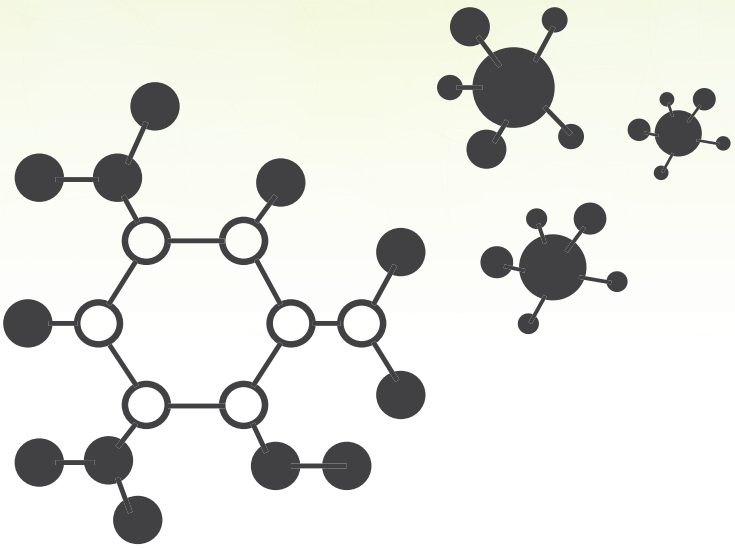
Ebola FAQs.

Ebola case investigation form.

Travel guidelines and advisory.

Centre for Vaccines and Immunology

Centre Head: Dr Melinda Suchard



National Polio Surveillance

As part of the Global Polio Eradication Initiative, the Centre for Vaccines and Immunology serves as the national reference laboratory for poliovirus isolation. South Africa is monitored by international bodies, such as the WHO, with regard to meeting adequacy indicators for surveillance of poliovirus, including a minimum case detection rate of two suspected acute flaccid paralysis cases per 100 000 population. Stool samples from cases of acute flaccid paralysis are inoculated into cell culture and any samples with suggestive cytopathic effects undergo molecular characterisation, including sequencing where applicable. South Africa has not had a case of endemic polio since 1989, but constant vigilance is required for imported cases. Molecular typing is required to differentiate circulating strains of Sabin vaccine virus from wild poliovirus. The centre processed more than 2 500 samples during the year under review. Data are shared and cases classified by the National Polio Expert Committee based on history, clinical notes and laboratory findings. In addition, the centre provides expertise to the National Task Force and National Certification Committees for polio containment in all laboratories nationally.

Measles Surveillance

The WHO African Region has a goal to eliminate measles by 2020. As we approach this goal, the field and laboratory surveillance indicators will change focus from the outbreak identification indicators to tracking chains of virus transmission and ultimately the verification of measles elimination.

The Centre for Vaccines and Immunology is the national referral laboratory for measles surveillance. Serology, specifically the detection of measles-specific IgM antibodies, is the mainstay of diagnosis of acute measles infection. The centre tested more than 4 800 specimens during the year under review in support of the National Measles Surveillance Programme, and identified 97 measles IgM-positive specimens. Following on from case investigations, 27 vaccine-associated cases were discarded, leaving 70 South African measles cases which could be divided into 23 sporadic cases and 47 cases in two clusters (ZF Mgcawu district in the Northern Cape and the City of Johannesburg Metro in Gauteng) spanning four months (September 2014–January 2015). The outbreaks were declared over in March 2015 after 42 consecutive days without further cases (two maximal incubation periods). A single strain of virus (genotype B3) was detected in both districts. The centre reports case-based data to the National Department of Health and WHO, and aggregated data to the Multisectoral National Outbreak Response Team (MNORT). The centre works closely with the National Expanded Programme on Immunisation Task Group to classify cases and monitor susceptibility.

