National Institute for Communicable Diseases

Annual Overview

2016/17
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List of Abbreviations

ACV  Acyclovir
AFCRN African Cancer Registry Network
AFENET African Field Epidemiology Network
AFP Acute Flaccid Paralysis
AMP Antibody-mediated prevention
AMR Antimicrobial resistance
AMRRL Antimicrobial Resistance Reference Laboratory
ART Antiretroviral Therapy
ASIR Age standardised incidence rates
BC Breast cancer
BCAH Burden of Cancers Attributable to HIV
BDQ Bedaquiline
BV Bacterial Vaginosis
CCHF Crimean-Congo hemorrhagic fever
CDC Centres for Disease Control and Prevention
CDW Corporate Data Warehouse
CED Centre for Enteric Diseases
CEZD Centre for Emerging and Zoonotic Diseases
CI Confidence interval
CrAg Cryptococcal antigen
CRDM Centre for Respiratory Diseases and Meningitis
CRE Carbapenem-resistant Enterobacteriaceae
CRS Congenital rubella syndrome
CTB Centre for Tuberculosis
DNA Deoxyribonucleic acid
DoH Department of Health
DRS Drug Resistance Survey
DST Department of Science and Technology
DTM&H Diploma in Tropical Medicine and Hygiene
EIA Enzyme immunoassay
EID Early infant diagnosis
EML Electron Microscope Laboratory
EOC Emergency Operations Centre
EPBCR Ekurhuleni population-based cancer registry
EPI Expanded Programme on Immunisation
ESC Extended-Spectrum Cephalosporins
ESKAPE Enterococcus, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas and ESBL
FDA Food and Drug Administration (US)
FELTP Field Epidemiology and Laboratory Training Programme
FETP Field Epidemiology Training Programme
FIC Fractional inhibitory concentration
GDOH Gauteng Department of Health
GERMS-SA Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa
GLASS Global Antimicrobial Resistance Surveillance System
GLI-AFRO Global Laboratory Initiative – Africa
GPEI Global Polio Eradication Initiative
GUS Genital ulcer syndrome
HAAstV Human Astrovirus
hc2 Hybrid Capture
HCC Hepatocellular carcinoma
HEU HIV-exposed uninfected
HIPSS HIV Incidence Provincial Surveillance System
HIV Human Immunodeficiency Virus
HIVDR HIV Drug Resistance
HPV Human Papillomavirus
HR High-risk
HR Human resources
HSRC Human Sciences Research Council
HSV Herpes simplex virus
HUU HIV-unexposed and uninfected
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>HVTN</td>
<td>HIV Vaccine Trials Network</td>
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<tr>
<td>IAEA</td>
<td>International Atomic Energy Agency</td>
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<td>IANPHI</td>
<td>International Association of National Public Health Institutes</td>
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<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<tr>
<td>IBBS</td>
<td>Integrated HIV Bio-Behavioral Surveillance</td>
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<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IHR</td>
<td>International Health Regulations</td>
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<tr>
<td>ILI</td>
<td>Influenza-like Illness</td>
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<td>IMD</td>
<td>Invasive Meningococcal Disease</td>
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<tr>
<td>IMS</td>
<td>Incident Management System</td>
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<tr>
<td>iNTS</td>
<td>Nontyphoidal <em>Salmonella</em></td>
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<td>IPD</td>
<td>Invasive Pneumococcal Disease</td>
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<td>IQC</td>
<td>Internal Quality Control</td>
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<td>IQR</td>
<td>Interquartile Range</td>
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<td>IRS</td>
<td>Residual insecticides</td>
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<td>ITNs</td>
<td>Insecticide treated bed nets</td>
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<td>ITS</td>
<td>Internal transcribed spacer</td>
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<td>JCS</td>
<td>Johannesburg Cancer Case-control Study</td>
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<td>KPIS</td>
<td>Key Population Implementation Science</td>
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<tr>
<td>KZN</td>
<td>KwaZulu-Natal</td>
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<tr>
<td>LARS</td>
<td>Laboratory-based Antimicrobial Resistance Surveillance</td>
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<td>LR</td>
<td>Liferisk</td>
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<td>LRTI</td>
<td>Lower Respiratory Tract Infection</td>
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<td>MADCaP</td>
<td>Men of African Descent Cancer of the Prostate</td>
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<td>MDR</td>
<td>Multi-drug-resistant</td>
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<td>MGIT</td>
<td>Mycobacteria Growth Indicator Tube</td>
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<td>MHCU</td>
<td>Mental health care users</td>
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<td>MIC</td>
<td>Minimal inhibitory concentration</td>
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<td>MLST</td>
<td>Multi-locus sequence typing</td>
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<td>MLVA</td>
<td>Multiple-locus variable number tandem repeat analysis</td>
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<td>mPTB</td>
<td>Microbiologically confirmed pulmonary TB</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>MRSA</td>
<td>Methicillin-Resistant <em>Staphylococcus aureus</em></td>
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<tr>
<td>MSM</td>
<td>Men-who-have-sex-with-men</td>
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<td>MUS</td>
<td>Male urethritis syndrome</td>
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<td>NAAT</td>
<td>Nucleic acid amplification test</td>
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<td>NADCs</td>
<td>Non-AIDS defining cancers</td>
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<td>NAPHISA</td>
<td>National Public Health Institute of South Africa</td>
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<td>NCR</td>
<td>National Cancer Registry</td>
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<td>NDoH</td>
<td>National Department of Health</td>
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<td>Necsa</td>
<td>South African Nuclear Energy Corporation</td>
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<tr>
<td>NHLS</td>
<td>National Health Laboratory Service</td>
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<td>NICD</td>
<td>National Institute for Communicable Diseases</td>
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<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
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<td>NIOH</td>
<td>National Institute for Occupational Health</td>
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<tr>
<td>NMC</td>
<td>Notifiable Medical Conditions</td>
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<tr>
<td>NNRTI</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
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<tr>
<td>NPSP</td>
<td>National Pneumonia Surveillance Programme</td>
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<tr>
<td>NRF</td>
<td>National Research Foundation</td>
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<tr>
<td>NSP</td>
<td>National Strategic Plan</td>
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<td>NTBRL</td>
<td>National TB Reference Laboratory</td>
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<td>NTP</td>
<td>National TB Programme</td>
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<td>NTPn</td>
<td>Nontypeable pneumococci</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>ORU</td>
<td>Outbreak Response Unit</td>
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<td>OSCC</td>
<td>Oesophageal Squamous Cell Carcinoma</td>
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<td>PCP</td>
<td><em>Pneumocystis jiroveci</em> Pneumonia</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
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<td>PEF</td>
<td>Polio Essential Facility</td>
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<td>PEPFA</td>
<td>President’s Emergency Plan for AIDS Relief</td>
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<td>PET</td>
<td>Provincial epidemiology team</td>
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<td>PFGE</td>
<td>Pulsed field gel electrophoresis</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>PHC</td>
<td>Primary Healthcare Centre</td>
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<td>PHIRST</td>
<td>Prospective Household Observational Cohort Study of Influenza, Respiratory Syncytial Virus and other Respiratory Pathogens Community Burden and Transmission Dynamics in South Africa</td>
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<tr>
<td>PHRU</td>
<td>Perinatal HIV Research Unit</td>
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<tr>
<td>PLHIV</td>
<td>People living with HIV</td>
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<tr>
<td>PMS</td>
<td>Post-marketing surveillance</td>
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<td>PMTCT</td>
<td>Prevention of mother-to-child transmission</td>
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<td>POC</td>
<td>Point-of-care</td>
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<tr>
<td>PRF</td>
<td>Poliomyelitis Research Foundation</td>
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<tr>
<td>PRL</td>
<td>Probabilistic record linkage</td>
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<tr>
<td>PS-MTM</td>
<td>PrimeStore molecular transport medium</td>
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<td>PT</td>
<td>Proficiency testing</td>
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<tr>
<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
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<tr>
<td>RAPIDD</td>
<td>Research and Policy for Infectious Disease Dynamics</td>
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<tr>
<td>REC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>REDCAP</td>
<td>Research Electronic Data Capture</td>
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<td>RMPRU</td>
<td>Respiratory and Meningeal Pathogens Research Unit</td>
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<tr>
<td>RPR</td>
<td>Rapid Plasma Reagin</td>
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<tr>
<td>RMR</td>
<td>Rifampicin mono-resistance</td>
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<tr>
<td>RR</td>
<td>Rifampicin-resistant</td>
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<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
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<tr>
<td>RT</td>
<td>Reverse transcriptase</td>
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<tr>
<td>RTQII</td>
<td>Rapid test quality improvement initiative</td>
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<tr>
<td>RVF</td>
<td>Rift Valley fever</td>
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<tr>
<td>RVFV</td>
<td>RVF Virus</td>
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<tr>
<td>SACIDS</td>
<td>Southern African Centre for Infectious Disease Surveillance</td>
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<td>SADC</td>
<td>Southern African Development Community</td>
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<tr>
<td>SAFETP</td>
<td>South African Field Epidemiology Training Programme</td>
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<td>SAM</td>
<td>South African HIV Cancer Match Study</td>
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<td>SaNTHNet</td>
<td>South African National Travel Health Network</td>
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<td>SARGDDC</td>
<td>South African Regional Global Disease Detection Centre</td>
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<tr>
<td>SARI</td>
<td>Severe Acute Respiratory Infections</td>
</tr>
<tr>
<td>SARI</td>
<td>Severe Acute Respiratory Illness</td>
</tr>
<tr>
<td>SASTM</td>
<td>South African Society of Travel Medicine</td>
</tr>
<tr>
<td>SCRIO</td>
<td>Severe Chronic Respiratory Illness</td>
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<tr>
<td>SIT</td>
<td>Sterile insect technique</td>
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<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
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<tr>
<td>SPI-RT</td>
<td>Stepwise Process for Improving the Quality of HIV Rapid Testing</td>
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<tr>
<td>SRI</td>
<td>Severe Respiratory Illness</td>
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<td>SSA</td>
<td>Sub-Saharan Africa</td>
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<td>STI</td>
<td>Sexually transmitted infection</td>
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<tr>
<td>TAC</td>
<td>TaqManR Array Card</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TEPHINET</td>
<td>Training Programme in Epidemiology and Public Health Interventions Network</td>
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<tr>
<td>TIV</td>
<td>Trivalent seasonal influenza vaccine</td>
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<tr>
<td>TK</td>
<td>Thymidine kinase</td>
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<tr>
<td>TWG</td>
<td>Technical working group</td>
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<tr>
<td>UCSF</td>
<td>University of California, San Francisco</td>
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<tr>
<td>UCT</td>
<td>University of Cape Town</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Emergency Fund</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>VDPV</td>
<td>Vaccine-derived poliovirus</td>
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<tr>
<td>VDS</td>
<td>Vaginal discharge syndrome</td>
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<tr>
<td>VHF</td>
<td>Viral hemorrhagic fever</td>
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<tr>
<td>VL</td>
<td>Viral load</td>
</tr>
<tr>
<td>VP-IBD</td>
<td>Vaccine-preventable invasive bacterial disease</td>
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<tr>
<td>WGS</td>
<td>Whole-genome sequencing</td>
</tr>
<tr>
<td>Wits</td>
<td>University of the Witwatersrand</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>XDR</td>
<td>Extensively drug-resistant</td>
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NICD Director’s Overview

In this age of precision medicine, the availability of robust data is pivotal to making informed decisions to inform public health policy. The National Institute for Communicable Diseases (NICD) has served, and continues to serve, as a publicly-trusted source of data on communicable diseases, both during outbreak threats and as part of its routine surveillance of priority infectious diseases affecting South Africans.

In 2016/17, the NICD expanded on its mandate of setting up a robust surveillance system on public health priority diseases, with a directive from the National Department of Health (NDoH) to re-engineer the South African Notifiable Medical Conditions notification system. This system, which transition from an outdated paper-based system to a state-of-the-art electronic system was piloted during 2016, will be launched in July 2017 across South Africa. The re-engineered system will provide the backbone with which to monitor and timeously respond to infectious disease outbreaks, as well as serve as a barometer in tracking progress in the prevention of morbidity and mortality associated with notifiable illnesses.

The burden and threat of infectious diseases and progress made in reducing the impact of these diseases in South Africa, were highlighted by ongoing laboratory-based and active field surveillance undertaken by the NICD during 2016/17. Included among these was the support given by the NICD Outbreak Response Unit, augmented by the Centre for Respiratory and Meningitis Diseases, to the KwaZulu-Natal DoH to investigate and control an outbreak of diphtheria. The NICD was also at the forefront in using Whole Genome Sequencing to show that an increase in numbers of *Salmonella enterica* serotype Typhi, identified in Gauteng in 2016, was related to a contemporaneous outbreak of typhoid fever in Zimbabwe. This emphasises the need for communicable disease surveillance in South Africa to be linked to similar surveillance in neighbouring countries.

The significance of the relationship between South Africa and its neighbours was further emphasised by the finding that the majority of malaria cases in South Africa are imported from neighbouring countries. However, in 2016/17 South Africa noted an increase in local transmission and acquisition of malaria, possibly due to abnormally high rainfall patterns in Mpumalanga. This poses a setback in terms of South Africa’s target to eliminate malaria in the near future. The NICD remains engaged with the DoH on surveillance and control of the malaria vector, including the testing of new compounds to address the challenge of insecticide resistance in malaria vector mosquitoes, which is critical in terms of disease epidemiology and vector control.

On the antimicrobial resistance (AMR) front, which is increasingly being recognised as a global threat to public health, drug resistance was highlighted at the United Nations General Assembly as a global priority. To address the threat, the NICD established a national surveillance data dashboard to identify and support efforts at combatting morbidity and mortality resulting from AMR bacterial disease. In acknowledgement of its expertise, the NICD became a Collaborating Centre for AMR for the WHO-AFRO region in 2016.

In terms of antibiotic resistance, the Centre for Tuberculosis (CTB) at the NICD released results of the largest ever study on the prevalence of tuberculosis (TB) drug resistance, globally. This study identified the emergence of rifampicin mono-resistant TB, which has occurred primarily among new cases, resulting in an almost doubling of the prevalence of rifampicin-resistant TB from 1.8% (95% CI: 1.3%–2.3%) in 2001/02 to 3.4% (95% CI: 2.5%–4.3%) in the latest survey of 2014. Additionally, high levels of resistance to second-line agents among multidrug-resistant TB (MDR-TB) cases were identified. These findings supported two key policy shifts, implemented by the National TB Programme. The first was the rollout of reflex second-line drug susceptibility testing, using the WHO-endorsed line probe assay for detection of rifampicin-resistant TB cases for early initiation of treatment, and the second was the introduction of a shortened treatment regimen for MDR-TB patients. To better assist the DoH in dealing with
this most important public health threat in South Africa, the NICD launched an online TB Surveillance Dashboard that is now accessible at www.nicd.ac.za. This was accompanied by a surveillance report on microbiologically confirmed pulmonary TB (mPTB) for the period 2004–2015, which shows consistent annual declines in mPTB since 2009. The report has also identified geospatial hotspots to sub-district level and highlights considerable heterogeneity in prevalence, requiring a targeted response.

In addition to supporting the DoH in its TB control programme, the NICD’s Centre for HIV and Sexually Transmitted Infections (STIs), is a partner to the DoH 2017–2021 National Strategic Plan for HIV, STIs and TB. The report on the sentinel surveillance of sexually transmitted infection syndrome aetiologies and human papillomavirus (HPV) genotypes among patients attending public health facilities in South Africa (2015–2016), provided important aetiological data for STI management, as well as baseline HPV genotype prevalence data for monitoring the effects of HPV vaccine implementation. These data have been used to inform policy formulation in STI syndromic management guidelines (Standard Treatment Guidelines and Essential Medicines List for both primary and adult hospital levels of care).

For monitoring HIV infections in the paediatric setting, the paediatric HIV viral load and CD4 dashboard and paediatric HIV VL and CD4 results for action reports were launched in November 2016. The DoH and its partners are now able to monitor the HIV programme nationally to improve patient outcomes. The antiretroviral (ARV) treatment programme in South Africa is the largest worldwide, with 3.2 million persons on treatment. Monitoring for drug resistance to inform treatment policy is an important activity for the CTB, which has established a clinic-based surveillance system for HIV drug resistance among persons initiating antiretroviral therapy (ART) in five provinces that showed 13% resistance to ARTs used in first-line regimens. The drug resistance level amongst participants with prior ARV exposure was 38%. Effective and continued monitoring of drug resistance is thus crucial.

The CTB remains involved in two key HIV prevention studies viz., the HVTN 702, the first HIV vaccine efficacy trial in seven years, and the HVTN 703 or antibody-mediated prevention (AMP) study, providing much of the specialised laboratory immunology services required for these studies. Also on the HIV front, the NICD led reflex screening and testing for Cryptococcus jirovecii in immunocompromised HIV-infected people; and is currently leading an evaluation of the effectiveness of this national intervention on patient outcomes. Globally, Cryptococcus infection was estimated to be responsible for 15% of AIDS-related mortality (95% CI: 10%–19%).

During 2016/17, the NICD Outbreak Response Unit (ORU), in close collaboration with the DoH and other stakeholders constituting a multi-sectoral national outbreak response team, continued to function as a source of technical expertise for outbreak detection, investigation and response activities. This included responding to 1 211 outbreak verification calls, 97% of which were responded to within 24 hours. The public was kept informed of such outbreaks and other communicable disease threats through 12 editions of the NICD Communicable Diseases Communiqué, which circulates to a wide audience, including general practitioners, specialists, infectious disease and travel medicine societies, and national and provincial public health personnel. Over the course of 2016/17, the ORU finalised the development and implementation of an infrastructural, policy and management framework for the Public Health Emergency Operations Centre, in fulfilment of a memorandum of agreement signed with the DoH in 2015. This will serve as a vital resource in the event of a major communicable disease outbreak occurring in South Africa.

The continual growth of the NICD, and its support to the DoH and the South African public at large, is very dependent on the training of adequately qualified epidemiologists. The NICD is now the single largest employer of epidemiologists in the country, and continues its training of epidemiologists through its South Africa Field Epidemiology Training Programme (SAFETP), which celebrated its 10th anniversary in 2016. Initially established in collaboration with the DoH and the Centres for Disease Control and Prevention (CDC) of the United States of America, the programme is now fully funded by the NICD. SAFETP has trained more than 80 health professionals since its inception, 88% of whom remain employed in the public service in South Africa. The team continues to work with the DoH in establishing epidemiology as a professional discipline in the Human Resource for Health Strategy, and is defining the epidemiology core competencies required for existing staff at the DoH.

During the review period, the National Cancer Registry was moved to the newly established Centre for Cancer at the NICD as South Africa moves toward the establishment of a National Public Health Institute of South Africa (NAPHISA). This will expand the surveillance platform from communicable to non-communicable diseases, as well as occupational health and injury prevention. The Centre for Cancer now provides the most updated information on the incidence of cancers in South Africa, benchmarked against global reporting standards. This data have been used to develop the South African National Cancer Control Plan, which includes breast and cervical cancer policies.

In conclusion, the NICD continues to entrench itself as a pivotal component in the effort to promote the health and well-being of South Africans. This is done through robust surveillance of current and imminent communicable disease threats to the country. As has been the case in the past, this would not have been achievable without the remarkable dedication of the NICD staff and the unwavering support of the DoH.

With the imminent establishment of NAPHISA, which is currently undergoing Cabinet and Parliamentary approval, providing robust communicable and non-communicable disease surveillance in South Africa will lay the foundation for the practice of precision medicine and in the process inform health policy for the benefit of all South Africans.
Centre for Enteric Diseases
BACKGROUND
The Centre for Enteric Diseases focuses on surveillance of pathogens associated with diarrhoea and enteric fevers, including typhoid fever. The centre also provides timeous identification of the potential causes of 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 provides policy advice and technical support to government and contributes to the training of medical professionals, including medical scientists, medical technologists, epidemiologists, public health workers, nurses and registrars.

SURVEILLANCE AND DIAGNOSTIC SERVICES
The number of diarrhoea cases in the 2016 season was lower compared to 2013–2015, with fewer rotavirus infections noted. The centre conducted diarrhoeal sentinel surveillance in all nine provinces and screened specimens using Taqman array real-time testing, which simultaneously detects multiple enteric viral, bacterial and parasitic pathogens. Rotavirus, Cryptosporidium spp. and Shigella spp. were the most frequently detected pathogens in hospitalised children <5 years of age in sentinel sites in 2016.

The centre provided laboratory testing and support for seven outbreaks, including ones of notifiable diseases. The increased case numbers of Salmonella enterica serotype Typhi identified in Gauteng in 2016 related to a contemporaneous outbreak in Zimbabwe, whereas well-described community-related clusters were identified in the Western Cape.

RESEARCH PROJECTS
Post-marketing intussusception monitoring after introduction of oral rotavirus vaccine in South Africa
NICD researchers: Prof. N Page, Ms S Nadan, Mr R Netsikweta, Ms T Kruger
Principle investigators: Prof. S Madhi, Dr M Groome (Department of Science and Technology/National Research Foundation (DST/NRF): Vaccine Preventable Diseases, University of the Witwatersrand (Wits); Respiratory and Meningeal Pathogens Research Unit (RMPRU))
Funding: Bill and Melinda Gates Foundation

Intussusception is a rare intestinal blockage associated with a human-simian rotavirus reassortant vaccine formulation. While current rotavirus vaccines did not demonstrate an increased risk of intussusception during large-scale vaccine trials, recent studies have indicated that there is a low-level risk after vaccine administration. There are currently no data on intussusception risk in African settings. Active surveillance was implemented in seven South African cities, with the study due to end in December 2017. Since the start of the study, 539 stool specimens have been collected (309 cases and 230 controls). Intussusception cases and controls will be tested using Taqman array card (TAC) real-time detection assays.

Re-analysis of stool specimens from Venda, South Africa, collected as part of the MAL-ED study, using Taqman array cards for the detection of multiple enteric pathogens
NICD researchers: Prof. N Page, Ms S Nadan
Principle investigator: Dr E Houpt (University of Virginia), Dr A Samie (University of Venda)
Funding: Bill and Melinda Gates Foundation

TAC technology has been adapted to simultaneously screen stool specimens for a variety of viral, bacterial and parasitic enteric pathogens. A total of 5 094 specimens from Venda, South Africa will be screened over an 18-month period with the University of Venda performing nucleic acid extractions and the centre performing the TAC reactions. Thus far, the assay has been validated, extraction problems solved and results generated for 2 768 specimens.
Laboratory testing for phase I/II double-blind, randomised, placebo-controlled, descending-age, dose-escalation study to examine the safety, tolerability and immunogenicity of the trivalent P2-VP8 subunit rotavirus vaccine in healthy South African adults, toddlers and infants

**NICD researchers:** Prof. NA Page, Ms S Nadan  
**Principle investigator:** Dr M Groome (DST/NRF: Vaccine Preventable Diseases, Wits; Respiratory and Meningeal Pathogens Research Unit (RMPRU))  
**Funding:** PATH Vaccine Solutions

The trivalent P2-VP8 vaccine will be administered intramuscularly to 30 adults, 30 toddlers and 450 infants with two concentrations evaluated (60 µg and 180 µg). Immune responses to the vaccine formulations will be evaluated for safety and immunogenicity. All infants will receive Rotarix after the third study injection, and a stool sample will be obtained from a subset of infants to assess shedding of Rotarix. Stool specimens will also be obtained from infants experiencing diarrhoea to test for rotavirus. Stool specimens will be analysed using rotavirus EIA and real-time polymerase chain reaction (RT-PCR) with standards to determine relative viral concentration.

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

**NICD researchers:** Ms S Nadan  
**Principle investigator:** Prof. NA Page  
**Funding:** Poliomyelitis Research Foundation, National Health Laboratory Service (NHLS) Research Trust

Between 2009 and 2014, human astroviruses (HAstVs) were detected in 6.6% (419/6 389) of stool specimens. A total of 245 specimens was further analysed by genotyping and sequencing of the ORF1a (serine protease protein) and ORF2 (capsid) regions. Only a quarter of the HAstV-positive specimens (26%; 63/245) could be typed using traditional methods. Of these classic strains, genotype 1 was detected most frequently (49.2%), followed by type 5 (28.6%), type 2 (11.1%), type 8 (7.9%) and type 6 (3.2%). The outcomes of the preliminary testing suggest that the current circulating HAstV strains in children with diarrhoea may not be identified using the traditional typing methods. These results highlight the urgent need to redesign the typing strategies for HAstV.

Invasive nontyphoidal salmonellosis in Gauteng province, South Africa, 2003–2013

**Principle investigator:** Dr KH Keddy  
**Co-researchers:** A Musekwa, A Sooka, A Karstaedt, S Takuva, AJ Puren, T Nana, S Seetharam, M Nchabaleng, R Lekalakala, FJ Angulo, KP Klugman, for GERMS-SA

This study defined factors associated with mortality in HIV-infected versus uninfected patients with invasive nontyphoidal Salmonella (iNTS) and changing iNTS incidence associated with increasing antiretroviral therapy (ART) availability. Laboratory-based surveillance for iNTS was conducted in Gauteng province from 2003 to 2013. Clinical isolates were serotyped at CED. Corporate Data Warehouse data on patient numbers obtaining HIV viral load measurements provided estimates of numbers of HIV-infected patients receiving antiretroviral therapy. Mortality due to iNTS in HIV-infected and uninfected patients in Gauteng remains high, primarily due to disease severity. The incidence of iNTS infections decreased significantly in Gauteng, in association with increased ART utilisation. Monitoring iNTS incidence may assist in monitoring the ART programme.

