



**NATIONAL INSTITUTE FOR
COMMUNICABLE DISEASES**

Division of the National Health Laboratory Service

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LIST OF ABBREVIATIONS

| | | | |
|-------------------|---|---------------|--|
| AFP | Acute flaccid paralysis | CVI | Centre for Vaccines and Immunology |
| Africa PGI | Africa Pathogen Genomics Initiative | DATCOV | Daily Hospital Surveillance for COVID-19 Report |
| AFRO | African Region Offices | DHIS | District Health Information System |
| AMR | Antimicrobial Resistance | DPHSR | Division of Public Health Surveillance and Response |
| ARL | Arbovirus Reference Laboratory | DRC | Democratic Republic of the Congo |
| ART | Antiretroviral Therapy | DTRA | Defence Threat Reduction Agency |
| BSL | Biosafety Level | DUT | Durban University of Technology |
| CCHF | Crimean-Congo Haemorrhagic Fever | EOC | Emergency Operations Centre |
| CDC | Centers for Disease Control and Prevention | EPBCR | Ekurhuleni Population-Based Cancer Registry |
| CDW | Corporate Data Warehouse | ESKAPE | <i>Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species</i> |
| CED | Centre for Enteric Diseases | FETP | Field Epidemiology Training Programme |
| CEZPD | Centre for Emerging Zoonotic and Parasitic Diseases | GERMS | Group for Enteric, Respiratory and Meningitis Surveillance – South Africa |
| CHARM | Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses | GIISER | Global Immunology and Immune Sequencing for Epidemic Response |
| CHIVSTI | Centre for HIV and STIs | GLASS | Global AMR Surveillance System |
| CoVICIS | Combating SARS-CoV-2 Pandemic | IgG | Immunoglobulin G |
| CRDM | Centre for Respiratory Diseases and Meningitis | IgM | Immunoglobulin M |
| CSIR | Council for Scientific and Industrial Research | INH | Isoniazid/ Isonicotinic Acid Hydrazid |
| CTB | Centre for Tuberculosis | IT | Information Technology |

LIST OF ABBREVIATIONS

| | | | |
|----------------|--|---------------|---|
| MRC | Medical Research Council | SADC | Southern African Development Community |
| MSM | Men-Who-Have-Sex-With-Men | SAFETP | South African Field Epidemiology Training Programme |
| NCR | National Cancer Registry | SAHPRA | South African Health Products Regulatory Authority |
| NDOH | National Department of Health | SAMVAC | South African mRNA Vaccine Consortium |
| NGS | Network for Genomic Surveillance in South | SANAS | South African National Accreditation Systems |
| NHLS | National Health Laboratory Service | SARS | Severe Acute Respiratory Syndrome |
| NICD | National Institute for Communicable Diseases | SBPRL | Special Bacterial Pathogens Laboratory |
| NIOH | National Institute for Occupational Health | SCF | Sequencing Core Facility |
| NMC | Notifiable Medical Conditions | STI | Sexually Transmitted Infection |
| ORU | Outbreak Response Unit | SVPL | Special Viral Pathogens Laboratory |
| PCR | Polymerase Chain Reaction | TB | Tuberculosis |
| PET | Provincial Epidemiology Team | TPT | TB Preventative Therapy |
| PGI | Pathogen Genomics Initiative | UNAIDS | Joint United Nations Programme on HIV/AIDS |
| POPIA | Protection of Personal Information Act | UP | University of Pretoria |
| RfA | Results for Action | US | United States of America |
| RNA | Ribonucleic Acid | VHF | Viral Haemorrhagic Fevers |
| RVF | Rift Valley Fever | WGS | Whole Genome Sequencing |
| SACCESS | South African Collaborative COVID-19 Environmental Surveillance System | WHO | World Health Organization |



EXECUTIVE DIRECTOR'S OVERVIEW

PROF ADRIAN PUREN

The important services of the NICD continue to be affected by the protracted COVID-19 pandemic and other communicable disease concerns affecting South Africans, the Southern African Development Community (SADC) region, and Africa. These strategic services include disease surveillance, specialised diagnostic services, outbreak response, research and training, and provincial epidemiology capacity building.

The institute plays a central role in detecting, containing, and responding to infectious disease threats and provides technical support and expertise to the National Department of Health (NDOH), World Health Organization (WHO), and the Africa Centres for Disease Control (Africa CDC). As a credible health partner, the institute offers the global health community valuable information on communicable diseases.

The NICD comprises seven disease-focused centres, and the staff complement includes pathologists, scientists, epidemiologists, medical technologists, technicians, and surveillance officers.

CENTRE FOR EMERGING ZOOONOTIC AND PARASITIC DISEASES (CEZPD)

The CEZPD is the national and regional hub for diagnosis, surveillance, outbreak response, research, teaching, and training related to zoonotic viral, bacterial, and parasitic diseases, particularly those associated with risk groups three and four pathogens.

These include:

- viral haemorrhagic fevers (VHFs) such as Ebola and Marburg viral diseases, Lassa fever, and Lujo haemorrhagic fever (LHF);
- arthropod-borne diseases such as Rift Valley Fever (RVF), Crimean-Congo haemorrhagic fever (CCHF), yellow fever, dengue fever, chikungunya fever, Sindbis fever, West Nile fever, Zika fever, malaria, plague, and rickettsioses;
- rabies and rabies-related infections;
- bacterial diseases such as anthrax, botulism, brucellosis, and leptospirosis;

- parasitic opportunistic infections – diarrhoeal diseases in children under five years of age and
- schistosomiasis and soil-transmitted helminthic diseases.

The centre operates highly specialised laboratory facilities, including:

- positive-pressure suit biosafety level (BSL) 4;
- BSL-3 laboratories and a transmission electron microscope laboratory, and insectaries for housing the vectors of malaria and
- arboviruses vectors for insecticide resistance and vector competence studies.

These facilities constitute an essential resource for diagnosis, surveillance, outbreak response, and research of priority zoonotic viral, bacterial, and parasitic diseases in Africa. The special viral pathogens laboratory (SVPL) has conducted passive laboratory-based surveillance for human rabies in South Africa since 1981. In 2021 a significant increase in dog rabies was noted in eThekweni (KwaZulu-Natal) and Buffalo City, and Nelson Mandela Bay (Eastern Cape) municipalities. The resurgence of dog rabies in these provinces is considerable and a high number of cases will be reported through the first quarter of 2022. The ongoing epizootics of dog rabies have also led to an increase in reported human rabies cases with 17 laboratory-confirmed cases reflected from 1 April 2021 to 31 March 2022 in these provinces.

The SVPL investigates South African VHF and provides laboratory testing for both endemic VHF including Crimean-Haemorrhagic fever (CCHF) and RVF and non-endemic VHF (Ebola and Marburg virus disease and Lassa fever).

In 2021 one CCHF case was confirmed from the Western Cape and another from the same province in February 2022. Historically CCHF cases have been reported from every South African province. The most significant cases were recorded from the Free State, Northern Cape, and North West. VHF is a category I notifiable medical condition in South Africa and the country's first imported case of hantavirus infection was confirmed in 2021. The latter involved a South African businessman, diagnosed and managed locally, with a travel and exposure history in Croatia.

To alert public health authorities to the possibility of increased human plague risk, the CEZPD SBPL surveilled for plague in susceptible rodent populations in the Nelson Mandela Bay (Coega area) and eThekweni municipalities. None of the rodents tested positive for plague anti-F1 antibodies.

The arbovirus reference laboratory (ARL) investigated endemic and exotic arboviral disease cases including chikungunya, RVF, dengue, Zika, Ross River, and Japanese encephalitis. The laboratory experienced a 20% increase in diagnostic submissions since the gradual return of the healthcare system and travel opportunities related to COVID-19 restrictions (from 71 recommendations in the previous year to 90 during the period under review).

CENTRE FOR ENTERIC DISEASES (CED)

The areas of focus include:

- food-borne diseases;
- waterborne diseases;
- priority enteric diseases under routine surveillance that comprise epidemic-prone conditions such as enteric fever, cholera, and listeriosis;
- rotavirus – a vaccine-preventable disease in South Africa;
- diarrhoeal disease syndromic surveillance;
- and genomic surveillance of priority enteric bacterial pathogens.

Diarrhoeal disease sentinel surveillance is active at five sites in three provinces; 383 cases were enrolled (229 from the Western Cape, 116 from the North West, and 37 from the Free State). Children under the age of five years constituted 90% of the cases (343/383) with an average age of 14 months. Testing of diarrhoeal specimens is ongoing. No rotavirus was detected in 2022 to date.

There were 72 cases of listeriosis reported from seven provinces with the majority being in the Western Cape (36%, 26/72) followed by Gauteng (31%, 22/72) and KwaZulu-Natal (19%, 14/72). No cases were reported from the Northern Cape or the North West. An average of one case per week (range: 0-4 cases per week) was recorded with the bulk being neonates under 28 days (33%, 24/72) followed by age groups 15-49 years (31%, 22/72); over 65 years (22%, 16/72), 50-64 years (13%, 9/72) and children between 30 days and 14 years (1%, 1/72).

By using whole genome sequencing (WGS) analysis, the NICD identified clusters (small localised outbreaks) in the Western Cape and North West. In the Western Cape, three clusters were identified in three districts, while in North West there is a cluster in the Dr. Kenneth Kaunda district. The first cluster cases occurred in 2020 and, as of 31 March 2022, the Cape Town cluster and

Garden Route cluster comprised 18 and 15 cases respectively. The last case of the Winelands cluster strain was identified in May 2021.

There were 35 confirmed cases of the Klerksdorp cluster strain in other provinces, namely North West (21), Gauteng (six), Mpumalanga (four) KwaZulu-Natal, and the Free State (two each). Most (43%) of the cases were working-age males (15-49 years). Investigations are ongoing for all clusters, but no definite infection source(s) have been identified for the Western Cape clusters.

In-depth interviews of 26/35 Klerksdorp cluster cases showed an association with consuming contaminated water in the district's gold mines. Due to the demographics and scale, contaminated municipal water is extremely unlikely to be the source in any of these clusters. Gauteng reported higher-than-usual numbers of enteric fever cases between January and March 2022. A new cluster was identified in Gauteng comprising 20 cases diagnosed between January 2020 and February 2022. The cases are not restricted to a single district and span a range of age groups. The CED provided technical advice and support to the provincial and district health departments with outbreak investigations. At the same time, local communities received educational support and information on enteric fever distributed via the media.

All alerts of suspected outbreaks reported through the notifiable medical conditions (NMC) system are followed up and epidemiological and laboratory support is provided. During the reporting period, the CED responded to ten outbreaks, while another 55 suspected food-borne disease outbreaks were reported, but insufficient epidemiological data and the absence of appropriate specimen collection precluded further investigation.

CENTRE FOR HEALTHCARE-ASSOCIATED INFECTIONS, ANTIMICROBIAL RESISTANCE AND MYCOSES (CHARM)

The centre incorporates two national reference laboratories for antimicrobial resistance (AMR) and mycoses, and houses the national stock culture collection of pathogenic bacteria and fungi. CHARM functions as a WHO collaborating centre for AMR and is the national focal point for WHO's global AMR surveillance system (GLASS). The centre's epidemiology team supports priority surveillance projects; conducts outbreak investigations, and establishes and evaluates public health programmes.

The centre implemented a real-time alert system to detect outbreaks of healthcare-associated bloodstream infections among neonates. Improvements to the application were completed and the surveillance was relaunched at Dora Nginza Hospital in 2022. Feedback received through informal consultations at this site highlighted additional development is required to enhance the application. A formal evaluation will be conducted in 2022 before further work commences.

CHARM members represented the NICD on a newly constituted ministerial advisory committee for AMR; WHO AMR surveillance and quality assessment collaborating centres network; WHO strategic and technical advisory group for AMR and WHO fungal pathogens priority list advisory group.

The AMR surveillance centre currently uses several approaches including:

- National or sentinel isolate-based surveys: bacterial and fungal isolates, cultured from patients meeting the surveillance case definitions, were submitted to the reference laboratories for identification, antimicrobial susceptibility testing, and genotyping. During the period under review, the centre conducted surveillance for bacteraemia caused by carbapenem-resistant Enterobacterales (2015-2021), enterococci and infections caused by *Candida auris* (2018-2021)
- Enhanced laboratory surveillance: detailed clinical information was collected from patients admitted to sentinel hospitals meeting the surveillance case definitions but was suspended for the period under review. More recently, electronic laboratory surveillance revealed that annual data compiled on bloodstream infections were caused by the ESKAPE bacterial pathogens and *Candida*. NICD merged and cleaned the line list data from the public and private sector pathology laboratory information systems and placed it on the AMR dashboard on the NICD website. The dashboard displays interactive and exportable AMR maps by geographic location, pathogen, antimicrobial agent, and health sector. AMR data for the public sector is available at the facility-level and a combined public and private AMR report on key organisms and antimicrobial agents is available at (<http://www.health.gov.za/index.php/antimicrobial-resistance>).

Since 2018 WHO has recommended a combination of amphotericin B and flucytosine (5-FC) as first-line induction treatment for cryptococcal meningitis. In December 2021 the South African Health Products Regulatory Authority (SAHPRA) registered 5-FC. Approximately 80 hospitals participated in a 5-FC access programme and the centre assisted with data collection and analysis coordination. A manuscript on the outcomes of 5-FC-containing combination treatment for cryptococcal meningitis was accepted in *The Lancet Infectious Diseases*. A member of the centre co-chaired the WHO guideline development group on cryptococcal disease in 2022 and WHO updated its recommendation for first-line treatment of cryptococcal meningitis.

Passive laboratory-based surveillance for rarer invasive mycoses continued. The centre led or participated in the investigations of several healthcare-associated outbreaks. Its contribution to outbreaks has shifted from epidemiological assistance to molecular studies and may signal changing

priorities, prompted by the COVID-19 pandemic, to investigate and manage healthcare-associated outbreaks.

As a WHO collaborating centre for AMR, the centre participated in the WHO AMR surveillance and quality assessment collaborating centres network formed to support the implementation of GLASS (<https://www.who.int/glass/reports/en/>). The NICD collaborated on activities to strengthen countries' capacity for developing and implementing AMR surveillance programmes and provided an external quality assessment programme (<https://ptschemes.nicd.ac.za/Home/Bacteriology>).

CENTRE FOR HIV AND STIS (CHIVSTI)

The HIV and SARS-CoV-2 virology section was involved with COVID-19-related research, focusing on characterising immune responses to variants of concern in various epidemiological cohorts and COVID-19 clinical trial vaccines.

The data provided insights that informed likely responses in cases of natural infections including previous infections and variants and responses in vaccines. Through the global immunology and immune sequencing for epidemic response (GIISER) and the coronavirus immunotherapy consortium (CoVICIS) projects, the laboratory was involved in establishing capacity development via new assays and sharing reagents in the networks forming part of these collaborative programmes.

Collaborations have also been established with pre-clinical developers of novel vaccines including the WHO-sponsored South African mRNA Vaccine Consortium (SAMVAC) and biotechnology company GreenLight Biosciences. The SARS-CoV-2 ELISA laboratory-developed assay passed SANAS accreditation in February 2022.

The centre also pursued studies of the ontogeny of broadly neutralising antibodies in HIV infection to inform vaccine design. There are ongoing adult HIV cure studies including conducting immunological and genetic analyses of studies.