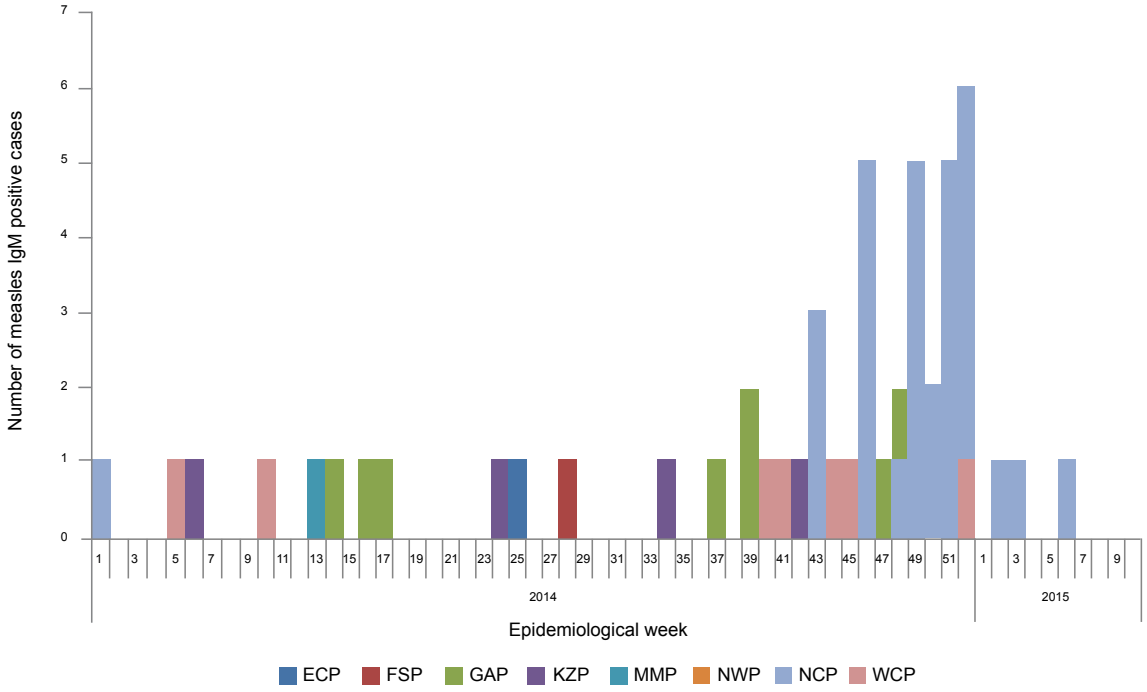


Figure 8: Measles IgM-positive cases in the South African outbreak of 2014/15

Congenital Rubella Syndrome Surveillance

Rubella infection during pregnancy can result in a number of severe abnormalities in newborns known as congenital rubella syndrome (CRS). Vaccination against rubella is mainly aimed at preventing CRS, as infection in children and adults is associated with low morbidity. The Centre for Vaccines and Immunology is planning a surveillance programme in preparation for rubella vaccine roll-out in South Africa. This will provide reliable baseline data on the disease burden, which will enable accurate comparison after the vaccine is introduced. The introduction of rubella vaccination has been known to lead to an increase in CRS cases when adequate coverage is not achieved. On the other hand, there is a tendency for increased reporting of cases with increased awareness among healthcare professionals. We therefore aim to obtain two years of surveillance data prior to introduction of the vaccine using a sentinel site approach that involves study sites in all nine provinces where case detection and laboratory testing will be performed. Applications have been submitted to relevant ethics committees and data collection will start as soon as clearance is obtained.

Research and Special Projects

Hepatitis B sero-prevalence in children in the general South African population

Most previous studies on hepatitis B prevalence and seroepidemiology focused on specific cohorts in localised healthcare facilities, such as patients at HIV clinics or other specialised clinics. This limitation makes it difficult to infer true population prevalence of the disease, which is necessary for monitoring and interventions with treatment and vaccine programmes. Our study will determine hepatitis surface antigen prevalence and sero-immunity in a sample representative of the general population of less than 15 years of age by using residual sera samples from the national rash-based surveillance programme at the NICD. Ethics approvals have been obtained to test 450 samples from all provinces in South Africa.

Mutational changes of the hepatitis C genotype 5a virus

The study identified mutations in the treatment of naïve patients attending the gastrointestinal clinic, Charlotte Maxeke and Chris Hani Baragwanath hospitals or asymptomatic South African blood donors. The core and NS5B regions were sequenced. Mega 6.0 and Bayesian inference were used for mutational and phylogenetic analyses respectively. This is the first study to describe pre-treatment viral mutations in HCV genotypes, particularly genotype 5a, for patients and anonymous blood donors in Johannesburg, South Africa. In the core region, R70Q and R70H were found to be the signature amino acids in genotype 5a in this study. These mutations were reported to be more significant in resistant than wild type viruses. In the NS5B region, the S282T mutation, associated with nucleotide inhibitor (Sofusbuvir) resistance, was not seen in any of the genotype 5a samples studied. This study provides new insight into one of the lesser-studied HCV genotypes and compares the diversity (and its implications) seen in a large pre-treatment genotype 5a cohort with other subtypes found in South Africa.