Synergy testing for Salmonella enterica subspecies Typhi

**NICD researchers:** Ms A Sooka, Dr KH Keddy  
**Funding source:** Liofilchem, Davies Diagnostics

The objective of this study is to evaluate combination therapy in vitro to aid therapeutic options for typhoid fever. Synergies testing of 25 invasive Salmonella Typhi strains that were resistant or intermediately resistant to ciprofloxacin were screened using Liofilchem MIC test strips. Antibiotic combinations included ciprofloxacin against ampicillin, amikacin, azithromycin, chloramphenicol, ceftriaxone and streptomycin. A fractional inhibitory concentration (FIC) index was calculated for each antibiotic combination to interpret synergistic, additive, indifference and antagonistic interactions. Synergy was seen in 15.3 (23/150) of combinations, additive inhibitions in 20% (30/150), indifference in 63.4% (95/150) and antagonism 1.3% (2/150). Ciprofloxacin in combination with streptomycin and ciprofloxacin in combination with ceftriaxone were the most active combinations.
Whole-genome sequencing analysis of human enteric pathogens in South Africa

**NICD researchers:** Dr AM Smith, Dr KH Keddy  
**Collaborator:** JCD Hinton, University of Liverpool, Liverpool, UK  
**Funding source:** UK Government Global Challenges Research Fund (awarded to University of Liverpool)

Whole-genome sequencing (WGS) analysis of human enteric pathogens isolated in South Africa over the years 2004–2015 is ongoing. This includes about 1 000 isolates of *Salmonella* species (*Salmonella Enteritidis*, *Salmonella Typhimurium* and *Salmonella Dublin*) and about 600 isolates of *Shigella* species (*Shigella flexneri* 2A and *Shigella sonnei*). Preparation and shipment of bacterial cells to the University of Liverpool is ongoing, where WGS and analysis of data is also ongoing. WGS data analysis will provide valuable information about the pathogens, including information concerning molecular epidemiology, relatedness of isolates, emergence and spread of clones, virulence, pathogenicity, antimicrobial resistance, etc.

Investigation of laboratory-acquired infections of *Salmonella enterica* serotype Typhi in South Africa

**NICD researchers:** AM Smith, N Tau, Sl. Smouse, KH Keddy  
**Collaborators:** P Naicker, C Bamford, V Moodley, C Jacobs, A Lourens, NHLS, Cape Town

We have investigated three cases of laboratory-acquired *Salmonella* Typhi infection which occurred over the period 2012–2016 in South Africa. To determine the source of the infections, various molecular subtyping methodologies were used to analyse isolates; these included pulsed-field gel electrophoresis analysis, multilocus sequence typing and single nucleotide polymorphism (SNP) profiling following whole-genome sequencing analysis. Of all methodologies used, SNP profiling was the most sensitive and provided the highest resolution of analysis. For all cases, we were able to identify the probable source (causal isolate) of the laboratory infection. All cases of infection were most likely the result of lapses in good laboratory practice and laboratory safety.

Whole-genome sequencing for surveillance of *Listeria monocytogenes* in South Africa

**NICD researchers:** ST Duze, AM Smith, KH Keddy

This study describes WGS data for *Listeria monocytogenes* in South Africa. In total, 53 *L. monocytogenes* isolates were analysed, mostly collected from the Western Cape. Multi-locus sequence typing (MLST) analysis showed 14 unique sequence types (STs). The most prevalent STs were ST6 (n=11) ST54 (n=9) and ST876 (n=6); the least prevalent were ST101 (n=1), ST403 (n=1), ST515 (n=1), ST219 (n=1), ST2 (n=1) and ST820 (n=1). Phylogenetic analysis using SNP data showed 11 distinct clusters. SNP data concurred with MLST data in that isolates with the same ST clustered together on the phylogenetic tree. This study has initiated the development of a WGS database for *L. monocytogenes* in South Africa, which will assist in future listeriosis outbreak investigations.

Application of molecular epidemiological methods to investigate strains of *Salmonella enterica* serovar Enteritidis in South Africa

**NICD researchers:** M Muvhali, AM Smith, KH Keddy  
**Funding source:** Global Disease Detection, grant 1U19GH000571-02

A newly described multiple-locus variable-number tandem-repeats analysis (MLVA) method was used to investigate the molecular epidemiology and relatedness of human and non-human *Salmonella Enteritidis* strains in South Africa. In total, 1 221 human isolates and 43 non-human isolates were included in the study. Eighty-six MLVA profiles were obtained; MLVA profiles 7, 21, 22 and 28 were the predominant MLVA profiles. MLVA profile 28 was the most common amongst both the human and non-human isolates. Furthermore, seven *Salmonella Enteritidis* outbreaks were investigated from six provinces and isolates from each individual outbreak showed an identical MLVA profile. MLVA showed that *Salmonella Enteritidis* strains circulating within the human and non-human population were clonal.

Characterisation of *Campylobacter* isolates from a South African population

**NICD researchers:** MS Thobela, AM Smith, KH Keddy  
**Funding source:** Global Disease Detection, grant 1U19GH000571-02

A multiplex real-time PCR targeting *Campylobacter jejuni* and *Campylobacter coli* was used to screen 848 bacterial isolates received from the GERMS-SA surveillance programme during 2014–2015. A total of 94% (801/848) of the submitted isolates were positive for *Campylobacter*. *C. jejuni* was the most predominant species detected (83%; 665/801), and *C. coli* was less frequently detected (12%; 97/801). Cases of coinfection (C. jejuni and C. coli) (2%; 16/801), and a few cases non-C. jejuni/C. coli infections (3%; 23/801), were identified. *C. jejuni* isolates (n=84) were further subtyped using multi-locus sequence typing and 30 sequence types were identified. The commonly detected STs were ST-227 and ST-572. Strains with novel STs were also identified (ST-8618, ST-8619, ST-8620, ST-8621, and ST-8622, ST-8619).
Whole-genome sequencing for surveillance and outbreak investigation of Salmonella enterica serotype Typhi in South Africa

**NICD researchers:** SL Smouse, AM Smith, NP Tau, KH Keddy  
**Funding source:** Global Disease Detection, grant 1U19GH000571-02 (for non-South African isolates)

In this study we aimed at investigating the utility of whole-genome sequencing (WGS) for outbreak detection and epidemiological surveillance of Salmonella Typhi in South Africa. For the period 2014–2017, 155 isolates were selected for WGS analysis using Illumina MiSeq technology. WGS data was analysed using single nucleotide polymorphism analysis, multi-locus sequence typing and phylogenetic analysis, using available web tools at the Centre of Genomic Epidemiology, Technical University of Denmark. We identified two typhoid clusters from the Western Cape that included nine and seven isolates, respectively. In addition, phylogenetic data allowed us to identify a large clade of isolates with similarities to Zimbabwean isolates, suggesting that the Zimbabwean outbreak strain is well established and circulating within the South African population.

The use of multiple-locus variable-number tandem-repeats analysis assay for the characterisation of Salmonella Typhi isolates from sub-Saharan Africa

**NICD researchers:** NP Tau, AM Smith, KH Keddy  
**Funding source:** Global Disease Detection, grant 1U19GH000571-02

Salmonella Typhi infections remain an important public health problem in Africa. Rapid and highly discriminatory molecular methodologies are fundamental for prompt and effective epidemiological investigation of typhoid fever outbreaks. In this study, a multiple-locus variable-number tandem-repeats analysis (MLVA) assay was developed and employed, along with pulsed-field gel electrophoresis (PFGE), to characterise 316 Salmonella Typhi isolates from nine countries in sub-Saharan Africa (SSA). A total of 226 MLVA types were identified, as compared to 143 PFGE fingerprint types. MLVA assay results suggested intracontinental spread of typhoid fever. MLVA can be used as a first-line assay for routine screening of Salmonella Typhi isolates in SSA and is a feasible alternative to PFGE, providing excellent discrimination of isolates.

TEACHING AND TRAINING

**Postgraduate level**

The centre trained registrars (microbiology and virology) as part of the NICD registrars' training course in the identification and epidemiology of enteric bacteria and viruses.

Medical intern scientists were trained as part of NICD training courses in bacteriology and virology disciplines.

Dr KH Keddy delivered lectures at the Annual African Vaccinology Course on 9 November 2016.

**Honours**

Dr AM Smith: C2 NRF-rating renewed until 31 December 2022.

**Professional development**

Postgraduates enrolled: 10 (3 PhD, 7 MSc/MPH)  
Postgraduate graduations: 2 (PhD, BSc Hons)
RESEARCH OUTPUT

Publications


Conference presentations:

a) International congresses: 6
Centre for Emerging and Zoonotic Diseases
BACKGROUND

The Centre for Emerging and Zoonotic Diseases (CEZD) provides national and regional capacity for the diagnosis and research of viral hemorrhagic fevers, arthropod-borne diseases, human rabies, anthrax, plague, botulism and leptospirosis. A range of diagnostic tests is accredited by SANAS against the ISO15189 standard. The centre is internationally recognised as a World Health Organization (WHO) Regional Reference Laboratory for Plague and Collaborating Centre for Reference and Research on Viral Hemorrhagic Fevers and Arboviruses. Members of the centre are actively involved in a number of regional and international networks concerned with research, surveillance and outbreak response to zoonotic pathogens, including Emerging and Dangerous Pathogens Laboratory Network, Southern African Centre for Infectious Diseases Surveillance, Global Outbreak Alert and Response Network and Global Virus Network. The centre houses several biosafety level 3 suites and the only positive pressure suit biosafety level 4 facility on the African continent. The CEZD also operates an Electron Microscope Laboratory (EML), which functions as a core facility for transmission electron microscopy. These facilities represent a strategic resource for the diagnosis and research of highly dangerous zoonotic and arthropod-borne pathogens.

SURVEILLANCE AND DIAGNOSTIC SERVICES

During the reporting period, the centre provided diagnostic support for suspected viral hemorrhagic fever (VHF) cases in South Africa (e.g. Crimean-Congo hemorrhagic fever – CCHF) and VHF outbreaks in South Sudan and Niger, and supported requests for diagnostic testing for yellow fever and CCHF in Namibia. A total of 671 suspected cases of arboviral diseases, both of endemic and exotic origins, were investigated, including suspected cases of dengue and Zika virus infections in travelers returning home from endemic areas of the world. Common endemic arboviral infections, such as West Nile and Sindbis fever, were detected in a number of cases. In collaboration with the NICD’s Outbreak Response Unit, we investigated a cluster of cases presenting with rash and fever in northern Johannesburg that was diagnosed as Sindbis virus infection. A number of suspected Zika cases with recent travel history to affected areas were investigated, including pregnant women and couples planning for pregnancy. The centre continued to serve as a regional arbovirus reference laboratory for other African countries, such as Seychelles, Angola and Namibia by assisting with specific arbovirus testing or confirmation. CEZD also provided diagnostic support for bacterial zoonoses (e.g. anthrax, botulism and leptospirosis) in South Africa and assisted with the identification of suspected other high consequence bacterial pathogens, such as *Brucella* spp., *Francisella tularensis*, and *Burkholderia* spp.

The CEZD continued surveillance for plague in susceptible rodent populations in the City of Johannesburg and the Nelson Mandela Bay Municipality (Coega area) to alert public health authorities to the possibility of increased human plague risk. More than 1 700 rodents were tested for plague antibodies, among which a Karoo bush rat (*Otomys unisulcatus*), trapped in July 2016 at the Port of Ngqura that tested positive. The trapping site was approximately 5 km from the epicentre of the 1982 plague outbreak.

A diverse array of pathogens was submitted to the Electron Microscope Laboratory for ultrastructural/phenotypic characterisation (Figure 1). The primary focus, in collaboration with the NICD Mycology Reference Laboratory, was the taxonomy of dimorphic fungal isolates from South African clinical cases. In the prokaryotic arena, e.g. group B Streptococcus, a novel technique is being developed for capsule stabilisation prior to processing for transmission electron microscopy, including latex bead agglutination/cationised ferritin. Viruses investigated included two new bat-associated viruses (*Orthobunyavirus* and *Adenovirus*), which were discovered under the centre’s ongoing programme on zoonotic pathogens in bats, as well as measles virus, and virus-like particles designed by the Antiviral Gene Therapy Research Unit at the University of the Witwatersrand. Variously-treated human herpes simplex virus 2 and *Neisseria gonorrhoeae* cultures were examined as part of the microbiocide research programme of the NICD.
**RESEARCH PROJECTS**

**South African bats as reservoir hosts for zoonotic pathogens**

**NICD investigators:** Prof. JT Paweska, Ms N Storm, Mr A Kemp, Dr P Jansen van Vuren  
**Collaborators:** Prof. W Markotter (University of Pretoria), Dr Gustavo Palacios (USAMRIID Centre for Genome Science)  
**Funding:** US CDC Global Disease Detection Programme and NRF

South African bat populations are being sampled on a regular basis and tested for evidence of infection with zoonotic pathogens. Continued sampling during 2016–2017 yielded further evidence of active circulation of Marburg virus in Egyptian fruit bats in a specific cave in Limpopo. The lyssavirus, Lagos bat virus, is also actively circulating in the population and the bats are infected with various corona and paramyxoviruses. In addition, three new viruses belonging to the families Reoviridae, Bunyaviridae and Reoviridae have been isolated from the bats or their ectoparasites. Biosurveillance of targeted vertebrate and invertebrate high-risk reservoir species for zoonotic pathogens improves preparedness and better understanding of spill-over potential to humans.

**Zika virus surveillance and vector competence**

**NICD investigators:** Prof. JT Paweska (PI), Mrs V Msimang, Mr A Kemp, Dr P Jansen van Vuren, Prof. B Brooke  
**Collaborators:** Dr S Williams, Dr T Lo, Dr J Fuller (US CDC)  
**Funding:** US CDC Global Disease Detection Programme, Poliomyelitis Research Foundation (PRF) research grant

A project was initiated to set up long-term active surveillance for arboviruses, focusing on Zika virus, in northern KwaZulu-Natal (KZN). The uMkhanyakude District of KZN has a subtropical climate, which provides a suitable environment for mosquito vectors of exotic arboviruses in peri-urban areas. A number of exotic viruses are endemic in neighbouring Mozambique. An exploratory visit to the district was conducted, during which a number of major public hospitals and clinics were identified where active sampling of patients presenting with pyrexias of unknown origin will be implemented. Several populations of *Aedes aegypti* from the main ports and towns of KZN and the Eastern Cape coastal region were collected and brought to the laboratory as seed material for establishing laboratory colonies for vector competence experiments.
Rift Valley fever ecology and epidemiology in South Africa

NICD investigators: Prof. JT Paweska, Mrs V Msimang, Mr A Kemp, Dr P Jansen van Vuren

Collaborators: Dr M Rostal, Dr W Karesh (Ecohealth Alliance), Dr C Cordel (ExecuVet), Prof. P Thompson (UP)

Funding: Ecohealth Alliance

One of the project objectives is to investigate circulation of Rift Valley fever virus (RVFV) in mosquitoes, animals and people, to better understand exposure risks and integrate data on climate, weather, soil and vegetation, to develop disease risk maps. A number of weather stations were successfully placed and operated in targeted sites. An association was found between sites of high RVF mortality and certain soils and wetland vegetation types. We found Immunoglobin G (IgG) seroprevalence to RVFV to be 9.6% (CI 95%: 6.9–12.2) amongst 711 participants from 212 farms and 8.2% (CI 95%: 6.2–10.2%) in 134 veterinarians. Given the participants’ age distribution (mean 39 y, 60% <40y), they were most likely exposed during the last (2010–2011) RVF epidemic.

TEACHING AND TRAINING

In addition to training of staff and national and international research fellows in laboratory techniques and introducing them to working in BSL3 and BSL4 biocontainment facilities, and to special laboratory techniques, such as electron microscopy, 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 CEZD was also involved in the training of microbiology and clinical pathology registrars, intern scientists and technologists on an ongoing basis. The CEZD provided routine training in support of its plague surveillance programme.

Professional development

CEZD staff members were involved in postgraduate training of 12 students, primarily in the field of virology. From this cohort, one student graduated with a PhD at Sokoine University in Tanzania, and one with a MSc and one with a BSc (Hons) at the University of Pretoria. Two postdoctoral fellows were also supported in their research through the Southern African Centre for Infectious Disease Surveillance (SACIDS). Dr Naazneen Moolla, a medical scientist at CEZD, was awarded a PhD at the University of the Witwatersrand. One CEZD staff member, Mrs Anastasia Trataris-Rebisz, is enrolled for a PhD at the University of Pretoria. Prof. Janusz Paweska contributed to the establishment of the SACIDS African Centre of Excellence for Infectious Diseases of Human and Animals in Southern and Eastern Africa, funded by the World Bank. Within this centre Prof. Paweska is tasked to co-lead PhD projects on emerging and vector-borne diseases.

Postgraduate students enrolled: 12

Postgraduate students graduated: 3

Figure 2: Zika surveillance study team visiting the Ndaba Clinic, uMkhanyakude Health District, northern KZN. Left to right: Mrs V Msimang (CEZD-NICD), Dr T Lo (US CDC), Dr J Fuller (US CDC), Dr T Lukhozi (Ndaba Clinic), Prof. B Brooke (VCRU-NICD).

Figure 3: Interviewing farm workers during the 2015/16 survey (Mrs V Msimang, Sr E Strauss and participants).

Figure 4: Setting up weather stations in Free State (Mr J Kgatitsoe).
Honours

Dr Jacqueline Weyer received a C2-rating from the National Research Foundation. Mr Alan Kemp, Dr Petrus Jansen van Vuren and Prof. Janusz Paweska were appointed by the National Department of Health (DoH) to the Zika and Yellow Fever Technical Working Group.

RESEARCH OUTPUT

Publications

Journal articles


**Chapters in books**


**Conference presentations**

1. International: 3

2. National: 1
Centre for HIV and Sexually Transmitted Infections
BACKGROUND

The 2012–2016 National Strategic Plan (NSP) came to an end and plans are underway for the implementation of the second NSP, 2017–2022. The centre has contributed to the development of the NSPs, with particular focus on sexually transmitted infections (STIs). The second NSP pays greater attention to STIs than the first. The implementation of the first NSP has seen remarkable activities, such as the numbers of persons tested for HIV and placed on combination antiretroviral therapy. Approximately 50% of the 7 million infected persons are now receiving therapy. These results are encouraging in terms of the UNAIDS 90-90-90 treatment targets to be achieved by 2020 in order to eradicate HIV by 2030. Critical to the success of such large-scale programmes are surveillance and monitoring and evaluation. The centre has demonstrated in four examples how ‘big data’ obtained from the Corporate Data Warehouse (CDW) can be used to support the NDoH’s efforts in surveillance and monitoring and evaluation. The first example relates to the continuum of care, and specifically the numbers of infected persons linked to care and virally suppressed (the second and third 90s) and determinants of outcome using CD4 recovery. In the second and third examples CDW data were used to demonstrate lab-based incidence of syphilis that can be triangulated with coverage of antenatal services and incidence of congenital syphilis. The fourth example was the development of routine ‘dashboards’ that can be used for purposes of data for action in the setting of early infant diagnosis of HIV. The centre has made progress in expanding its integrated HIV and TB drug resistance programme using the GERMS facility-based platform. The results of the aetiological STI surveillance and antimicrobial drug resistance can inform baseline data requirements for the second NSP key indicators. The centre continued its support through various collaborations or laboratory-based activities for HIV and STI surveillance studies in high-risk populations, including young women, sex workers and men-who-have-sex-with-men (MSM). The centre conducted wide-ranging research that focused on HIV prevention studies, HIV pathogenesis in search for a cure, vaccine-related research, and microbicides. The two key HIV prevention studies are the HIV Vaccine Trials Network (HVTN) 703 or AMP (antibody-mediated prevention) study and HVTN 702, the first efficacy HIV vaccine trial in seven years. HVTN 703 is a phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralising monoclonal antibody in reducing acquisition of HIV-1 infection among women in sub-Saharan Africa. HVTN 702 involves a new version of the only HIV vaccine candidate ever shown to provide some protection against the virus. HVTN 702 aims to enrol 5 400 men and women, making it the largest and most advanced HIV vaccine clinical trial to take place in South Africa. The studies on anti-HIV broadly neutralising antibodies have yielded finer details that will inform vaccine development. The centre has continued its investment in the development of appropriate technologies to better answer surveillance questions and diagnostic challenges. The activities have yielded a number of peer-reviewed publications and participation in various national and international conferences and meetings. Integral to the centre’s activities are several national and international collaborations and funding that have been sustained and expanded. In preparing for the future, the centre has continued the extensive training for various professional staff and postgraduate mentoring and technical assistance at both a national and regional level.

SURVEILLANCE

STI surveillance

Syphilis surveillance

Analysis of prevalence of maternal syphilis among females ages 12 years and older was undertaken and was a follow-up of a previous study that used the NHLS CDW as a source of surveillance data. Data on all Rapid Plasma Reagin (RPR) tests conducted on females aged 12 years or older during the period 2010–2015 was obtained from the CDW. A probabilistic matching algorithm was used to link test results to unique individuals and de-duplicated syphilis incidence determined at national, provincial and district levels. The syphilis positivity was determined as the proportion of women who tested RPR-positive, regardless of titre. Future studies using CDW data will assess coverage of syphilis testing at first antenatal visit.
Analysis of presumptive early congenital syphilis among children less than two years of age was undertaken for the period 2010–2016. Using the CDW probabilistic matching algorithm, tests were linked to unique individuals and de-duplicated. The number of children tested and the number of RPR-positive children were determined at national, provincial and district levels. In addition, the incidence of presumptive early congenital syphilis was determined for children less than one year of age, as the number of children less than one who tested RPR-positive divided by the number of live births for the year and province. The future plans are to link laboratory and clinical data as part of congenital syphilis screening.

STI clinical syndrome, aetiological and gonococcal antimicrobial resistance surveillance

Sentinel surveillance of sexually transmitted infection syndrome aetiologies and HPV genotypes among patients attending public health facilities in South Africa (2015–2016)

Laboratory-based STI surveillance was undertaken in 36 primary healthcare centres (PHCs) across all nine South African provinces as part of the new National Aetiology Surveillance Programme of Sexually Transmitted Infections. The targeted sample size was 25 cases of each STI syndrome per PHC, which equated to 900 cases of each syndrome nationally. Surveillance was conducted for male urethritis syndrome (MUS); vaginal discharge syndrome (VDS) and genital ulcer syndrome (GUS); and high-risk human papillomavirus (HPV) infection in adolescent girls and young women. The aetiological study commenced in April 2014 and was completed in September 2015. The NICD/NHLS and the NDoH were the implementing partners. These data have been analysed and the report finalised for submission to the DoH and CDC. This analysis, and the resultant trends that will be observed over time, will provide important intelligence for monitoring interventions to reduce STI/HIV transmission, and will also provide crucial HPV prevalence genotyping data following the introduction of the HPV vaccine into South Africa. The data have also been used towards policy formulation in STI syndromic management guidelines (Standard Treatment Guidelines and Essential Medicines List for both primary healthcare and adult hospital level of care).

Aetiological surveillance of STI syndromes in patients attending public health facilities in South Africa (NICD GERMS-SA) and early warning surveillance for antimicrobial resistance in Neisseria gonorrhoeae

The syndromic approach to the management of STIs in PHCs is based on the identification of a group of symptoms and easily recognisable signs associated with a number of well-defined aetiologies. Periodic aetiological surveillance of STI syndromes is critical in validating the existing treatment algorithms. Aetiological surveillance at selected sentinel sites (at least one per province) has been carried out under the umbrella of NICD GERMS-SA from 2015 onwards.

The main objective of this surveillance was to determine the microbial aetiologies of the three major STI syndromes, i.e. MUS, VDS and GUS among adult (>18 years) patients. Secondary objectives were to determine (a) the prevalence of HIV co-infection in patients presenting with STI syndromes; (b) the antimicrobial susceptibility of Neisseria gonorrhoeae isolates from MUS patients to extended-spectrum cephalosporins (ESCs); and (c) the sero-prevalence of HSV-2, infectious hepatitis B and syphilis.

The NICD GERMS-SA STI surveillance protocol required the recruitment of a total of 150–200 MUS, 100 VDS, and 100 GUS cases from each sentinel site. In 2015–2016, surveillance was conducted at various sentinel sites in KwaZulu-Natal (Phoenix (mobile) Clinic in Durban and Eastboom Clinic in Pietermaritzburg), Mpumalanga (Kabokweni Clinic in Nelspruit and Hluvukani Clinic near Bushbuckridge); North West (Jouberton Clinic); and Gauteng (Alexandra Health Centre). The plans are to expand surveillance to other provinces, including the Free State (Heidedaal Clinic), Eastern Cape and Western Cape.
Sentinel surveillance of HPV genotypes among patients attending public health facilities in South Africa (2013–current)

Sexually transmitted infections, including HIV infection, continue to be highly prevalent among individuals of reproductive age within South Africa. A total of 330 endocervical samples collected as part of national surveillance of 18–20 year-old women attending family planning clinics, were tested for HPV to determine the prevalence and genotypes. Overall, HPV infection was detected in 57.6% (190/330) of participants. Of these, single HPV infection was detected in 23.0% (76/330) while multiple (2–14) HPV infection was detected in 34.5% (114/330). HR-HPV infection was detected in 37.9% (125/330) of women, probable HR-HPV infection in 15.5% (53/330) and LR-HPV infection in 40.0% (132/330). HPV infection was found to be significantly higher among women who reported a sexual debut of ≤16 years compared to those with a >16 years sexual debut (68.5% 76/111; 52.9% 92/174 P=0.001 respectively). A proportion of 11.5% (38/330) of women were infected with one or more HPV types targeted by Cervarix HPV vaccine, 19.1% (63/330) with one or more HPV type(s) targeted by Gardasil HPV vaccine, and 29.4% (97/330) with one or more HPV type(s) targeted by Gardasil-9 HPV vaccine. The high prevalence of HPV types found in current HPV vaccines in South African women demonstrates that this population will greatly benefit from the current HPV vaccine and encourages rollout of a vaccine that covers many HPV types.