The HIV and STI surveillance and monitoring and evaluation of HIV antiretroviral treatment programmes were critical activities. The centre supported the NDOH Operation Phuthuma programme to improve the quality of healthcare management at the facility-level. The NICD provided routine HIV laboratory reports and supported validation of facility District Health Information System (DHIS) data and validation in meeting the UNAIDS targets for:

- number of HIV-positive people who know their status and
- number of HIV-positive people on treatment and virally suppressed.

Results from the 2019 antenatal HIV sentinel survey showed an association between the unsuppressed viral load and unintended pregnancy among pregnant women who had initiated antiretroviral therapy (ART) before pregnancy. This

highlighted the need to strengthen the routine assessment of fertility preferences and contraceptive provision services for HIV-positive women receiving ART.

Case surveillance of congenital syphilis and STI sentinel aetiological surveillance continued at three primary healthcare centres, namely Alexandra Health Centre (Gauteng), Prince Cyril Zulu Communicable Diseases Centre (KwaZulu-Natal) and Spencer Road Clinic (Western Cape).

A new surveillance site was established for MSM surveillance at a sentinel men's health centre in central Johannesburg that aims to develop early warning for evolving resistance to extended-spectrum cephalosporins in *Neisseria gonorrhoeae* and emerging STIs such as lymphogranuloma venereum. HIV incidence is a key indicator of epidemic control, but is difficult to measure. Cross-sectional surveys, like general population and antenatal surveys, can provide the necessary sample sizes but are logistically difficult to implement and the results are not in real-time. Developing a point-of-care assay to detect recent infections may provide an alternative to monitoring recent infections. The centre is part of a multi-facility study currently assessing the utility of the test and specifically assessing its integration as part of the routine workflow and yield of recent infections. The results will determine a national rollout programme.

CENTRE FOR RESPIRATORY DISEASES AND MENINGITIS (CRDM)

The CRDM is a resource for surveillance, diagnostics, expertise, and research in communicable respiratory diseases and meningitis in South Africa and Africa. The centre is a WHO COVID-19 international and regional reference laboratory and provides technical support and training across Africa. It generates data and provides expertise to the NDOH, healthcare providers and regional and international collaborators to plan public health policies and programmes and respond to respiratory and meningitis disease outbreaks.

COVID-19 data advised several policy recommendations including the ministerial advisory committee and NDOH on health system planning for emerging SARS-CoV-2 variants and implementing non-pharmaceutical interventions and policies to control COVID-19 in schools. Influenza vaccination guidelines were updated in light of new data on effectiveness and safety when co-administering vaccines.

The CRDM is responsible for six category one NMC (acute rheumatic fever, COVID-19, diphtheria, meningococcal disease, pertussis) and

respiratory disease caused by a novel respiratory pathogen) and two category two NMCs (Haemophilus influenzae type b (Hib) disease



and legionellosis). The centre provided ongoing laboratory and epidemiological support to the NDOH for suspected diphtheria, pertussis, legionella and meningococcal disease.

During the review period, it continued with response activities to the COVID-19 pandemic and its core surveillance function through syndromic and laboratory-based surveillance programmes. The CRDM supported the national COVID-19 incident management team, particularly in the epidemiology and laboratory streams. It produces regular COVID-19 surveillance reports including but not limited to the weekly epidemiological brief, weekly testing summary and COVID-19 reproductive number. Several detailed epidemiologic reports were also published in the Communicable Diseases Surveillance Bulletin.

CRDM staff consulted on numerous expert committees and working groups for WHO, Africa Centres for Disease Control (Africa CDC) and WHO African Region (AFRO). The Centre is a founding member of the network for genomic surveillance in South Africa (NGS-SA), using routine genomic surveillance of SARS-CoV-2 in detecting new SARS-CoV-2 variants as the pandemic progressed locally and regionally including detecting Omicron in November 2021. CRDM obtained funding to conduct a range of COVID-19-related research activities, mainly focused on the burden of disease, transmission, seroepidemiology and viral sequencing. CRDM staff participated in numerous media engagements to educate the public on COVID-19 risks, how to reduce transmission, and updates on the epidemic's progression.

CENTRE FOR TUBERCULOSIS (CTB)

The CTB's core functions are to execute TB surveys and population research; conduct laboratory-based public health surveillance of TB and contribute to advancing TB epidemiology, diagnostics and treatment, thus guiding South African policy. The centre also houses the national TB reference laboratory and is a member of the WHO sub-Saharan Africa TB supranational reference laboratory network.

The CTB provided the national TB programme with a bi-weekly analysis of Xpert MTB/RIF (Xpert) TB testing volumes, positive tests, positivity rate and rifampicin-resistant rates to support the TB COVID-19 recovery plan. Xpert TB testing volumes recovered during 2021 have exceeded upper confidence bounds since November 2021.

The national TB prevalence survey, begun in mid-August 2017 as a collaboration between the MRC, HSRC, NICD (CTB) and NDOH, aims to establish the burden of South Africa's pulmonary TB disease and was conducted according to the WHO global task force on TB impact measurement international recommendations. Over 35,000 people agreed to participate

with the NICD processing 15,268 sputum samples and the findings were presented on 27 January 2021.

The overall TB prevalence was 852 (95% CI 679-1,026) per 100,000 with a higher prevalence in males (1,094 per 100,000) versus females (675 per 100,000). Most of the survey cases were HIV-negative and 57.8% did not report any symptoms during specimen submission. Surveillance findings are still regularly analysed and reported to national and provincial TB programmes.

The weekly results for action (RfA) reports cover both drug-susceptible and drug-resistant TB. Quarterly reporting of TB cases (drug-susceptible and drug-resistant) nationally and further stratified by province and sub-district are ongoing with automated reports regularly emailed to the relevant stakeholders. With support from the Global Fund, enhanced TB surveillance reports were developed for nine priority TB districts to target local interventions and improve the TB programme. The enhanced reports include detailed facility-level epidemiological, geospatial and trajectory analyses. The 2021 quarterly reports were distributed and presented to stakeholders and discussions are ongoing for the added support and further expansion of the enhanced TB surveillance reports to all districts.

Developing the TB module on the NMC system has significantly advanced the public health surveillance and response front. The module allows users to electronically capture cases and then viewed in near real-time by public health responders. Electronic capturing removes paper-based notifications and reduces notification time and catching errors. This ultimately reduces the initial loss to follow-up among TB patients.

The module will also integrate clinical and laboratory notifications to measure South Africa's TB burden accurately. Internal piloting of the NMC-TB module has been completed with the next phase expanding to several healthcare facilities. The GERMS surveillance TB section focuses on participants with rifampicin-susceptible TB diagnosed at hospitals to detect isoniazid (INH) mono-resistance and monitor the relative contribution of HIV/ART, TB preventative therapy (TPT), and pathways to care to reduce the incidence and achieve the expectations of the NDOH strategic plan expectations. Hospitals in five provinces are included in the surveillance, but the global pandemic severely hampered the surveillance programme with only 267 samples received, of which 184 were culture-positive and 14 (7.6%) were found to be INH-resistant.

CENTRE FOR VACCINES AND IMMUNOLOGY (CVI)

The CVI provides the NDOH with epidemiological, virological, and immunological support for vaccine-preventable diseases and conducts testing and surveillance for poliovirus, measles,

rubella, tetanus, and viral hepatitis targeted for either eradication or elimination in the next few years. The target indicators for polio and measles, set by the WHO and NDOH, guide the centre to improve surveillance detection and sensitivity.

The centre tests wastewater samples for poliovirus and SARS-CoV2 detection and remains committed to reaching the viral hepatitis elimination goals by 2030. CVI performs passive laboratory-based surveillance for hepatitis A, B, and C using data NHLS corporate data warehouse (CDW) and NMC data.

The poliovirus isolation laboratory serves Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, Swaziland, and South Africa for acute flaccid paralysis (AFP) surveillance and Angola, Malawi, Mozambique, Namibia, and South Africa for environmental surveillance. The poliovirus regional reference laboratory is one of two sequencing laboratories in Africa. During the period under review, 3,452 samples were processed for poliovirus isolation – 696 from South Africa and the balance from the other seven countries. Between January and March 2022, the country's AFP detection rate in children under 15 years old was 3.2 per 100,000 population, meeting the WHO indicator of 2/100,000, but below the South African 4/100,000 target indicator.

A wild poliovirus type 1 was detected in a Malawian AFP case sample. Local sampling and testing of the community, household contacts, and environmental samples from the area showed no new cases. Heightened surveillance continues in an attempt to detect any circulation. Vaccine-derived poliovirus type 1 (VDPV1) was identified in 53 Madagascar case samples and VDPV2 in 149 samples from cases of Burkina Faso, Democratic Republic of the Congo (DRC), Ivory Coast, Liberia, Mali, Niger, Republic of the Congo (Congo Brazzaville), South Sudan and Sierra Leone and two cases in Mozambique. Type 2 Sabin polioviruses were detected in 96 samples, mostly from countries using monovalent oral polio vaccine type 2 to halt VDPV2 transmission (Burkina Faso, Ivory Coast, Mali, DRC, South Sudan, Congo Brazzaville, and Uganda).

The NICD has partnered with the National Institute for Occupational Health (NIOH), Lumegen Laboratories, GreenHill laboratories, Praecautio, Waterlab, Durban University of Technology (DUT), South African Medical Research Council-Tuberculosis (SAMRC-TB) platform, and the Council for Scientific and Industrial Research (CSIR) in the South African collaborative COVID-19 environmental surveillance (SACCESS) network to detect and geographically locate SARS-CoV-2 distribution in sewage.

In total, 548 wastewater samples were processed for SARS-CoV-2 surveillance from sites in Gauteng, the Western Cape, Free State, KwaZulu-Natal, the Eastern Cape, and the Northern Cape. SARS-CoV-2 was identified in 498 samples (91%) and quantitated using the optimised methodology to obtain copies of SARS-

CoV-2 RNA/ml of wastewater. Quantitative PCR has documented increases and subsequent decreases in viral load in wastewater correlating with clinical caseloads in each metropolitan area. NICD also collates and reports results from 73 additional sites from SACCESS partners. Reports are compiled and shared with stakeholders every Friday and published online. Next-generation sequencing successfully detected mutations of the SARS-CoV-2 variants Beta, Delta, Omicron, and C.1.2 in wastewater. SARS-CoV-2 is considered non-infectious from sewage samples, but the viral RNA remains detectable in raw sewerage. This monitoring may provide additional information to the NDOH for planning geographically localised interventions.

The centre is the national and WHO regional reference laboratory for measles and rubella testing and surveillance. Laboratory results (detection of measles-specific IgM antibodies, the avidity of anti-measles IgG antibodies, RT-PCR and genotyping) are used with epidemiologic case investigations to diagnose acute measles infection. In total 960 South African febrile rash samples were tested during the period under review with five confirmed measles cases, two compatible, and eight cases still requiring classification (case notes are needed). Measles genotype B3 was detected in a patient who had recently returned from the DRC, but no clusters of cases were detected. Only 20 rubella cases were identified via febrile rash surveillance, considerably lower than in previous years but a likely reflection of lower health-seeking behaviour due to COVID-19 and lower transmission because of social distancing and lockdown measures. For January to March 2022, South Africa met the WHO indicator of a non-measles non-rubella discard rate of $\geq 2/100\ 000$ population.

DIVISION OF PUBLIC HEALTH SURVEILLANCE AND RESPONSE (DPHSR)

The DPHSR facilitates communication and data sharing between the national and provincial health departments and the NICD and provides epidemiological input to other NICD centres through collaborative projects. It also supports surveillance, epidemiological and research activities, and outbreak responses. DPHSR incorporates the GERMS-SA surveillance programme, provincial epidemiology team (PET), NMC surveillance unit and the outbreak response unit (ORU) that works closely with the emergency operations centre (EOC). Together, these teams contribute to national communicable disease surveillance and response efforts by providing systems for rapid alert and disease notification of public health importance and technical expertise to the country's provinces, districts and healthcare workers. In the past year, the DPHSR has been integral to the national and provincial COVID-19 pandemic responses, providing valuable epidemiological expertise and creating data platforms to monitor trends, testing, hospitalisations and deaths. DPHSR



representatives attended the national COVID-19 incident management team meetings with the NDOH.

The division undertakes several research activities in collaboration with NICD centres and national and international partners and teaches and trains intern scientists (SAFETP) students public health registrars, and microbiology registrars from various South African universities.

GERMS-SA collaborates with NICD centres to provide a national active surveillance programme for laboratory-confirmed bacterial and fungal infections, complemented by enhanced surveillance at sentinel hospital sites. This data informs and guides public health policymakers.

PET comprises epidemiologists based in eight South African provinces who support provincial health departments with the epidemiological interpretation of TB, HIV, and NMC data and support outbreak investigation and management activities. During the pandemic, this epidemiological support brought about better coordinated and structured data flow, management, and analysis processes within provincial response teams. PET also works with stakeholders to improve data collection and COVID-19-related death reports, including post-mortem COVID-19 testing on natural deaths outside of hospitals. The NMC unit provides a coordinated approach to South Africa's collection, collation, analysis, interpretation, and dissemination of public and private sector NMC through a real-time surveillance system. It provides information for targeted public health response, decision-making, and resource allocation. Since March 2021, the expanded NMC App is now available on all device platforms. The ORU and EOC provide technical support to national, provincial, and district health departments for communicable disease outbreaks and control and facilitate coordinating outbreak detection, investigation, and response activities, together with the appropriate NICD centres. The DATCOV hospital surveillance system has informed understanding of the SARS-CoV-2 epidemic evolution and is an

important alert mechanism for COVID-19 resurgences. The data informs hospital resource needs and provides insight into the severity and mortality during each wave.

NATIONAL CANCER REGISTRY (NCR)

The NCR is responsible for cancer surveillance, including its systemic collection, storage, analysis, interpretation, and reporting. Its primary roles are national pathology-based cancer surveillance and implementing population-based cancer registration. For the year under review, the NCR expanded its primary roles to include childhood cancer surveillance.

Within NHLS/NICD, the NCR is the only unit specialised in non-communicable disease surveillance. The registry's information offers an essential insight into South Africa's cancer landscape and affirms the NCR's vital role in cancer surveillance, a growing non-communicable disease of importance in the country.

The NCR met its key performance indicators for the year including publishing two national cancer incidence reports. The population-based surveillance team made every effort to catch up on data collection despite the difficulties faced during COVID-19. High-quality and complete cancer data collection was hindered with hospital wards closed, outpatient clinics suspended, and restrictions on surveillance officers' movements. Consequently, the overall case finding and data collection for 2020 decreased by 33.3% compared to 2018.

The newly established national childhood cancer registry published its first report on childhood cancer incidence (from birth to 14 years old) in 2018. There is a need for accurate childhood cancer estimates globally, but this is particularly difficult and scarce in sub-Saharan Africa. Annual reports of childhood cancers are the first steps toward improving this reporting and raising awareness. The cancer incidence reports for 2018 and 2019 was published on the NCR website (<https://>

www.nicd.ac.za/centres/national-cancer-registry/). In 2019 there was a 5.58% increase in cancer cases compared to 2018.