Collaborators: *JT Blackard, A Mahomed, W Abuelhassan, J Mahlangu, M Vermeulen, S Bowyer*

Regional Polio Surveillance

The centre serves as a regional reference laboratory for polio detection in the WHO-AFRO as well as other African countries. Detection of poliovirus requires labour-intensive cell culture isolation methods followed by molecular typing and sequencing. Strict laboratory containment measures are essential for working with a pathogen that has been eliminated in South Africa. The centre confirmed two wild poliovirus type 1 (WPV1) cases from Cameroun. Over ten months have passed since the last WPV1 case had onset of paralysis in central Africa (the last case was from Cameroun with the onset date 9 July 2014). There has been a noticeable increase in confirmed vaccine-derived poliovirus (VDPV) cases. A total of nine VDPV-2 cases were reported from Niger, Guinea, Republic of South Sudan, Uganda, Chad, Ethiopia and the Democratic Republic of Congo. In the same period Madagascar had six confirmed cases of VDPV-1. The last globally reported circulating VDPV-1 was reported in 2011. These results helped inform the regional outbreak response to identification of wild type virus in previously polio-free countries. The early identification of wild poliovirus and VDPVs is vital for immediate action in the endgame strategy for global polio eradication.

In addition, the centre provided on-site support to the Inter-Country Polio Laboratory at the Uganda Virus Research Institute as a WHO consultant. The objectives of this successfully completed mission were to critically review current and previous quality control data to identify gaps in the procedure and feedback accordingly for implementation of corrective actions, and to observe cell culture and cell sensitivity laboratory techniques and provide feedback on areas for improvement.

The Polio Molecular Unit participated in a pilot study of the Quanta ToughMix® real-time PCR assay. This assay now replaces the previous CDC in-house protocol used by the Polio Laboratory Network. The study was completed in mid-November 2014 and a validation report was submitted to the CDC. The protocol was phased into the AFRO laboratories from the beginning of 2015.

Collaborator: *WHO*

The assessment of HIV infection or exposure on immune responses to routine oral polio vaccination in infants

Deficiencies in poliovirus immunity in HIV-infected and/or exposed infants following the routine immunisation schedule could impact adversely on the overall population immunity and may pose a risk for the development of clusters or even localised outbreaks of circulating vaccine-derived polioviruses. Where the deficiency is substantial, it would be a motivation for supplementation of the routine polio immunisation schedule for HIV-infected and/or exposed infants. Infant sera archived at Chris Hani Baragwanath Hospital were tested for polio-neutralising antibodies at six weeks to assess serotype-specific response to birth OPV dose and at 18 weeks following primary vaccine administration. Neutralising antibody responses will be compared between non-exposed, exposed and HIV-infected infants with or without antiretroviral therapy.

Collaborator: *Respiratory and Meningeal Pathogens Unit, Soweto*

Regional Measles and Rubella Surveillance

In Africa, only 16 of 46 countries currently offer a second measles vaccine dose in their routine immunisation schedules, thus most countries still rely on periodic supplementary campaigns to provide the second dose. The measles first dose coverage varies considerably in the region: 16 countries reported a coverage ≥90%, 19 between 80–89% and 11 between 50–79%. Only one country reported a coverage <50%.

The centre retested 1 100 serum specimens from nine southern African countries (Botswana, Lesotho, Madagascar, Malawi, Mozambique, Namibia, Swaziland, Zambia and Zimbabwe) for measles and rubella as part of the WHO Regional Quality Assurance Programme. Additionally, serology support was given to Namibia during several measles outbreaks. Kenya and Namibia sent throat swabs for genotyping of outbreak strains: three strains of measles virus genotype B3 were shown to be circulating in Namibia and one of these strains of genotype B3 was identified as the cause of the outbreak in Kenya (and in the two South African outbreaks during September 2014 and January 2015). Regionally, intensified efforts are required to increase coverage with two doses of measles vaccine through routine immunisation services, sustaining the implementation of the 'reaching every district' approach, use of supplementary immunisation activities and introduction of a second dose in the routine immunisation schedule where it is not yet offered.

Collaborator: *WHO*

Environmental Polio Surveillance

The environmental laboratory provides virological testing for polioviruses in support of the global poliomyelitis eradication initiative. The laboratory provides a regional reference service to the WHO for samples from Angola. To date samples have been received from four selected sites in Angola. Only non-polio enteroviruses and Sabin vaccine strains have been isolated to date, indicating good quality of sample processing and laboratory techniques in use.

Teaching and Training

We have two intern scientists training in the unit (in the disciplines of molecular biology and immunology) and three MSc, two MMED, one MTech, one MPH and two PhD candidates in training. We are a placement site for one resident training in field epidemiology (FETP) and one intern medical scientist in the disciplines of virology and molecular biology.

Courses Hosted

Polio Laboratory Training, 9–27 June 2014

The overall objective of this training was to strengthen laboratory capacity for the detection and characterisation of polioviruses. There were four participants in total: one each from national polio laboratories in Zambia, Zimbabwe, Kenya and Uganda.