HIV surveillance

HIV paediatric surveillance

The centre continues to perform paediatric HIV surveillance activities, reporting to national, provincial and district health departments, as well as providing early infant diagnosis (EID) support across the country. The menu of reports available can be accessed on the NICD website under M&E Reporting. New national EID reports to monitor prevention of mother-to-child transmission have been developed to include HIV polymerase chain reaction (PCR) testing at birth and ten weeks of age. HIV PCR, viral load (VL) and CD4 results for action reports, detailing weekly results at provincial, district, sub-district and facility level, have been developed and can be accessed through the NICD’s Self Service Portal allowing better control and management of reporting services. Missed diagnostic opportunity reports, detailing HIV PCR test requests that receive neither a positive or negative result, have also been developed to improve efficiency within the EID programme. A paediatric (0–<19 years) version of the HIV M&E Dashboard is now available. Mapping paediatric and adolescent care in South Africa, as well as monitoring mobility of mother-to-infant pairs receiving antiretroviral prophylaxis is ongoing. EID point-of-care (POC) testing using two different HIV PCR technologies have been evaluated with further studies planned to evaluate POC VL assays. The use of cellular phone technology has been investigated to close prevention of mother-to-child transmission (PMTCT) cascade gaps for the elimination of mother-to-child transmission, in collaboration with the United Nations Children’s Emergency Fund (UNICEF).

HIV surveillance and monitoring and evaluation

The results of ‘big data’ obtained from the NHLS CDW were demonstrated in two studies. The first study looked at the progress to meet the UNAIDS 90-90-90 targets. For the period of the study (namely 2012) of the 6 511 000 people living with HIV (PLHIV) in South Africa, 3 300 000 individuals (50.7%) accessed care and 32.9% received ART. Linkage to HIV care was lower among men (38.5%) than among women (57.2%). Viral suppression was 73.7% among the treated population in 2012, and the overall percentage of persons with viral suppression among all PLHIV was 23.8%. The second study was a collaborative project with the World Bank, HE2RO and NHLS and was an impact evaluation of ART adherence and retention programmes in South Africa. A total of 1 070 900 individuals were included in the analysis. Of these, 30.3% were male. The median CD4 count at ART initiation was 213 cells/µl (interquartile range (IQR) 117–324 cells/µl), the median of duration of follow-up was 24 months (IQR 12.2–36.9 months); and 85.9% achieved viral suppression by the end of follow-up. Of the 6 511 000 people living with HIV (PLHIV) in South Africa, 3 300 000 individuals (50.7%) accessed care and 32.9% received ART. Linkage to HIV care was lower among men (38.5%) than among women (57.2%). Viral suppression was 73.7% among the treated population in 2012, and the overall percentage of persons with viral suppression among all PLHIV was 23.8%. The second study was a collaborative project with the World Bank, HE2RO and NHLS and was an impact evaluation of ART adherence and retention programmes in South Africa. A total of 1 070 900 individuals were included in the analysis. Of these, 30.3% were male. The median CD4 count at ART initiation was 213 cells/µl (interquartile range (IQR) 117–324 cells/µl), the median of duration of follow-up was 24 months (IQR 12.2–36.9 months); and 85.9% achieved viral suppression by the end of follow-up. Of the 46.6% of individuals who initiated ART with a CD4 count less than 200 cells/µl, 79.7% achieved CD4 count recovery to 200 cells/µl in a median of 9.5 months. Among those who were virally suppressed by the end of follow-up, the proportions who recovered to CD4 count thresholds of 200, 350 and 500 cells/µl were 85.3%, 68.3% and 44.4% in a median time to recovery of 9.4, 12.4 and 17.3 months respectively. The proportion who achieved CD4 count recovery beyond the specified thresholds was lower among older individuals, males, those with low CD4 counts, and those with a shorter duration of follow-up. The extent of CD4 count recovery during the first 12 months of follow-up was greatest among those who were virally suppressed by the end of follow-up and those with the lowest CD4 counts at ART initiation. The two studies demonstrated that the analysis of large sets of routine data and novel approaches in record linkage can contribute to better targeting and more efficient implementation of the South African ART programme.

HIV drug resistance surveillance

The HIV Drug Resistance (HIVDR) Laboratory is a designated laboratory for national surveillance activities and serves as a WHO regional HIV drug resistance testing laboratory and quality control reference centre. During the past year, the laboratory performed HIVDR testing for assessment of acquired DR levels amongst specimens collected for surveys conducted in Zimbabwe. The laboratory has validated systems to detect mutations associated with Integrase inhibitor resistance, mutations in the protease and reverse-transcriptase regions using next generation sequencing technologies. Surveillance for TB drug resistance among persons initiating TB treatment and/or HIVDR among persons initiating ART in the same clinic, was expanded to four new clinics in Mpumulanga, KwaZulu-Natal and Gauteng. To date,
850 specimens have been collected, constituting two-thirds of sample size targets. Amongst specimens analysed, pre-treatment resistance rates were 22%; 19% of specimens has resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and 3% to NRTI+NNRTI. Resistance level amongst participants with prior ARV exposure was 38%. Assessment of HIV viraemia and resistance levels amongst sex workers was conducted in collaboration with PHRU. Amongst 264 whole blood specimens tested, 53% were virologically suppressed, whereas 38% of viraemic participants displayed resistance to standardised first-line regimens. Phylogenetic linkage between specimens was detected at low rates (<2%).

The FIRST 90 and HIV-1 rapid testing quality assurance and post-marketing surveillance of HIV rapid test devices

The centre supported the HIV rapid test quality improvement initiative (RTQII). The specific focus was the assessment of quality assurance implementation and scale-up of participation in the use of independent quality controls (IQC) and proficiency testing (PT) programmes at facility level. The standard tool used to assess quality assurance implementation was the WHO-CDC Stepwise Process for Improving the Quality of HIV Rapid Testing (SPI-RT) Checklist. Of 1 896 participating health facilities, approximately 1100 sites have been assessed using SPI-RT Checklist. The purpose of the IQC is to provide testers with a key control step prior to testing and an early warning indicator of test-kit performance. IQC was distributed to various facilities, both government-run and implementation partner-supported. In 2016, the laboratory distributed 31 500 panels to the various testing facilities. Participation in PT increased, with over 1 500 facilities enrolled. Post-marketing surveillance (PMS) continued and 58 batches of the HIV rapid tests were tested through the system established in the centre.

HIV prevention trials

The centre conducted validated end-point antibody and molecular diagnostic assays for the HIV HTN. Data generated for the HTN 100 trial, in which vaccines have been redesigned to target clade C viruses that circulate in South Africa, contributed to the important decision to proceed to a large-scale efficacy trial called HTN702. This is the first efficacy trial in South Africa in seven years and aims to test whether a canarypox prime plus protein boost will elicit protective antibody responses. The centre is also involved in the antibody-mediated protection (AMP; HTN703) trial, which aims to test whether passive infusion of the broadly neutralising antibody VRC01 will provide protection from HIV infection. Both trials are expected to run for the next 3–4 years, and assessing and understanding the correlates of protection will be a major focus for the centre. The centre continued to supported end-point testing protocols including HTN 802, 110, 910, 100, 702, 703, 107, 108 and 111 that used revised testing algorithms in line with current diagnostic approaches.

SELECTED CURRENT RESEARCH PROJECTS

Investigation of GeneXpert human papillomavirus performance on anal specimens

Collaborators: Prof. A-L Williamson, Dr ZZA Mbulawa (NICD) T Wilkin (Weill Cornell Medical College, New York), BJ Goeieman (Right to Care), E Jong M (Julius Clinical Research, Zeist, The Netherlands), P Michelow (Wits and NHLS), A Swarts (Wits) JM Smith (University of North Carolina), P Kegorilwe (Right to Care), CS Firnhaber (Right to Care)

This study investigated anal high-risk HPV (HR-HPV) prevalence in South African HIV-infected women using the Cepheid Xpert HPV assay, and compares its performance with that of Hybrid Capture-2 (hc2). A total of 199 HIV-infected women aged 25–65 years were recruited from Themba Lethu Clinic, Helen Joseph Hospital, Johannesburg. Stored ThinPrep anal swabs that had previously been tested using hc2 were tested for HPV using Xpert according to manufacturer’s instruction. Anal cytology and high resolution anoscopy had previously been performed. The HR-HPV prevalence by Xpert was 40.8% (80/196) and similar to hc2 (41.8% [82/196]), with overall agreement of 86.7%; Cohen’s kappa 0.73 (95% CI: 0.63–0.82). High grade squamous intraepithelial lesions (HSIL) was associated with increasing number of multiple HPV infection (P<0.001). Xpert and hc2 were similarly sensitive (77.4% and 77.4%, respectively) and specific (66.1% and 64.8%) for HSIL detection. HPV16 (OR: 14.0, 95% CI: 3.9–48.0, P<0.0001), HPV39/68/56/66 (OR: 4.1, 95% CI: 1.4–12, P=0.01) and HPV51/59 (OR: 2.8, 95% CI: 1.1–7.6, P=0.04) were independently associated with anal HSIL. Xpert HPV typing is a promising anal screening test in HIV-infected women that performs similarly to hc2, and should be investigated for use in anal cancer screening programmes.

The assessment of the testing accuracy of HIV rapid testing in diverse settings

Collaborators: A Kharsany, L Lewis, A Grobelaar (Centre for the AIDS Programme of Research in South Africa (CAPRISA)), C Cawood (EPICENTRE), T Lane, MGA Manyuchi, Z Ishdal, T Osmand (UCSF), J McIntyre, H Struthers (ANOVA Health)

The accuracy of HIV rapid testing was assessed in two settings. (1) HIV rapid test performance during wave 2 of the HIV Incidence Provincial Surveillance System (HIPSS) survey. This involved the secondary comparison of rapid HIV testing conducted during a population-based household survey with laboratory-based 4th generation enzyme-linked immunoassays and determining the accuracy, sensitivity, specificity, positive and negative predictive values, as well as false positive and false negative rates. (2) HIV rapid test performance during the MSM
Thymidine kinase mutations associated with acyclovir resistance in herpes simplex virus-2 in Gauteng, South Africa

Acyclovir (ACV) has been the drug of choice for the treatment of herpes simplex virus type 2 (HSV-2) infections. The antiviral activity of ACV is based on the phosphorylation to its monophosphate form by the virus-encoded thymidine kinase (TK), which is then further phosphorylated by cellular thymidylate kinases to its active triphosphate form. The active ACV is incorporated into the growing deoxyribonucleic acid (DNA) chain by the viral DNA polymerase, resulting in replication inhibition through chain termination. HSV-2 resistance to ACV is mainly due to mutations in the viral TK (encoded by the UL23 gene), resulting in the defective production of TK or in the alteration of TK substrate specificity. Mutations related to ACV resistance are nucleotide insertions, deletions or substitutions, accounting for 50% of resistance cases. Resistance is also associated with substitutions in conserved regions of the TK gene and the substitution of cysteine at codon 337 of HSV-2 TK. The main aim of this study will be to perform phenotypic and genotypic characterisation of 100 clinical HSV-2 strains, obtained through the GERMS-SA programme, from patients presenting with genital ulcer disease at the Alexandra Health Centre in Alexandra, Gauteng, comparing the ACV antiviral susceptibility profiles of these HSV-2 isolates with their TK sequence profiles to identify mutations that are associated with ACV resistance. Several studies have shown that minor drug-resistant variants that are not detected by conventional sequencing are clinically relevant, in that they are often responsible for the virological failure of new antiviral treatment regimens. We will therefore determine the presence of wild-type and resistant HSV-2 virus co-infection in all HSV-2 positive patients and evaluate the prevalence of minority ACV resistant HSV-2 variants using next-generation deep sequencing.

Comparison of the in-house discharge multiplex PCR and the Aptima Combo GC/CT assay for the qualitative detection of Neisseria gonorrhoeae and Chlamydia trachomatis in anal swabs, oropharyngeal swabs and urine from MSM in Cape Town, South Africa

Effective screening and diagnosis of STIs are important for STI prevention and care of infected individuals and their partners, as well as for public health as a whole. Chlamydia trachomatis and Neisseria gonorrhoeae are amongst the most prevalent STIs worldwide. The majority of chlamydial and gonococcal infections are asymptomatic and regular screening by using nucleic acid amplification tests (NAATs) for sexually active individuals is recommended. Simultaneous infection with both gonorrhoea and chlamydia is not uncommon and can easily be left undetected in asymptomatic patients. In MSM, STIs occur at both urethral and non-urethral sites, yet screening of the ano-rectum and oropharynx remains uncommon. The most common site of gonococcal infection in MSM, however, is the oropharynx, and approximately 90% of those infected have no symptoms at all, indicating that this could be an important reservoir for infection at genital sites. Culture-based techniques have always been the gold standard for detection of N. gonorrhoeae infections and testing is mainly performed on specimens from symptomatic patients. The sensitivity of N. gonorrhoeae culture techniques depends on the optimal collection, transport and handling of the specimens. Recently published data support the fact that NAATs are more sensitive and specific than culture for the diagnosis of N. gonorrhoeae across a range of specimen types and under varying conditions. Culture techniques do, however, allow for the detection of emerging antibiotic resistance patterns and is therefore still an important surveillance tool. NAAT specificity varies by assay used and by anatomical site tested. NAATs have not yet been approved by the US Food and Drug Administration (FDA) for testing extragenital specimens, and each laboratory is required to perform their own validation and verification of data to support the results obtained from these sample sites. The objective of this study was to evaluate and compare the performance of a validated in-house multiplex PCR assay with the Gen-Probe APTIMA Combo 2® 16S rRNA-based assay for the detection of N. gonorrhoeae and C. trachomatis in MSM patients using urine and samples from non-genital sites.

Near real-time monitoring of PMTCT gaps in three districts of KwaZulu-Natal Province, South Africa

Collaborators: Dr S Bhardwaj (UNICEF), Dr K Ng’oma (UNICEF), Mr B-A Smith (UNICEF), Ms O Mhlongo (KZN DoH)

The aim of this study was to describe in near real-time potential reasons for mother-to-child transmission amongst HIV-infected infants in three districts of KwaZulu-Natal. The findings reveal critical gaps within the PMTCT cascade that require urgent intervention, as South Africa works towards eliminating mother-to-child transmission. Timing of maternal HIV diagnosis and subsequent access to ART remain strong predictors of HIV transmission, with a third of women in our study diagnosed at or after delivery. However, our results suggest that the majority of infant transmissions occurred among women who accessed HIV testing services prior to conception or at first ANC visit, yet received suboptimal treatment and monitoring services.
Paediatric HIV point-of-care (POC) testing: field evaluation of the performance of Cepheid and Alere qualitative HIV assays in a Soweto academic hospital

Collaborators: S Carmona (Wits and NHLS), Dr F Nakwa (Wits), Prof. W Macleod (Boston University), Prof. S Velaphi (Wits), Dr N Sipambo (Wits)

This study aimed to evaluate the performance of two EID POC technologies in a hospital environment. Results demonstrate excellent performance of both EID POC technologies in comparison to the laboratory standard. Both EID POC assays detected all HIV-infected children with acceptable error rates observed for both technologies evaluated. Viral loads taken around the time of EID POC testing ranged from log VL of 2.6 (368 copies/ml) to 7 (1x107 copies/ml), suggesting adequate limits of detection by EID POC. Although EID POC is an accurate alternative for HIV PCR testing in the field, the manner in which POC may be integrated into a busy hospital setting is yet to be determined.

Cepheid Xpert® HIV-1 point-of-care test evaluation for neonatal diagnosis of HIV in the birth testing programme of a maternity hospital

Collaborators: Dr K-G Technau (Wits), Prof. A Coovadia (Wits), Dr P Murnane (Columbia University), Prof. L Kuhn (Columbia University)

In this study, a field evaluation of HIV PCR birth POC testing was conducted at a busy maternity hospital in Johannesburg. Point-of-care testing was found to be an accurate and useful tool for birth HIV testing, increasing the overall result return rates, reducing time to result and enabling earlier ART initiation for HIV-infected neonates. However, implementation was challenging and will require careful consideration and innovative approaches if POC testing is to be introduced for routine use within busy maternity units. Further research is required to assess the benefits of very early ART initiation in infected children to establish whether this specific consequence of POC testing warrants the additional resources required to implement birth POC testing.

Maternal-infant HIV-1 transmission (MTCT) and a role for Fcγ receptor-mediated immune functions

Collaborators: Prof. L Kuhn (Columbia University, NY), Prof. GE Gray (Medical Research Council (MRC), PHRU)

Fcγ receptors bind the Fc portion of antibodies and mediate many functions in the immune response. To explore the role of HIV-specific antibodies in innate effector immune responses more broadly, we have utilised all known variants of the low-affinity FcγR locus as proxies for immune function and studied these in the context of MTCT. The maternal FcγRIIIa-158V allele that confers enhanced antibody binding affinity and antibody-dependent cellular cytotoxicity capacity significantly associated with reduced HIV-1 transmission (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.28–0.79, P = 0.004; P矫正 > 0.05). In particular, the FcγRIIIa-158V allele was underrepresented in the in utero transmitting group (P = 0.048; P矫正 > 0.05) and in utero-enriched transmitting groups (P = 0.0001; P矫正 < 0.01). In both mother and infant, possession of an FcγRIIIb-HNA1b allotype that reduces neutrophil-mediated effector functions associated with increased transmission (OR: 1.87, 95% CI: 1.08–3.21, P = 0.025; P矫正 > 0.05) and acquisition (OR: 1.91, 95% CI: 1.11–3.30, P = 0.020; P矫正 > 0.05), respectively. Conversely, the infant FcγRIIIb-HNA1a|1a genotype was significantly protective of perinatal HIV-1 acquisition (OR: 0.42, 95% CI: 0.18–0.96, P = 0.040; P矫正 > 0.05). Findings suggest a role for FcγR-mediated NK/monocyte (FcγRIIIa) and neutrophil (FcγRIIIb) functions in perinatal HIV-1 transmission (maternal infectiousness and infant susceptibility/protection).

Paediatric HIV functional cure and early antiretroviral treatment

Collaborators: Prof. L Kuhn (Columbia University), Prof. A Coovadia (ESRU, RMMCH), Dr K Technau (ESRU), Renate Strehlau (ESRU), Faeezah Patel (ESRU), the LEOPARD study team (funded as a NIH U01 grant: PI Kuhn, RSA PI CT Tiemessen)

This research area encompasses a single-arm clinical trial (called LEOPARD-CT) that commenced in August 2015 at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa. The trial has been designed to better understand viral latency in early treated HIV-infected children to develop more effective treatment strategies for children, with the ultimate goal of achieving functional cure or viral remission. We have established the HIV reservoir assays that quantitate integrated and episomal provirus to gain a better understanding of the effects of early antiretroviral treatment on the size of the reservoir. Furthermore, we have evaluated and optimised four multicolour flow cytometry panels that in detail will characterise longitudinally in infants all the known T cell subsets that can serve as reservoirs for HIV, as well as B cell subsets. In parallel we have been recruiting an observational cohort of mothers and their infants (called LEOPARD-O, commenced March 2015) where there has been a delay in treatment to the infant (i.e. did not start within 48 hours of birth as for the LEOPARD-CT protocol); the same viral and immunological parameters are being measured in these infants to establish effects of delayed treatment. To date, 75 birth-identified HIV-1 infected infants have been enrolled, 30 of whom started treatment within 48 hours of birth.
South African HIV-1 infected long-term non-progressors and elite controllers

Collaborators: Dr N Martinson (PHRU), Dr D Spencer (Right to Care), Dr P Ise (CHRU), Prof. M Ramsay (SBIMB), Dr P Kiepiela (MRC), M Vermeulen (SANBS), M Papathanosopoulos (Wits)

This study explores natural control of HIV-1 that occurs in rare individuals called elite controllers, and includes other phenotypic groups of patients that may control their disease progression through different mechanisms. We have continued to identify and recruit HIV-1 controllers and progressors across South Africa, with the aim of identifying viral and host targets that can be developed for functional cure strategies in our populations. To date, we have samples from 200 elite controllers (136 from SANBS testing), 270 viraemic controllers, 525 progressors, and 11 high viral load long-term nonprogressors (a very rare group among HIV-1 infected adults; >10,000 RNA copies/ml and healthy CD4 T cell counts for >7 years). The approach includes establishing biosignatures (combinations of host, viral, bacterial, environmental factors) that ultimately will distinguish different clinical phenotypes of HIV-1 control, and the incorporation of unbiased systems biology approaches, such as whole genome DNA sequencing, whole genome transcriptional profiling of mRNA and microRNA. Assays have been established and analyses are ongoing with an initial focus on a cohort from Johannesburg/Soweto. This study will contribute to the discovery of novel factors that play a role in natural control of HIV-1 infection.

Metal complexes as broad spectrum microbicides for HIV and STIs

Collaborators: Dr M Fernandes (Molecular Sciences Institute, School of Chemistry, Wits)

This study describes the synthesis of various metal complexes, and to date 47 compounds (silver, copper, bismuth) have been synthesised and tested for their antimicrobial activity against HIV-1, HSV-2 and Neisseria gonorrhoeae, and for toxicity towards lactobacilli (L. crispus and L. jensenii) and a vaginal cell line (SiHa). Those compounds, with good antimicrobial activity and low toxicity, are then further tested for antimicrobial activity against HIV-16, Chlamydia trachomatis and Trichomonas vaginalis. Findings to date have identified: (i) A silver saccharinate benzimidazole complex and a silver saccharinate 8-hydroxyquinoline complex that exhibit low toxicity, excellent broad spectrum activity and good chemical stability, and (ii) bismuth-based complexes with potent antiviral activity (HIV-1, HSV-2, HPV) and low toxicity.

Structure of an N276-dependent HIV-1 neutralising antibody targeting a rare V5 glycan hole adjacent to the CD4 binding site

Collaborators: J Gorman (VRC, CS Anthony (UCT), SS Abdool-Kanim (CAPRISA), JR Mascola (VRC), C Williamson (UCT), PD Kwong (VRC)

The conserved CD4 binding site on gp120 is a major target for HIV-1 vaccine design, but key events in the elicitation and maturation of antibodies against this site remain elusive. Since earlier strain-specific antibodies can evolve into broadly neutralising antibodies, characterising the epitopes of strain-specific antibodies may help to inform the design of HIV-1 immunogens able to elicit broadly neutralising antibodies. In this study, we isolate a narrowly neutralising N276 glycan-dependent antibody and use X-ray crystallography and viral deep sequencing to describe how gp120 lacking glycans in V5 might have elicited these early glycan-dependent CD4 binding site antibodies. These data highlight how glycan holes can play a role in the elicitation of B-cell lineages targeting the CD4 binding site.

Structure and recognition of a novel HIV-1 gp120-gp41 interface antibody that caused MPER exposure through viral escape

Collaborators: J Gorman (VRC), G Ozorowski (Scripps), DJ Sheward (UCT), DR Burton (Scripps), M Connors (NIAID), SS Abdool-Kanim (CAPRISA), JR Mascola (VRC), JE Robinson (Tulane), AB Ward (Scripps), C Williamson (UCT), PD Kwong (VRC)

Our understanding of which regions of the HIV-1 envelope are targets for broadly neutralising antibodies (likely required for an HIV-1 vaccine) has expanded greatly in recent years. In this study, we isolated the neutralising monoclonal antibody CAP248-2B from an HIV-infected individual, and used structural biology to characterise its epitope, which spanned both the gp120-gp41 and gp41-gp41 interfaces in a manner distinct from other antibodies. Analysis of viral escape pathways identified a cluster of unusual mutations in the gp160 cleavage sites that made HIV-1 viruses more sensitive to antibodies targeting highly conserved membrane-proximal epitopes. These mutations might improve the immunogenicity of gp41, and thereby inform HIV-1 immunogen design.