A decade-long cancer trend analysis (2010-2019) report was produced, providing a comprehensive and up-to-date overview of South African trends. Enacting Regulation 380, which made cancer reporting obligatory in 2011, is reflected by the increase in incidences between 2010 and 2012. The report's key findings are that breast cancer among women increased between 2010 and 2019 and is still the leading cancer diagnosis among women in the country. There was also a significant increase in prostate cancer incidence in men from 2010 to 2019.

The Ekurhuleni population-based cancer registry (EPBCR) report detailed the fourth year of population-based cancer registration in the Ekurhuleni metropolitan municipality. This includes cancers diagnosed in the 2020 calendar year. Data collection was conducted in 2020 and 2021, but the global pandemic posed significant international challenges to public health programmes, and the EPBCR was no exception. The overall case finding and data collection for 2020 decreased by 33.31% to 3,131 (2018: 4,695).

The challenges included:

- restricted access for EPBCR surveillance officers to collect cancer data in health facilities during the lockdown;
- misinterpretation of the Protection of Personal Information Act (POPIA), resulting in facilities being less willing to report cancer data and
- closure of Charlotte Maxeke Johannesburg Academic Hospital (a significant data source for EPBCR) due to the fires that occurred in 2021.

Despite these challenges, the report provides valuable information for key stakeholders to guide decision-making, planning of cancer initiatives and intervention programmes and essential data for evaluating health interventions.

A South African first was publishing a childhood cancer registry as a standalone report using the International Classification of Childhood Cancers Third Edition (ICCC-3). In total 975 cancers were diagnosed in children from birth to 14 years old in South Africa in 2018. This equated to an overall age-standardised rate of 59.8 cases per million (95%CI: 48.6-73.2), the most common group diagnosed with leukaemia followed trends. After that following lymphomas aligned with previous South African reports on childhood cancer incidence. Almost half of the cases (n=441) were diagnosed in children aged from birth to four years old and most of the results are comparable with regional and global trends.

DEPUTY DIRECTOR'S OFFICE

COVID-19's exceptional and protracted demands emphasised the importance of biosafety and biosecurity transversal functions, communication, information technology (IT), field epidemiology, and occupational health services. Despite challenging conditions, the teams remained resolute in achieving future-orientated goals. The biosafety and biosecurity division championed the secure operation of the NICD's high and maximum containment laboratory infrastructure under the biorisk management umbrella for biosafety biosecurity and biocontainment engineering.

The division was instrumental in developing several policies, including the regional training and certification programme and a regulatory and certification framework for African institutions handling high-risk pathogens. This work was subjected to rigorous review including numerous regional consultative meetings convened by Africa CDC and the division's team now leads the development of training materials with the support of a NIOH sub-committee and the University of the Witwatersrand's (Wits) Steve Biko Centre for Bioethics. In supporting the delivery of COVID-19 diagnostic services, the division facilitated the NHLS's mobile laboratory fleet biocontainment enhancements. The collaboration with Canada's Weapons Threat Reduction Programme supported the NHLS COVID-19 mobile diagnostic laboratories to enhance its national capacity to respond to the pandemic.

Construction of the 600m² regional diagnostics demonstration training centre, built in collaboration with the US Defence Threat Reduction Agency (DTRA), was finalised in March 2022. The modern facility provides secure and dedicated laboratory space for routine diagnostic procedure training. The design mimics the real laboratory environment meaning learners experience the appropriate infrastructure and operation that adhere to biosafety and biosecurity standards.

During the period under review, the communications unit fulfilled its vision of being a premier source of trustworthy and fact-based information for public stakeholders including healthcare providers and media professionals. In response to the ongoing epidemic, the team drafted and syndicated media statements and public health alerts and was instrumental in releasing daily and weekly COVID-19 surveillance reports.

The NICD website remains a reliable communicable disease information source and holds a significant content repository that requires frequent reviewing and updating. Since 2019 the website has recorded more than 45.2 million page views of which 15.1 million happened in the year under review. More than 10.2 million users have frequented the website since

2019 of which 4.1 million were in the past financial year. The unprecedented social media growth volume is testimony to the content quality shared across various platforms.

Since 2019 Twitter followers have increased by 113%, YouTube subscribers by 444%, and LinkedIn and Facebook communities recorded astounding growths of 1,654% and 3,640%, respectively.

The IT team focused on improving the COVID-19 laboratory test automation for public and private sectors while maintaining service levels above 98%. There was a soft launch of the re-engineered notifiable medical condition system with further developments underway.

One highlight was successfully implementing the sequencing centre's high-performance clustering system that enabled the rapid throughput required for sequencing data.

The South African field epidemiology training programme (SAFETP) uses an established applied epidemiology curriculum. It provides an accredited Master of Science (MSc) degree from either the University of Pretoria (UP) or the University of the Witwatersrand (Wits) with mentored practical field experience.

In addition to the advanced tier, SAFETP offers the frontline and intermediate tiers. Launched in 2016 the three-month in-service frontline tier training programme is the first step in the three-tiered FETP training model. The intermediate tier, launched in November 2021, is a nine-month in-service programme designed for health professionals and teaches the essential surveillance skills.

The programme has more than 104 graduates employed in the public sector, NDOH, private sector, Africa CDC, US CDC (in-country office) and WHO. The NICD employs 42 graduates located provincially or at NICD centres. Currently, the programme has 29 residents.

SAFETP's significant impact in this reporting period involved graduates and residents in COVID-19-related surveys and the SARS-CoV-2 school transmission research study in collaboration with MRC, the Western Cape health and education departments, and the University of Cape Town.

SEQUENCING CORE FACILITY (SCF)

The transversal SCF supports the NICD centres' NGS needs by providing sustainable solutions and enabling early outbreak or epidemic detection to respond to or anticipate imminent outbreaks or epidemics effectively. The Illumina SCF has received SANAS 17025 accreditation for Illumina sequencing and WGS.

The facility supported the Africa CDC, ASLM, and Africa Pathogen Genomics Initiative (Africa PGI) for SARS-CoV-2 sequencing for Namibia, Sudan, Eswatini, Lesotho, and Mauritius. With support from the Fleming Fund SEQAFRICA funding, bacterial sequencing (*Salmonella* sp, *E. coli*, *S. typhi*, *P. aeruginosa*, *K. pneumoniae*) was performed for participating African countries to monitor MLST, AMR, and virulence genes.

APPRECIATION

The NICD thanks the NHLS for its innovative leadership and ongoing laboratory support during the global pandemic. It also acknowledges the technical and financial support from the NDOH, the National Treasury, and its development and technical partners. The institute remains resolute and unswerving in its efforts to manage communicable diseases and inform public health policies. It believes that improving regional and global collaborative efforts will contribute to everyone's betterment, and its successes will ultimately benefit society.





DEPUTY DIRECTOR'S OVERVIEW

DR NATALIE MAYET

The exceptional and protracted demands of the COVID-19 pandemic emphasised the importance of transversal functions of biosafety and biosecurity, communication, information technology (IT), field epidemiology and occupational health services.

Despite challenging conditions, the teams remained resolute in achieving future-orientated goals.

The NICD operates in a complex environment with interdependence on multiple stakeholders at local, national, regional and international levels both within government and non-state sectors. Against this backdrop, the NICD consolidated its partnerships and strengthened networks through dialogue, shared expertise, research collaboration and joint exploration to improve global health security.

BIOSAFETY AND BIOSECURITY

The Biosafety and Biosecurity Division championed the NICD's secure operation of the high and maximum containment laboratory infrastructure under the biorisk management umbrella for biosafety, biosecurity and biocontainment engineering.

The NICD imports and exports biological materials in collaboration with other institutions in 30 countries including 25 in Africa and the division manages the National Department of Health (NDOH) diagnostic and research import/export blanket permit. During the review period, it reported on the use of 376 diagnostic and 136 research permits.

The division has been instrumental in developing several policies including the regional training and certification programme and the regulatory and certification framework for institutions handling high risk pathogens for Africa. This work has been subject to rigorous review including numerous regional consultative meetings convened by Africa CDC and with support from the National Institute for Occupational Health (NIOH) and the University of the Witwatersrand's (Wits) Steve Biko Centre for Bioethics, the Biosafety and Biosecurity Division team is now leading the development of training materials. The specialist team provides expertise for national, regional and international institutions:

NATIONAL

- Leading the local communication and advocacy for the Africa CDC regional biosafety and biosecurity legal framework for African Union (AU) member states.
- Voting membership on the South Africa Bureau of Standards (SABS) technical working committees and sub-committees in developing BSC national standards.

REGIONAL

- Developed the Africa CDC regional training and certification programmes in four specialised areas: the selection, installation, maintenance and certification of biological safety cabinets; biorisk management; design and maintenance of facilities handling high risk pathogens (biocontainment engineering) and biological waste management.
- Membership of the Africa CDC Southern Africa regional collaborating centre regional biosafety and biosecurity regional technical working group (RBB-TWG).
- The biorisk specialist served as the African Biological Safety Association vice-president in the 2020-2021 cycle and is the current 2021-2022 president-elect.

INTERNATIONAL

- South Africa nominated experts for the secretary-general's mechanism for the alleged use of chemical and biological weapons (UNSGM).
- Contributed to establishing the signature initiative to mitigate biological threats in Africa and has representation on the biosafety and biosecurity working group. The signature initiative (SI) is being developed by the global partnership against the spread of weapons and materials of mass destruction in collaboration with the Africa CDC and other partners.
- The biorisk specialist served as an International Federation of Biosafety Associations (IFBA) mentor in the IFBA mentorship programme.

As part of efforts to support the delivery of COVID-19 diagnostic services, the division facilitated the biocontainment enhancements of the NHLS's mobile laboratory fleet. The collaboration with Canada's weapons threat reduction programme supported the NHLS COVID-19 mobile diagnostic laboratories, enhancing the national capacity to respond to the pandemic.

TEACHING AND TRAINING

In total 355 participants benefited from the 13 CPD-accredited training events specifically aimed at improving the NICD's biosafety and biosecurity awareness and capacity in topics of:

- bio risk management;
- BSL3 staff training;
- working safely in BSCs;
- dual use research of concern and bioethics and
- IATA shipping course and practical exams.

Construction of the regional diagnostic demonstration centre was achieved in March 2022. Built in collaboration with the US Defence Threat Reduction Agency (DTRA), the 600m² modern facility is designed to provide secure and dedicated laboratory training space in routine diagnostic procedures. The design mimics the laboratory environment to ensure learners experience the operations of high containment laboratories.

The division's staff attended various virtual conferences including:

- the inaugural Biosecurity Virtual Symposium, American Biological Safety Association, Chicago, US. 2021 and
- the 64th Annual Biosafety and Biosecurity Virtual Conference, American Biological Safety Association, USA. 25-27 October 2021.

COMMUNICATIONS

During the period under review, the communications unit remained committed to ensure that the NICD was the premier source of trustworthy and fact-based information for its various public stakeholders including healthcare providers and media professionals. In response to the epidemic, the team drafted and syndicated media statements and public health alerts and were instrumental in releasing daily and weekly COVID-19 surveillance reports.

The NICD website remains a reliable source of communicable disease information and holds a significant repository of content that requires frequent reviewing and updating. Since 2019 the website has recorded more than 45.2 million page views of which 15.1 million are attributed to the year under review. Furthermore, over 10.2 million users have frequented the website since 2019 an increase from the 4.1 million users in the past financial year.

The growth volume experienced on social media was unprecedented and testimony to the quality of the content shared across the NICD's various platforms. Since 2019 each platform has enjoyed notable year-on-year growth. Twitter followers have increased 113%; YouTube subscribers 444%, LinkedIn 1,654% and Facebook 3,640% respectively – an outstanding growth record and notable achievement in engaging communities with science.

The internal newsletter NICD Pulse delivers employees with important content about relevant topics while the public dissemination of the Communicable Diseases Communiqué shares information concerning communicable diseases of interest to both public and international readers.

Distributed quarterly, the research publication The Science Focus contained an impressive 254 peer-reviewed publications for the year under review.

INFORMATION TECHNOLOGY

The IT team focused on improving COVID-19 laboratory test automation for both the public and private sector while maintaining service levels above 98%. There was a soft-launch of the re-engineered notifiable medical condition system with further developments underway. A highlight was the successful implementation of the high-performance clustering system for the sequencing centre, enabling rapid throughput required of sequencing data.

SOUTH AFRICAN FIELD EPIDEMIOLOGY TRAINING PROGRAMME (SAFETP)

SAFETP uses an established applied epidemiology curriculum, providing an accredited Master of Science (MSc) degree from either the University of Pretoria (UP) or University of the Witwatersrand (Wits) with mentored practical field experience.

In addition to the advanced tier, SAFETP offers frontline and intermediate tiers. Launched in 2016, the frontline tier is a three-month in-service training programme and the first step in the three-tiered FETP training model. The intermediate tier was launched in November 2021 as a nine-month, in-service programme designed for health professionals and providing participants with essential surveillance skills.

To date, the programme has more than 104 graduates employed in the public sector or ministry of health, private sector, Africa CDC, US CDC (in-country office) and the World Health Organisation (WHO). There are 42 graduates employed by the NICD and located in the provinces or NICD centres. Currently, the programme has the largest cohort of 29 residents. Over 90 scientific manuscripts have been published in peer-reviewed scientific journals by SAFETP residents who participate in major scientific conferences including AFENET, TEPHINET, EIS, PHASA and PathRed.

SAFETP's significant impact in this reporting period was involving graduates and residents in COVID-19 related surveys and research, such as the SARS-CoV-2 school transmission study in collaboration with the South African Medical Research Council (MRC), Western Cape departments of health and education and the University of Cape Town.

The programme secured \$905,000 (R15.4 million) from the US CDC and \$9,852 (R167,582) from AFENET to continue its training activities.

OUTBREAKS

Residents and NICD centre staff, alongside provincial or district communicable diseases control (CDC) coordinators, responded to more than 30 outbreaks in this reporting period. These include COVID-19 clusters, avian influenza, diphtheria, adverse events following COVID-19 vaccines, rabies, typhoid fever, suspected tetanus cases, food-borne illnesses and others.

The food-borne outbreaks highlight the need to collect food samples and strengthen the laboratory component to isolate the suspected microbial agents.

The rabies cases investigated emphasise the need to increase dog bite awareness and animal vaccination in the community

and increase the index suspicion of rabies and wound management among healthcare workers.

The typhoid fever outbreak among illegal miners demonstrated the gaps in hand hygiene, sanitary and water safety practices while they work underground. Targeted messaging for illegal miners was recommended to focus on treating water with bleach and optimising hand hygiene.

COVID-19 RELATED SURVEYS AND RESEARCH STUDIES

- SAFETP residents and staff, in collaboration with WHO, supported the Mpumalanga Department of Health to conduct a KAP survey regarding COVID-19 vaccinations among healthcare workers and the general population.
- The SAFETP team were deployed to support a KAP survey in collaboration with the Free State and Thabo Mofutsanyane district COVID-19 incidence management team. The findings will secure a better understanding of the knowledge gaps, perceptions and behaviour toward COVID-19 in the community.
- Residents were involved in six other studies as part of their core learning activities.



TEACHING AND TRAINING

In the year under review, six residents graduated; four from the 2019 cohort graduated with a Master of Public Health (MPH) conferred by UP and two a MSc in epidemiology conferred by Wits.