Tissue Culture Refresher Workshop, 11–23 August 2014

The overall objective of this workshop was to provide practical orientation on the mechanisms of cell culture propagation and technical orientation on monitoring cell sensitivity. There were 15 participants, one each from polio reference laboratories within the African region.

Environmental Surveillance Workshop 2–13 March 2015

The first week of the workshop was focused on the harmonisation of laboratory procedures for environmental surveillance of polio and included facilitators from Switzerland, India, USA, Egypt and Finland. The second week was hands-on training of key staff in laboratories currently performing testing and those selected for implementation, with participants from South Africa, Bangladesh, Kenya, Cameroon, and the Philippines.

Research Output

Gumede N *et al.* JID. 2014 S1 S361–7 Phylogeny of imported and re-established wild polio viruses in the DRC, 2006–2011.

Kinge CN, Espiritu C, Prabdial-Sing N, Sithebe NP, Saeed M, Rice CM. HCV genotype 5a subgenomic replicons for evaluation of direct acting antiviral agents. *Antimicrob Agents Chemother.* 2014; 58 (9): 5386–5394.

Shibeshi ME, Masresha BG, Smit SB, Biellik RJ, Nicholson JL, Muitherero C, Shivute N, Walker O, Reggis K, Goodson JL. Measles resurgence in southern Africa: challenges to measles elimination. *Vaccine.* 2014; 32 (16): 1798–1807.

Conference Presentations

National: six

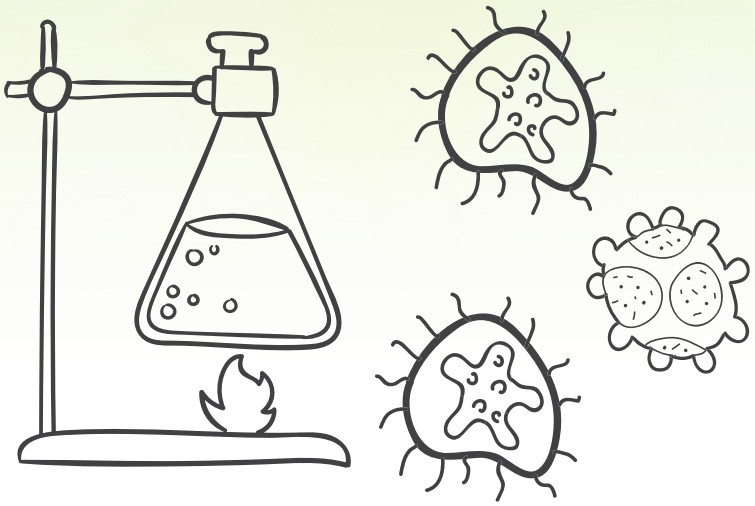
International: two

Figure 9: The Centre for Vaccines and Immunology hosting the Environmental Surveillance Workshop, March 2015

Figure 10: The Centre for Vaccines and Immunology hosting and facilitating a WHO tissue culture course at the NICD, August 2014

Division of Public Health Surveillance and Response

Centre Head: Prof. Lucille Blumberg



Background

The Public Health Surveillance and Response Division includes the Outbreak Unit, the GERMS-SA Surveillance Programme, Travel Health and the Communications Unit. During the year under review the division expanded significantly to include a Data Management Unit, an Emergency Operations Centre (EOC) to respond to public health emergencies, and a Provincial Epidemiology Team to strengthen the footprint of the NICD within provinces. The division facilitates communication and data sharing between the National and Provincial Departments of Health, the NICD and the public. It provides epidemiology and public health input into other NICD units through collaborative projects and support of surveillance and epidemiological activities and outbreak responses.

The Ebola outbreak in west Africa required that the division play a key role ensuring national preparedness and response to the possible introduction of Ebola virus disease (EVD) into South Africa. The expansion of the GERMS Programme from primarily laboratory-based surveillance to clinic-based surveillance for a number of priority conditions in rural and urban clinics in the provinces continued, supported by a network of NICD-appointed epidemiologists.

The Mass Gatherings Centre, which is part of the WHO Mass Gathering Global Network, supported research and operational activities on communicable disease monitoring and risk assessments for mass gatherings in the region. The South African National Travel Health Network (SaNTHNeT), established together with the DoH and the South African Travel Medicine Society in August 2013, continued to provide reliable and current information and guidelines for travellers to the southern African region. The NICD Communications Unit played a key role in conveying important public health messages and outbreak alerts to medical and allied professionals, as well as to the public through extensive interaction with the media, and other channels.