Ontogeny-based immunogens for the induction of V2-directed HIV broadly neutralising antibodies

Collaborators: G Gorman (VRC), N Doria-Rose (VRC)

Antibodies that recognise the V2 region of the HIV-1 envelope often exhibit remarkable breadth and potency. These antibodies are derived from rare precursors with long anionic antigen-binding loops that are often deleted in the B cell repertoire, posing challenges for their elicitation. However, once engaged, these precursors contain many of the structural elements required for neutralisation, and can rapidly acquire breadth through moderate levels of somatic hypermutation in response to emerging viral variants. Commonalities in the precursors and mechanism of neutralisation have enabled the identification of viral strains that show enhanced reactivity for V2 precursors from multiple donors, and may form the basis of germline-targeting approaches for vaccine design.
POLICY FORMULATION

The centre was part of the technical working group (TWG) nominated by the NDoH to develop a comprehensive strategy for STI management in South Africa, which includes the use of rapid syphilis point-of-care tests. Several meetings of the TWG were held in 2016/17, at which significant contributions were made to the following documents, based on epidemiological and surveillance data generated by the centre:

1. South African National Strategic Plan on HIV, TB and STIs 2017–2022

Additionally, the centre has contributed data for policy formulation, as well as written recommendations for incorporation into national STI syndromic management guidelines at meetings of the Essential Medicines List, NDoH:

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

TECHNICAL AND REFERENCE SUPPORT

The laboratory performed HIV-1 testing for the Prospective Household Observational Cohort Study of Influenza, Respiratory Syncytial Virus and other Respiratory Pathogens Community Burden and Transmission Dynamics in South Africa (The PHIRST Study) and for the Alcohol, Tobacco and Other Drug Research Unit (MRC) Project that assessed the effectiveness of an alcohol-focused intervention in improving adherence to ART and HIV treatment outcomes.

HIV-1 viral load testing was performed for various Southern African Development Community (SADC) incidence studies: Swaziland Link4Health (linkage and retention in HIV care), Swaziland HIV Incidence Measurement Survey (SHIMS 2), the LePHIA study (Lesotho Population-based HIV Assessment), ZAMPHIA (Zambia Population-based HIV Impact Assessment survey).

The laboratory performed HIV-1 incidence testing and HIV-1 viral load testing on samples received for the Human Sciences Research Council (HSRC) educator study. Dried blood spot samples were tested for this survey and the major challenge experienced was quality of the dried blood spot samples and resulted in sample rejection and compromised HIV viral load results.

Wits Reproductive Health and HIV Institute Unit: CHOICES study – a prospective observational study of the association between injectable contraception, HIV and other STIs among young women in South Africa. Laboratory testing over a two-year study period will include quarterly visits for serology (rapid HIV, syphilis, HSV-2) and annual molecular testing (M-PCR) of vaginal swab specimens for VDS pathogens. Started April 2016 and recruitment is ongoing.

Foundation for Professional Development: ASPIRES Study – prevalence of STIs (Neisseria gonorrhoeae, Chlamydia trachomatis and Trichomonas vaginalis) among school-going children (four schools in the Tshwane District). Post-intervention recruitment and testing started in December 2016.

AYAZAZI: Cohort study of adolescents and young adults in Soweto and Durban, sponsored by the Canadian HIV Vaccine Initiative and the Canadian Institutes for Health Research. The primary objective was to identify, understand and link socio-behavioural, clinical, and biomedical patterns of risk for HIV acquisition and vaccine trial preparedness. Baseline and annual STI testing were performed on urine and/or genital swab specimens. The study was completed in September 2016.

UChoose a Star: Study of hormone (contraceptive) induced mucosal changes due to effects on the genital microbiome, and HIV susceptibility in adolescent females. Endocervical and vaginal swabs specimens for STI testing will be taken at screening, crossover (week 16) and termination (week 32). Recruitment is ongoing for screening, crossover and termination.

Human papillomavirus prevalence in HIV-negative South African adolescents and young women (UCT collaboration). This study investigated prevalence, incidence and clearance of cervical HPV infection in adolescents and young women in South Africa, along with the influence of other STIs (Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma genitalium, herpes simplex virus-2 (HSV-2)), bacterial vaginosis (BV), sociodemographic characteristics and sexual behaviour.

The adequacy of syndromic management of high HIV-risk African adolescents: an observational cohort study (UCT collaboration) to evaluate the prevalence of STIs and BV in adolescent women from two low-income communities in South Africa, and identify behaviour/s that increased the risk of STI/BV acquisition. The appropriateness of syndromic management of STIs/BVs in these young women was evaluated.
HPV in men (HIM-SA/CANSA study): The prevalence of anogenital and oropharyngeal HPV infection, genotype distribution and associations with anogenital disease, according to HIV-related factors and exposure to antiretroviral treatment. The study will aim to describe and report on the epidemiology of anogenital and oropharyngeal cancer patterns and trends in men, including incidence and mortality rates and differences by ethnicity in SA between 1994 and 2010. Furthermore, the influence of HIV status on epidemiology of these cancers will be explored.

GRANT FUNDING

CDC Global Disease Detection
Clinton Health Access Initiative
Discovery Foundation
Medical Research Council (South Africa)
National Health Laboratory Service Research Trust
National Research Foundation Incentive Funding for Rated Researchers
National Research Foundation Professional Development Programme
Department of Science and Technology/National Research Foundation Chair of HIV Vaccine Translational Research
PEPFAR
Poliomyelitis Research Foundation
National Institutes of Health (NIH)
South African Society of Obstetrics and Gynaecology
UNICEF
Unitaid
USAID

TEACHING AND TRAINING

1. The teaching and field supervision of Field Epidemiology Training Programme (FETP) residents.
2. Specialist registrar and postgraduate teaching and training in HIV and STIs.
3. Postgraduate training to postgraduate students enrolled for the Diploma in Tropical Medicine and Hygiene (DTM&H).
4. Training for undergraduate medical and dental/pharmacy/nursing students.
5. Technical training and support 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. Technical training was provided to laboratory staff from Kenya on post-marketing surveillance of HIV rapid test kits. Centralised and on-site training by NICD for various studies e.g. Key Population Implementation Science (KPIIS) study and SABSMM V national survey.

Professional development

Postgraduate students enrolled: 22 (16 PhD, 4 MSc, 2 BSc (Hons))

Postdoctoral fellows: 6

Postgraduate students graduated: 5 (2 PhD, 2 MSc, 1 BSc (Hons))

Honours

Prof. Tiemessen received a university award for top postgraduate supervisor in the Faculty of Health Sciences, and a certificate was awarded by the Faculty of Health Sciences, University of the Witwatersrand for dedication and achievement in research for 2016.

Prof. Lynn Morris is listed on the Thompsons Reuters ISI list of the 3 000 highest cited researchers in the world for two consecutive years (2015 and 2016).

Prof. Lynn Morris was inducted as a Fellow of the Royal Society of South Africa.

Dr Jinal Bhiman was awarded the 2016 James Gear Fellowship by the Poliomyelitis Research Foundation (PRF), to enable her to join Prof. Dennis Burton's laboratory at the Scripps Research Institute in California as a Postdoctoral Research Associate, where she will continue to study HIV envelope immunogens.
RESEARCH OUTPUT

List of publications


43. Shaffer JS, Moore PL, Kardar M, Chakraborty AK. Optimising immunisation protocols to maximise the probability of evolving broadly neutralising antibodies against highly mutable pathogens. *PNAS* 2017; 112 (49): pii: 201614940. [Epub ahead of print]


Chapters in books


Conferences/Congresses

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Centre for Opportunistic, Tropical and Hospital Infections
BACKGROUND

The surveillance, reference and research activities of the centre include opportunistic infections, particularly those related to HIV/AIDS, tropical infections, especially malaria, and nosocomial infections, concentrating on antimicrobial resistance, molecular epidemiology and outbreak investigations in the hospital setting. Since the introduction of antimicrobial agents, antimicrobial resistance (AMR) has become a global problem, and as the use of antimicrobial drugs increases, the complexity of resistance mechanisms demonstrated by bacterial, fungal and parasitic pathogens becomes increasingly important. With the South African government’s 2018 target for elimination of local transmission of malaria, surveillance and research activities around malaria parasites, their vectors, and the human hosts, are priorities for the NICD in supporting the NDoH. The burden of opportunistic infections caused by certain fungal pathogens in the country’s large HIV-positive population, is another major focus of attention for the centre.

SURVEILLANCE, DIAGNOSTIC AND REFERENCE SERVICES

Due to the increase in antibiotic resistance, the prevalence of hospital and community-acquired infections is high, with a significant number of deaths. 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)) and especially focused on Staphylococcus aureus, Klebsiella pneumoniae and Pseudomonas aeruginosa, with the aim to complete situational analysis of resistance patterns through national sentinel site surveillance. Once baseline data have been collected, periodic surveillance for ESKAPE pathogens will follow. A reference service was offered for all multidrug-resistant organisms, such as emerging colistin resistance in Gram-negative bacteria, efflux mechanism of resistance in non-fermenting organisms, carbapenem-resistant Enterobacteriaceae (CRE), vancomycin and linezolid resistance in Gram-positive bacteria, and others. AMRRL serves as a Collaborating Centre for AMR for the WHO and is the focal point for Global Antimicrobial Resistance Surveillance System (GLASS) at national level.

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 has played a leading role in the national implementation and monitoring of a screen-and-treat intervention for cryptococcal disease included in South Africa’s Care and Treatment HIV Programme.

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 carried out by the Vector Control Reference Laboratory for the Mpumalanga and KwaZulu-Natal Provincial Malaria Control Programmes. Malaria parasite infection surveillance has been expanded to support the NDoH’s plans to halt malaria transmission in selected districts in South Africa; these activities include antimalarial drug resistance studies, submicroscopic and gametocyte infection detection, malaria serology, rapid diagnostic test quality assessment, and the evaluation of novel POC malaria case management tools. Advice and expertise was provided to the Department of Health at national and provincial levels, with active participation on the SA Malaria Elimination Committee.

In the field of laboratory quality improvement, the centre has played an active role in reporting on clinical laboratory capacity in the WHO African region for the past 14 years, and has supported African laboratories involved in crucial 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 the year. These included cases of malaria affecting Gauteng residents without recent travel history, that is, Odyssean malaria. Entomological investigations revealed no evidence of local breeding of vector anophelines. The interrelated issues of antimicrobial resistance and nosocomial infections are growing public health problems. In this regard, the centre led investigation of outbreaks of neonatal candidaemia at a Gauteng tertiary hospital, Klebsiella pneumoniae in a Mpumalanga provincial hospital, and carbapenem-resistant Enterobacteriaceae in private health facilities.

RESEARCH PROJECTS

Insecticide resistance in malaria vectors

Collaborators: Dr M Paine and Prof. J Hemingway, Liverpool School of Tropical Medicine

Malaria vector control relies principally on the use of insecticides via the distribution of insecticide treated bed nets (ITNs) or indoor spraying of residual insecticides (IRS). However, wide-scale use of insecticides has led to the development of insecticide resistance. Insecticide resistance in target Anopheles malaria vector populations is now extremely common and is increasing, especially in sub-Saharan Africa. However, phenotypic resistance, as measured using diagnostic dosages of insecticides, does not always translate into operational vector control failure because there is no direct relationship between diagnostic dosages and the amounts of insecticide used to treat ITNs and to spray the inside walls of dwellings. Reviews of the evidence to date show that insecticide resistance can lead to vector control failure, especially in an IRS setting. This has been demonstrated in the southern African region over the past two decades.

Anopheles arabiensis and An. funestus are major malaria vectors in much of sub-Saharan Africa, including South Africa. Resistance to insecticides in populations of these species is widespread, necessitating ongoing research into the mechanisms conferring resistance. Recent investigations showed that multiple blood feeding augments the expression of resistance in insecticide resistant adult females of these species. This is because multiple blood-feeding induces increased glutathione peroxidase activity, which leads to a reduction in oxidative stress in adult female mosquitoes. This mechanism also reduces the oxidative burden induced by DDT and pyrethroid insecticides, leading to increased insecticide tolerance.

Malaria vector control and transmission dynamics

Collaborators: Dr C Lyons, University of Stellenbosch; Dr J Gilles, International Atomic Energy Agency (IAEA)

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 the influence of temperature on larval development rate and survival from egg/larva to adult differ across Anopheles species, and that the upper thermal limits of wild and laboratory strains of the major malaria vector An. funestus are unaffected by resistance to insecticides. Resistant populations can therefore be expected to perform as well as, if not better, than susceptible strains in terms of survival and reproduction under changing environmental conditions, such as those associated with climate change. The adaptation mechanisms in these populations likely involve variations in the expression of certain enzyme systems, including esterases.

Possible alternative methods of malaria vector control include the use of the sterile insect technique (SIT) and plant-derived larvicides. It was shown that sterile males from a laboratory-reared genetic sexing strain of the major malaria vector An. arabiensis are suitably competitive in terms of mating against their fertile wild counterparts under semi-field conditions. This is an important step in establishing the feasibility of the SIT for the control of malaria vectors. It was also shown that black pepper and its primary constituent, piperine, are effectively larvicidal against insecticide resistant and susceptible strains of certain, but not all, malaria vector species.
Laboratory-based antimicrobial resistance surveillance (LARS) programme for nosocomial bacteria

**Collaborators:** A Whitelaw, A Duse, C Bamford, M Nicol, J Wadula, P Naicker, S Haffejee, K Mlisana, Y Coovadia, K SweSwe Han, P Ramjathan, P Bohla (all NHLS)

Laboratory surveillance for antimicrobial resistance (AMR) provides a platform for generation of reliable AMR data from different geographical regions. Surveillance for carbapenem-resistant Enterobacteriaceae (CREs) is included in the GERMS-enhanced surveillance programme. Baseline antimicrobial resistance data on other ESKAPE organisms and tests for genes implicated in emerging resistance is planned.

Molecular testing includes an array of assays (real time and conventional PCRs) for the detection of various mechanisms of resistance, including antibiotic resistance genes, efflux pumps and porin loss. The presence of the methicillin resistance determinants mecA and mecC were investigated in *Staphylococcus aureus* along with the linezolid resistance gene (*cfr*) and the Panton-Valentine leukocidin (*pvl*) toxin. In Gram-negative organisms, the following antibiotic resistance genes were investigated: extended spectrum beta-lactamases (*bla*<sub>TEM</sub>, *bla*<sub>SHV</sub>, and *bla*<sub>CTX-M</sub>); carbapenemase-producing genes (*bla*<sub>NDM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>IMP</sub>, *bla*<sub>OXA-48</sub> & variants, *bla*<sub>KPC</sub> and *bla*<sub>GES</sub>); plasmid-mediated *ampC* and colistin resistance (*mcr-1*) genes and *VEB*-I. Porin loss (*OprD*) and efflux pumps were also investigated. Molecular characterisation techniques also include SCCmec element and spa typing in *Staphylococcus aureus*, and multi-locus sequence typing (MLST) and pulsed field gel electrophoresis (PFGE) in various organisms.

Antimicrobial resistance prevalence and transmission between animal feed and humans

**Collaborators:** Prof. M van Vuuren, Faculty of Veterinary Science, University of Pretoria; Dr D Petty, private veterinary practitioner

Given that antimicrobial resistance is a major global health concern, and that South Africa has high-density industrial farming of food animals, including cattle, poultry and pigs, the routine use of antibiotics for therapeutic, prophylactic and growth promotion on these farms is worrying, as antibiotics in food animals have been linked to increases in clinical resistance in human medicine. There has been little regulation of antibiotics administered to animals, with overlaps in the classes of antibiotics used for farming and human therapy. These animals, animal products, farm workers and the farming environment itself are potential reservoirs for resistance determinants. Antimicrobial resistance has been detected on farms; however, the extent of resistance and spill-over in the country remain largely unknown. This project aims to describe the antibiotic resistance genes present in food animals and livestock workers, reservoirs from which spill-over may occur into the community and/or hospital environments.

Carbapenemase characterisation in *Klebsiella pneumoniae*

**Collaborators:** LARS members

Carbapenem non-susceptible isolates obtained during sentinel surveillance from four provinces were confirmed at the NICD, and further characterisation of carbapenemase genes and plasmid-mediated *ampC* were performed.

Enhanced surveillance for hospital versus community-associated infections by methicillin-resistant *Staphylococcus aureus*

**Collaborators:** T Nana, R Lekalakala, A Whitelaw, P Naicker, C Bamford (all NHLS)

*Staphylococcus aureus* is one of the most significant pathogens responsible for nosocomial and community-associated infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), which has a high prevalence worldwide, as well as high morbidity and mortality rates. Previously MRSA was considered a nosocomial pathogen, but now it is recovered from some patients on admission to hospitals. Community-associated MRSA (CA-MRSA) occurs in patients that may never have been exposed to healthcare settings. MRSA has spread increasingly to the community over the past three decades, becoming endemic in most countries. The aim of this project is to identify virulence factors and evolution patterns of *S. aureus* to determine the prevalence and extent of these nosocomial and community-acquired infections in the South African setting.

Enhanced surveillance for carbapenem-resistant Enterobacteriaceae

**Collaborators:** C Bamford, P Bohla, N Basman, V Chibabhai, Y Coovadia, H Dawood, A Duse, S Haffejee, K SweSwe Han, A Hoosen, N Mbelle, Y Mahabeer, M Maloba, C Maluleka, K Mlisana, P Naicker, M Nchabeleng, S Mahlangu, P Ramjathan, T Thomas, J Wadula, A Whitelaw (all NHLS)

The Enterobacteriaceae are part of the commensal human gut flora and are the cause of community- and healthcare-associated infections. Over the last decade, Enterobacteriaceae have increasingly developed resistance to all beta-lactam antibiotics, fluoroquinolones and aminoglycosides. Of particular concern are carbapenem-resistant Enterobacteriaceae (CREs) that have become a threat to healthcare and patient safety worldwide. This LARS project gathers information about the spread of CPEs in South Africa from sentinel site at public healthcare facilities.
**Pneumocystis jirovecii** pneumonia (PCP) in hospitalised patients with severe acute respiratory infections (SARI) using an existing surveillance network in South Africa

**Collaborators:** Centre for Respiratory Diseases and Meningitis, NICD

Surveillance for PCP in adults and children has been done at sentinel sites in North West and KwaZulu-Natal since 2012, to determine the relative contribution of PCP to the burden of severe acute respiratory infections. A total of 15 136 samples was tested, of which 14% were positive for *P. jiroveci*. Because colonisation, rather than infection, can confound the interpretation of molecular detection of *P. jiroveci*, to the correlation between gene copy number and serum β-D-glucan levels was examined. Preliminary results showed a 'fair' agreement (Cohen’s kappa agreement coefficient = 0.44) between the two measurements.

**Sentinel surveillance for parasitic causes of diarrhoea in hospitalised children**

**Collaborators:** Centre for Enteric Diseases, NICD

Five sentinel sites provided stool samples from under-five children with diarrhoea, as part of a rotavirus surveillance programme; residual samples were screened for bacterial and parasitic pathogens. Of approximately 4 000 samples tested, 12.2% contained pathogenic parasites; the vast majority (>95%) were *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. Molecular detection of microsporidial species in these samples was carried out; of 358 samples tested, 2% were positive by PCR, compared to 0.3% by microscopy. These organisms are underappreciated as diarrhoeal agents, because they are difficult to detect by conventional laboratory methods.

**Malaria parasite infection surveillance**

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

The NICD has re-established the country’s only molecular antimalarial drug resistance surveillance programme, as well as initiated surveillance for sub-microscopic malaria infections and gametocyte carriage. These efforts are all in support of the NDoH’s plans to eliminate the transmission of malaria in South Africa by 2018. Of the 300 samples analysed, 100% agreement between the malaria rapid diagnostic test and the molecular parasite detection assay was found. In addition, none of the molecular markers associated with resistance to artemisinins were detected in any of the parasite isolates tested.

**Assessing the safety and efficacy of single low-dose primaquine**

**Collaborators:** Provincial Malaria Control Programmes of Limpopo and Mpumalanga; Prof. KI Barnes, University of Cape Town (UCT); Prof. L Braack and Dr H Swanepoel, University of Pretoria

In 2015, the WHO recommended that single low-dose primaquine be incorporated into standard antimalarial treatment in regions nearing malaria elimination. This recommendation is based on preliminary data, which showed that the addition of single low-dose primaquine greatly reduced the number of circulating gametocytes, the parasite stage associated with onward transmission. Unfortunately, high doses of primaquine are associated with acute haemolysis, particularly in glucose-6-phosphate dehydrogenase-deficient individuals. To inform a single low-dose primaquine policy in South Africa, a primaquine safety, efficacy and tolerability clinical trial was initiated at selected high malaria-burdened clinics in Mpumalanga during the 2016/17 malaria season. Since the start of the trial, 81 potential participants have been screened, with 36 that met the study criteria enrolled in the trial. Twenty of the 36 enrolled participants have successfully completed their 42-day follow-up period, with no adverse effects due to primaquine reported to date.

**Global burden of disease of HIV-associated cryptoccocal meningitis: an updated analysis**

**Collaborators:** R Rajasingham and DR Boulware, University of Minnesota; RM Smith, TM Chiller, and BJ Park, CDC, Atlanta; JN Jarvis, University of Pennsylvania; DW Denning, University of Manchester; A Loyse, University of London

To estimate the global burden of disease of HIV-associated cryptoccocal meningitis, we used 2014 Joint United Nations Programme on HIV/AIDS estimates of adults with HIV and antiretroviral therapy (ART) coverage. Estimates of CD4 <100 cells/µL, virologic failure incidence, and loss-to-follow-up of adults were from published multinational cohorts in low and middle-income countries. We calculated those at risk for cryptoccocal disease, specifically those with CD4<100 cells/µL not on ART, and those with CD4<100 cells/µL on ART but lost-to-follow up or with virologic failure. We estimated an average cryptococcal antigen (CrAg) prevalence of 6.0% among CD4 <100 cells/µL, with 278 000 CrAg+ persons globally and 223 100 incident cryptoccocal meningitis cases globally in 2014. Sub-Saharan Africa accounted for 73% of the estimated cryptoccocal meningitis cases (162 500 cases). Cryptoccocal-related deaths were estimated at 181 100 globally, with 135 900 (75%) deaths in sub-Saharan Africa. Globally, Cryptococcus was responsible for 15% of AIDS-related mortality. Our analysis highlights the substantial ongoing burden of HIV-associated cryptoccocal disease, primarily in sub-Saharan Africa.
Implementation and evaluation of a public health intervention: cryptococcal antigen screening and pre-emptive treatment

**Partners:** Department of Health, NHLS, USAID, CDC, President’s Emergency Plan for AIDS Relief (PEPFAR) partners, Boston University, University of Minnesota

Cryptococcal meningitis has a fatal outcome in >50% of cases in routine care in South Africa. In a randomised-controlled clinical trial conducted in Tanzania and Zambia, cryptococcal antigen (CrAg) screening of HIV-infected persons with a baseline CD4 count <100 cells/µL and pre-emptive antifungal treatment, together with ART adherence support, resulted in a ~30% relative reduction in 6-month mortality. In January 2016, the NDoH made a decision to implement reflex laboratory CrAg screening across the country based on strategic information compiled by the centre. By 1 November 2016, reflex screening had been set up at 50 NHLS CD4 laboratories with a projected 250 000 HIV-infected persons to be screened each year. If properly implemented, this intervention has the potential to directly reduce deaths associated with cryptococcal disease. The centre is currently involved in evaluating the effectiveness of this national intervention on patient outcomes through the NIH-funded CAST-NET project.

Further description of novel dimorphic fungal pathogens in humans

**Collaborators:** Prof. C Kenyon, University of Cape Town; Dr I Schwartz, University of Antwerp; Prof. S de Hoog, K Dukik (CBS); and others

Recent discoveries of novel systemic fungal pathogens with thermally dimorphic yeast-like phases have challenged the current taxonomy of the Ajellomyctaceae, a family currently comprising the genera Blastomyces, Emmonsia, Emmonsiellopsis, Helicocarpus, Histoplasma, Lacazia and Paracoccidioides. Our morphological, phylogenetic and phylogenomic analyses demonstrated species relationships and their specific phenotypes, clarified generic boundaries and provided the first annotated genome assemblies to support the description of two new species. A new genus, Emergomyces, accommodates Emmonsia pasteuriana as type species, and the new species, Emergomyces africanus, the etiological agent of case series of disseminated infections in South Africa. Both species produce small yeast cells that bud at a narrow base at 37°C and lack adiaspores classically associated with the genus Emmonsia. Another novel dimorphic pathogen, producing broad-based budding cells at 37°C and occurring outside North America, proved to belong to the genus Blastomyces, and is described as Blastomyces percursus.

Antifungal-resistant *Candida* species causing bloodstream infections

**Collaborators:** GERMS-SA network

We aimed to determine the genetic diversity of *Candida parapsilosis* causing fungaemia in South African neonatal intensive care units (NICUs). From February 2009 through to August 2010, cases of candidaemia were reported through laboratory-based surveillance. *C. parapsilosis* isolates from neonatal cases were submitted for identification by internal transcribed spacer (ITS) region sequencing, antifungal susceptibility testing and microsatellite genotyping. Of 1 671 cases with a viable *Candida* isolate, 393 (24%) occurred among neonates. Many isolates were resistant to fluconazole (77/143; 54%) and voriconazole (20/143; 14%). Seven clusters, comprising 82 isolates, were identified at five hospitals in three provinces. Isolates belonging to certain clusters were significantly more likely to be fluconazole resistant. *C. parapsilosis*-associated candidaemia in public-sector NICUs was caused by closely-related genotypes and there was molecular evidence of undetected outbreaks as well as intra-hospital transmission.