In January 2022 the SAFETP staff welcomed 14 residents in the sixteenth cohort of six medical technologists, two nurses and nutritionists and one veterinarian, physiotherapist, forensic scientist and health technologist. The programme builds field epidemiology capacity in neighbouring countries with two eSwatini residents in the 2022 cohort.

INTERMEDIATE TRAINING

To increase epidemiologic capacity for outbreak response and public health surveillance, intermediate level training was launched in November 2021. This nine-month competency-based training course saw 16 Eastern Cape provincial Department of Health healthcare professionals enrolled as residents in the initial cohort.

Four workshops were conducted in this reporting period.

FRONTLINE TRAINING

In the period under review, SAFETP conducted four additional frontline training sessions for 50 healthcare professionals in Limpopo and Mpumalanga as well as the Lesotho Ministry of Health and Tshwane University of Technology (TUT) environmental health students, using a hybrid approach.

In addition to Frontline training, the SAFETP team has conducted two virtual basic epidemiology short courses. Thirty health officials from the Gauteng Research and Evaluations Training Programme attended a virtual "Introduction to Epidemiology" training.

Fifty-two Environmental Health Practitioners (EHPs) from Gauteng Department of Health attended "Basic Epidemiology" training. The curriculum included an introduction to epidemiology, public health surveillance and outbreak investigations.

WORKSHOPS

The programme hosted a virtual scientific writing workshop for 10 participants who will support SAFETP second-year residents and recent graduates. The Dale Carnegie Leadership training and the team attended PurpleZa Google workspace training relating to the Google Workspace platform.



OCCUPATIONAL HEALTH

The on-site occupational health clinic provided SARS-CoV-2 testing with 209 staff testing positive for SARS-CoV-2 at the Sandringham campus since the March 2020. In the previous financial year 121/764 test recipients (15.8%) tested positive against 173/731 (23.7%) in the 2021/2022 financial year; an increase coinciding with South Africa's fourth wave.

Wellness visits averaged 12 per month, consistent with previous years, and include blood pressure and glucose checks and general consultations with referrals when necessary. The clinic performed 72 immunity checks with 16 vaccines administered. A significant achievement was the partnering with Gauteng DOH Travel Clinic who provide vaccines including yellow fever and malaria prophylaxis to staff travelling for work purposes.

There were 16 injuries on duty this year (2020/2021: 40) largely attributed to fewer man-hours and less construction on-site. There was one trip and fall injury requiring hospitalisation from a wrist fracture. One occupational disease was reported to the Department of Labour of an employee who tested positive for pulmonary TB, but based on investigations, it is unlikely the exposure was at the workplace. There were 39 possible workplace COVID-19 exposures due to the inherent risks of surveillance officers being in close contact with patients.

The NICD occupational health nurse trained and evaluated about 200 registered nurses on procedures to obtain blood through skin prick and phlebotomy as part of a Centre for HIV project.

DEPUTY DIRECTOR

The deputy director has participated in COVID-19 IMT meetings since the beginning of the pandemic and is involved in the case management working group and recently the long-COVID surveillance working group.

Extensive Engagement with Africa CDC continues as a member of the African Taskforce for Coronavirus steering committee (AFCOR) and as the case management working group co-chair. The deputy director also serves on the INAPHI and BMGF executive committees to support developing the WHO Berlin Hub and serves on the two TEPHINET strategic leadership groups promoting FETP institutionalisation and integrating the FETP Enterprise with key global health programmes and priorities.

Over the last year the deputy director mentored a fellow as part of the Africa CDC Kofi Anan Leadership Programme and continues as a board member of the Institute of Social and Health Science (ISHS), focusing on injury and violence prevention and burn injury surveillance.

There is extensive collaboration with WHO to advance provincial epidemiological capacity with the organisation employing three FETP alumni on short-term contracts in Mpumalanga, KwaZulu-Natal and Limpopo. Equally, engagement continues with the non-government organisation Right to Care for coordinating \$1.5 million (R25.5 million) USAID funding to support sequencing laboratory and information technology capacity.



The NICD secured four rapid responders from Africa CDC – three epidemiologists and a graphic designer to support the Emergency Operating Centre (EOC), Mpumalanga, NICD centres and communications. The deputy director also managed grants secured in the last quarter worth \$2.49 million (R42.46 million) including funding from the US CDC Foundation for three Data for Health Projects. The non-government organisation Gift of the Givers donated a modular office unit to accommodate social distancing for FETP staff and residents. The estimated value is R1.5 million and construction is now completed.

A diversity talk, organised with Prof Jonathan Jansen, on 23 March 2022 was attended by 191 people. The deputy director's office also hosted two Namibian delegations during the year under review.

RESEARCH OUTPUTS

ARTICLES

- Norlock, S.M., Okanya, P.W., Trataris, A. et al. South-to-south mentoring as a vehicle for implementing sustainable health security in Africa. *One Health Outlook* 3, 20 (2021). <https://doi.org/10.1186/s42522-021-00050-x>
- Amar S, De Boni L, de Voux A, Heath L and Geertsma P. An outbreak of African swine fever in small-scale pigs,

Gauteng, South Africa, July 2020 <https://doi.org/10.1016/j.ijid.2021.04.003>

- Ndlovu BC, Sengayi-Muchengeti M, Kellett P, Kuonza L, Cubasch H, Singh E and Chen WC. Completeness of Reporting for Breast Cancer Data in the National Pathology-based Cancer Registry in South Africa.
- De Boni L, Msimang V, De Voux A and Freaun J. Trends in the prevalence of microscopically confirmed schistosomiasis in the South African public health sector, 2011–2018 <https://doi.org/10.1371/journal.pntd.0009669>
- De Boni L, Mall S, Msimang V, de Voux A, Rossouw J and Freaun J. Exposure of South African Abattoir Workers to *Coxiella burnetii*. *Tropical medicine and infectious disease*. 2022 Feb 16; 7(2):28. <https://doi.org/10.3390/tropicalmed7020028>

PRESENTATIONS

NICD staff made presentations at two international and five local conferences.





CENTRE FOR EMERGING ZOO NOTIC AND PARASITIC DISEASES (CEZPD)



CENTRE FOR EMERGING ZOOONOTIC AND PARASITIC DISEASES

PROF JANUSZ PAWESKA

BACKGROUND

CEZPD is a national and regional hub for diagnosis, surveillance, outbreak response, research, teaching and training which is related to zoonotic viral, bacterial and parasitic diseases, particularly those associated with risk group three and four pathogens, and including the following:

- Viruses causing haemorrhagic fever (VHF) such as Ebola and Marburg virus disease, Lassa fever and Lujo haemorrhagic fever
- Arthropod-borne diseases such as Rift Valley fever (RVF), Crimean-Congo haemorrhagic fever (CCHF), yellow fever, dengue fever, chikungunya, Sindbis fever, West Nile fever, Zika virus disease, malaria, plague and rickettsioses
- Rabies and other lyssavirus infections
- Bacterial diseases such as anthrax, botulism, brucellosis and leptospirosis
- Parasitic opportunistic infections
- Diarrhoeal disease in children under five years of age
- Schistosomiasis
- Soil-transmitted helminthic diseases

The CEZPD contributes to policy advice and technical support, as well as training of scientists, epidemiologists, health care workers and medical doctors in the field of emerging and re-emerging zoonotic and parasitic diseases. It is an internationally recognised resource of expertise for referral diagnostic services, outbreak response and consultations under the World Health

Organization's (WHO) Regional Reference Laboratory for Plague mandate and the WHO Global Outbreak Alert and Response Network (GOARN).

The Centre plays an important role in supporting the provincial, national and regional malaria control and elimination programmes and operates highly specialised laboratory facilities including:

- An array of different containment facilities including biosafety level (BSL) 2, BSL3 and positive-pressure suit BSL4 laboratories.
- An transmission electron microscope laboratory
- Insectaries for housing the vectors of malaria and arboviruses for insecticide resistance and vector competence studies.

These facilities constitute a key resource capacity for diagnosis, surveillance, outbreak response and research of priority zoonotic viral, bacterial and parasitic diseases in Africa.

SURVEILLANCE

The Special Viral Pathogens Laboratory (SVPL) continued passive laboratory-based surveillance for human rabies, arboviruses and VHFs. Figure 1 reflects the provincial distribution of laboratory-confirmed human rabies cases for 2011 to 2022 with KwaZulu-Natal, the Eastern Cape and Limpopo provinces reporting the majority of cases. Human rabies is a Category I notifiable medical condition (NMC) in South Africa.

During 2021 the SVPL confirmed a single case of CCHF from the Western Cape and another case from the same province in February

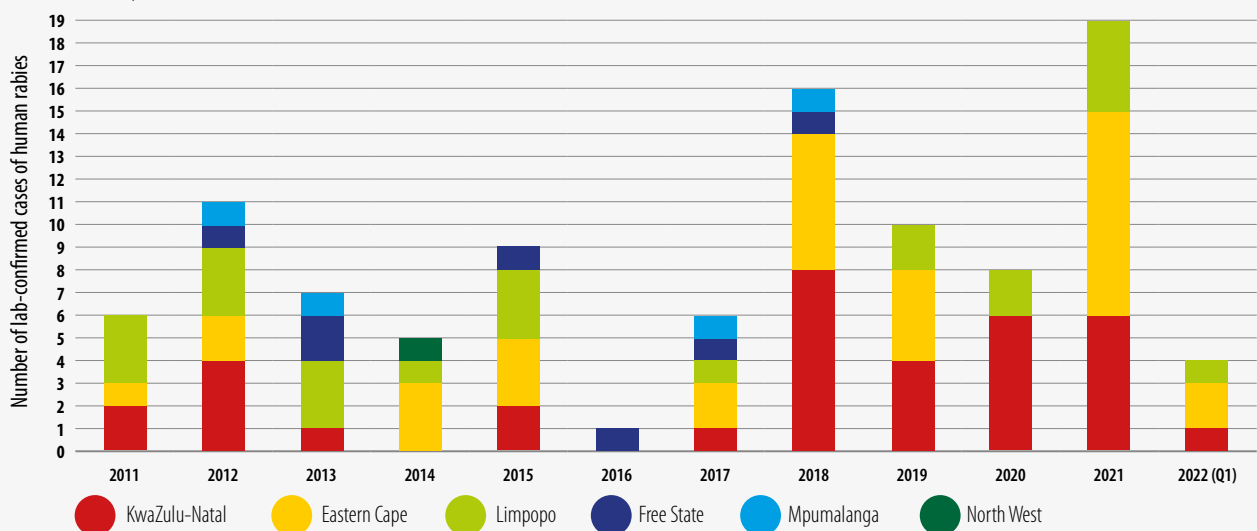


Figure 1. Laboratory-confirmed human rabies cases by province, South Africa, 2011-2022 (Quarter 1: 1 January - 31 March)

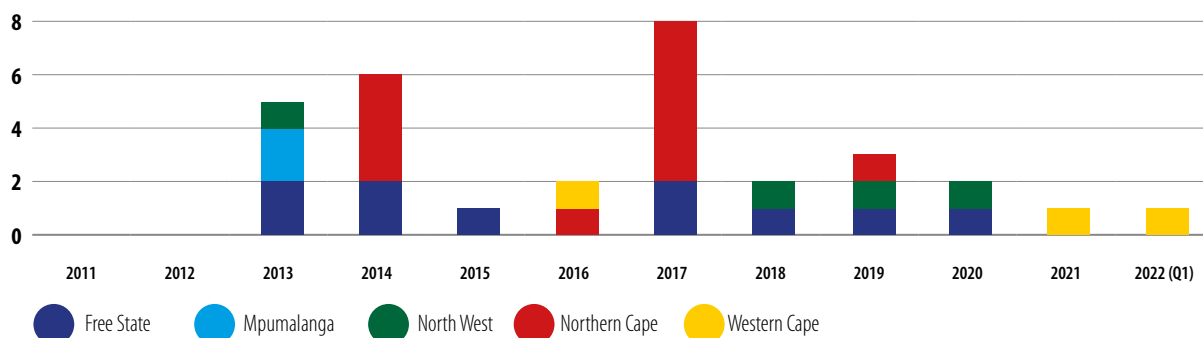


Figure 2. Laboratory-confirmed CCHF cases by province, South Africa, 2011-2022 (Quarter 1: 1 January - 31 March)

2022. The provincial distribution of laboratory-confirmed CCHF cases from 2011 to 2022 is shown in Figure 2. Although historically CCHF cases have been reported across the country, the majority have been recorded from the Free State, Northern Cape and North West. VHF is a Category I NMC in South Africa.

To alert public health authorities to the possibility of increased human plague risk, the CEZPD Special Bacterial Pathogens Reference Laboratory (SBPRL) continued surveillance for plague in susceptible rodent populations in the Nelson Mandela Bay (Coega area) and eThekweni municipalities. No rodents tested positive for plague anti-F1 antibodies.

A total of 9,465 *Anopheles* mosquitoes was referred to the CEZPD Vector Control Reference Laboratory (VCRL) from sentinel sites in the KwaZulu-Natal, Mpumalanga and Limpopo provinces. The presence of five malaria vector species (*Anopheles arabiensis*, *An. merus*, *An. vaneedeni*, *An. funestus* and *An. parensis*) that contribute to South Africa's ongoing residual malaria transmission were identified among these collections (Figure 3).

The CEZPD Parasitology Reference Laboratory (PRL) conducts smear cross-checking on blood smears made for malaria surveillance in Mpumalanga Provincial Department of Health. All positive and 20% of negatives were checked by microscopy (n=1,049 for 2021) and polymerase chain reaction (PCR).

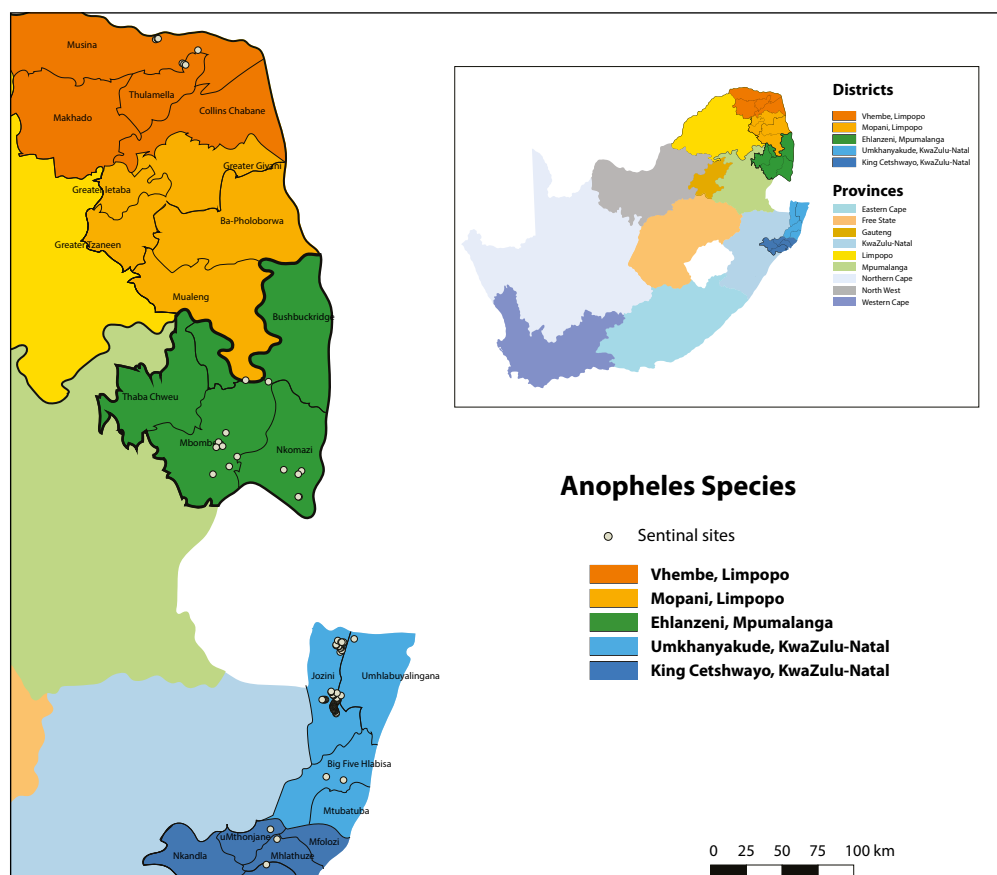


Figure 3. Sentinel sites in KwaZulu-Natal, Mpumalanga and Limpopo from which *Anopheles* specimens were collected

OUTBREAKS

During 2021 there was a significant increase in dog rabies from eThekweni (KwaZulu-Natal) and Buffalo City and Nelson Mandela Bay (Eastern Cape) municipalities. The resurgence of canine rabies in these provinces is considerable and a high number of cases were also reported in the first quarter of 2022. The ongoing epizootics of dog rabies have fuelled the number of reported human rabies cases with 17 laboratory-confirmed cases between 1 April 2021 and 31 March 2022 from these two provinces.