GERMS-SA

Surveillance/diagnostic services

GERMS-SA is a laboratory-based surveillance programme for diseases of public health importance. It is co-ordinated by a core team within the DPHSR and spans many of the centres at the NICD. The laboratory surveillance pathogens include: *Candida spp, Salmonella enterica, Shigella spp, Vibrio cholerae, Campylobacter spp, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus, Pseudomonas aeruginosa* and *Cryptococcus* spp. GERMS-SA is an active surveillance programme and relies not only on participating laboratories to submit isolates, but also makes use of the NHLS Corporate Data Warehouse to ensure that all cases meeting the case definition are included in the database. Annually, approximately 200 microbiology laboratories nationally report roughly 13 000 cases meeting the GERMS-SA case definitions. The enhanced surveillance arm is operational at 25 sentinel sites across the country, where 30 surveillance officers collect clinical information on patients relating to specific pathogens: *invasive S. pneumoniae, H. influenzae, N. meningitidis; S. aureus* and *Candida* spp bacteraemia*; Cryptococcus* spp and Rifampicin-resistant TB.

The aim of GERMS-SA is to use the data 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 the HIV/AIDS Comprehensive Care, Management and Treatment Programme in South Africa on HIV-associated opportunistic infections, and evaluating the impact of vaccines included in the Expanded Programme of Immunisation (EPI). The work carried out by the GERMS-SA team contributed significantly to the development of clinical guidelines for pneumonia, meningococcal disease, cholera, cryptococcosis and typhoid fever, which in turn contributed to the situational analysis of antibiotic resistance in South Africa, and the introduction of pneumococcal conjugate vaccine as well as a booster dose for *Haemophilus influenzae* type b into the EPI. Data emanating from the GERMS-SA activities also contributed to the DoH roll-out of the cryptococcal antigen (CrAg) screening programme to facilitate the early diagnosis, and hence treatment, of cryptococcal meningitis. With these interventions in place, it is imperative that surveillance continues in order to monitor the burden of *S. pneumoniae* and *H. influenzae*. *Cryptococcus spp* surveillance will help monitor the CrAg screening and treatment programme.

GERMS-SA is also a platform for nested studies. The *Case-control study to estimate the effectiveness of a pneumococcal conjugate vaccine against invasive pneumococcal disease in South Africa* has just been completed, and data cleaning and manuscript write-up are in process.

GERMS-SA work is funded through the NHLS and a CDC co-operative agreement, and more recently by the DoH.

Expansion of the GERMS platform: XpertMTB/RIF

XpertMTB/RIF, a rapid diagnostic test that detects both *Mycobacterium tuberculosis* and resistance to Rifampicin, was implemented in all NHLS laboratories nationally and will now be the initial diagnostic test for all TB suspects in South Africa. In response to this implementation, enhanced surveillance for Xpert rifampicin resistance TB was initiated at the Chris Hani Baragwanath Hospital and selected surrounding clinics late in October 2012, and has subsequently been

introduced into six other provinces. This surveillance will monitor trends over time, estimate the proportion of MRD TB among RR TB cases and the burden of resistance to other TB drugs, and provide information on risk factors, including close contact, occupational history and HIV status.

Surveillance will be initiated in the remaining two provinces during 2015.

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

GERMS-SA recently expanded to include clinic-based surveillance. Two sites have been initiated to date in the North West and Eastern Cape provinces. Clinic-based surveillance includes integrated TB/HIV surveillance which aims to characterise the burden of TB-HIV co-infection, describe the proportion of patients actively managed through care and to describe the epidemiology of drug resistance among HIV-infected persons initiating ART and/or TB treatment at the selected sites, as well as STI surveillance. The STI component includes surveillance of STI syndrome aetiologies, gonococcal antimicrobial resistance and HPV genotypes among patients attending the clinic. Additional sites will be established in KwaZulu-Natal, Mpumalanga and Gauteng during 2015.

The acute febrile illness (AFI) surveillance project was built on the zoonotic diseases study, which was funded by the Swedish Civil Contingencies Agency (MSB) and the Swedish International Development Cooperation Agency (SIDA) and by the Global Disease Detection Program in 2012–2014. This project has been incorporated into clinic-based syndromic surveillance 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 done in collaboration with veterinary practitioners and researchers from the University of Pretoria Veterinary Faculty.