*Candida auris* is an emerging, multidrug-resistant fungal pathogen responsible for a wide spectrum of clinical manifestations and is associated with high mortality. We investigated the genetic relatedness of a sample of clinical *C. auris* isolates circulating in South Africa. Isolates, which were suspected or confirmed to be *C. auris* from patients admitted to either public and private-sector hospitals, were submitted to a reference laboratory from 2012 through to 2015. Susceptibility testing for ten antifungal agents was performed. Clustering was performed using multi-locus sequence typing (MLST). Eighty-five isolates were included in the study and confirmed as *C. auris*. MLST analysis grouped isolates into two clusters: cluster 1 and cluster 2 comprising 83 and two isolates respectively. Azole-resistant *C. auris* strains circulating in South African hospitals were highly related and the possibility of nosocomial transmission should be explored using a more discriminatory technique, such as whole genome sequencing or microsatellite genotyping.
RESEARCH FUNDING SOURCES

Carnegie-Wits Alumni Diaspora Programme
Centers for Disease Control and Prevention through NHLS/CDC Cooperative Agreement
Deutscher Akademischer Austausch Dienst
Gates Grand Challenges Explorations
Hillel Friedland Fellowship
Innovative Vector Control Consortium
International Atomic Energy Agency
London School of Hygiene and Tropical Medicine
International Centre of Excellence in Malaria Research – National Institutes of Health (ICEMR – Johns Hopkins Malaria Institute)
Medical Research Council of South Africa
South African National Energy Commission (Necsa)
NHLS Research Trust
National Institutes of Health
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 RatanjiDalal Research Scholarship
Stellenbosch University Hope Project
UK-MRC/DFID/Wellcome Trust Joint Global Health Trials Scheme
WHO African Region

TEACHING AND TRAINING

Teaching and training in various aspects of bacteriology, parasitology, mycology, medical entomology and communicable diseases was provided to students at postgraduate level (MSc, PhD), medical students, technicians, medical technologists, intern medical scientists, pathology registrars, South African Society of Travel Medicine (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 NDoH with the development of laboratory and clinical training materials for the relevant disease programmes.

Professional development

Postgraduate students enrolled: 10 (7 MSc, 3 PhD).

Postgraduate students graduated: 2 (MSc).

Honours

Prof. Maureen Coetzee: Certificate of Distinction awarded by the Council for International Congresses of Entomology at the ICE meeting in Orlando, Florida, USA, 2016; finalist, Standard Bank Top Women Awards in the Science category; Member of the Malaria Policy Advisory Committee of the WHO Global Malaria Programme, 2016–2019, reporting to the Director-General, WHO.


Nelesh Govender: Member of WHO Guidelines Development Group for Advanced HIV Disease.
RESEARCH OUTPUT

Publications

Journal Articles


9. Oliver SV, Brooke BD. The role of oxidative stress in the longevity and insecticide resistance phenotype of the major malaria vectors *Anopheles arabiensis* and *Anopheles funestus*. *Parasites & Vectors* 2016; 11(3): e0151049.


**Book Chapters**


**Conferences**

a. International conferences and meetings: 21

b. National conferences: 7

c. Local conferences: 11
Centre for Respiratory Diseases and Meningitis
BACKGROUND

The centre maintained ongoing syndromic surveillance for pneumonia and influenza-like illness (ILI) at sentinel sites within South Africa, and expanded ILI surveillance to include an additional rural site in Mpumalanga. Laboratory-based national surveillance continued for important causes of invasive bacterial disease and meningitis through the GERMS-SA platform. We published new guidelines for diagnosis, prevention and management of diphtheria as well as Middle East respiratory syndrome coronavirus. We investigated several outbreaks, including a diphtheria outbreak in KwaZulu-Natal and an influenza outbreak in a boarding school in the Eastern Cape. Several new research projects were initiated, the largest being the Prospective Household Observational Cohort Study of Influenza, Respiratory Syncytial Virus and other Respiratory Pathogens Community Burden and Transmission Dynamics in South Africa (PHIRST).

SURVEILLANCE PROGRAMMES

Pneumonia surveillance

The National Pneumonia Surveillance Programme (NPSP) is operational in five provinces. The protocol includes surveillance for severe respiratory illness (SRI), irrespective of duration of symptoms, and testing for core pathogens of public health importance. In the year under review, at all surveillance sites, the NPSP described the contribution of influenza, respiratory syncytial virus (RSV) and Bordetella pertussis to the syndrome of SRI. At two of the surveillance sites, enhanced surveillance continued to describe the pathogens associated with more chronic respiratory illness, including collection and testing of specimens for atypical causes of pneumonia: Pneumocystis jirovecii, Mycobacterium tuberculosis, Streptococcus pneumoniae, Bordetella pertussis, Haemophilus influenzae, Legionella species, Chlamydia pneumoniae and Mycoplasma pneumoniae. Surveillance for influenza-like illness is ongoing at outpatient clinics at two sites and a new site was initiated in Mpumalanga in early 2017.

Influenza surveillance

The 2016 influenza season started in week 19 (9 May) when the influenza detection rate increased to 19%. The influenza season was dominated by influenza B early in the season, accounting for 53% of influenza virus positive cases. Influenza A(H3N2) circulation followed as the dominant influenza A subtype in 66% of influenza A-positive cases. Influenza B/Victoria lineage strains dominated all influenza B virus detections. In the two influenza-like illness (ILI) surveillance programmes (Viral Watch and systematic surveillance for ILI at public health clinics), influenza B viruses were detected at frequencies of 57% and 47%, respectively, compared to 66% in pneumonia surveillance. Regional differences were observed in the circulation of influenza A viruses with A(H3N2) dominant in the Western Cape, A(H3N2) and A(H1N1)pdm09 co-dominant in KwaZulu-Natal, and A(H1N1)pdm09 dominating in Gauteng.

Cell culture-derived influenza virus isolates were obtained with a 90% success rate. A four-fold or greater reduction in hemagglutination inhibition titre against relevant vaccine strain antisera was observed at frequencies of 30% for B/Victoria and 58% for A(H3N2) virus isolates. All influenza A(H1N1)pdm09 viruses were in the 6B.1 genetic lineage and almost all influenza A(H3N2) viruses were in the 3C.2a genetic lineage. Influenza B/Victoria viruses identified in 2016, compared to South African B/Victoria strains from 2012, showed continued drift associated with the following amino acid substitutions: I117V, N129D and V131I. No genetic mutations associated with reduced susceptibility to oseltamivir were observed in the neuraminidase protein sequences of influenza A and B viruses. This report includes the analysis of influenza virus sequence data generated by WHO Collaborating Centres (in Atlanta, London and Australia) from representative 2016 South African clinical specimens and associated influenza virus isolates.
Laboratory-based surveillance for Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae (GERMS and WHO Vaccine Preventable Invasive Bacterial Disease)

CRDM continued national laboratory-based, population-based active surveillance for invasive disease caused by S pneumoniae, H. Influenzae and N. meningitidis. Surveillance data contribute to the evaluation and understanding of the impact of both pneumococcal conjugate vaccine (PCV) and H. influenzae serotype b conjugate vaccine (Hib CV). CRDM also contributes data on numbers and serogroups of N. meningitidis and supports diagnostic testing and outbreak response for suspected cases of meningococcal meningitis. Data generated allows for descriptive epidemiology of invasive disease and emergence of resistance in these three pathogens. Additionally we continued our role as a WHO regional reference laboratory for the vaccine-preventable invasive bacterial disease (VP-IBD) surveillance network.

RESEARCH PROJECTS

Effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) against invasive pneumococcal disease (IPD) in South African children: a case-control study

C Cohen, C von Mollendorf, L de Gouveia, S Lengana, S Meiring, V Quan, A Nguweneza, DP Moore, G Reubenson, M Moshe, SA Madhi, B Eley, U Hallbauer, H Finlayson, S Varughese, K L'Obrien, ER Zell, KP Klugman, CG Whitney, A van Gottberg, for the South African IPD Case-Control Study Group

PCV13 was designed to include disease-causing serotypes that are important in low-income and middle-income countries. Vaccine effectiveness estimates are scarce in these settings. We assessed the effectiveness of ≥2 doses of PCV13 against invasive pneumococcal disease (IPD) in HIV-infected and -uninfected children using a matched case-control study. Between January 2012 and December 2014, we enrolled 240 HIV-uninfected and 75 HIV-infected cases and 1 118 HIV-uninfected and 283 HIV-infected controls. The effectiveness of two or more doses of PCV13 against PCV13-serotype invasive pneumococcal disease was 85% (95% CI: 37–96) in HIV-uninfected and 91% (35–100) among HIV-infected children. PCV13 effectiveness was 52% (95% CI: 12–79) against all-serotype invasive pneumococcal disease and 94% (44–100) for serotype 19A in HIV-uninfected children. Vaccine effectiveness against PCV7-serotype invasive pneumococcal disease was 87% (95% CI: 38–97) in children exposed to HIV but uninfected, and 90% (CI: 53–98) in malnourished children not infected with HIV. These findings support recommendations for widespread use of pneumococcal conjugate vaccine in low- and middle-income countries. (Lancet Global Health 2017; 5: e359-369)


Syndromic surveillance for hospitalised severe acute respiratory illness (SARI) and outpatient ILI was conducted in two provinces of South Africa, 2012–2015. Characteristics of influenza-positive patients with SARI and ILI were compared to identify factors associated with SARI hospitalisation. Influenza virus was detected in 5.9% (110/1,861) of SARI and 15.8% (577/3,652) of ILI cases. Factors significantly associated with increased risk of influenza-associated SARI hospitalisation on multivariable analysis were: age <6 months (aOR: 37.6), 6–11 months (aOR: 31.9), 12–23 months (aOR: 22.1), 24–59 months (aOR: 7.1) and ≥65 years (aOR: 40.7) compared to 5–24 years, underlying illness (aOR: 4.5), HIV (aOR: 4.3); and S. pneumoniae colonisation density (aOR: 4.8). Miners (aOR: 13.8) and pregnant women (aOR: 12.5) were also at higher risk. (Open Forum Infectious Disease 2017; 4(1): ofw262)

Molecular characterisation of invasive capsule null Neisseria meningitidis in South Africa


Encapsulation is an important virulence determinant for invasive meningococcal disease (IMD). Many colonising meningococci are unencapsulated and regarded as non-pathogenic. Rare cases of IMD caused by unencapsulated, capsule null locus (cnl) meningococci belonging to clonal complex (cc) 192, cc845 and cc198 have been reported. The clinical significance of these isolates remains unclear. Through national laboratory-based surveillance for IMD, from 2003–2013, four cnl meningococci were identified and characterised using whole genome sequencing. The isolates belonged to cc192 or cc53, and contained loci for fHbp and NHBA, which are included in protein-based vaccines for serogroup B (Bexsero and Trumenba). In addition, cnl strains may have a tendency to cause IMD in immunocompromised hosts, potentially coupled with unknown non-capsular virulence mechanisms. (BMC Microbiology 2017; 17(1): 40)
Estimating vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings in South Africa

JM McAnerney, S Walaza, S Tempia, L Blumberg, FK Treurnicht, SA Madhi, Z Valley-Omar, C Cohen

The effectiveness of trivalent seasonal influenza vaccine (TIV) against influenza-associated medically-attended acute respiratory illness was assessed using a test-negative case control study design. Patients with ILI presenting to an outpatient influenza sentinel surveillance programme were enrolled during the 2015 influenza season. Nine hundred and fifty-seven individuals were eligible for the VE analysis, with an overall influenza vaccine coverage of 1.8% (9/490) in cases and 4.3% (20/467) in controls (p=0.03). The overall VE estimate, adjusted for age, underlying conditions and seasonality, was 56% (95% CI: 3%–81%) against any influenza virus type, 60% (95% CI: 9%–85%) against influenza A(H1N1)pdm09, 71% (95% CI: 28%–93%) against influenza A(H3N2) and 19% (95% CI: -26%–82%) against any lineage of influenza B. Despite low vaccine coverage, influenza vaccine effectiveness was moderate. (Influenza and Other Respiratory Viruses 2017; 11(2): 177–181)

Enterovirus D68 and other enterovirus serotypes identified in South African patients with severe acute respiratory illness, 2009–2011

O Hellferscee, FK Treurnicht, S Tempia, E Varavara, H Dawood, K Kahn, AL Cohen, M Pretorius, C Cohen, SA Madhi, M Venter

Human enteroviruses (EV) have been associated with SARI in South Africa. This study describes the molecular epidemiology of EV serotypes among patients hospitalised with SARI during 2009–2011. Study samples from patients were tested for the presence of enterovirus using PCR. For SARI cases, 8.2% (842/10260) tested positive for enterovirus. Of the EV positive cases that were genotyped, 16% (7/45) were species EV-A, 44% (20/45) EV-B, 18% (8/45) EV-C and 22% (10/45) EV-D. Seventeen different EV serotypes were identified within EV-A to EV-D, of which EV-D68 (22%; 10/45) and Echovirus 3 (11%; 5/45) were the most prevalent. Therefore EV-D68 should be monitored to assess the emergence of highly pathogenic strains. (Influenza and Other Respiratory Viruses 2017; Jan 25)

Genomic analysis of nontypeable pneumococci (NTPn) causing invasive pneumococcal disease (IPD) in South Africa, 2003–2013

T Mohale, N Wolter, M Allam, K Ndlangisa, P Crowther-Gibson, M du Plessis, A von Gottberg

The capsule is the principal virulence factor of S. pneumoniae and is targeted by current pneumococcal vaccines. Some pathogenic pneumococci are serologically nontypeable. Invasive NTPn (n=39/32,824, 0.1%), detected through GERMS surveillance, were characterised by whole genome analysis. Twenty-two (56%) had partial capsular genes (Group I), 17 (44%) had complete capsular deletion. Seventy-nine percent (31/39) were derived from encapsulated S. pneumoniae. 59% (13/22) of ancestral serotypes were serotypes included in the 13-valent pneumococcal conjugate vaccine. A variety of mutations were identified within the capsular region of Group I NTPn. Nonsusceptibility to tetracycline and erythromycin was higher in NTPn than encapsulated S. pneumoniae. NTPn are currently a rare cause of IPD in South Africa and represent a genetically diverse collection of isolates. (BMC Genomics 2016; 17: 470; 1–11)

Epidemiology of acute lower respiratory tract infection (LRTI) in HIV-exposed uninfected infants in South Africa, 2010–2013

C Cohen, J Moyes, S Tempia, M Groome, S Walaza, M Pretorius, F Naby, O Mekgoe, K Kahn, A von Gottberg, N Wolter, AL Cohen, C von Mollendorf, M Venter, SA Madhi

The epidemiology of LRTI hospitalisation in HIV unexposed uninfected (HUU) and HIV-exposed uninfected (HEU) infants aged <6 months was studied. Hospitalised infants with LRTI from four provinces were prospectively enrolled. Using PCR, nasopharyngeal aspirates were tested for ten viruses. Incidence for 2010–2011 was estimated at one site. The annual incidence of LRTI was elevated in HEU (incidence rate ratio [IRR] 1.4; 95% CI: 1.3–1.5) and HIV infected (IRR 3.8; 95% CI: 3.3–4.5), compared with HUU infants. Relative incidence estimates were greater in HEU than HUU, for RSV (IRR 1.4; 95% CI: 1.3–1.6) and human metapneumovirus-associated (IRR 1.4; 95% CI: 1.1–2.0) LRTI, with a similar trend observed for influenza (IRR 1.2; 95% CI: 0.8–1.8). HEU infants overall, and those with RSV-associated LRTI had greater odds (odds ratio 2.1, 95% CI: 1.1–3.8, and 12.2, 95% CI: 1.7–infinity, respectively) of death than HUU. (Pediatrics 2016; 137(4): e20153272)
Severity of respiratory syncytial virus (RSV) lower respiratory tract infection with viral coinfection in HIV-uninfected children


Molecular testing was performed for respiratory viruses in nasopharyngeal aspirates collected from children aged <5 years during sentinel surveillance for severe acute respiratory illness hospitalisation during February 2009–December 2013. The primary outcome was life-threatening disease, defined as mechanical ventilation, intensive care unit admission or death. Of 2,322 HIV-uninfected children with RSV-associated lower respiratory tract infection, 1,330 (57.3%) had RSV monoinfection and 38 (1.6%) had life-threatening disease. RSV and any other viral coinfection was not associated with severe disease (OR: 1.4; 95% CI: 0.7–2.6), ADV coinfection had increased odds of life-threatening disease (aOR: 3.4, 95% CI: 1.6–7.2, p=0.001), and influenza coinfection had increased odds of life-threatening disease and prolonged length of stay (aOR: 2.1, 95% CI: 1.0–4.5, p=0.05) compared to RSV monoinfection. (Clinical Infectious Diseases 2017; 64(4): 443–450)

Factors associated with nasopharyngeal pneumococcal colonisation and increased nasopharyngeal pneumococcal density in children

N Wolter, C Cohen, J Moyes, S Walaza, F Treurnicht, O Hellferssee, H Dawood, E Variava, SA Madhi, A von Gottberg

From 2011–2015, children <5 years, hospitalised with LRTI were enrolled at two sentinel sites. Nasopharyngeal aspirates and blood were tested for *S. pneumoniae* by quantitative lytA PCR. A total of 2,072 children were tested, of which 65% (1,356/2,072) were colonised with *S. pneumoniae*. Older age [6–11 months (adjusted odds ratio (aOR): 1.9, 95% CI: 1.4–2.6), 12–23 months (aOR: 2.2, CI: 1.6–3.1)] or 24–59 months (aOR: 1.9, CI: 1.4–2.7) compared to <6 months of age, crowded living conditions ([≥3 compared to <3 individuals per room: aOR: 1.3, CI: 1.1–1.7]), HIV infection (aOR: 1.5, CI: 1.1–2.1), influenza virus infection (aOR: 1.8, CI: 1.1–3.2), and adenovirus infection (aOR: 1.4, CI: 1.0–1.9), were associated with increased risk of colonisation. Amongst children colonised with pneumococcus, increased colonisation density was associated with malnutrition (aOR: 1.5, CI: 1.1–2.1), HIV infection (aOR: 1.7, CI: 1.1–2.6), influenza infection (aOR: 1.9, CI: 1.0–3.6), respiratory syncytial virus infection (aOR: 1.4, CI: 1.0–1.9), enterovirus infection (aOR: 1.8, CI: 1.1–3.1) and testing positive for pneumococcus in blood (aOR: 1.8, CI: 1.1–2.9).

Non-vaccine pneumococcal serotypes in children and adults pre- and post-pneumococcal conjugate vaccine introduction in South Africa


Invasive pneumococcal disease non-vaccine serotypes cases, reported through GERMS in 2005–2008 (pre-PCV) and 2012–2015 (post-PCV), were reviewed. Among children aged <5 years, serotype 35B incidence increased 77% (95% CI: 32%–94%) from 0.08 to 0.34/100,000 population (p=0.001), while 8 and 12F; increased 32% (95% CI: 25–64%) and 30% (95% CI: 48–68%) from 0.37 to 0.54/100,000 (p=0.1) and 0.25 to 0.36/100,000 (p=0.2), respectively. The majority of 35B isolates were clonal complex (CC) 361 (23/30, 78%). Predominant CCs did not change pre- and post-PCV among serotype 8 and 12F (serotype 8:CC53 (13/14 and 44/44, respectively), 12F:CC989 (4/10 and 17/26, respectively) and CC2416 (6/10 vs. 9/26, respectively). Among adults aged ≥25 years, 15A increased 64% (95% CI: 36%–81%) from 0.06 to 0.18/100,000 population (p<0.001). 12F increased 40% (CI: 20%–56%) from 0.31 to 0.51/100,000 population (p<0.001). CC63 and CC989 were identified among serotypes 15A (1/2) and 12F (23/37), respectively.


The characteristics of influenza-positive patients were compared between those with SARI and those with ILI to identify factors associated with severe disease (hospitalisation). Factors significantly associated with increased risk of influenza-associated SARI hospitalisation were: younger and older age (<6 months [aOR: 37.6], 6–11 months [aOR: 31.9], 12–23 months [aOR: 22.1], 24–59 months [aOR: 7.1], and ≥65 years [aOR: 40.7] compared with 5–24 years of age), underlying medical conditions (aOR: 4.5), HIV infection (aOR: 4.3), and *Streptococcus pneumoniae* colonisation density ≥1,000 copies/mL (aOR: 4.8). Underlying medical conditions in children <5 years included asthma (aOR: 22.7), malnutrition (aOR: 2.4), and prematurity (aOR: 4.8); in persons aged ≥5 years, included asthma (aOR: 3.6), diabetes (aOR: 7.1), chronic lung disease (aOR: 10.7), chronic heart disease (aOR: 9.6), and obesity (aOR: 21.3). Mine workers (aOR: 13.8) and pregnant women (aOR: 12.5) were also at increased risk for influenza-associated hospitalisation.

S Tempia, S Walaza, J Moyes, AL Cohen, C von Mollendorf, F Treurnicht, M Venter, O Hellferscee, N Walter, A von Gottberg, H Dawood, E Variava, SA Madhi, C Cohen

Age group-specific influenza prevalence among ILI, SARI and severe chronic respiratory illness (SCRI) cases was compared to those of controls, stratified by HIV-serostatus. Overall attributable fraction (AF) for influenza virus detection to illness was 92.6% (95% CI: 89.3%–94.8%), 87.4% (95% CI: 81.3%–91.5%) and 86.2% (95% CI: 77.7%–91.5%) among ILI, SARI and SCRI cases, respectively. Among HIV-uninfected patients the AF was highest among persons aged <1 and ≥65 years and lowest among persons aged 25–44 years for all syndromes. This trend was not observed among HIV-infected patients. Influenza viruses when detected in patients with ILI, SARI or SCRI are likely attributable to illness overall, especially among children and the elderly, irrespective of the HIV-serostatus and among HIV-infected individuals irrespective of age.

Systematic review of influenza and tuberculosis co-infection

Collaborators: S Walaza, C Cohen, S Tempia, J Moyes, A Nguweneza, M McMorrow, AL Cohen

We assessed 3 739 abstracts, reviewed 108 articles and included 25. Of the 25, 20 reported data from human studies and five were animal experimental studies. Of the 20 human studies, 15 reported individual level data and six were ecologic studies (one included both). Six of the 11 papers with laboratory-confirmed influenza suggested an association with poor outcomes in individuals with influenza-tuberculosis coinfection. Four of the six ecologic studies suggested increased mortality in individuals with TB during influenza pandemics. In mouse models, four studies noted increased severity of illness among TB-infected mice challenged with influenza viruses. Although experimental animal studies suggest increased severity of influenza illness with underlying TB infection, observational studies on influenza and TB in humans were of low quality and reported mixed findings.

Epidemiology of influenza-like illness (ILI) among HIV-infected and -uninfected patients, South Africa, 2013–2015


Active syndromic surveillance was conducted for outpatient ILI at two sentinel sites. Patients were tested for respiratory viruses using PCR. Unconditional logistic regression was used to assess factors associated with ILI among HIV-infected and HIV-uninfected outpatients. Among 3 845 enrolled patients, the median age was 26 years (interquartile range [IQR], 6–40 years), and 22% (794/3 667) were male. Data on HIV status were available for 95.4% (3 667/3 845) of ILI patients, HIV prevalence was 2% (27/1 034) among children <5 years and 38% (896/2 363) among individuals ≥5 years. Comparing HIV-infected and -uninfected ILI patients ≥5 years, individuals aged 25–44 years aOR 19.6, 95% CI: 7.03–54.477.9) were more likely to be HIV-infected compared to those aged 5–24 years and males (aOR: 0.49, 95% CI: 0.41.7–0.6) were less likely to be HIV-infected than females. There was clear seasonality of ILI for some respiratory pathogens, but individual pathogen seasonality varied and higher detection rates for most viruses were in children <5 years.

Molecular epidemiology of invasive serogroup C meningococcus in South Africa, 1999–2014

Collaborators: M du Plessis, M Allam, L de Gouveia, C Cohen, C von Mollendorf, S Meiring, A von Gottberg

Several countries have reported outbreaks of N. meningitidis among MSM, caused by a serogroup C (MenC) clonal complex (cc) 11 strain with a high case-fatality ratio. A sporadic case of fatal MenC meningitis was reported in 2008 in an MSM individual in South Africa. Cases of MenC reported through GERMS surveillance were reviewed. Overall, 33% (104/319) and 24% (76/319) of MenC occurred in children <5 years and young adults (15–24 years), respectively. Clonal complex (cc) 865 and cc11 represented 54% (150/276) and 24% (65/276), respectively. For cc11 isolates, the MSM genotype accounted for 37% (24/65). The case-fatality ratio was higher among patients with cc11 (7/16, 44%) compared to those with cc865 (6/55, 11%) (p=0.007). The cc11 MSM outbreak strain accounted for 9% of MenC disease, showed increased virulence and was more common in young adults than cc865.
Legionnaires’ disease among patients hospitalised with pneumonia in South Africa


Individuals hospitalised with severe pneumonia at two sentinel sites were enrolled from June 2012 through March 2016. Nasopharyngeal specimens and induced/expectorated sputum were collected and tested for Legionella spp. by real-time PCR. Of 5 662 patients tested, Legionella spp. was detected in 28 (0.5%, 95% CI: 0.3–0.7%). Case patients were aged 19 months to 59 years, with a median of 38 years. The highest detection rate was in the 25–44 year age group (0.9%, 16/1 780). HIV infection amongst Legionella cases was documented in 68.2% (15/22) of cases and males accounted for 15 (53.6%) cases. Species were identified for three cases, of which two were L. longbeachae and one was L. pneumophila serogroup 1.