The CEZPD PRL and VCRL investigated eight outbreaks of Odyssean malaria. This form of malaria is acquired in non-endemic areas by persons with no travel history, transmitted by infected mosquitoes that are likely imported in road vehicles such as minibus taxis. These outbreaks affected 14 individuals, with one death. The outbreaks highlight the large flow of traffic into Gauteng province from surrounding malaria-endemic provinces and neighbouring countries.

DIAGNOSTIC SERVICES

The SVPL confirmed 21 human rabies cases from 1 April 2021 to 31 March 2022, reported from the Eastern Cape (n=11); KwaZulu-Natal (n= 6) and Limpopo (n=4)(Figure 4).

There were 17 suspected viral haemorrhagic cases during the period under review with two confirmed CCHF cases. South Africa's first imported case of hantavirus infection was confirmed in 2021, involving a South African businessman with travel and exposure history in Croatia. The CEZPD ARL investigated endemic and exotic arboviral disease cases including chikungunya, RVF, dengue, Zika, Ross River and Japanese encephalitis. The laboratory experienced around a 20% increase in diagnostic submissions to 90 (2020/2021: 71). The CEZPD SBPRL provided specialised diagnostic services for zoonotic

bacterial pathogens causing diseases including anthrax, plague, leptospirosis, botulism and brucellosis. There were 26 probable cases of leptospirosis and two cases of brucellosis caused by *Brucella abortus* detected, while a case of melioidosis (caused by *Burkholderia pseudomallei*) was confirmed in a Namibian patient. No cases of anthrax, botulism or plague were detected during the reporting period. The CEZPD PRL provided specialised diagnostic services for parasites of medical importance both by conventional methods and, increasingly, PCR assays. There was a high rate of positives among the *P. jirovecii* PCR tests (28%, 62/220). Many malaria PCR tests were positive for *P. falciparum*. Interesting Parasitic helminths identified by microscopy included *Bertiella* species and *Echinococcus* species. The CEZPD PRL, with financial support from the Global Fund and the Eliminating Eight (E8) countries, maintained and managed the Regional Malaria Slide Bank and Proficiency Testing (PT) scheme for supporting malaria laboratory diagnosis in southern African countries. In 2021, 9,851 slides in 44 batches were manufactured for microscopist training and external quality assessment by participating regional laboratories. A total of six (three per year) PT surveys were conducted. Training slide sets were also prepared and supplied to each country.

RESEARCH ACTIVITIES

REDUCING THE THREAT OF RIFT VALLEY FEVER (RVF) THROUGH ECOLOGY, EPIDEMIOLOGY AND SOCIO-ECONOMICS (2019-2024)

NICD investigators: J Paweska, V Msimang, A Kemp, O Hellferscee and J Weyer

Collaborators: P Thompson (University of Pretoria), M Rostal, W Karesh, W Whitney, C Machalaba (EcoHealth Alliance, USA); C Cordel (ExecuVet, South Africa), A Lubisi and Z Mdlulwa (Agriculture Research Council – Onderstepoort Veterinary Research)

This ongoing One Health RVF study, coordinated by the NICD, University of Pretoria and EcoHealth Alliance, aims to investigate the disease's impact and improve the capacity to predict future outbreaks. It addresses the socio-economic consequences of RVF on individuals and national levels and monitors satellite-collected meteorological data to create an early warning system. The projects encompass 40 000 km² in the Free State and Northern Cape including areas affected by major RVF outbreaks like the 2010-2011 epidemic. In the Free State long-term research studies continue on:

- RVF virus infection rates in sheep between outbreaks;
- duration of humoral immunity in sheep following vaccination with RVF (Smithburn vaccine) and
- seasonal dynamics in mosquito populations.

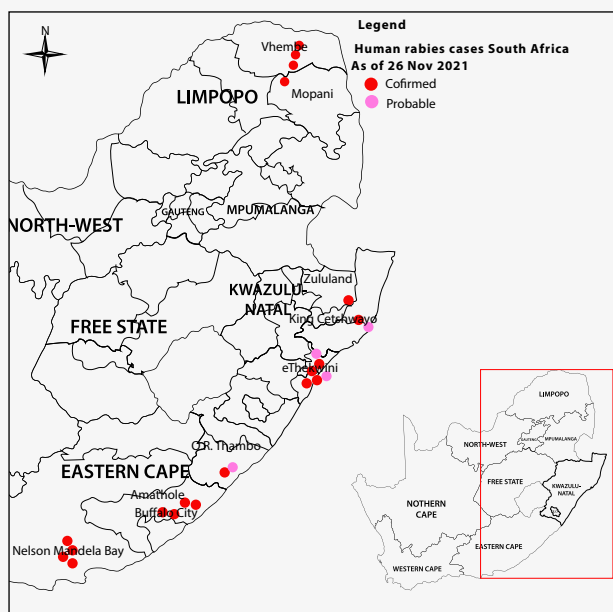


Figure 4. Geographic distribution of laboratory-confirmed human rabies in South Africa, 1 April 2021-31 March 2022

Since 2019 the study has expanded to a 1000km² area in northern KwaZulu-Natal where no major outbreaks have been reported to date, but recent studies demonstrate an active circulation of RVF virus among domestic and wild ruminants and humans.



Figure 5a. One Health RVF project in the Free State – collecting of mosquitoes using CO₂ traps



Figure 5b. Identifying the collected mosquitoes under a light microscope in the field-established laboratory with post-graduate students (left); Prof P Thompson (University of Pretoria, top right) and J Kgatitsoe (NICD CEZPD - bottom right).

DETECTION OF MAMMARENAVIRUSES FROM RODENTS FROM SELECTED SOUTH AFRICAN AND ZIMBABWEAN LOCATIONS

NICD investigators: A Grobbelaar, J Weyer and J Paweska

Collaborator: R Swanepoel (University of Pretoria)

A bio-surveillance study conducted targeting myomorph rodents from South African and Zimbabwean locations between 1964 and 1994 found wide-scale seropositivity against mammarenavirus antigens. From 5,363 serum samples taken from 39 rodent species, the positivity rate ranged between 1.2% and 31.8% in 14 species of myomorph rodents. In addition, 19 mammarenavirus isolates were obtained from serum specimens and viscera of four seropositive species. Phylogenetic analysis on the basis of partial nucleoprotein sequences indicates 14 isolates from *Mastomys natalensis* (Natal multimammate mouse) were Mopeia virus, whereas the Merino Walk virus was characterised as novel in a separate study. The remaining four isolates from three rodent species potentially constitute novel viruses pending full characterisation.

DEVELOPMENT OF A PAN-FILOVIRIDAE REAL-TIME PCR FOR BIO-SURVEILLANCE AND DIAGNOSIS

NICD investigators: J Coertse, A Grobbelaar, N Moolla and J Weyer

Collaborators: W Markotter (University of Pretoria)

Filovirus outbreaks are of zoonotic origin and associated with high mortality and morbidity rates and improved, rapid filovirus assays allowing for the detection of diverse filovirus species are needed. In collaboration with the Southern African Bat Research Network (SABRENet), a SYBR green-based real-time PCR assay was developed to detect the currently known filovirus species to enhance surveillance efforts and build regional capacity.

VECTOR COMPETENCE OF BAT-ASSOCIATED FLIES FOR MARBURG VIRUS TRANSMISSION IN EGYPTIAN ROUSETTE BATS

NICD investigators: J Paweska, P Jansen van Vuren, N Storm and A Kemp

Collaborators: W Markotter (University of Pretoria)

The Egyptian rousette bat (ERB) is implicated as a natural reservoir host for Marburg viruses, but their maintenance and transmission among ERB remain elusive. This knowledge gap hampers our understanding of spill-over mechanisms and the potential role of bat ectoparasites in transmission of these viruses has been postulated.

This study aimed to determine the vector competence of bat-associated nycteribiid flies (*Eucamsipoda africana*) for Marburg virus in the ERB. The study also tested bat flies collected from a wild ERB colony in Mahune Cave, Limpopo, South Africa, where enzootic transmission of Marburg virus occurs. While results from this preliminary study potentially demonstrate bat flies do not act as biological vectors, their role in mechanical and oral transmission through direct consumption (namely during auto-and allo-grooming) of bat flies engorged with Marburg virus contaminated blood has not yet been excluded. Refer to figures 6a-c.

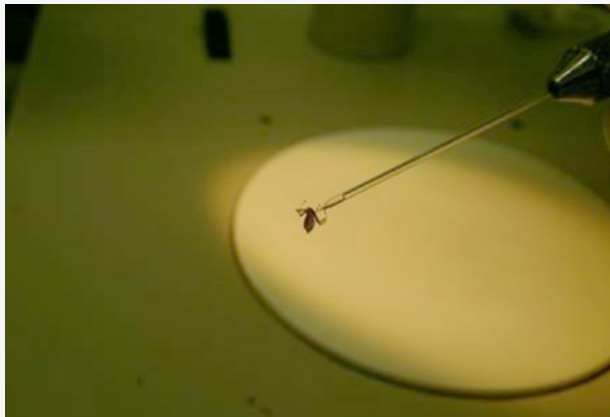


Figure 6a. Inoculating bat flies with Marburg virus under a stereomicroscope



Figure 6b. Releasing Marburg virus-inoculated flies on bats



Figure 6c. Collecting flies experimentally inoculated with the Marburg virus with Dr N Storm (right) and Prof J Paweska (left)

VALIDATION OF AN INDIRECT ELISA BASED ON RECOMBINANT NUCLEOCAPSID PROTEIN OF THE RVF VIRUS FOR THE DETECTION OF IgG ANTIBODY IN DOMESTIC RUMINANTS

NICD investigators: J Paweska, P Jansen van Vuren and V Msimang

Collaborators: M Lo, Y Thiongane (Laboratoire National de l'Elevage et de Recherches Vétérinaires, Senegal), L Mulumba-Mfumumu (University of Kinshasa), A Mansoor (Central Veterinary Laboratory, Yemen), J Fafetine (Modlane University, Mozambique), J Magona (National Livestock Resources Research Institute, Uganda), H Boussini (Central Veterinary Laboratory, Burkina Faso), B Bazanow (University of Environmental and Life Sciences, Poland), W Wilson (US Department of Agriculture), M Pepin (L'Agence Française de Sécurité Sanitaire des Aliments, France), H Unger and G Viljoen (International Atomic Energy Agency, Austria)

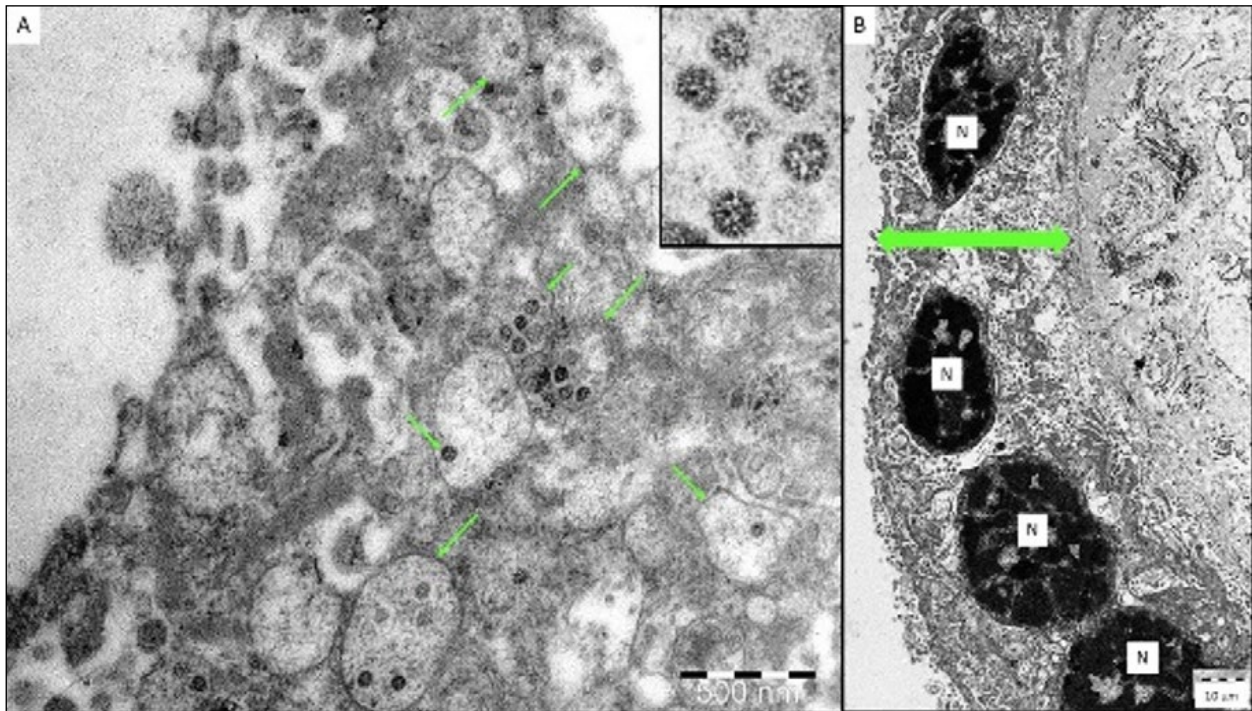
Diagnostic performance of an indirect enzyme-linked immunosorbent assay (I-ELISA) based on a recombinant nucleocapsid protein (rNP) of the RVF virus was validated for detecting the IgG antibody in domestic ruminants from RVF-endemic (Burkina Faso, Democratic Republic of Congo, Mozambique, Senegal, Uganda and Yemen) and RVF-free countries (France, Poland and USA). The results of this large-scale international validation study demonstrate the high diagnostic accuracy of the RVFV rNP I-ELISA. Standard incubation and inactivation procedures evaluated did not adversely affect the detectable levels of the anti-RVFV IgG in ruminant sera and thus, together with recombinant antigen-based I-ELISA, provide a simple, safe and robust diagnostic platform that can be automated and carried out outside expensive bio-containment facilities. These advantages are particularly important for less-resourced countries where there is a need to accelerate and improve RVF surveillance and research on epidemiology while advance disease control measures.