The aim of the surveillance is to describe the prevalence of zoonotic infections in adult patients presenting with acute febrile illness and for whom the clinic sisters do a malaria test. Laboratory testing includes PCR and serology for brucellosis, *Bartonella* infections, leptospirosis, Q fever, tick bite fever (TBF), West Nile virus, Sindbis, Rift Valley fever and chikungunya virus infections. An initial study of patients with acute febrile illness and herders attending cattle dip tanks with their livestock showed TBF, Q fever, leptospirosis and *Bartonella* to be causes of AFI. A study using cellphone technology for data submission to a central server was conducted in parallel, to improve timeliness of reporting of malaria cases, diarrhoeal cases and dog bites. A key component of the malaria elimination strategy is a 24-hour reporting time for confirmed malaria cases to allow rapid follow-up and management of additional cases by malaria field staff. The use of a notification sent via SMS from a cellphone for each newly diagnosed malaria case was acceptable to users and was technically feasible in this rural area, and significantly improved the timeliness of data transmission. Consideration should be given to large-scale use by the provincial malaria control programmes, possibly using a toll-free phone service.

Provincial Epidemiology Team

The NICD has historically supported the DoH in its role of responding to priority diseases, such as HIV and TB, and to outbreaks of infectious diseases. Support of Provincial departments of health has primarily been from teams based at the NICD until 2014, when the NICD set up a Provincial Epidemiology Team (PET) comprising one senior epidemiologist based at the NICD and nine provincial field epidemiologists, one in each of the nine Provincial DoH offices. Currently there are five provincial epidemiologists in the KwaZulu-Natal, Mpumalanga, Free State, Eastern Cape and North West provinces. The process of filling the vacant positions is under way. Having an NICD epidemiologist in each province ensures that epidemiology, public health and diagnostic and clinical expertise within the NICD is available to provinces in a timely manner to effectively support communicable disease surveillance, prevention and control, epidemiology research, training and outbreak response at provincial and district level.

The main focus for the next few years will be on HIV/TB and CDC (surveillance of notifiable medical conditions) and outbreak response. PET provides expert technical advice and assistance on the design, maintenance, analysis and interpretation of surveillance databases. Additionally, they support synthesis and analysis of surveillance and routine clinical and DHIS data collected at provincial, district and sub-district levels by both the NICD and the DoH to determine populations at risk, monitor disease trends and distribution, detect outbreaks and subsequently advise on interventions required to curb morbidity and address public health needs and resource allocation. To highlight one example, provincial epidemiologists analyse data generated via the NICD Centre for TB to describe and report on trends and numbers of patients diagnosed with drug-susceptible and drug-resistant TB. These reports, which are analysed together with provincial data from electronic TB registers showing the actual number of patients starting TB therapy, are used to identify and address gaps in the TB treatment cascade. PET is also responsible for the implementation and management of the clinic-based surveillance of HIV/TB drug resistance and STIs, and provides some supervision for the GERMS surveillance.

NICD Data/Information Centre

The NICD Data/Information Centre has been established within the division, and its aims are to centralise data generated by the NICD, provide technical expertise for data management within the EOC, establish and maintain the data systems

for the national notification system, manage the national malaria information system, provide technical support/expertise for the GIS, provide a data repository for the NICD, including the dashboards, and provide analysis tools for reporting.

A manager was appointed and there are plans to expand the staff complement. Key events planned to date are the migration of the MIS from the National DoH to the NICD and the establishment of data systems to support the functioning of the EOC.