Utility of real-time PCR for the identification and speciation of Legionella in South Africa


Individuals hospitalised with severe respiratory illness were enrolled from June 2012 through March 2016. Nasopharyngeal (NP) and sputum specimens were tested for Legionella spp. Of the 5 662 patients tested, Legionella spp. was detected in 28 (0.5%, 95% CI: 0.3–0.7%) with 22 (79%) detected in sputum only, five (18%) in NP only and one (4%) in both sputum and NP specimens. The overall mean Ct-value was 38.4±3.9, with a mean Ct-value of 38.1±4.3 and 39.1±1.9 in sputum and NP specimens, respectively (P=0.47). Species was identified for three cases: L. longbeachae (n=2) and L. pneumophila serogroup 1 (n=1). Mean Ct-values of specimens for which a species was identified (30.7±8.7) differed to specimens for which a species could not be identified (39.1±1.9) (P<0.001).

Ongoing pneumococcal disease declines and an indirect effect of vaccination, South Africa, 2005–2015

Collaborators: A von Gottberg, L de Gouveia, S Tempia, V Quan, S Meiring, C von Mollendorf, SA Madhi, KP Klugman, CG Whitney, C Cohen, for GERMS-SA

We continued national, active, laboratory-based surveillance for IPD. We calculated the percentage change in incidence, comparing post-vaccine (2015) and pre-vaccine years (2005–2008). Surveillance identified 42 602 cases. Overall disease incidence (per 100 000 population) declined from 9.9 cases prior to PCV immunisation to 4.4 in 2015, including a PCV13-serotype (additional six serotypes) IPD declined 75% (3.3 to 0.8, 95% CI: -78%, -72%), with a significant increase in nonvaccine-serotype IPD (2.5 to 3.0, +18%; 95% CI: +11%, +24%). Among children <2 years IPD rates declined from 57.4 to 12.3: PCV13-serotype IPD declined 93% (14.4 to 1.0; 95% CI: -95%, -89%). Non-vaccine serotypes increased significantly in the 45–64 year-old (+39%; 95% CI: +28%, +49%; [2.7 to 4.4) and >64 age groups (+56%; 95% CI: +38%, +69%; [2.0 to 4.6). PCV-serotype disease continues to decrease in children and adults in South Africa due to direct and indirect effects. Non-vaccine serotype disease increases were driven by increases in older adults.

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TEACHING AND TRAINING
CRDM staff lecture at the Universities of the Witwatersrand and Pretoria and are involved in registrar training, medical scientist intern training and technical training for other healthcare professionals. Specifically, A/Prof. Cohen co-ordinated the Infectious Diseases Epidemiology 1-week module at the Wits School of Public Health for MSc Epidemiology. CRDM senior staff are also involved in the teaching of undergraduate and supervision of postgraduate students from the Schools of Public Health and Pathology at Wits.

Professional development
Postgraduate students enrolled: 8 (6 PhD, 2 MSc)
Postgraduate student graduated: 3 (PhD, MSc, B. Tech)

Honours
Cheryl Cohen was awarded the MRC SA Silver Scientific Achievement Award in recognition of the excellence of her research.

RESEARCH OUTPUTS

Publications


Conference presentations

a. International: 22

b. National: 0

c. Local (research days): 6

World Pneumonia Day at CRDM
Centre for Tuberculosis
BACKGROUND

The year under review continued to see important progress for the Centre for Tuberculosis (CTB), in line with the mandate of the National Institute for Communicable Diseases and the Centre for Conducting Laboratory-based Public Health Surveillance of TB in South Africa and serving as a National TB Reference Laboratory (NTBRL) for South Africa, as well as a WHO supranational TB reference laboratory. Involvement in microbiology and epidemiology-oriented training programmes continued, and the CTB initiated applied public health research aimed at providing enhanced intelligence on the drivers and protective factors that underlie the TB epidemic in South Africa.

The period has been an exciting one for TB research in South Africa and for the CTB. It released the results of the largest drug resistance survey conducted globally, published a surveillance report that provided extensive analysis of trends in microbiologically-confirmed TB incidence rates across all parts of South Africa between 2004 and 2015, and concurrently launched an open access online TB surveillance dashboard. These significant developments came at an opportune time, as the country began the development of the new National TB Strategic Plan: 2017–2021, which emphasises a data-driven approach to TB efforts, which the centre will co-lead in the new five-year plans.

SURVEILLANCE AND DIAGNOSTIC SERVICES

The CTB has successfully integrated public health surveillance and reference laboratory functions to provide enhanced and strategic information to guide TB control activities for South Africa. National surveillance covers new cases of laboratory-confirmed TB, as well as new drug-resistant TB, including rifampicin-resistant (RR), multidrug-resistant (MDR) and extensively drug-resistant (XDR) cases identified by NHLS laboratories, which serve over 80% of the population. Surveillance findings are regularly analysed and reported to the National TB Programme (NTP) and now are visually presented using the online TB surveillance dashboard. Weekly alerts continue to be sent out, and with the planned introduction of a revised treatment initiation indicator, will further strengthen public health responses. Information on drug resistance prevalence determined through a national survey has been important in revising the approach to management of drug-resistant TB, and the use of newer technologies aimed at improving effective and early management of this public health problem.

Specialised molecular techniques for Mycobacterium tuberculosis have now been integrated into the surveillance system to better define drug resistance mutation profiles and clonal strains, using next generation sequencing (NGS), and have modernised approaches to molecular epidemiological tracking of TB transmission. Globally, the centre has played an important role in the development and standardisation of methods for drug resistance determination for new anti-mycobacterial agents.

Survey of drug resistance in TB – South Africa

The South African Tuberculosis Drug Resistance Survey (DRS), 2012–2014, was the largest TB DRS conducted globally, with over 200 000 persons screened. The prevalence of MDR-TB nationally was measured at 2.1% (95% CI: 1.5%–2.7%) in new cases and 4.6% (95% CI: 3.2%–6.0%) in retreatment cases with an overall MDR-TB estimate of 2.8% (95% CI: 2.0%–3.6%). Compared to the previous survey in 2001/02, the MDR-TB prevalence has remained relatively stable over the ten-year period, with the overall MDR-TB rate in the previous survey being 2.9% (95% CI: 2.4%–3.5%). Provincial MDR-TB prevalence varied, with six of the nine provinces showing MDR-TB rates below 2% among new cases in the current survey. The highest rate observed was in Mpumalanga, with an overall rate of 5.1% (95% CI: 3.7%–7.0%), including both new and previously treated cases, which was higher than the national rate (2.8%; 95% CI: 2.0%–3.6%). This is a particular concern requiring urgent intervention.

Contrasted to the MDR-TB prevalence nationally, the rate of any rifampicin resistance prevalence has increased since the previous survey, with the overall prevalence being 4.6% (95% CI: 
3.5%–5.7%) nationally in the current survey, compared with 3.4% (95% CI: 2.8%–3.9%) in the previous survey. The increase was primarily seen among new cases, almost doubling from 1.8% (95% CI: 1.3%–2.3%) to 3.4% (95% CI: 2.5%–4.3%), highlighting the likely role of transmission. The use of Xpert MTB/RIF as the primary diagnostic tool will be important to detect these cases with any RR early, together with rapid initiation of therapy to halt further transmission. Rifampicin mono-resistance (RMR), which showed a low prevalence in the previous survey, has emerged as a concern.

Second-line drug resistance prevalence among MDR-TB cases was evaluated for the first time in this survey, and findings are concerning. The prevalence of resistance to ethionamide and pyrazinamide, both used empirically in the treatment of MDR-TB, was found to be high at 44.7% (95% CI: 25.9%–63.6%) and 59.1% (95% CI: 49.0%–69.1%) respectively. This compromises the effectiveness of the standard MDR regimen and could lead to further selection of resistance to other drugs. Additionally, resistance levels to the key drug classes, fluoroquinolones and injectable agents, were both 13% (95% CI: 5%–21%), highlighting the relatively high frequency of pre-XDR cases among those with MDR confirmation, and the need to identify these cases early. Taking into consideration the high pre-existent levels of second-line drug resistance and the loss of one or both key drugs among pre-XDR and XDR cases, achieving improved outcomes is likely to require the use of a new regimen that incorporates newly-introduced drugs.

### Surveillance of microbiologically-confirmed TB in South Africa

The WHO’s END TB strategy has set two primary targets aimed at reducing incidence of TB and mortality significantly by 2035. Previously we published a study in the *Lancet Infectious Disease* journal outlining a trend analysis of microbiologically-confirmed pulmonary TB (mPTB) between 2004 and 2012 and showed a decline in mPTB incidence since 2008, which coincided with the upscaling of ART as a contributory factor. In 2015, the analysis was updated and the report was launched on World TB Day (24 March 2017). These latest findings provide further encouragement as the year-on-year declines in mPTB incidence rates have continued since 2012 and were -4.8%, -6% and -4.8% nationally for the years 2013–2015. Although this is half of what is required, it is better than the global average of 1.5%. The national achievements are a sum total of the efforts of the nine provinces in South Africa.

**Figure 5: Trends in mPTB incidence rates by province, South Africa: 2005–2015.**

KwaZulu-Natal, which carries the highest absolute burden in the country, has shown the greatest success in the recent past, with annual reductions of mPTB incidence rates in line with the END TB targets, namely -13.4%, -9.7% and -8.5% for 2013–2015. This trend was also observed in Limpopo, but with a much lower burden. Similarly encouraging has been the Free State, with successive improvement in its year-on-year reductions: -2.5% in 2013, -4.8% in 2014 and approaching the target in 2015 at -9.2%. Gauteng, North West and the Western Cape showed excellent reductions in the early years, but these slowed down in recent years. For the latter, the annual change was -0.8%, -1.3% and +1.8% for the period 2013–2015. The impact of the ART programme on reducing mPTB incidence is an important contributor; however this alone will not be enough. These provinces initiated ART programmes much earlier than other provinces and as a result have reaped...
those rewards in the earlier years, but more needs to be done. An outlier province was the Northern Cape. Although it carries a relatively low mPTB burden, by incidence it is one of the highest, and more concerning is the observed increase in the mPTB incidence rate. This will need to be investigated and is an example of an area where health systems and access are key elements impacting on success or failure.

A striking clue to the success and failure of the achieved reduction in incidence was observed by disaggregating by gender. Most of the declines observed across provinces and reflected nationally have been driven by successes achieved among females between 25–44 years of age, with a 33.6% reduction between 2008 and 2015 nationally. This links closely with the large emphasis of the HIV programme on this population, as well as the greater health-seeking behaviour in this population. In stark contrast, the reduction among males in the same age category was only 13.4% for the same period and in addition, this is the age group with the highest mPTB incidence. Specific strategies aimed at this population are urgently required if the SA is to reach the END TB targets. Public messaging targeting this population group and increasing access to this group through men’s health and wellness centres or days, as well as male role models will need to be used. Breaking through this barrier is likely to see even greater reductions than have been seen in the past, but will be more challenging.

Online TB surveillance dashboard

A major new development for the reporting period has been the launch of an online TB surveillance dashboard (Figure 7). This was launched by the Minister of Health on 24 March 2017 and is now available online (www.nicd.ac.za) as an open access tool that allows the tracking of the TB epidemic across time and space. The dashboard provides trend analyses of TB incidence over a moving 11-year period and can monitor the impact of activities on incidence rates, from national down to sub-district level, anywhere in South Africa. Additionally, the incidence trends are disaggregated by age and gender, which provides useful insights into the relative contribution of different population groups for targeted interventions. Most importantly, the dashboard provides hotspot maps that allow easy visualisation of areas of greatest concern at the click of a button. The distribution of TB is not homogenous in South Africa, and being able to easily see this will allow resources to be strategically placed to ensure the greatest impact with the least amount of resources. The dashboard provides a view of the incidence rate, which in the local context is a proxy for transmission; however, it also provides a view of the absolute burden of incident cases, which is valuable to operational planning as well. To foster greater trust with the public and ensure that the information reaches as wide an audience as possible to stimulate further efforts and research aimed at ending TB by 2035, there is open access to the dashboard and users can select the ‘guest login’ without requiring further approval. A restricted access dashboard with further functionality is also being made available for relevant programme managers that lead the TB response.

Provincial and district-wide rifampicin resistance alerts for public health action

The new National TB Strategic Plan 2017–2021 has identified an initial lack of follow-up as a major concern, and an important area that requires attention. These are cases that have been diagnosed with active TB and have not been started on treatment, which results in increased risk of mortality and further transmission. Weekly alerts providing a line listing of cases diagnosed with RRTB by the NHLS were introduced to address this concern and are emailed to the nine provincial and 52 district managers in each province for public health action. This has provided an important tool for case management in the health system and to support continued patient-tracing efforts by the respective teams in the field. To ensure that these alerts have the prerequisite effects, the current rifampicin-resistant TB treatment initiation rate indicator has been revised, and will now incorporate the alerts as part of the reporting. Additionally, attention is increasingly being placed on drug-susceptible TB and alerts will now be generated for these cases and integrated into the quality improvement intervention arm of the new strategic plan, which will allow responses to be activated and monitored at a facility level.

Surveillance for bedaquiline resistance

Bedaquiline (BDQ) is a di-arylquindoline antimycobacterial drug that specifically inhibits mycobacterial adenosine triphosphate synthase. It is the first new drug class with a novel mechanism of action. Since October 2014, Sirturo (bedaquiline, BDQ) from Janssen Pharmaceutica, has been registered in South Africa for use in HIV-negative or HIV-infected, ART-naïve patients that are 18 years or older, who have laboratory-confirmed MDR-TB. Surveillance for early detection of BDQ resistance is advised by the WHO and is incorporated into the South African policy framework, according to which all patients starting BDQ treatment will have samples tested at baseline, week 8, and week 24, using BDQ minimal inhibitory concentration (MIC) determination. Results from the first 280 patients under surveillance were included, and used to determine local epidemiological cut-offs for bedaquiline in South Africa. MICs against BDQ were determined on the three phenotypic methods: Mycobacteria Growth Indicator Tube (MGIT) 960, 7h11 agar proportion and broth microdilution. In addition, whole genome sequencing was performed to determine the relevance of putative genes associated with resistance. Findings have been shared with the WHO and will be used to inform global policy. Among BDQ naïve patients only two had a significantly high MIC, which is reassuring. The genetic basis of resistance at this stage has been difficult to determine, however some genes (e.g. \( Rv1979 \)) have been clearly shown not to be associated with resistance. Monitoring is ongoing for the emergence of resistance and mechanisms associated with resistance in the South African context.
Supporting NTBRLs and surveys in Africa – supra-national TB reference laboratory

The reference laboratory has had a busy year in supporting the introduction of the new line probe assay (LPAslt) that provides rapid identification of fluoroquinolone and second-line injectable drug resistance. This included validation of the method and ensuring that the selected regional centres were proficient in the methodology. In addition, we have been actively working with the NDoH and the MDR advisory committee in revising the new diagnostic algorithm for RR-TB and ensuring that there is good synergy between the diagnostic services and clinical services.

On the regional front, we have successfully completed the third round of external quality assessments of the 16 high-burden countries in Africa through the WHO African Region. Findings have shown consistent improvements in performance across many countries and show the impact of QA activities in the region. In addition, we are now key role players in the newly formed Global Laboratory Initiative – Africa (GLI-AFRO) Consortium that will oversee laboratory improvement initiatives in Africa. Last, the centre has continued to provide support to the reference laboratories in Malawi and Namibia and has also, on an ad-hoc basis, supported training staff from the Swaziland reference laboratory.

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

Outbreaks of drug-resistant TB have been reported in South Africa, but are usually identified late and often with an accompanied high mortality. An early warning surveillance system has been introduced where strain typing of all RR-TB cases is aimed at identifying areas of high risk transmission. This is being implemented at district level, with one district targeted per province. Although large clusters of transmission are not expected to be identified within at least two years of implementation, the surveillance programme has already produced early results.

A cluster of genetically-identical RR-TB cases were identified in one of the districts being monitored just after the first year, and were predominantly XDR-TB patients. An investigation was conducted in collaboration with the outbreak unit at NICD and the provincial and district representatives of the NDoH. As such investigations are complex due to the nature of TB, a social network component was included, as well as geospatial mapping of cases undertaken. The findings provided fascinating insight into the complex transmission patterns. Nosocomial transmission was not found to be a major contributor. Most of the transmission occurred in the community, primarily affecting multiple generations in individual households. Social links were more complex to ascertain, although geographically, the cases clustered in two main hotspots. The insight provided is expected to improve public health responses to curbing further transmission events in this area, and will hopefully assist in improving control efforts nationally.

RESEARCH PROJECTS

Preliminary analysis of the spatial distribution of microbiologically-confirmed tuberculosis in clinics in South Africa, 2015

Collaborators: A van Rie (University of Antwerp, Antwerp, Belgium), S Madhi (RMPRU, Wits, Johannesburg)

Incidence of TB is highly variable within districts and sub-districts in South Africa, but the administrative boundaries used in health statistics are arbitrary and thus not optimal for the design of geographically-targeted interventions. Clustering of individuals with mPTB has been described in many settings. However, national geospatial analysis of mPTB has not yet been conducted in South Africa. We aimed to characterise facility level mPTB caseload hotspots across public health facilities in South Africa. Incident cases of mPTB in 2015 were identified from the NHLS central data warehouse. A combination of direct linkages and probability matching were used to link facilities where samples were collected to a database containing the GPS co-ordinates of NDoH facilities. Clustering and hotspot analysis of clinic level mPTB caseloads in South Africa, including three metropolitan areas, was conducted using Global Moran’s I and Getis-Ord Gi* in ArcGIS (ESRI, v10.3). Almost all (298 616 of 307 764, 97%) mPTB cases in the 2015 NHLS database were linked to geolocated health facilities. There was strong evidence of global clustering (p<0.001, Global Moran’s I). Cluster analysis revealed mPTB caseload hotspots in and around all eight metropolitan municipalities, with two additional hotspots in Klerksdorp and Richards Bay. Possible coldspots were identified in Limpopo, KwaZulu-Natal and the Eastern Cape. In the Cape Town Metropolitan Municipality, a cluster of 24 (21%) clinics accounted for 44% of mPTB cases, whereas there was little evidence of a local cluster within eThekwini. The identified mPTB hotspots are likely a result of the higher populations in these areas. Coldspots could reflect lower TB case-finding rates. Further analysis incorporating facility catchment populations and TB case-finding rates is required to identify areas with high mPTB incidence rates and inform targeted interventions.
Implementing whole-genome sequencing (WGS) as a clinical decision-making tool

Collaborators: T Walker, D Crook (Nuffield Department of Medicine, University of Oxford, and John Radcliffe Hospital, Oxford) D Wilson (Wellcome Trust Centre for Human Genetics, University of Oxford)

Phenotypic drug susceptibility testing is slow, can be poorly reproducible, and is expensive for low income, high incidence settings. WGS can accurately identify single nucleotide polymorphisms (SNPs) with the promise of ‘field technology’ within five years. Common drug resistance mutations are known, but a more complete catalogue is required before WGS can replace phenotyping. A total of 2 153 clinical Mtb isolates from the UK, Sierra Leone and South Africa were sequenced on Illumina platforms. Reads were mapped to the H37Rv reference genome and a minimum 88% of the genome called. Phenotypes were performed for clinical use through WHO-accredited methods. Excluding clade defining SNPs, all non-synonymous SNPs within 23 genes previously linked to drug resistance were identified. Each time a solitary SNP was seen within a subset of genes relevant to a resistant phenotype, that SNP was defined as ‘resistant’. All isolates containing the SNP were then counted as genotypically resistant. Also, SNPs from across the whole genome were assessed for homoplasy to screen for resistance-associated loci. 1920/2153 (89%) isolates had phenotypic data available, and all isolates were used to calculate homoplasy. In total, 340 (18%) isolates were resistant to ≥1 drugs and 94 (4.5%) were MDR. Furthermore, 81% of sensitive and 4.7% of resistant phenotypes had no SNPs in the relevant gene subset, whereas 13.3% of sensitive and 72.5% of resistant phenotypes had one SNP only. We defined 111 resistant SNPs, predicting resistance across all isolates with a mean sensitivity and specificity of 93.3% and 98.7%. In total, 66% of resistant SNPs were known to the literature and 44% were homoplastic, 3.3% of other SNPs within the 23 genes and 1.9% of SNPs elsewhere in the genome were homoplastic. Outside the 23 genes, only 3.2% of homoplastic SNPs were associated with resistance, and none significantly. Our heuristic approach identifies known and novel SNPs that accurately predict resistance. WGS is rapidly becoming a promising tool that will soon be adopted by several European countries as routine. This approach can be applied iteratively to new data, contributing to a comprehensive catalogue of resistance SNPs.

Field evaluation of a novel preservation medium to transport sputum specimens for molecular detection of *Mycobacterium tuberculosis* in a rural African setting

Collaborators: R Peters (Anova Health Institute, Johannesburg), PB Fourie (University of Pretoria)

This project assessed the performance of an innovative method of transporting sputum to centralised facilities for molecular detection of *Mycobacterium tuberculosis*, using a swab to inoculate sputum in a transport medium, PrimeStore molecular transport medium (PS-MTM). Two sputum specimens were obtained from suspected patients with TB at rural healthcare facilities in South Africa. A swab was taken from each specimen and placed into PS-MTM, prior to it being processed by either liquid culture or Xpert MTB/RIF assay (Xpert). 141 patients (including 47 with laboratory-confirmed TB) were included in this analysis. *M. tuberculosis* was detected at 29% by culture and 29% by Xpert, whereas 31% tested positive by IS6110 real-time PCR of PS-MTM from the culture and 36% from the Xpert-paired specimen. Concordance between the method under evaluation with culture was 82% (McNemar, p = 0.55) and 84% (McNemar, p = 0.05) for Xpert. Stratified by culture result, the detection rate by IS6110 real-time PCR of PS-MTM was similar to Xpert for patients with positive culture (p = 0.32), but significantly higher if culture was negative (p = 0.008). These results suggest that swab collection of sputum into PS-MTM for transport is a promising method for diagnosis of TB in rural healthcare settings, thereby potentially improving the options available for molecular diagnosis of TB in countries incapable of applying decentralised high-tech molecular testing. (Tropical Medicine & International Health 2016; 21(6), doi: 10.1111/tmi.12701)

A multicenter non-inferiority evaluation of Hain GenoType MTBDRplus Version 2 and Nipro NTM+MDRTB line probe assays for the diagnosis of rifampin and isoniazid resistance

Collaborators: D Hilleman (National Reference Laboratory for Mycobacteria, Forschungszentrum Barstel, Barstel, Germany), C Boehme (FIND, Geneva, Switzerland)

Due to laboratory constraints, less than 30% of MDR-TB patients are currently diagnosed. Molecular diagnostics enable rapid and simplified diagnosis. Newer-version line probe assays have not been evaluated against the WHO-endorsed Hain GenoType MTBDRplus (referred to as Hain version 1 [V1]) for the rapid detection of RIF and isoniazid (INH) resistance. A two-phase non-inferiority study was conducted in two supranational reference laboratories to allow head-to-head comparisons of two new tests, Hain Genotype MTBDR plus version 2 (referred to as Hain version 2 [V2]) and Nipro NTM+MDRTB detection kit 2 (referred to as Nipro), to Hain V1. In phase 1, the results for 379 test strains were compared to a composite reference standard that used phenotypic drug susceptibility testing (DST) and targeted sequencing. In phase 2, the results for 644 sputum samples were compared to a phenotypic DST reference standard alone. Using a challenging set of strains in phase 1, the values for sensitivity and specificity for Hain V1, Hain V2, and Nipro, respectively, were 90.3%/98.5%, 90.3%/98.5%, and 92.0%/98.5% for RIF resistance detection and 89.1%/99.4%, 89.1%/99.4%, and 89.6%/100.0% for INH resistance detection. Testing of sputa in phase 2 yielded values for sensitivity and specificity of 97.1%/97.1%, 98.2%/97.8%, and 96.5%/97.5% for RIF and 94.4%/96.4%, 95.4%/98.8%, and 94.9%/97.6% for INH. Overall, the rates of indeterminate results were low, but there was a higher rate of indeterminate
results with Nipro than with Hain V1 and V2 in samples with low smear grades. Non-inferiority of Hain V2 and Nipro to Hain V1 was demonstrated for RIF- and INH-resistance detection in isolates and sputum specimens. These results have resulted in an updated WHO policy recommendation on the use of line probe assays, including the Hain V2 and Nipro assays, for MDR-TB detection. (Journal of Clinical Microbiology 2016; 54(6). doi:10.1128/JCM.00251-16)

Identifying lineage effects when controlling for population structure improves power in bacterial association studies

Collaborators: DCrook (Nuffield Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford), DWilson (Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford)

Bacteria pose unique challenges for genome-wide association studies because of strong structuring into distinct strains and substantial linkage disequilibrium across the genome. Although methods developed for human studies can correct for strain structure, this risks considerable loss-of-power because genetic differences between strains often contribute substantial phenotypic variability. Here, we propose a new method that captures lineage-level associations, even when locus-specific associations cannot be fine-mapped. We demonstrate its ability to detect genes and genetic variants underlying resistance to 17 antimicrobials in 3 144 isolates from four taxonomically diverse clonal and recombinating bacteria: Mycobacterium tuberculosis, Staphylococcus aureus, Escherichia coli and Klebsiella pneumoniae. Strong selection, recombination and penetration confer high power to recover known antimicrobial resistance mechanisms and reveal a candidate association between the outer membrane porin rmpC and cefazolin resistance in *E. coli*. Hence, our method pinpoints locus-specific effects, where possible, and boosts power by detecting lineage-level differences when fine-mapping is intractable. (Nature Microbiology 2016; 1: 16041. doi:10.1038/nmicrobiol.2016.41)

ACKNOWLEDGEMENTS

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TEACHING AND TRAINING

Training accommodating experiential and didactic learning was provided on site in Malawi at their second and newly-established TB reference laboratory. Additionally, CTB provided instruction in a train-the-trainer course for NTP/national reference laboratory managers with participants from SADC countries. 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, training on Xpert MTB/RIF, LPA and WGS was conducted at an international skills-building workshop, with participants from Africa, Europe and Asia.