THE ULTRASTRUCTURE OF PATHOGENS

NICD investigators: M Birkhead

Collaborators: AJ Glass (Lancet Laboratories, University of the Witwatersrand), H Allan-Gould (Sandton Mediclinic), C Goossens (Sandton Mediclinic) and CA Wright (Lancet Laboratories, University of the Witwatersrand)

The ultrastructural identification of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in infected tissues has been globally problematic. A placental sample from a mother and neonate, both testing positive by PCR for the virus in which histological observations supported a case of vertical transmission, was processed for electron microscopy. This resulted in the first publication of micrographs confirming virion presence in placental tissue. Refer to figure 7.



(A) Numerous membrane-bound vesicles (arrows) containing spherical virions. Inset: black dots within the sectioned virions are nucleocapsid profiles.

Figure 7. SARS-CoV-2 virions in placental tissue.

(B) The multinucleate (N), infected syncytiotrophoblast layer (arrow) of the placental tissue. This is the outermost layer of the placental membrane of foetal villi.

EXPOSURE TO Q FEVER AMONG SOUTH AFRICAN ABATTOIR WORKERS

NICD investigators: L De Boni, Alex De Voux, V Msimang, J Rossouw, and J Frean

Collaborators: S Mall (School of Public Health, University of the Witwatersrand)

Abattoir workers may contract the zoonotic bacterial infection Q fever (QF) by inhaling the pathogen in aerosols from slaughtered animals or in contaminated dust. This study examined the seroprevalence of QF and associated factors in South African abattoir workers. Among 382 workers from 16 facilities, the overall seroprevalence was 33% (95%CI: 28–38%) and ranged from eight to 62% at facility-level. Prolonged contact with carcasses and/or meat products (odds ratio OR: 4.6, 95%CI: 1.51–14.41) and prior abattoir and/or butchery work experience (OR: 1.9, 95%CI: 1.13–3.17) were associated with QF seropositivity.

TRENDS IN THE PREVALENCE OF MICROSCOPICALLY-CONFIRMED SCHISTOSOMIASIS IN THE SOUTH AFRICAN PUBLIC HEALTH SECTOR, 2011–2018

NICD investigators: L De Boni, A De Voux, V Msimang and J Frean

This descriptive analysis of secondary data from the National Health Laboratory Service (NHLS) included records of patients for whom microscopic examination detected *Schistosoma* species eggs in the urine or stool. Crude estimates of the prevalence

were calculated and simple linear regression used to analyse prevalence trends. The prevalence remained consistent during the eight-year period, independent of increasing annual testing volumes. The groups with the highest burden included males aged five to 19 years with highest-burdened schistosomiasis-endemic areas being Limpopo, Mpumalanga and KwaZulu-Natal. There is also an ongoing outbreak in the Eastern Cape.

ASSESSING NOVEL/ALTERNATIVE METHODS OF MALARIA VECTOR CONTROL IN SOUTH AFRICA

NICD investigators: G Munchenga, S Oliver, Y Dahan-Moss, M Kaiser, E Jamesboy, P Manana, L Koekemoer and B Brooke

Anopheles arabiensis is a major malaria vector in South Africa and assessing the feasibility of the sterile insect control technique involved a key field exercise to establish the population size and dispersal range of *An. arabiensis* in northern KwaZulu-Natal. The data obtained is essential for subsequent field trials of this novel control method.

Additionally, a recent study shows recombinant Akirin vaccines can develop a protective response against *An. arabiensis*, providing an important step in developing novel interventions against this vector species. It was also shown that exposure of *An. arabiensis* larvae to cigarette pollution increases their tolerance to certain insecticides formulated for vector control, thus adding to the database on those environmental factors affecting the development and expression of insecticide resistance in vector species.



Figure 8. Assessing *Anopheles* mosquito dispersal distances in northern KwaZulu-Natal.

POLICY CONTRIBUTIONS

The Centre contributed to reviewing and developing policies, guidelines, operating procedures and strategies for the following:

- contributions to the latest WHO guidelines (manual for monitoring insecticide resistance in mosquito vectors and selecting appropriate interventions) for detecting insecticide resistance in malaria vector populations;
- developing national guidelines for preventing human rabies in South Africa: review of the Hazardous Biological Agent Regulations of the Occupational Health and Safety Act on request by the Department of Employment and Labour;
- contributing to the WHO manual for plague surveillance, diagnosis, prevention and control review;
- contributing to the strategic development and operations policies of the WHO global outbreak alert and response network and inputs to strengthening the global ecosystem and architecture for pandemic preparedness and response and
- contributing to and providing technical advice for South Africa's national and provincial malaria control policies and programmes.

TEACHING AND TRAINING

CEZPD staff provided and contributed various teaching and training activities:

TRAINING COURSES AND WORKSHOPS

- NICD rotation, virology and parasitology intensive courses for registrars;
- NICD medical scientist intern rotation for virology, microbiology and parasitology;

- PCR training on malaria vector species identification; KwaZulu-Natal and Mpumalanga Provincial Departments of Health;
- Specialist training for the medical entomology component of the University of Witwatersrand School of Public Health Master's degree by coursework program;
- Special pathogens course for the infectious disease fellow training programme;
- Laboratory diagnosis of parasites for Diploma in Tropical Medicine and Hygiene (DTM&H) programs for University of Glasgow and Sheffield University;
- Malaria microscopy and rapid diagnostic testing (RDT) and stool parasitology refresher training conducted for NHLS technologists.
- Malaria microscopy and RDT refresher training conducted for the Malaria Control Program for Limpopo, Mpumalanga and KwaZulu Natal provinces.

GUEST AND SPECIAL LECTURES

- Lectures for the University of Witwatersrand Master's degree in Epidemiology and Vaccinology and DTM&H programs;
- Lectures for the University of Pretoria One Health course for fifth year undergraduate veterinary program students;
- Lectures for the University of Pretoria ELEPHANT One Health in theory workshop;
- Lectures for the University of Pretoria, ERFAN RVF course;
- Chairing the dual-use issues in research webinar hosted by the Academy of Sciences of South Africa (ASSAf);
- Chairing the One Health pre-congress workshop (NHLS Pathred Congress 2021).

CURRICULUM DEVELOPMENT

- Curriculum development for the Africa CDC certification of biorisk management in Africa programme in collaboration with the NICD Division of Biosafety and Biosecurity (DBB).

POSTGRADUATE STUDENTS

During the period under review, CEZPD staff supervised or co-supervised 23 post-graduate students (six BSc Hons, eight MSc, one MPH and eight PhD) at national and international universities.

PROFESSIONAL DEVELOPMENT, AWARDS AND HONOURS

PROFESSIONAL DEVELOPMENT

- Dr V Dermaux-Msimang was awarded a PhD from the University of Pretoria.



Figure 9. Prof. Janusz Paweska receiving the Benedict the Pole major award, University of Warsaw, Warsaw, Poland 25 June 2022. The Benedict Polak Award is awarded annually to two laureates, a Pole and a foreigner, in recognition of their outstanding exploration and research achievements on land, at sea, in the air and in space. The Chapter of the Award was appointed by the Polish Branch of the Explorers Club, the Municipality of Łęczyca, the County of Łęczyca and the Warsaw Scientific Society.

AWARDS

- Prof Paweska was honored with the Benedict the Pole Major Award for 2022, an annual presentation to individuals with outstanding contributions to science.
- Dr N Moolla won the Best Oral Presentation in Public Health Award at the NHLS PathRed Congress 2021;
- Drs J Coertse and O Hellferscee received Y2 ratings from the National Research Foundation.

HONOURS

- Dr J Weyer was appointed as the Deputy Chair to the ASSAf Standing Committee on Biosafety and Biosecurity;
- Drs J Weyer and J Rossouw were appointed Qualified Experts to the United Nations Secretary-General's Mechanism (UNSGM) for investigating the alleged use of chemical, biological or toxin weapons;
- Dr J Weyer was appointed as a member of the South African Centre for Infectious Disease Surveillance (SACIDS) International Scientific Board;
- Prof B Brooke engaged with the WHO World Malaria Programme monthly as a member of the guidelines development group (GDG) for malaria vector control;
- Dr G Munhenga engaged with WHO on the AFRO-II project for the demonstration of the effectiveness of diversified, environmentally sound and sustainable interventions and strengthening the national capacity for innovative implementation of integrated vector management (IVM) for disease prevention and control in the WHO AFRO region;
- Profs B Brooke (Chair) and L Koekemoer participated in the E8 Vector Control Technical Working Group meetings;

- Prof Brooke and Dr Munhenga participated in the WHO Malaria Drug Resistance Work Stream, the Vector Control component;
- Prof Paweska continued his membership and contributions to the WHO GOARN, WHO Blueprint for RVF Roadmap and the Coalition for Epidemic Preparedness and Innovation (CEPI) RVF Task Force.

RESEARCH OUTPUT JOURNAL ARTICLES

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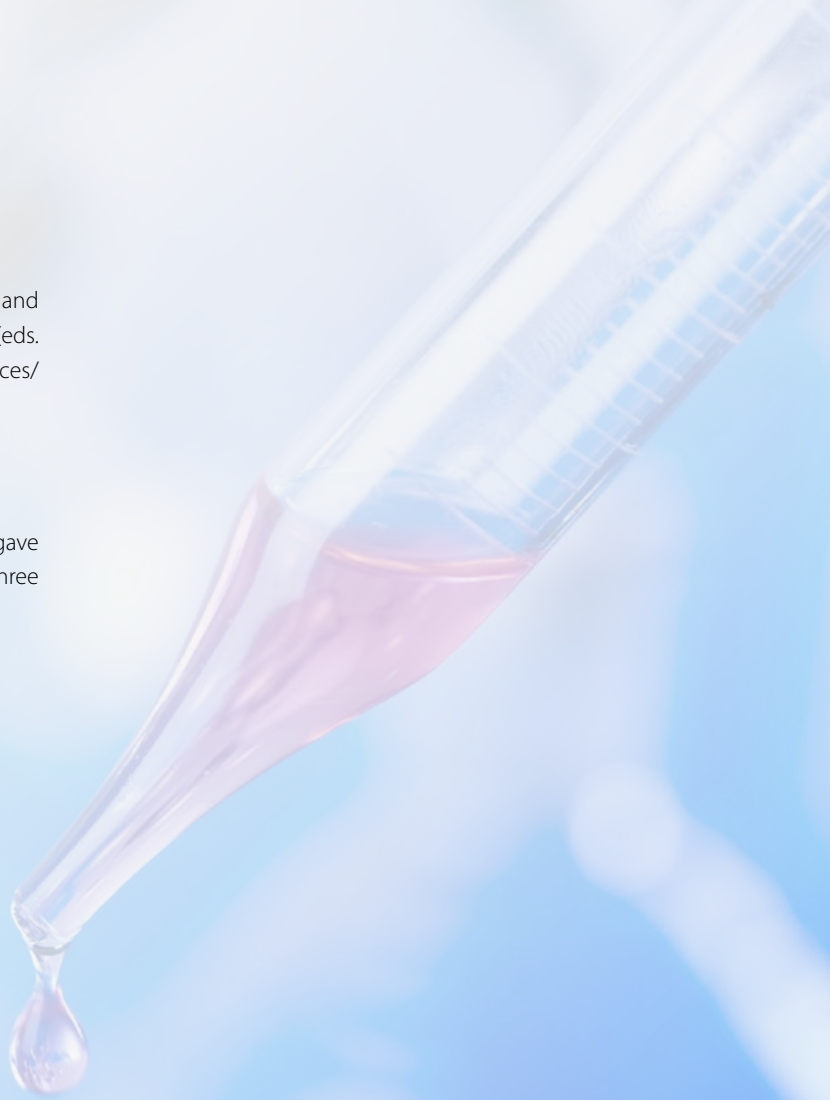
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BOOKS

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CONFERENCES

During the year under review, staff from the centre gave five presentations at international congresses and three presentations at local conferences.





CENTRE FOR ENTERIC DISEASES (CED)



CENTRE FOR ENTERIC DISEASES

DR JUNO THOMAS

BACKGROUND

The CED facilitates the understanding, management and prevention of enteric diseases by providing up-to-date and locally relevant information. The current areas of focus are:

1. Foodborne diseases globally recognised as a threat to food safety and security;
2. Waterborne diseases affecting public health where unsafe water is used and often associated with large outbreaks;
3. Priority enteric diseases under routine surveillance comprising epidemic-prone conditions including enteric fever, cholera and listeriosis;
4. Rotavirus, a vaccine-preventable disease in South Africa;
5. Diarrhoeal disease syndromic surveillance, and
6. Genomic surveillance of priority enteric bacterial pathogens.

The centre comprises a small team of specialists with extensive experience in enteric diseases. Activities include surveillance, public health-orientated research, outbreak investigation and response, reference laboratory services, regional technical and laboratory testing assistance and international collaborations.

SURVEILLANCE

ACUTE DIARRHOEAL DISEASE SURVEILLANCE

Sentinel surveillance for diarrhoeal disease is active at five sites in three provinces. A total of 414 cases were enrolled (260 from the Western Cape, 117 from the North West and 37 from the Free State). Children under the age of five years constituted 90% of cases (374/414) with an average age of 14 months. Most cases (390/414, 94%) were in-patients.

Rotavirus was detected in 15% of the ELISA-tested samples (57/376) with detection rates and case numbers highest in June (in keeping with the typical rotavirus season). Multiplex PCR testing for other enteric viruses, bacteria and parasites was performed. Excluding rotavirus, the most common enteric viruses detected were norovirus (46/302, 15%), adenovirus (37/302, 12%) and astrovirus (15/302, 5%).

Shigella spp. was the most common enteric bacterial pathogen identified (51/300, 17%) followed by *Campylobacter* spp. (16/300, 5%) and nontyphoidal *Salmonella* (5/300, 2%). The most common parasites detected were *Cryptosporidium* spp. (36/300, 12%) and *Giardia lamblia* (15/300, 5%).

NATIONAL LISTERIOSIS SURVEILLANCE

The centre's staff followed up on every listeriosis case alerted through the notifiable medical conditions (NMC) system and NHLS corporate data warehouse (CDW) to collect additional data, a comprehensive food history and isolate referral. All listeria isolates underwent whole-genome sequencing (WGS).

Seventy-two cases of listeriosis were reported from seven provinces; the majority were from the Western Cape (36%, 26/72) followed by Gauteng (31%, 22/72) and KwaZulu-Natal (19%, 14/72). No cases were reported from the Northern Cape and North West. An average of one case per week (range: 0-4 cases per week) was recorded. Most cases were neonates ≤ 28 days (33%, 24/72) followed by persons in the following age groups: 15-49 years (31%, 22/72), ≥ 65 years (22%, 16/72), 50-64 years (13%, 9/72) and children between 30 days and 14 years (1%, 1/72).

NATIONAL ENTERIC FEVER SURVEILLANCE

By using WGS analysis, clusters (small localised outbreaks) of *Salmonella* Typhi were identified in the Western Cape and the North West: three clusters in different Western Cape districts and one in the Dr Kenneth Kaunda district in the North West. The first cases in each cluster occurred in 2020 and as of 31 March 2022, the City of Cape Town cluster and the Garden Route cluster comprised 18 and 15 cases respectively. The last case of the Winelands cluster strain was identified in May 2021.