Provincial Epidemiology Team

Major focus for the next 3–5 years is on outbreak support, TB/HIV and CDC

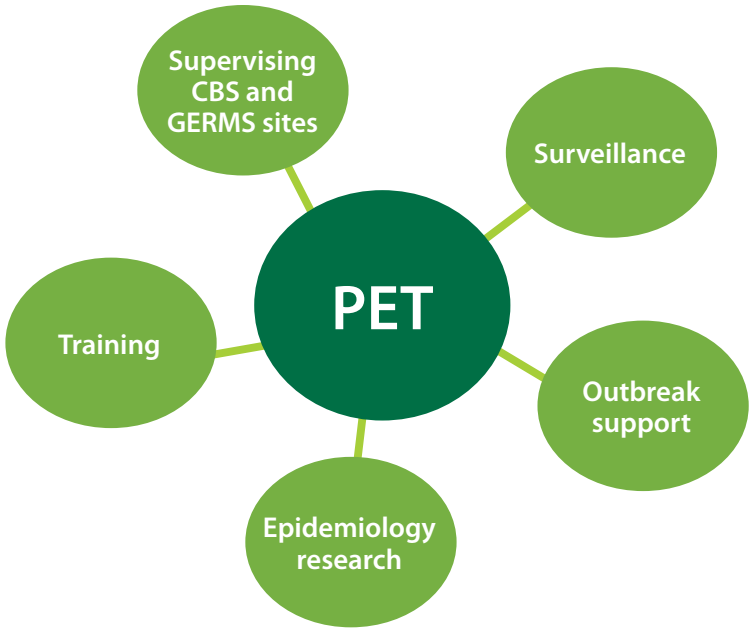


Figure 11: Functional areas of Provincial Epidemiology Team

Outbreak Response Unit

The Outbreak Response Unit (ORU) provides technical support for all aspects of communicable disease outbreaks and control in South Africa. Through close collaboration with Provincial and National DoH and other stakeholders, together with systems for early detection and improved reporting of epidemic-prone communicable diseases, the ORU functions as a source of intelligence for outbreak detection and facilitates comprehensive outbreak response activities. In addition, close partnerships with the NHLS's diagnostic laboratories and NICD centres provide appropriate laboratory diagnostic services during outbreaks and specialised diagnostic testing as required. The National DoH's Communicable Diseases Directorate and the ORU are functionally integrated as the National Outbreak Unit, a platform for synergistic outbreak detection and response activities throughout the country.

Public Health Services

The ORU's role in outbreaks includes, but is not limited to, outbreak detection and reporting, field investigation, development of clinical and laboratory guidelines, management of laboratory data and interpretation of results, and recommendations for prevention and control.

Ebola virus disease outbreak in West Africa

During the year, the ORU assisted with the investigation of and response to a wide spectrum of outbreaks (in excess of 100). A major focus for 2014 was the response to the Ebola virus disease (EVD) outbreak in West Africa. Once confirmed in February 2014, the division, together with the Centre for Emerging and Zoonotic Diseases (CEZD,) initiated a response to the Ebola outbreak in West Africa to prepare the country for possible introduction of the disease into South Africa and to support the personnel deployed to Sierra Leone to assist with laboratory diagnosis and treatment of patients.

The NICD gave guidance on the diagnosis, infection control and entry risk assessment, and EVD risk communication to the general public and other stakeholders, and carried out various training activities to support responses to EVD in other countries. With the outbreak of EVD in west Africa, the NICD also established an Emergency Operations Centre (EOC) in South Africa to prepare and respond better to high-risk disease outbreaks such as Ebola in the country, in line with its mandate from the DoH. The NICD's 24-hour emergency call facility received more than 600 calls of suspected cases. From February 2014 to April 2015 a total of 37 suspected cases were subjected to testing at the CEZD at the NICD in Johannesburg. Eight of these cases were referred from other African countries, including Zimbabwe (n=2), Namibia (n=4), Angola and Ethiopia (not SADC). The remainder were patients presenting at South African healthcare facilities, who required follow-up for suspected EVD. All of these cases tested negative for EVD.

The differential diagnosis of these cases revealed infectious and non-infectious causes of disease. Ten cases were diagnosed with malaria, but laboratory testing also supported trypanosomiasis (n=1), dengue (n=1) and parvovirus infection (n=1). Two cases involving Nigerian patients were related to complications of sickle-cell anaemia, a common hereditary condition in the Nigerian population. One patient was diagnosed with severe complications of autoimmune disease, while another died of a possible drug reaction. Overall, in excess of 600 incidents were reviewed, leading to laboratory testing of almost 40 patients with acute febrile illness, but to date there have been no cases of laboratory-confirmed EBV in South Africa or the southern African region.

Diphtheria outbreak, KwaZulu-Natal

In March 2015, the ORU assisted with the investigation of a case of suspected diphtheria in KwaZulu-Natal. This case marked the beginning of the first diphtheria outbreak reported in South Africa in at least the last two decades. The ORU assisted the provincial outbreak response team by participating in field investigations, producing clinical management and public health response guidelines, and facilitating specialised toxigenicity testing of *C. diphtheriae* isolates. Prof. Blumberg facilitated a generous donation of diphtheria antitoxin treatment by the Japanese government.

Other outbreaks that were responded to included:

- Foodborne illness outbreaks, countrywide
- Institutional outbreaks: TB, hepatitis A, hepatitis B, scabies
- Healthcare-associated infection outbreaks: ESBL-producing *Klebsiella pneumoniae*, suspected carbapenemase-producing *K. pneumoniae*, NDM-1-producing Enterobacteriaceae, B*urkholderia cepacia*
- Measles outbreak in Gauteng and the Northern Cape, prompting local vaccination campaigns
- Clusters of odyssean malaria in Gauteng.

Cases of suspected rabies and suspected viral haemorrhagic fever infections were routinely referred to the ORU for follow-up in order to conduct risk assessments and guide diagnostic testing and clinical management, and initiate public health responses where appropriate.