Professional development

Postgraduate students enrolled: 9 (5 PhD, 3 MSc, 1 MPH).

Postgraduate students graduated: 1 (MPH).

Honours

The MRC UK/SA Newton Grant for Implementation Science was awarded to S Madhi and N Ismail.

RESEARCH OUTPUT

Publications


Conference presentations

a. International: 8

b. National: 1
BACKGROUND

The Centre for Vaccines and Immunology comprises the national and WHO regional referral laboratories for acute flaccid paralysis and measles surveillance. The centre provides epidemiological, virological and immunological support to the NDoH for vaccine preventable diseases, and conducts research projects on viral hepatitis and rubella.

The centre was established in 2012 by merging the existing polio and measles laboratories. It forms an integral part of the Global Polio Laboratory Network and the Global Measles Laboratory Network, and is the only laboratory in South Africa, and one of only a handful of reference laboratories world-wide, that process samples containing wild type polio virus, and is the only sequencing polio laboratory in Africa.

SURVEILLANCE AND DIAGNOSTIC SERVICES

National polio surveillance

The Acute Flaccid Paralysis (AFP) Laboratory serves as a national reference laboratory for poliovirus isolation as part of the Global Polio Eradication Initiative (GPEI). The laboratory serves seven countries within the southern African region in this capacity, namely Angola, Botswana, Lesotho, Mozambique, Namibia, Swaziland and South Africa. WHO protocols are strictly followed to ensure standardisation of methods globally. Samples are inoculated into cell cultures and any sample with suggestive poliovirus cytopathic effects is subjected to molecular typing and characterisation to confirm poliovirus serotype and differentiate poliovirus intratype. During the reporting period, 2,905 samples were processed.

Data are shared on a weekly basis with the WHO and NDoH, and specific cases are subjected to classification by the National Polio Expert Committee based on history, clinical notes and laboratory findings. The centre also provides expertise to the National Task Force and National Certification Committees for polio containment in all laboratories nationally. The case-based acute flaccid paralysis detection rate for 2016 was 3.0/100,000 children under five years.

Regional polio surveillance

The centre serves as a regional reference laboratory for poliovirus identification and characterisation for the WHO African Region. In April 2016, a global switch was implemented from trivalent oral polio vaccine to bivalent oral polio vaccine, as wild poliovirus type 2 was certified globally eradicated in September 2015. Following this declaration, any isolation of type 2 polioviruses are events of global significance.

The laboratory confirmed a vaccine-derived poliovirus (VDPV) type 2 case from Mozambique, with 30 November 2016 as the date of onset of paralysis. Classification of this case resulted in vaccination campaigns with monovalent oral polio vaccine type 2 (mOPV2), released from the global stockpile. Additional to the Mozambique VDPV, three VDPV type 2 viruses were detected by our laboratory during this period; two from the Democratic Republic of Congo and one from Somalia, with dates of onset of paralysis prior to the vaccine switch in April 2016.

To continue to support the WHO and our surrounding countries as a regional reference laboratory, the NICD applied to the NDoH to host a Polio Essential Facility (PEF). This PEF will enable the NICD to work with poliovirus type 2 under high containment following global certification of eradication and the vaccine switch. Operation in the proposed PEF began in 2016, and the application was approved by NDoH in March 2017. A subsequent application has been made to the WHO, with the outcome pending. Structural requirements for the PEF have all been met, and a regulatory body will be implemented by the NDoH to oversee and certify the PEF following all approvals.
National measles surveillance

The Centre for Vaccines and Immunology is the national reference laboratory for measles surveillance. In support of the global measles elimination initiative, which has an African measles elimination goal of 2020, the centre provides serological and molecular testing for measles virus. Serology, specifically the detection of measles-specific IgM antibodies, and molecular methods (RT-PCR and genotyping) are used in conjunction with epidemiologic case investigations in the diagnosis of acute measles infection.

During the reporting period, 3,300 samples were tested; 71 tested positive either for measles IgM or for measles virus RNA. These cases related to a confirmed measles outbreak in the Western Cape in January 2017, currently with 29 positive cases. Identical sequences of a genotype D8 measles virus were detected in this outbreak. There have been ten confirmed cases in Gauteng in an unrelated outbreak, as well as a single case from North West, mostly affecting primary schoolchildren previously unvaccinated against measles. A slightly different strain of genotype D8 measles virus was detected in the cases in Gauteng and North West, representing separate importation events not linked to the Western Cape cases. All samples submitted for measles testing were also tested for rubella infection. There were 988 rubella IgM positive cases identified for the review period (29.9%).

Measles and Rubella Regional Reference Laboratory

As part of the WHO regional quality assurance programme, the centre retests approximately 10% of serum samples from nine southern African countries, namely Botswana, Lesotho, Madagascar, Malawi, Mozambique, Namibia, Swaziland, Zambia and Zimbabwe. A total of 442 samples was received, of which 3 (0.7%) were measles IgM positive and 43 (9.7%) were rubella IgM positive. There was generally good concordance for the measles IgM results (90–100%) with slightly poorer concordance for rubella IgM results (70–100%).

Viral hepatitis testing

Serological testing for hepatitis B was accredited by SANAS in February 2017. This testing will support surveillance for hepatitis B prevalence, as well as occupational testing for laboratory staff.

RESEARCH AND SPECIAL PROJECTS

Congenital rubella syndrome surveillance (CRS)

The centre established a sentinel site surveillance programme for CRS in 2015. The aim is to obtain baseline data on the burden of CRS in South Africa prior to the introduction of the rubella vaccine in the National Expanded Programme for Immunisation, and to monitor the impact of the vaccine thereafter. There are 29 study sites across the nine provinces of South Africa. During the reporting period, there were seven laboratory-confirmed CRS cases from six sentinel sites.

Environmental polio surveillance

The centre provides an environmental surveillance service to four sites in Angola in support of GPEI. From 1 April 2016 to 31 March 2017, 48 samples were received from Angola. There were three Sabin-like poliovirus type 3 isolated from one site and 39 non-polio enteroviruses isolated from all four sites.

The Regional Reference Laboratory received 86 samples that were referred to NICD. Of these, 43 were non-polio enterovirus and 40 were poliovirus positive for Sabin vaccine strains type 1, 2 or 3, the latter from Niger, Cameroon, Senegal and Madagascar.

Pertussis serology

Several ELISA pertussis anti-toxin IgG test formats were evaluated and validated by testing a panel of specimens provided by a reference laboratory (CDC, Atlanta). The results of this inter-laboratory comparison compared very well and we are therefore able to perform pertussis anti-toxin IgG testing to assist with confirmation of cases.
TEACHING AND TRAINING

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

A group of virology registrars was trained in polio, measles and hepatitis on 24–25 May 2016.

Two delegates from Uganda and Zambia attended training on the intratypic differential PCR for polioviruses in June 2016.

Mrs M Mashele conducted on-site training of laboratory staff in measles and rubella serology and quality assurance procedures in Mauritius to support the establishment of a national measles/rubella laboratory. This training took place on 6–10 June 2016 at the request of the WHO.

Dr N Prabdial-Sing was invited to speak at a World Hepatitis Day event held on 28 July 2016 at Kgapanne Hospital, Limpopo.

The centre hosted an ITD and VDPV version 5.0 training course on 10–14 October 2016 and again on 14–18 November 2016 at NICD.

Various centre staff attended national and international meetings and workshops, including the 19th Inter-Country Certification Committee (ICCC) meeting from 14–15 June 2016 in Johannesburg, a sequencing training workshop in Morocco from 31 October–04 November 2016; the Multi-Regional GAPIII Implementation and Certification Training Workshop in Bangkok, Thailand from 24–28 October 2016; basic phylogenetic training in Pretoria from 1–4 November 2016; and advanced phylogenetic training in Pretoria from 7–11 Nov 2016.

Professional development

Postgraduate students enrolled: 5 (5 MSc, 2 PhD).

Postgraduate students graduated: 4 (2 MSc, 1 MTech, 1 BSc (Hons)).

RESEARCH OUTPUT

Publications

Journal articles


Book


Book chapter


Conference presentations

a. International: 1

b. National: 1
BACKGROUND

The Public Health Surveillance and Response Division includes the Outbreak Response Unit, the Epidemiology Support Unit, the GERMS-SA surveillance programme, Travel Health, and the Communications Unit. It provides evidence-based epidemiological and public health expertise and guidance to national and provincial government health departments through support for surveillance and epidemiological activities, and outbreak response. Additionally, the division supports other NICD units through collaborative surveillance projects. It facilitates communication and data sharing between the national and provincial health departments, the various centres within the NICD and the public.

During the past year, the division continued to expand significantly and now includes a Data Management Unit and an Emergency Operations Centre (EOC) to respond to public health emergencies. The provincial epidemiology team aimed to increase the footprint of the NICD within the provinces to facilitate timely provision of relevant epidemiological data. Presently, the Epidemiology Support Unit has an epidemiologist in seven provinces. Under a directive from the NDoH, the Epidemiology Support Unit is leading the development of an integrated Notifiable Medical Conditions (NCM) national surveillance system that builds on existing resources to provide a co-ordinated approach to the collection, collation, analysis, interpretation and dissemination of public and private sector NMCs in South Africa. Significant progress has been made, including the development, approval and commencement of the implementation of a national surveillance strategy.

The expansion of the GERMS-SA programme for surveillance for a number of priority conditions in rural and urban clinics in the provinces has continued, supported by a network of NICD-appointed epidemiologists. The Mass Gatherings Centre, as part of the WHO Mass Gathering Global Network, has supported research and operational activities in communicable disease monitoring and risk assessments for mass gatherings in the region and is currently in the process of being appointed as a WHO collaborating centre. The South African National Travel Health Network (SaNTHNet), established together with the NDoH and 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 the medical sector, allied professionals and the public, through extensive interaction with the media around a number of outbreaks, including leptospirosis, malaria, Zika, Ebola, diphtheria and rabies.

The division also took responsibility for submission of the application for ethics clearance for routine surveillance and outbreak investigation activities to the University of the Witwatersrand Human Research Ethics Committee. This was approved on 24 June 2017 and is valid until 2020.

SURVEILLANCE/DIAGNOSTIC SERVICES

GERMS-SA

The GERMS-SA laboratory-based surveillance programme for diseases of public health importance is co-ordinated by a core team within the division and spans most of the centres at the NICD. The laboratory surveillance pathogens routinely include: Candida spp, Salmonella Typhi, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus, carbapenem-resistant Enterobacteriaceae (CRE), and Cryptococcus spp. and for outbreak-related Salmonella non-Typhi, Shigella spp, Vibrio cholerae, Campylobacter spp, Enterohaemorrhagic E.coli, Diantheraogenic E.coli. 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 that meet the case definition are included in the database. Annually, approximately 50 laboratories that do cultures on cerebrospinal fluid and blood send specimens (from both the private and public sector). However, the drainage for our surveillance specimens includes all ~150 NHLS microbiology laboratories as there is a set referral system for the flow of microbiology cultures. These laboratories report roughly 18 500 cases meeting the GERMS-SA case definitions. The enhanced surveillance arm is operational at 25 sentinel public sector sites across the country, where nurse surveillance
officers collect clinical information on patients relating to specific pathogens, namely invasive *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, *Salmonella* Typhi, *S. aureus*, CREs and *Candida* spp bacteraemia, *Cryptococcus* spp, and RR-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 SA on HIV-associated opportunistic infections; and evaluating the impact of vaccines included in the Expanded Programme on Immunisation (EPI). The Laboratory Antimicrobial Resistance Project was set up to establish a functional, integrated, antimicrobial resistance surveillance system for common, nosocomial, bacterial pathogens. The work carried out by the GERMS-SA team has significantly contributed to the development of clinical guidelines for pneumonia, meningococcal disease, cholera, cryptococcosis and typhoid fever; 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 GERMS-SA activities have also contributed to the DoH rollout 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 essential that surveillance continues to monitor the burden of *S. pneumoniae* and *H. influenzae*. Cryptococcus spp surveillance will help to monitor the CrAg screen and treatment programme. GERMS-SA’s work is funded through the NICD/DoH.

**Expansion of the GERMS platform: Xpert MTB/RIF**

Xpert MTB/RIF, a rapid diagnostic test that detects both *Mycobacterium tuberculosis* and resistance to rifampicin, has been implemented in all NHLS laboratories nationally and has become the initial diagnostic test for all suspected TB cases in South Africa. In response to this implementation, enhanced surveillance for Xpert RR-TB was initiated at Chris-Hani Baragwanath Academic Hospital and selected surrounding clinics in late October 2012, and has subsequently been introduced in seven other provinces. This surveillance will monitor trends over time, estimate the proportion of MDR-TB among RR-TB cases and the burden of resistance to other TB drugs, and provide information on risk factors, including close contact, previous TB treatment and HIV status. Surveillance was initiated in the Free State during 2016.

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

GERMS-SA recently expanded to include clinic-based surveillance. Eight sites have been initiated to date in the North West, Mpumalanga, Eastern Cape, KwaZulu-Natal, Gauteng and Free State. Clinic-based surveillance includes TB and HIV surveillance to describe the epidemiology of drug resistance among HIV-infected persons initiating ART and/or TB treatment at the selected sites, as well as undertake STI surveillance. The STI component includes surveillance of STI syndrome aetiologies, gonococcal antimicrobial resistance and HPV genotypes among patients attending the clinic’s STI surveillance will be initiated in the Western Cape later in 2017.

Building on the zoonotic diseases study, funded by the Swedish Civil Contingencies Agency, the Swedish International Development Cooperation Agency and the Global Disease Detection Programme in 2012–2014, the Acute Febrile Illness Surveillance Project continues to be 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 and takes place in collaboration with veterinary practitioners and researchers from the University of Pretoria Veterinary Faculty. The aim is to describe the prevalence of zoonotic infections in adult patients presenting with acute febrile illness and for whom the clinic sisters would do a malaria test. Laboratory testing includes PCR and serology for brucellosis, bartonella infections, leptospirosis, Q-fever, tick bite fever, West Nile virus, Sindbis, Rift Valley fever and chikungunya virus infections. Study data published show a high seroprevalence of tick bite fever, Q-fever and leptospirosis in parallel with significant exposures at the human/animal interface.

**Surveillance of notifiable medical conditions (NMCs)**

Following the resurgence of fatal epidemics in recent years, the Global Health Security Agenda was launched to enhance global capacities to prevent, detect, and rapidly respond to infectious diseases in line with International Health Regulation (IHR) requirements. To help achieve the set national public health surveillance goals in South Africa, the NDoH in 2015 directed the NICD to develop an integrated NMC national surveillance system that builds on existing resources to provide a co-ordinated approach to the collection, collation, analysis, interpretation and dissemination of public and private sector NMCs in South Africa. Additionally, the NICD is building the required field epidemiology and analytical capacity in the public health service to maximise the utility of NMC surveillance. Following in-depth consultations with national, provincial and local DoH and relevant key stakeholders, a national surveillance strategy was developed and adopted. The initial phase of the implementation strategy, which involved facility and district level assessments to determine the deficiencies of the current NMC clinical and laboratory surveillance systems and identify best practice with regards to policies, guidelines, systems and tools, processes, infrastructure and human resource capacity, was conducted between March and June 2016. A total of 71 health facilities ranging from tertiary hospitals to PHCs were utilised, resulting in 276 interviews with mainly nurses and doctors. Key findings highlighted the need for:
• Updated NMC-related regulations and guidelines
• Standardised and up-to-date notification processes and systems with built-in continuous in-service training of all surveillance system users
• A detailed NMC-related module within the academic training curriculum for nurses and doctors
• Integration of the private sector and other key stakeholders.

Efforts are underway to address these gaps and implement a functional real-time surveillance system for NMC.

Guided by the results of the national assessments, a new surveillance system has been developed with two notification streams, namely the laboratory and clinical-based notification streams. Data from both streams are merged and stored in a central database that is accessible to all users with different access levels and stringent privacy and confidentiality protocols for protection of patient information. All supporting and guiding documents have been developed, including a new and easy-to-use case notification form. The new surveillance system was piloted in Gauteng between October 2016 and March 2017, and full implementation is scheduled for June 2017. National rollout is expected to be completed by March 2018.

PROVINCIAL EPIDEMIOLOGY TEAM (PET)

Epidemiology is a rare skill in South Africa, but one that is critically needed at provincial and local levels to ensure efficient and real-time data analysis, the results of which are used to direct public health activities, resource allocation and policy decisions at regional and local levels. To address this deficiency, the NICD has deployed provincial epidemiologists since 2014 to each of the nine provinces. The aim of this service, integral to the NICD’s functions, is to ensure that the NICD’s core services of surveillance, outbreak response, specialist microbiology and public health research are available at the local level in a timely, flexible and rapid manner. The team in managed centrally by a senior epidemiologist at the NICD Sandringham campus. Currently the team has an epidemiologist in each province except for Mpumalanga, KwaZulu-Natal and the Northern Cape where efforts are underway to fill these vacancies. Based on the successes achieved over the past three years in providing epidemiology support and strengthening health service delivery, additional epidemiologists have been placed at the district DoH to provide district-level support in the Eastern Cape and Limpopo. Through the PET, the NICD is better able to understand the diverse needs of each province, enabling relevant and timely communication between the NICD and local DoHs and deployment of required information, guidance and expertise. The provincial epidemiologists also assist in the implementation of the NICD’s clinic-based surveillance programmes.

To date, provincial epidemiologists played a pivotal role in strengthening surveillance of infectious diseases, through routine analyses of surveillance data to identify and address any deficiencies in data collection and collation. The results are used to assist disease programme managers in identifying and implementing interventions to improve programme performance within the set national, provincial and district strategic plans. Of note is their role in supporting the implementation of the new notifiable medical conditions surveillance system that will ensure efficient and real-time reporting of infectious diseases that are of public health importance to enable rapid outbreak investigation and response.

The provincial epidemiology team is instrumental in supporting outbreak response and forms part of the provincial outbreak response teams. In their respective provinces, provincial epidemiologists played a crucial role in case investigation, contact tracing and monitoring, case mapping and the establishment of epidemiologic links and use of these data to contain transmission and direct vaccination efforts during the measles outbreaks in the Western Cape and Gauteng, the malaria outbreak in the North West, the polio case in Limpopo and several food-borne outbreaks across all provinces.

Significant milestones have been achieved in supporting the TB directorate to achieve the national 90-90-90 strategy. The PET, in collaboration with the relevant stakeholders and partners, co-ordinates data collation and integration to facilitate linking patients diagnosed via GeneXpert to care. Laboratory-based alerts of all diagnosed RR-TB patients are sent weekly to the provincial teams, including the respective provincial epidemiologist who ensures that the alerts are distributed to local levels to facilitate rapid patient tracing and timely treatment initiation. Additionally, TB programme provincial data from patient records are consolidated with laboratory-based diagnosis data to identify gaps between patient diagnosis and initiation onto TB therapy. Furthermore, results from epidemiological analyses of these data are utilised in identifying TB hotspots and high-risk groups, and direct resource allocation and interventions to curb TB transmission. In the Eastern Cape, the provincial epidemiologist has developed a quarterly TB bulletin that highlights TB burden and TB programme performance and this will be rolled out to all provinces in 2017.

SOUTH AFRICAN FIELD EPIDEMIOLOGY TRAINING PROGRAMME (SAFETP)

SAFETP celebrated its 10th anniversary since its development. The programme was developed as a vehicle to build field epidemiology in collaboration with the NDoH, the NICD and the USA CDC. The programme achieved a significant milestone in April 2016 with it being
fully funded by the NICD. The CDC continued to support the costs of technical assistance. To date, the programme has trained more than 80 health professionals in field epidemiology, 88.3% of whom remain employed in the public service in South Africa. Six graduates were appointed at the NICD in roles as either provincial or centre epidemiologists.

In 2016, FETP had an intake cohort of seven first and ten second-year students; this was the largest number of residents in a cohort. Another milestone saw ten residents graduating with an MPH – this was the highest number of graduates in a year, with a graduation attainment rate of 85%.

The team continues to work with NDoH in having epidemiology recognised as a professional discipline in the Human Resource for Health Strategy and are defining the epidemiology core competencies required for current health staff in the NDoH.

The FETP team has assisted in regional outbreak investigations: Dr Timothy Doyle provided epidemiological support for the yellow fever outbreak in Luanda, Angola in 2016, and the team was invited to conduct the investigation of a cluster of eight cases of paediatric hydrocephalus that was identified Lesotho during 2016.

Residents participated in more than 26 outbreak investigations, conducted 12 large database analyses and produced the following dissertations as part of their core learning activities:

5. Knowledge, attitude and practices regarding the transmission of malaria in Mamfene, Jozini, KwaZulu-Natal, 2015.
9. Knowledge, attitudes and practices of healthcare professionals and caregivers regarding immunisation of children 0 to 72 months, Johannesburg, 2015.

**NICD DATA/INFORMATION CENTRE**

Work continues within the NICD Data/Information Centre, which aims to centralise the management of data generated within the NICD, provide technical support/expertise for GIS and provide a data repository for the NICD, including disease-specific dashboards. Efforts are continuing to build the team required and to align the goals of the data centre with those of the DoH’s Information Management Directorate.

**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 DoHs and other stakeholders, and together with systems for early detection and improved reporting of epidemic-prone communicable diseases, the ORU functions as a source of technical expertise for outbreak detection, investigation and response activities. The Outbreak Response Unit facilitates interaction between the NHLS diagnostic laboratories and NICD centres, and the provincial and district communicable disease structures to provide appropriate laboratory diagnostic services during outbreaks and when specialised diagnostic testing as required. The unit is also kept abreast of international developments in outbreaks and outbreak preparedness through representation on key WHO advisory committees and international interest groups. Representatives from the unit attend the monthly Multisectoral National Outbreak Response meeting, and report on surveillance and outbreak investigation activities.

The Outbreak Response Unit co-ordinates the provision of the 24-hour emergency hotline, which is staffed on a rotational basis by pathologists and medically qualified staff of the NICD. The hotline serves as a resource for public and private sector healthcare workers for emergency information pertaining to the post-exposure management of rabies and other infectious disease, requests and advice for diagnostic tests for suspected epidemic-prone disease and technical advice regarding the management of cases of infectious disease.

The ORU continues to publish its monthly *Communicable Diseases Communiqué*, which reports recent outbreaks and communicable disease cases/issues of relevance. This is distributed to a wide audience, including general practitioners, specialists, infectious diseases and travel medicine societies, and national and provincial public health personnel. In addition, the unit published special urgent advisories and communiqués in response to acute events requiring immediate dissemination of information.
During the reporting period, 1,211 outbreak verification calls were attended to by ORU directly or through the NICD hotline, 97% of which were responded to within 24 hours. Figure 8 represents the number of calls per category, indicating that enquiries regarding the management of rabies post-exposure prophylaxis followed by investigation of persons with suspected infectious disease account for over 60% of calls. The majority of calls to the ORU originated from Gauteng, followed by KwaZulu-Natal and the Western Cape (Figure 9).

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

1. Investigation of a cluster of genotypically identical drug-resistant TB cases in Nelson Mandela Bay, 24–26 May 2016
2. Investigation of suspected nosocomial cases of legionellosis at two academic hospitals (Western Cape and Gauteng) in April and May 2016
3. Investigation of a suspected *Klebsiella pneumoniae* outbreak at a district hospital in Mpumalanga, June 2016
4. Investigation of an influenza outbreak at a school in Grahamstown, July 2016
5. Investigation of a suspected hepatitis B outbreak at an institution of mentally impaired persons, Gauteng, October 2016
6. Investigation of Leptospirosis cases from Tshwane, November 2016
7. Investigation of a case of brucellosis in Mpumalanga, November 2016
Investigation of a cluster of *Listeria monocytogenes* cases in Johannesburg, December 2016

Investigation of typhoid fever cases in the Western Cape and Gauteng, 2015–2016

Investigation and management of measles cases in the Western Cape and Gauteng, January–March 2017.