The Klerksdorp cluster strain associated with the outbreak in North West, has also been identified in other provinces; there are 35 confirmed Klerksdorp cluster strain cases across the North West (21), Gauteng (six), Mpumalanga (four), and KwaZulu-Natal and the Free State (two each). Most (43%; 15/35) of the cases were working age males (15-49 years) and outbreak investigations are ongoing for all clusters.

No definite source(s) of infection have been identified for the Western Cape clusters, while in-depth interviews of 26/35 Klerksdorp cluster cases showed an association with consuming contaminated water in gold mines located in the district. Municipal water contamination is extremely unlikely to be the infection source in any of these clusters due to the demographics of the cases and the scale.

Gauteng reported higher-than-usual numbers of enteric fever cases in January to March 2022 and a new cluster has been identified in the province comprising 20 cases diagnosed between January 2020 and February 2022. The cases are not restricted to a single district and span a range of age groups. CED continued providing technical advice and support to the provincial and district health departments with outbreak investigations and local communities were supported through education and information on enteric fever distributed via the media.

OUTBREAKS

The centre plays a leading role in the investigation and response to outbreaks of food- and water-borne disease and clusters or suspected outbreaks of epidemic-prone enteric pathogens. The staff routinely follow up on alerts of suspected enteric disease outbreaks reported through the NMC system and other sources and provide epidemiological and laboratory support. During the 2021/2022 reporting period, the CED responded to 12 outbreaks with a selection detailed below.

FOODBORNE DISEASE OUTBREAKS

Outbreaks were detected at the following institutions:

- A secondary school in Tshwane Metro, Gauteng (May 2021) where 120 learners presented to several health facilities with

vomiting and abdominal cramps after consuming food (including rice and tinned fish) provided by the feeding scheme. No enteric pathogens were isolated from the single stool sample collected, but testing for bacterial toxins was not done. No food samples were available for testing.

- A correctional facility in Caledon, Western Cape (June 2021) where eight inmates were affected by *Salmonella* Enteritidis.
- A correctional facility in the uThukela district, KwaZulu-Natal (August 2021) where 66 inmates were affected. No pathogens were identified from the single stool sample collected for testing or from the food samples tested. An audit by environmental health practitioners found the facility's kitchen and cold room unsatisfactory.
- An old-age home in Overberg, Western Cape (February 2022) where 12 cases of acute diarrhoea were reported. Nine stool samples were submitted for multiplex PCR testing and *Cryptosporidium* spp. was detected in six of them.

Outbreaks were recorded at the following events:

- An inaugural ceremony in the Mopani district, Limpopo (May 2021) where 51 people presented with gastroenteritis following the consumption of home-made mageu (a fermented maize drink) served at the ceremony. Fifteen cases were admitted to hospital, but no fatalities were reported. No clinical samples were collected and no mageu



samples were available for testing.

- A funeral in West Rand district, Gauteng (November 2021) where 42 people were affected by a *Salmonella* Enteritidis outbreak after eating food served at the funeral. Three fatalities were reported.

Outbreaks were reported from the following healthcare facilities:

- A psychiatric hospital in the Harry Gwala district, KwaZulu-Natal (April 2021) where eight patients were affected, but no clinical samples were obtained for testing and no specific food(s) were identified as the likely infection vehicle(s). Environmental assessment of the hospital kitchen showed gaps in health and hygiene processes. Health promotion activities were conducted and no further cases reported.
- The neonatal unit of a City of Cape Town hospital, Western Cape (October 2021) where a *Salmonella* Enteritidis outbreak, characterised by person-to-person transmission affected at least four babies. WGS of isolates confirmed their close genetic relatedness and proved the outbreak to be healthcare-facility associated.

Outbreaks were reported in the following household or localised community settings:

- Sedibeng, Gauteng (July 2021) where four children ate sweets bought at a nearby spaza shop. Two of the children (both aged six years) fell ill, apparently experiencing dizziness and foaming at the mouth; no diarrhoea or vomiting was reported. They were rushed to the closest clinic but declared dead on arrival. No clinical samples were collected for testing, but the symptoms suggested a chemical rather than a microbial food-borne disease.
- Uthukela, KwaZulu-Natal (November 2021) where a family of six developed gastroenteritis after eating beef from a cow that had died after a short illness. Multiplex PCR testing of stool samples collected from three of the patients identified nontyphoidal *Salmonella*.

There were another 57 suspected food-borne disease outbreaks reported to NICD/CED through NMC or other sources and followed up. However, due to insufficient epidemiological data and the absence of any clinical, food or environmental sample collection and testing, these are not described in detail.

DIAGNOSTIC SERVICES

The virology and bacteriology reference laboratories provide a range of specialised tests to support diagnostic laboratories in public and private health sectors and provide rapid diagnostic and confirmatory testing for epidemic-prone pathogens. These include:

- Specialised rotavirus testing and rotavirus typing;
- Specialised testing for other enteric viruses including

astrovirus, adenovirus, norovirus and bocavirus;

- Specialised molecular screening for enteric pathogens including multiplex PCR;
- Specialised testing for *Vibrio cholerae*;
- Specialised testing for diarrhoeagenic *E. coli* including Shiga toxin-producing *E. coli*;
- Specialised testing for *Salmonella* species including serotyping and molecular testing;
- Specialised testing for *Listeria* species and
- Experimental metagenomics for investigation of patients with pathogen-negative diarrhoeal disease.

COMPLETED RESEARCH ACTIVITIES

Genomic characterisation of toxigenic *Vibrio cholerae* O1, February 2018 to January 2020:

From February 2018 to January 2020, the NICD received 102 *Vibrio cholerae* isolates for testing of which nine were identified as toxigenic *V. cholerae* O1. The isolates were phenotypically and genotypically characterised including WGS, comparative genomics and phylogenetic analysis. Two isolates were identified as ST69 (7PET lineage) and seven as ST75. The ST69 isolates were recovered from two patients with cholera in a family cluster in October 2018 associated with travel to Zimbabwe.

The seven ST75 isolates (five from patients and two environmental samples) originated from KwaZulu-Natal and Limpopo. The three KwaZulu-Natal cases occurred between February 2018 and January 2020 and were located between 200 and 600km apart. The two Limpopo cases occurred in November 2018 and were located in the same district (about 70km apart). The cases between the two provinces were more than 900km apart. There was no evidence of importation from another country; no epidemiological links between cases and no secondary transmission.

Phenotypic characterisation of the O1 ST75 isolates confirmed toxigenic *V. cholerae* O1 serotypes Ogawa and Inaba. Further phylogenetic analysis showed the isolates were closely related, but split into two clusters based on their province of origin. The Limpopo isolates differed from the KwaZulu-Natal isolates by 4-5 alleles on core-genome multilocus sequence typing (cg-MLST).

In keeping with reports of O1 ST75 cases from other countries, the South African cases have been sporadic with no secondary cases and no demonstrable epidemiological links. No associated outbreaks occurred, even when the strains were present in surface water sources used by multiple vulnerable communities with poor WaSH (safe water, sanitation and hygiene). The O1 ST75 isolates were found across large spatial and geographical distances, suggesting local spread.

The emergence and dominance of O1 ST75 in South Africa has major implications for the public health response to cholera cases. The level of public health response must be commensurate with

the risk of outbreak and WGS and cgMLST must be expedited to guide the response. Ongoing WGS of all clinical and environmental *V. cholerae* isolates is essential to describe the dynamics of O1 ST75 in South Africa and identify the emergence of other strains.

- NICD training course rotations in enteric bacteriology and virology laboratories: six medical intern scientists (microbiology, molecular biology and virology) and
- Virology registrars attended the intensive virology training course

TEACHING AND TRAINING

CED staff provided and contributed to various teaching and training activities during the period under review:

- SAFETP hosted by the NICD at Wits University;
- Field Epidemiology Training Programme (FETP) and
- MSc Epidemiology and Biostatistics, MSc Vaccinology and Diploma in Tropical Medicine and Hygiene (DTM and H) courses, Clinical Associate programme presented by Wits.

POST-GRADUATE STUDENTS

The centre's staff participated in the following specialised NICD training courses:

- NICD registrar training course: 20 pathology registrars (microbiology and virology);

PROFESSIONAL DEVELOPMENT

- One intern medical scientist was registered with the HPCSA for independent practice.
- Three intern medical scientists are currently training at the CED.
- Senior CED staff are supervising three PhD students and one MPH student.



RESEARCH OUTPUT

JOURNAL ARTICLES:

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- Moura A, Lefrancq N, Wirth T, Leclercq A, Borges V, Gilpin B, Dallman TJ, Frey J, Franz E, Nielsen EM, Thomas J, Pightling A, Howden BP, Tarr CL, Gerner-Smidt P, Cauchemez S, Salje H, Brisse S, Lecuit M, The Listeria CC1 Study Group (including Smith AM). 2021. Emergence and global spread of *Listeria monocytogenes* main clinical clonal complex. *Science Advances* 7:eabj9805. <https://doi.org/10.1126/sciadv.abj9805>.
- Colston JM, Zaitchik BF, Badr HS, Burnett E, Ali SA, Rayamajhi A, Satter SM, Eibach D, Krumkamp R, May J, Chilengi R, Howard LM, Sow SO, Jahangir Hossain, M, Saha D, Imran Nisar M, Zaidi AKM, Kanungo S, Mandomando I, Faruque ASG, Kotloff KL, Levine MM, Breiman RF, Omoro R, Page N, Platts-Mills JA, Ashorn U, Fan Y-M, Shrestha PS, Ahmed T, Mduma E, Yori PP, Bhutta Z, Bessong P, Olortegui MP, Lima AAM, Kang G, Humphrey J, Prendergast AJ, Ntozini R, Okada K, Wongboot W, Gaensbauer J, Melgar MT, Pelkonen T, Freitas CM, Kosek MN. Associations between Eight Earth Observation-derived climate variables and enteropathogen infection based on large surveillance studies with broad spectrum nucleic acid diagnostics. *GeoHealth*. 2021 Nov 6, e2021GH000452.
- Ntshoe G, Shonhiwa AM, Govender N, Page N. A systematic review on mobile health applications for foodborne disease outbreak management. *BMC Public Health*. 2021 Dec 8; 21(1):2228.
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The background of the page is a solid green color with a pattern of various green, semi-transparent bacterial shapes, including chains, clusters, and individual cells, scattered across the surface. A dark green horizontal bar is positioned in the middle of the page, containing the text.

CENTRE FOR HEALTHCARE-ASSOCIATED INFECTIONS, ANTIMICROBIAL RESISTANCE AND MYCOSES (CHARM)



CENTRE FOR HEALTHCARE-ASSOCIATED INFECTIONS, ANTIMICROBIAL RESISTANCE & MYCOSES

PROF NELESH GOVENDER

BACKGROUND

CHARM incorporates two national reference laboratories for antimicrobial resistance (AMR) and mycoses, both accredited to ISO 15189:2012 requirements, and houses the pathogenic bacteria and fungi national stock culture collection. It functions as a World Health Organization (WHO) AMR collaborating centre and is the national focal point for WHO's global AMR surveillance system (GLASS). CHARM's epidemiology team supports priority surveillance projects; conducts outbreak investigations and is involved in the set-up and evaluation of public health programmes.

SURVEILLANCE

HEALTHCARE-ASSOCIATED INFECTIONS (HAI) SURVEILLANCE

NICD investigators: NP Govender, L Shuping and H Ismail

Collaborators: S Abrahams, L Mngokoyi, B Banda, F Khan, A Thomas, S Mahmud Yakoob, J Black, N Ramncwana, F Naby, S Haffeejee, H Dawood, J Green, T Martin, A Abrahams, E Mosenye, M Maila, A Abraham and C Ndobe

The centre implemented a real-time alert system to detect outbreaks of healthcare-associated bloodstream infections among neonates. Improvements to the application were completed and the surveillance was relaunched at the Dora Ngizwa Hospital (Eastern Cape) in 2022. Informal feedback highlighted additional development is required to enhance the application and a formal evaluation will be conducted this year before further work is undertaken.

ANTIMICROBIAL RESISTANCE SURVEILLANCE

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

Collaborators: GERMS-SA network, SA Society for Clinical Microbiology

CHARM members represented NICD on a newly constituted AMR ministerial advisory committee, WHO AMR surveillance and quality assessment collaborating centres network, WHO AMR strategic and technical advisory group and the WHO fungal pathogens priority list advisory group. The centre currently uses several approaches for AMR surveillance including:

- National or sentinel isolate-based surveys: bacterial and fungal

isolates, cultured from patients who meet the surveillance case definitions, were submitted to the centre's reference laboratories for identification, antimicrobial susceptibility testing and genotyping. During the period under review, the centre conducted surveillance for bacteraemia caused by carbapenem-resistant Enterobacterales (2015-2021), enterococci and all infections caused by *Candida auris* (2018-2021).

- Enhanced laboratory surveillance: detailed clinical information was collected from patients admitted to sentinel hospitals who met the surveillance case definitions. This was suspended during the review period.
- Electronic laboratory surveillance: annual data was compiled on bloodstream infections caused by the ESKAPE bacterial pathogens and more recently *Candida*. NICD cleaned and merged line list data from public and private-sector pathology laboratory information systems and made these available through the AMR dashboard on the NICD website. The dashboard displays interactive and exportable AMR maps by geographic location, pathogen, antimicrobial agent and health sector; AMR data for the public sector is available to facility level. A combined public/private AMR report on key organisms-antimicrobial agents is available from the NDOH (<http://www.health.gov.za/index.php/antimicrobial-resistance>).
- Wastewater-based surveillance for ESKAPE pathogens: a pilot study was planned for a six-month period at sites in South African provinces to determine the presence of selected ESKAPE bacterial pathogens from wastewater.

SURVEILLANCE FOR MYCOSES

NICD investigators: NP Govender, R Mashau, R Mpembe, T Maphanga, S Naicker and J Paxton

Collaborators: GERMS-SA network, Clinton Health Access Initiative (CHAI)

Since 2018, the WHO has recommended a combination of amphotericin B and flucytosine (5-FC) as first-line induction treatment for patients with cryptococcal meningitis. In December 2021 the South African Health Products Regulatory Authority (SAHPRA) registered 5-FC. Approximately 80 hospitals participated in a 5-FC access programme and the centre assisted with data collection and analysis coordination. A manuscript on outcomes of 5-FC-containing combination treatment for cryptococcal meningitis was published in *The Lancet Infectious*

Diseases. A CHARM staff member co-chaired the WHO guideline development group on cryptococcal disease in 2022 and the WHO updated its recommendation for first-line treatment of cryptococcal meningitis. Passive laboratory-based surveillance for rarer invasive mycoses continued.

OUTBREAKS

The centre led or participated in investigating several healthcare-associated outbreaks during the period under review. Increasingly, its contribution to outbreaks has shifted from epidemiological assistance to molecular investigations. This may signal changing priorities prompted by the COVID-19 pandemic in investigating and managing healthcare-associated outbreaks.