The ORU continued to strengthen networks for the reporting and investigation of food-borne illness, with close to 60 food-borne illness outbreaks reported and followed up. The emergency NICD hotline and the CDW alert system, managed by the ORU, facilitated timely notification of outbreaks and laboratory-confirmed cases of priority communicable diseases detected by NHLS laboratories throughout the country (*Salmonella* Typhi*, Vibrio cholerae, Neisseria meningitidis* and *Bordetella pertussis*) to healthcare and public health workers. The ORU assisted with the development of provincial and national guidelines for priority communicable diseases.

Residents of the Field Epidemiology Programme were seconded to the ORU for 4–8 weeks to gain field experience of outbreaks under supervision. Public health registrars from the University of the Witwatersrand were hosted for six-month placements in the ORU to participate and gain experience of the range of public health activities undertaken by the unit.

The ORU continues to publish a 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 requiring immediate dissemination of information.

Figure 12: Genevie Ntsoe (left) and NICD team at the Diphtheria outbreak site visit to Umlazi, KwaZulu-Natal

Figure 13: DPHSR and the Vector Control unit, NICD and DoH team investigating a case of Odyssean malaria in Gauteng

Research Projects

Pertussis surveillance project

This hospital-based project based at two sites in Gauteng aims to describe the prevalence and characteristics of pertussis disease amongst children under ten years of age who are hospitalised with suggestive respiratory illness, or in the case of infants and young children, present with apnoea for investigation. With informed consent from caregivers, key clinical data are recorded and nasopharyngeal swabs are collected for *B. pertussis* and *B. parapertussis* PCR testing as well as culture for *Bordetella* spp. Case enrolment is ongoing and will continue until December 2015.

Teaching and Training

The following students were supervised: one MMed student, one MSC (University of Johannesburg), one PhD (University of the Witwatersrand).

Travel Health Unit

This unit provides a consultative service for health practitioners on 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 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.

South African National Travel Health Network (SaNTHNeT)

http://www.santhnet.co.za

SaNTHNeT is a travel health network run by the National 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 and attracts over 5 000 visits a month, many of international origin. The network focuses on developing guidelines on travel-related health matters. It serves as a surveillance platform to gather information on imported communicable diseases, e.g. dengue fever, trypanosomiasis and leishmaniasis as well as expert advice on the 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.

WHO Collaborating Centre on Health at Mass Gatherings

http://www.who.int/ihr/publications/mass_gatherings/en/

The Mass Gatherings (MG) Centre was established for communicable disease surveillance and risk assessment for the 2010 FIFA World Cup and has now become part of the WHO 6-centre Mass Gatherings Collaborating Centre network (Disaster Research Centre, Flinders University, Australia; Public Health England, United Kingdom; NICD, South Africa; Institute of Public Health of Vojvodina, Serbia; School of Public Health, University of Washington, United States; Ministry of Health, Saudi Arabia).

The WHO consultancy was conducted to Botswana in April 2014 for the African Youth Games in Gaberone. These games attracts participants from 52 African countries. The centre provided support to establish a number of systems and guided specific preparations to respond to any introduction of EVD by participants in the games or their support teams.

NICD Communications Unit

The NICD Communications Unit continued to expand its role in conveying important public health messages and outbreak alerts to both the medical and allied professionals through guidelines and information sheets, as well as to the general public through media releases, interviews on TV, radio and the print media and through the introduction of social media. During the past year, the NICD set up a Twitter account, which is an effective tool for public health messaging.

The NICD website is proving to be an invaluable resource for information on outbreak response, diseases surveillance and infectious diseases information. A case in point is the setting up of a portal on the NICD website dedicated to updating information on a daily basis during the Ebola virus disease outbreak in West Africa. The information on the NICD centres is updated monthly; the Alerts and News sections are updated twice weekly. Over the past year, the NICD website continued to grow in attracting the general public, the media and health professionals. To meet the increasing demands for this, media training for senior staff was undertaken. A general review of the NICD website is planned for the coming year, with an interim updating of all centre information.

A new electronic format was successfully developed for disseminating NICD publications to stakeholders in the public and private sector and National and Provincial DoH. These include the monthly Communicable Disease Communiqué, which highlights current communicable disease events and outbreaks, the monthly NICD Surveillance Bulletin, which collates data from the NICD surveillance programmes, and the quarterly bulletin which documents more formally outbreaks and surveillance programmes.

The unit continues to produce internal publications, namely the NICD's Science Focus, a quarterly compilation of abstracts of scientific publications by NICD staff members published in peer-reviewed journals, and the NICD Newsletter, which has a more informal focus on events and happenings at the NICD, and staff awards and profiles of individual staff members and their work.

Over the past year a good partnership was forged with the National DoH's communications teams – there are now collaborations in media relations during high-profile occurrences such as outbreaks with international and local significance.

RP272/2015
ISBN: 978-0-621-43930-4

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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