EMERGENCY OPERATIONS CENTRE

During the financial year, the infrastructural, policy and management framework for the Public Health Emergency Operations Centre of the NICD was developed and implemented. IT systems, including a call centre, wifi, servers, independent internet connectivity and contractual arrangements with a service provider were set up. Standard operating procedures regarding the Incident Management System (IMS) were developed. NICD staff were familiarised with the principles of the IMS through presentations and paper-based simulation exercises regarding the activation and implementation of the project-planning cycle. A paper-based, discursive simulation to familiarise the Multi-Sectoral National Outbreak Response Team with the IMS was conducted. Mr N Govender, the centre manager, attended the Working Group Meeting on Public Health Emergency Operations Centres from 17–19 October 2016 and the EOC-NET Annual Meeting 20–21 October 2016, in Geneva, Switzerland and contributed to the editing and revision of the EOC-NET Handbook on Training and Exercises. In addition, Mr Govender participated in the WHO International Health Regulations Joint External Evaluation in Liberia 5–9 September 2016 on behalf of the NDoH. On 27 February 2017, the EOC was activated by the Director-General of the NDoH for a non-public health emergency to facilitate relocations of former Life Esidimeni mental healthcare users (patients, MHCU) from non-governmental organisations to appropriate care facilities identified by the GDoH. A project management team, drawn from NICD EOC, NDoH and GDoH staff, used the EOC IMS to plan and execute the safe, humane and compassionate relocation of 751 MHCU within 38 working days. This first activation of the EOC provided an opportunity to apply and review the policies and procedures.

RESEARCH AND SPECIAL PROJECTS

**Representation on committees and advisory groups**

Prof. Blumberg serves on the:

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

TRAVEL HEALTH

This unit provides a consultative service for health practitioners regarding pre-travel advice for travellers and clinical consultations for returning travellers with suspected infectious diseases; develops guidelines for a number of travel-related diseases and neglected diseases; serves as a point of contact and liaison internationally for infectious diseases acquired in southern Africa, and assists with the training of travel health practitioners and those studying tropical diseases. There is a focus on zoonotic diseases and emerging pathogens through the One-Health approach brought about by the interactions between animal and human health and the environment. The unit was recently accepted as a Geosentinal Programme member. This programme includes 64 global sites that monitor imported infectious diseases in business and leisure travellers, as well as migrants and displaced persons.

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

SaNTHNet is a travel health network run by the DoH, the NICD and the South African Society of Travel Medicine (SASTM). SaNTHNet provides up-to-date information on health risks for travel in the southern African region, with a primary South African focus by developing and providing guidelines on communicable diseases and up-to-date information on disease outbreaks. An informative website has been developed, which attracts over 5 000 visits a month, a significant number of which are of international origin. The network will focus on developing further guidelines around travel-related health matters and will serve as a surveillance platform to gather information around imported communicable diseases, e.g. dengue, trypanosomiasis and leishmaniasis, as well as expert advice on diagnosis and management of tropical and travel-related diseases. The unit also manages a supply of essential drugs for a selection of tropical and neglected diseases, e.g. leishmaniasis, trypanosomiasis and severe malaria.
Following the communicable disease surveillance and risk assessment for the 2010 FIFA World Cup, the DPHSR has now become part of the WHO Mass Gatherings Collaborating Centre Network, which includes the Disaster Research Centre, Flinders University, Australia; Public Health England, United Kingdom; NICD, South Africa; Institute of Public Health of Vojvodina, Serbia; School of Public Health, University of Washington, United States of America; Ministry of Health, Saudi Arabia.

TEACHING AND TRAINING

Staff delivered lectures for training activities related to communicable diseases for the national and provincial DoHs to under- and postgraduate students of the University of the Witwatersrand (School of Public Health, Departments of Medicine, Obstetrics and Gynaecology, Community and Family Medicine, Diploma in Tropical Medicine and Hygiene), University of Pretoria, Onderstepoort Veterinary Institute, North-West University (School of Pharmacology) and Stellenbosch University (Department of Medicine).

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

Professional development

Dr Kerrigan McCarthy is registered for a PhD at the University of the Witwatersrand, School of Public Health.

One MSc.

Honours

Prof Lucille Blumberg delivered the Arnold Theiler Memorial Lecture at the Faculty Day of the Faculty of Veterinary Science at Onderstepoort Veterinary Institute on 5 September 2016.

RESEARCH OUTPUTS

Publications


**NICD publications**

1. Monthly NICD Communiqué
2. Quarterly NICD Communicable Diseases Surveillance Bulletin
3. Surveillance Officer Monthly Communiqué
5. Monthly MNORT Reports
6. Quarterly GERMS-SA ESSORs, Provincial Statistics and PEPFAR Report

**Conference presentations**

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South African Regional Global Disease Detection Centre
BACKGROUND

In its fifth year since inception, the South African Global Regional Global Disease Detection Centre (SARGDDC) focused mainly on the core capacity of surveillance system strengthening by supporting the re-engineering of the Notifiable Medical Conditions Surveillance System in collaboration with partners.

SARGDDC remained a conduit and a platform that facilitated the fast-tracking of projects of mutual interest through research and non-research co-operative agreements. A total of 26 staff members were employed through these agreements, six of whom were located at the NDoH.

The Non-research Cooperative Agreement is in a no-cost extension phase and projects have been streamlined into five projects: analysing the South African notifiable disease surveillance system, including strengthening malaria surveillance; PulseNet Africa; emergency funds for VHF outbreaks in Africa – mobile laboratory; supporting capacity for field epidemiology in South Africa; and partnering with NDoH to address the import and export of biological agents.

The Research Cooperative Agreement is in year five and has seven projects: investigation of influenza burden – interaction with other pathogens and nosocomial transmission at sentinel surveillance sites; household transmission of influenza amongst HIV infected and uninfected; effectiveness of trivalent inactivated influenza maternal vaccination and evaluation of the vaccination program among pregnant women and their newborns in South Africa; healthcare utilisation survey – Johannesburg and Cape Town; additional methods for controlling malaria in South Africa; harbouring of viral zoonotic agents by southern African bat populations; and investigating the contribution of swine and or avian influenza-like illness and pneumonia in South Africa.

SPECIAL PROJECTS

The re-engineering of the Notifiable Medical Conditions Surveillance kicked off with exploratory discussions with numerous providers with expertise in managing large data sets. SARGDDC facilitated discussions with the NDoH representatives, the NICD, and the National Health Information Repository Data representatives, aimed at resource optimisation.

Fruitful engagement with stakeholders from the Board of Healthcare Funders of Southern Africa, Council for Medical Schemes, Alliance of South African Independent Practitioners Association, Health Professions Council of South Africa, the National Pathology Group, AMPATH, Hospital Association of South Africa, South African Medical Association, KZN Doctors Healthcare Coalition, and the South African Nursing Council, resulted in opportunities for the sharing of data and using common communication platforms to share information relating to notifiable diseases.

SARGDDC contributed to the development of the Social and Environmental Impact Assessment document required for the National Public Health Institute for South Africa (NAPHISA) Bill and continues to support the development of the business case for the establishment of NAPHISA after the passing of the NAPHISA Bill by Cabinet in March 2017.

The NICD is a member of the International Association of National Public Health Institutes (IANPHI) and Dr Mayet was elected as the INAPHI – Africa Chairperson at the annual meeting in China in October 2016. IANPHI-Africa has 21 members in the network and activities are underway aimed at expanding the network and strengthening public health institutional capacity across Africa.

The year under review saw the Co-Director take on the role as the Acting NICD Human Resources (HR) Manager. An NICD HR strategic plan with specific HR performance indicators was drafted; the plan for a comprehensive induction programme was developed; input was made on seven HR policies and HR supported the achievement of 93% of the training target for the Workplace Skills Plan.
COLLABORATORS

1. South African Malaria Elimination Committee in driving the malaria elimination agenda and activities.
2. The Defense Threat Reduction Agency on the establishment of the Regional Diagnostic Demonstration Centre at the NICD.
3. China CDC exploring the opportunity on various projects.
4. African CDC in supporting the First Advisory and Technical Council meeting to finalise the Africa CDC 5-year strategic plan.
5. Wits School of Public Health in finalising an MSc Field Epidemiology course.
7. University of South Africa Institute for Social and Health Sciences as a Board member.

TEACHING AND TRAINING

SARGDD and FETP staff lecture at the Universities of Pretoria and Witwatersrand and are involved in teaching of infectious disease epidemiology and surveillance short courses for the NDoH.

A total of 123 participants benefited from the training as follows:

1. A 12-week pilot of the Frontline Course aimed at strengthening public health surveillance and promoting data use for decision-making at the district level in Port Elizabeth, attended by 19 DoH officials in Port Elizabeth.
2. Outbreak Investigation and Management course for environmental health practitioners from the Sedibeng and West Rand districts in June 2016. The course was conducted in Randfontein, 25 participants attended.
3. A week-long Basic Applied Epidemiology short course for health practitioners at Sizwe Hospital for Gauteng region in April, 25 participants in attendance followed up by the second week in July 2016.
4. SAFETP facilitated a short course on Basic Applied Epidemiology for health practitioners organised by the DoH in the North West in July 2016, 24 participants attended the course.
5. Mr Alfred Musekiwa conducted training on statistical analysis at the NICD for 28 participants and has taken up the statistician position with the CDC-South Africa Division of Global HIV & TB from November 2016.

Professional development

Dr Lazarus Kuonza attended the Using Quantitative Bias Analysis with Epidemiologic Data short course at Stellenbosch University in May 2016 and has incorporated some of the concepts into the FETP Epidemiology courses.

Hetani Ngobeni attended the Introductory Research Electronic Data Capture (REDCAP) workshop held at the Faculty of Health Sciences, University of the Witwatersrand. This is a web-based system that allows one to create research databases.

Hetani Ngobeni and Gloria Motshudi attended a MS Project workshop held at AFENET in Kampala in May 2016. This was practical training on MS Project, which benefited the programme in developing annual work plans and dividing activities into manageable activities.

Hetani Ngobeni and Gloria Motshudi attended the ISO9001 training hosted by the NICD, which covered the importance of total quality management.

Dr Reddy attended the training programme in Epidemiology and Public Health Interventions Network (TEPHINET) accreditation training in Stockholm, Sweden. This will be used to inform the SAFETP application process for TEPHINET accreditation.

FETP staff participated in the Hermann Brian Dominance workshop. Other participants included the Provincial Epidemiologist Team and the Outbreak Response Unit as part of Work Skills Plan.

Charmaine Singh attended a 2-day, Effective Executive Secretary/PA training course, and key lessons learnt are being implemented.

Honours

Dr Reddy was elected Chairman of the TEPHINET Advisory Board at the TEPHINET Programme Directors Meeting in Madrid. He is also a member of the African Field Epidemiology Network (AFENET) Board, Chairman of the Finance and Audit Subcommittee and a member of the Human Resources and Quality Assurance Subcommittees of AFENET.
Dr Lazarus was appointed to the Advisory Board of the Department of Environmental Health at the University of Johannesburg for the next three years.

Husna Ismail won the third prize at the AFENET Conference in Abuja, Nigeria, in August 2016, for her poster presentation titled ‘Epidemiology of drug-susceptible tuberculosis in Gauteng, South Africa, 2012–2014.’

**RESEARCH OUTPUT**

**Publications**


**PRESENTATIONS**

a. International conferences: 10
b. National conferences: 17
National Cancer Registry
The core functions of the NCR are national cancer surveillance through the pathology-based cancer registry and the implementation of population-based cancer registration as per Regulation 380 of the National Health Act, together with cancer research and training. 2016/17 has been a year of extensive growth and change for the NCR. It joined the NICD from the National Institute for Occupational Health (NIOH), and moved to the Sandringham campus in May 2016. Several vacant posts for epidemiologists, medical scientists and surveillance officers were filled, allowing for adequate personnel to move surveillance and research forward. NCR staff members were trained in cancer registration methods by international cancer registration experts. The backlog in cancer coding from previous staff shortages has been greatly reduced, with cancer coding for 2014 completed and 2012 incidence data published. Establishment of the pilot population-based registry in Ekhuruleni is underway, with surveillance officers placed in both private and public health facilities.

The NCR published key research in breast cancer patterns in South Africa, which highlighted the increased risk of breast cancer and younger age at diagnosis in white and Asian women compared to other population groups. Using probabilistic record linkage techniques, we linked HIV cohort data to NCR data and demonstrated a high cancer incidence in the HIV-infected population. We also reviewed current evidence on HIV-related malignancies in children in the context of ART availability. We found that cancer risk remains high in children who start ART at older ages or more advanced immunosuppression as compared with children who start ART at younger age and with mild immunosuppression. Starting ART before severe immunosuppression develops is key to cancer prevention in HIV-infected children.

**SURVEILLANCE PROGRAMMES**

**Pathology-based cancer registry**

In the year under review, the pathology-based cancer registry data was captured and coded for 2012, 2013 and 2014. Data from 2012 were analysed and the annual report was published on the NCR website (www.ncr.ac.za). Data cleaning for 2013 and 2014 is underway. The main challenges have been data extraction errors from the CDW. All NCR staff attended a two-week training course from the African Cancer Registry Network (AFCRN), the African partner for the International Agency for Research on Cancer (IARC). Data from the NCR have been used for the development of the National Cancer Control Plan, as well as the Breast and Cervical policies of the DoH. In addition, there has been an increase in the use of our data by local and international researchers.

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

Mrs Lerato Khoali, a medical scientist at the NCR, was assigned to manage the EPBCR. Nine surveillance officers were recruited and trained in CanReg software and in ICD-O-3 cancer coding. Surveillance officers have been placed in all public hospitals that diagnose cancer in the Ekurhuleni district and their respective referral hospitals. One surveillance officer has been assigned to cover private hospitals and private oncology centres in Ekurhuleni. Data collection is underway and officers attend monthly feedback and progress meetings at the NCR. Development is underway to establish a Research Electronic Data Capture (REDCAP) database to allow mobile data capturing of notifications into the EPBCR. Seven out of the nine surveillance officers are funded by the South African Medical Research Council (SAMRC) and quarterly progress reports are sent to the funder. Year 2 funding of the population-based registry was secured from the MRC. However, there is a need for surveillance officers to be funded under the NCR operational budget since population-based cancer registration is a core function and mandate of the NCR.

**RESEARCH PROJECTS**

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

The SAM study is a national cohort of HIV-positive people created from NHLS HIV data (HIV tests, CD4 count and HIV viral load tests) and linked probabilistically to the NCR to determine the spectrum and risk of cancer in the HIV population. In 2016/17, we recruited a data analyst
and epidemiologists to work on the SAM study. Dr Adrian Spoerri (linkage specialist from Bern, Switzerland) visited the NCR twice to train the SAM staff. We purchased a server, software and a laptop. Data extraction and data cleaning of both HIV and cancer data are complete. De-duplication of HIV data is in progress using machine learning techniques for record linkage.


The BCAH study is a sub-study within the SAM Study which aims to estimate the burden of laboratory-diagnosed cancer attributable to HIV in the South African public sector and the additional cancer risk of HIV-positive people compared to HIV-negative people in the era of antiretroviral therapy. The BCAH study is funded by CDRF Global through the Beginner Investigator Grant for Catalytic Research in Cancer (BIG Cat) awarded to Dr Mazvita Sengayi. An MSc cancer epidemiology fellowship is funded within the BCAH study, and the post has been advertised for recruitment of a suitable candidate.

**Johannesburg Cancer Case-control Study (JCS)**

The JCS is a case-control study of newly (<6 months) diagnosed black cancer patients (1995–2016) with over 26 000 patients interviewed and over 20 000 blood samples stored to examine genetic and emerging and/or novel risk factors for cancer. Data collection, data entry and cancer coding for the JCS was completed in 2016. Quality checks of cancer coding are underway. Several genetic studies are using JCS samples:

**Newton Grant (Breast, Oesophageal and Cervical Cancer)**

The main objective of this collaborative study is to identify genetic variants associated with susceptibility to breast, cervical and oesophageal cancer in African cancer patients. Ethics approval was received for the Newton Grant and the recruitment of PhD fellows is in progress.

**Men of African Descent Cancer of the Prostate (MADCaP) Consortium**

The MADCaP consortium is an Africa-wide collaborative research with US partners to explore genetic causes of prostate cancer in men of African origin. Ethics approval has been granted from Wits Human Research Ethics Committee. Prospective data collection has been established at the Chris Hani Baragwanath Hospital Urology Clinic, with more than 100 cases and 75 controls enrolled.

**Genetic aetiology of inherited breast cancer in black South African women**

The study aims to perform targeted sequencing of all known breast cancer susceptibility genes (currently 65 genes on the BROCA panel), in young (<50) black South African women diagnosed with breast cancer.

**Genetic aetiology of oesophageal squamous cell carcinoma (OSCC)**

Mr Wenlong Chen, a medical scientist at the NCR, is conducting this study for his PhD. The aim of this project is to test the hypothesis that genetic variation in the South African black population contributes significantly to the risk of OSCC. We tested genetic risk factors for OSCC which were identified by genome-wide association scans in other populations for association with OSCC in the South African black population. All individuals were from the black population of the Western Cape, with 98.2% being from the Xhosa ethnic group. A total of 513 OSCC cases and 820 controls were genotyped for 15 single nucleotide polymorphisms (SNPs). No significant evidence of association was observed for the index SNPs at the previously reported loci. We are now expanding the power and density of this study by genotyping 36 SNPs from loci of interest in 1 000 South African OSCC cases and 940 controls from the Johannesburg Cancer Study by mass spectrometry using the MassArray genotyping system (Agena Bioscience).

**The Uranium Health Study: An epidemiological study of uranium mineworkers**

This is a collaboration between a uranium mine in Namibia, the University of Manchester UK, the Namibian Cancer Registry and the National Cancer Registry of South Africa. The main objective is to determine retrospectively whether there have been excess work-related cancer risks in uranium mineworkers employed at a selected mine. A specific concern in this Namibian mine arises from an unpublished cohort study report by Sitas et al. (2001) indicating a possible excess cancer mortality amongst the workforce of this mine, with a possible higher incidence of brain cancer. The NCR will conduct a probabilistic record linkage to improve cancer ascertainment in Namibian mineworkers since some of them seek cancer care in South Africa. Ethics approval was obtained from Wits REC, the University of Manchester REC and the Ministry of Health and Social Services in Namibia. Currently the NCR is working on data security compliance to ensure confidentiality and the establishment of IT infrastructure to perform the linkage.

**Anatomical distribution of colorectal cancer in South Africa**

This is a study being conducted by an MMED surgery student, Dr Akrem Amer, in the Department of General Surgery at the University of Cape Town. Historically, two-thirds of colorectal malignancies are located in the left colon and rectum. However, recent studies suggest a trend towards an increase of right-sided tumours. The main objective of this study is to describe the anatomic location of colorectal cancer in South Africa from 2006–2010. Ethical approval was obtained from the University of Cape Town’s, Human Research Ethics Committee.
HPV-related cancers and HIV

Dr Admire Chikandiwa, a PhD student at the Wits School of Public Health, is studying HPV-related cancer trends (anogenital, head and neck cancers) in context of the HIV epidemic in South Africa.

Hepatocellular carcinoma (HCC) and hepatitis viruses

Mr Daniel Mak, a PhD student at the Hepatitis Virus Diversity Research Unit, Wits School of Clinical Medicine, is working on the relationship between the hepatitis viruses and HCC in the context of HIV and other environmental factors. He conducted a retrospective case-control study of 150 HCC cases and 450 sex and age-matched controls recruited between June 2000 and December 2012 from the JCS study. High rates of Hepatitis B and C virus infections were found in JCS HCC patients, with a considerable proportion of burden being borne by rural migrants moving into urban areas. He is also working on national liver cancer incidence and mortality trends in the context of the increasing HIV prevalence and the introduction of hepatitis B vaccination in 1995.

ACKNOWLEDGEMENTS AND COLLABORATORS

1. Prof. Matthias Egger, Dr Julia Bohlius, Dr Adrian Spoerri. Institute of Social and Preventive Medicine, University of Bern, Switzerland.
2. Prof. Tim Rebbeck. Harvard TH Chan School of Public Health, Harvard University, Boston, USA.
3. Prof. Chris Mathew. Department of Medical and Molecular Genetics, Guy’s Hospital, King’s College London, United Kingdom.
4. Prof. Debbie Bradshaw. Medical Research Council of South Africa.
5. Prof. Amanda Krause, Dr Fiona Baine. Division of Human Genetics, University of the Witwatersrand.
6. Dr Kathryn Chu, Dr Akrem Amer. Department of General Surgery, University of Cape Town.
7. Prof. Raymond Agius, Prof. Roseanne McNamee, Prof. Richard Wakeford. School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, United Kingdom.
8. Prof. Anna Kramvis, Mr Daniel Mak. Hepatitis Virus Diversity Research Unit, Department of Internal Medicine, University of the Witwatersrand.
9. Dr Pedro Pisa, Dr Admire Chikandiwa. Wits Reproductive Health Institute, University of the Witwatersrand.

TEACHING AND TRAINING

Dr Elvira Singh and Dr Mazvita Sengayi taught MPH and MSc epidemiology students at the Wits School of Public Health. Ms Lactatia Motsuku gave lectures to SAFETP students. Dr Mazvita Sengayi gave practical tutorials at the monthly epidemiology methods seminars at the NICD and at the GERMS surveillance officers training meeting. Dr Singh has also lectured and presented a seminar at the University of Cape Town School of Public Health.

Professional development

Dr Mazvita Sengayi attended NIH NIAID training on grants policy and management in May 2016. The African Cancer Registry Network team gave a five-day practical course on cancer registration methods and use of CanReg 5 training to all NCR staff in June 2016. NCR staff attends ongoing epidemiology seminars at the NICD. Dr Sengayi has been appointed as an honourary lecturer and Dr Singh continues as a joint appointment at Wits School of Public Health.

Additional students supervised and registered during 2016/17

Three students registered for PhD degrees (Mr Carl Chen, Mr Daniel Mak and Dr Admire Chikandiwa).

Four students registered for MSc/MPH/MMed degrees (Dr Gbenga Olorunfemi, Ms Lerato Khoali, Ms Natasha Abraham and Dr Akrem Amer).

One student registered for Hons BSc Computer Science (Ms Matshidiso Mohlala).

Honours

Dr Mazvita Sengayi was awarded the CRDF Beginner Investigator Grant for Catalytic Research in Cancer (BIG Cat), which is an early-career investigator grant for first-time Principal Investigators totalling USD50 000 over two years. She is using these funds for a study entitled ‘Burden of Cancers Attributable to HIV in South Africa (2004–2014)’, which is a sub-study within the SAM Study.
RESEARCH OUTPUTS

Top publications


Breast cancer is the most common cancer in South African women. This paper describes breast cancer (BC) incidence (1994–2009) and mortality (1997–2009) by ethnicity in South Africa. For the Black, Coloured and Asian groups, increases in age standardised incidence rates (ASIR) and lifetime risk (LR) were observed between 1994 and 2009. In 2009, the ASIR for the total population, Blacks, Whites, Coloureds and Asians were 26.9, 18.7, 50.2, 40.9 and 51.2 per 100,000, respectively. For Asians, an increase in proportion of BC as a percentage of all female cancers was observed between 1994 and 2002 (11.1%) and continued to increase to 2009 (a further 4.5%). Whites and Asians presented higher incidences of BC at earlier ages compared with Blacks and Coloureds in 2009. In 1998, there were 1,618 BC deaths in SA compared with 2,784 deaths in 2009. ASMR between 1997 and 2004 increased, but stabilised thereafter. We demonstrated that SA BC incidence rates are similar to other countries in the region, but lower than other countries with similar health systems. Ethnic differences in BC trends were observed. However, the reasons for observed ethnic differences are unclear.


The surveillance of HIV-related cancers in South Africa is hampered by the lack of systematic collection of cancer diagnoses in HIV cohorts and the absence of HIV status in cancer registries. To improve cancer ascertainment and estimate cancer incidence, we linked records of adults (aged ≥ 16 years) on antiretroviral treatment (ART) enrolled at Sinikithemba HIV Clinic, McCord Hospital in KZN with the cancer records of public laboratories in the province using probabilistic record linkage (PRL) methods. We calculated incidence rates for all cancers, Kaposi sarcoma (KS), cervix, non-Hodgkin’s lymphoma and non-AIDS defining cancers (NADCs) before and after inclusion of linkage-identified cancers with 95% CIs. A total of 8,721 records of HIV-positive patients were linked with 35,536 cancer records. Between 2004 and 2010, we identified 448 cancers, 82% (n=367) were recorded in the cancer registry only, 10% (n=543) in the HIV cohort only and 8% (n=538) both in the HIV cohort and cancer registry. The overall cancer incidence rate in patients starting ART increased from 134 (95% CI: 91–212) to 877 (95% CI: 744–1,041) per 100,000 person-years after inclusion of linkage-identified cancers. Incidence rates were highest for KS (432, 95% CI: 341–555), followed by cervix (259, 95% CI: 179–390) and NADCs (294, 95% CI: 223–395) per 100,000 person-years. Ascertainment of cancer in HIV cohorts is incomplete; PRL is both feasible and essential for cancer ascertainment.


We reviewed the current literature on the epidemiology and prevention of cancer in HIV-infected children. ART reduces the risk of developing cancer in HIV-infected children. Cancer risk remains high in children who start ART at older ages or more advanced immunosuppression as compared with children who start ART at a younger age and with mild immunosuppression. Starting ART before severe immunosuppression develops is key to prevent cancer in HIV-infected children, but most children in low-income countries start ART at severe immunosuppression levels. Vaccination against high-risk variants of human papillomavirus may protect against human papillomavirus-associated cancer later in life. However, tailoring of human papillomavirus vaccination guidelines for HIV-infected children and young women awaits answers to determine the best vaccination strategies.

List of publications


Conferences

There were three presentations at international conferences and five presentations at national conferences for the financial year.