WHO COLLABORATING CENTRE FOR AMR

As a WHO collaborating centre for AMR, the centre participated in the WHO AMR surveillance and quality assessment collaborating centres network formed to support the GLASS implementation (<https://www.who.int/glass/reports/en/>). The NICD collaborated on activities to strengthen countries' capacity for developing and implementing AMR surveillance programmes and provided an external quality assessment programme (<https://ptschemes.nicd.ac.za/Home/Bacteriology>).

RESEARCH ACTIVITIES

CAST-NET

NICD investigators: NP Govender, GS Greene, D Desanto, J Paxton, R Mashau, A Shilubane and N Valashiya

Collaborators: University of Minnesota, US CDC, Epicentre

The CAST-NET project, supported by an NIH R01 grant (2016-2023), aims to evaluate the effectiveness of the national reflex cryptococcal antigen screen-and-treat intervention and pilot programmatic approaches to optimising this. With the assistance of field data collection partner Epicentre, the centre completed a retrospective collection of clinical information from a cohort of nearly 3,000 people with cryptococcal antigenaemia screened between February 2017 and February 2019 in 27 sub-districts nationally. In February 2022 the project team completed abstracting 2010 health facility records from individuals ultimately included in the final study cohort and data analysis and manuscript preparation are underway. In February 2021, the CAST-NET team began the second part of the study aimed at addressing operational gaps identified in the cascade of care for people with cryptococcal antigenaemia. This proof-of-concept study was concluded in October 2021 and data collection completed in February 2022.



BABY GERMS-SA: NEONATAL INFECTION SURVEILLANCE IN SOUTH AFRICA

NICD investigators: NP Govender, S Meiring, R Mashau, O Perovic, M Smith, R Mpembe, V Quan, A von Gottberg, L de Gouveia, S Walaza and C Cohen

Collaborators: A Dramowski, C Mackay, R Phayane, T Mailula, O Mekgoe, C Kapongo and Dr Maphosa

Through tier one of this project, the centre conducted a national surveillance of culture-confirmed neonatal bloodstream infections and meningitis across South Africa's public sector hospitals. A manuscript was submitted in December 2021, summarising data for approximately 40,000 neonatal infection cases. Tier two focused on a detailed characterisation of neonatal infections occurring at six secondary-level institutions (provincial/regional neonatal units). Clinical data collection on 935 laboratory-confirmed neonatal infection episodes is complete and data are being analysed with several manuscripts in preparation.

PREVALENCE OF AMR GENES IN ANIMALS AND HUMANS

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

Collaborators: EMC Etter, JM Mokoee, A Jonker (University of Pretoria)

This project, expected to be completed by June 2022, aims to describe antibiotic resistance genes present in food animals and livestock workers at a commercial pig farm. The following activities were completed:

- description and quantification of antimicrobial usage at the study farm (a manuscript is in the final stages of approval for publication);
- culturing, identification and antimicrobial susceptibility testing of *Campylobacter spp.*, *Enterococcus spp.*, *Escherichia coli* and non-typhoidal *Salmonella* from pig faecal droppings and self-collected human rectal swabs;
- whole genome sequencing (WGS) of isolates to determine strain diversity and molecular epidemiology and direct detection of resistance genes from faecal droppings;
- metagenomics for comparison of the genes from crude and cultured samples
- testing retail meat for presence of indicator organisms and antibiotic residues.

ATLAS: SURVEILLANCE AND EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE PROGRAMME (PILOT)

NICD investigators: O Perovic, M Smith, R Kganakga, N Bulbulia and A Sesoko

Collaborators: NICD Sequencing Core Facility

This multi-year initiative will develop a scalable surveillance platform using the antimicrobial leadership testing and surveillance (ATLAS) core methodology. Supported by a public-private partnership that expands surveillance capacity to low and middle-income countries, the pilot study is being conducted in Ghana, Kenya, Malawi and Uganda. The centre serves as a central reference laboratory and performed phenotypic and genotypic work. CHARM has received batches of isolates from the pilot sites; completed identification and antimicrobial susceptibility testing and sent reports to the investigators. The centre has completed isolate testing for 30% of the estimated sample size.

MOLECULAR EPIDEMIOLOGY OF *CRYPTOCOCCUS GATTII* IN SOUTH AFRICA

NICD investigators: S Naicker, T Maphanga, E van Schalkwyk and NP Govender

Collaborators: Translational Genomics Research Institute, Westmead Institute for Medical Research (University of Sydney), Universidad del Rosario (Bogota, Colombia)

Cryptococcus gattii is divided into six molecular types: VG1, VG2, VG3, VG4, VG5 and VG6. Earlier molecular epidemiology studies, including relatively few isolates, most southern African isolates were confirmed as molecular type VG4. The study aimed to determine the molecular diversity of *C. gattii* in South Africa by genotyping patient isolates obtained through laboratory surveillance between 2005 and 2013. The investigation confirmed VG4 was the dominant molecular type and HIV-seropositive patients were more likely to be infected with VG4 compared to those who are HIV-seronegative. Analysis of the South African VG4 genomes isolates revealed they spanned the whole VG4 clade and confirmed most isolates do not cluster specifically. However, two interesting clusters of closely related isolates, originally cultured from patients from three neighbouring provinces (Gauteng, Limpopo and Mpumalanga) were observed, suggesting a similar environmental source.

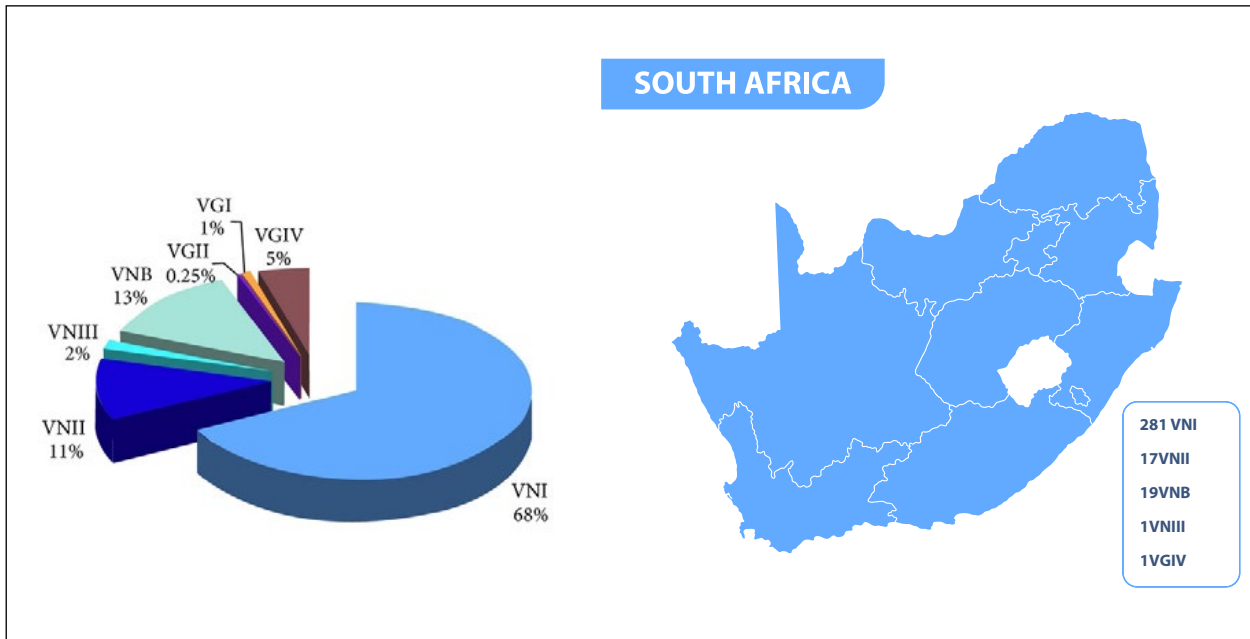


Figure 1. The geographic distribution of *Cryptococcus* molecular types identified in Africa (left) and the molecular type distribution in South Africa (right) (Cogliati, 2013).

ANTIMICROBIAL RESISTANCE IN ETHIOPIA AMONG PREGNANT WOMEN AND NEWBORNS

NICD investigators: O Perovic, M Smith and P Mashupye

Collaborators: Harvard Medical School, Harvard T.H. Chan School of Public Health, SPHMMC/BIRHAN, Debre Birhan Hospital

A maternal and newborn colonisation study is being undertaken in Ethiopia focusing on Gram-negative resistant pathogens (ESBL-producing and carbapenem-resistant Enterobacterales) and Group B Streptococcus. All specimens were sent to the centre for culture, identification and antimicrobial susceptibility testing and, based on these findings, CHARM will perform additional testing including WGS.

FUNGAL DISEASE SURVEILLANCE AND CAPACITY IN SOUTHERN AFRICA

NICD investigators: NP Govender, S Jallow, R Mashau, TM Mwamba, R Mpenbe, T Maphanga, S Naicker and G Greene

Collaborators: Africa CDC, National Departments of Health for Angola, Botswana, Eswatini, Lesotho, Mozambique, Namibia, Zambia and Zimbabwe

This project aims to improve capacity to perform surveillance, identification and genomic epidemiology of fungal pathogens in southern Africa. During the reporting period, the centre began work to set up a regional network for fungal genomic surveillance, collaborating with Ministry of Health-supported national reference laboratories to ensure the sustainability of surveillance activities.

TEACHING AND TRAINING

CHARM staff provided and contributed to various teaching and training activities:

- NICD course for registrars and ID fellows
- Mycology online workshop for registrars and ID fellows
- MMed (Pathology) molecular course (University of the Witwatersrand)
- BHSc Molecular Medicine III (innate and adaptive immunology) (University of the Witwatersrand)
- BHSc biochemistry (vaccines) (University of Johannesburg)
- MSc epidemiology and biostatistics (University of the Witwatersrand)
- MPH (University of Pretoria)
- MSc Vaccinology (University of the Witwatersrand)
- DTM and H (University of the Witwatersrand)
- PhD, MSc, MTech, MPH (SAFETP) and MMed supervision

POST-GRADUATE STUDENTS

Seven students were enrolled for post-graduate studies, specifically one each for MPH, MTech and MSc and four PhDs. Three students graduated during the review period, namely one each with MPH, MTech and PhD qualifications.

RESEARCH OUTPUT

JOURNAL ARTICLES:

- [1] Govender NP, Todd J, Nel J, Mer M, Karstaedt A and Cohen C for GERMS-SA. HIV Infection as Risk Factor for Death among Hospitalised Persons with Candidemia, South Africa, 2012-2017. *Emerg Infect Dis*. 2021 Jun;27(6):1607-15. doi: 10.3201/eid2706.210128.
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TECHNICAL REPORTS AND GUIDELINES

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CONFERENCES

CHARM members contributed to 10 international, three national and no local conferences during the year under review.



The background of the page is a solid green color with a pattern of semi-transparent, circular virus particles. Each particle has a textured, spherical core and is surrounded by numerous thin, hair-like spikes or filaments extending outwards, characteristic of certain types of viruses.

CENTRE FOR HIV AND STIS(CHIVSTI)



CENTRE FOR HIV AND STIS

PROF ADRIAN PUREN

BACKGROUND

Sexually transmitted infections (STIs), including those caused by the human immunodeficiency virus (HIV) types one and two, remain a major public health problem in Africa. Published estimates of the joint United Nations (UN) Programme on HIV/AIDS show South Africa has the highest burden of HIV infections with recent estimates reflecting 7.8 million people live with HIV.

The National Institute for Communicable Diseases (NICD) centre for HIV and STIs (CHIVSTI) has a strong track record in the research disciplines of HIV virology, HIV immunology, HIV/STI epidemiology, HIV/STI diagnostics and HIV-STI interactions.

- CHIVSTI addresses the challenges of HIV and STI diseases through various programmes:
- Surveillance of disease burden and antimicrobial resistance;
- Measurement of endpoint infections and detection;
- Broadly neutralising antibodies as part of prophylactic HIV vaccine and antibody-mediated protection clinical trials;
- Exploring an HIV cure strategy and
- Developing and implementing reference diagnostics and implementation science.

CHIVSTI consists of the following four sections:

- HIV virology;
- Cell biology;
- HIV molecular and serology and
- STIs.

The centre provides a suitable academic environment for the successful supervision of undergraduate and post-graduate

students and post-doctoral fellows. It also has well-established links and collaborations with various key national and international organisations in the field of HIV and STIs.

SURVEILLANCE

STIS

The STI aetiological surveillance continued in 2021/22 in the three primary healthcare centres in Gauteng, KwaZulu-Natal and the Western Cape. The surveillance validates the current STI syndromic management guidelines and the 2019 and 2020 reports were submitted to the facilities and the provincial and national health departments. The section monitors antimicrobial susceptibility patterns to detect the emergence of extensively drug-resistant *Neisseria gonorrhoeae*, while the antimicrobial resistance data is also reported annually to the World Health Organization Global Antimicrobial Resistance and Use Surveillance System (WHO GLASS).

The section entered into discussions with WHO to be one of the regional focal points submitting data as part of the enhanced Gonococcal Surveillance Programme (eGASP). The improved programme aims to standardise the sampling and testing methodologies and collect demographic, behavioural and clinical data associated with *Neisseria gonorrhoeae* isolates. This will ensure timely reporting of critical alerts in the country and the global GASP network for action.

The section initiated STI surveillance among a priority population, namely men who have sex with men (MSM cohort) at a sentinel Men's Health Centre in central Johannesburg. The survey's overall aim surveillance is to establish an early warning system in an at-risk priority population to monitor for evolving resistance to extended-spectrum cephalosporins in *Neisseria gonorrhoeae* and emerging STIs such as lymphogranuloma venereum.

PAEDIATRIC SURVEILLANCE

The centre supports the National Department of Health (NDOH) through the analysis and reporting of HIV-related data from the National Health Laboratory Service (NHLS) data warehouse. Reporting is provided at national, provincial and district levels to the national and provincial departments of health and other stakeholders. This includes secure online distribution via the NICD's self-service portal of results for action (RfA) reports as per the 2019 national HIV guidelines; monthly reports on early infant diagnosis, paediatric and adolescent HIV viral load (VL) monitoring and maternal PMTCT HIV VL monitoring; validating the UNAIDS 95-95-95 target achievement at the district level and various programmatic data requests from the field. The centre provides disaggregated monthly reporting for early infant diagnosis (both testing coverage and positivity); paediatric, adolescent and adult HIV VL (monthly and rolling annual test-level and patient-level numbers of HIV VL done and suppression rates) and the uptake of maternal HIV VL electronic gatekeeping codes including antenatal, delivery and post-natal suppression rates. These reports highlight sub-populations who require additional support within the HIV treatment programme and enable effective intervention monitoring in the field.

SARS-COV-2 SURVEILLANCE

The centre has made significant contributions to genomics surveillance for SARS-CoV-2 by contributing to bioinformatics support for SARS-CoV-2 sequencing and identifying variants associated with increased transmissibility, neutralisation resistance and disease severity of public health importance.

HIV SURVEILLANCE IN PREGNANT WOMEN

The 29th edition of the antenatal HIV sentinel survey (ANCHSS) data was collected during this financial period. The survey was conducted between 28 February and 30 April 2022 and included 41,236 pregnant women from 1,589 public health facilities nationally. The survey sought to address the questions:

- where, why and in which group(s) of pregnant women the HIV response has an impact and
- assess groups/populations who are lagging.

While the survey findings will only be shared in the next financial year, four papers were published from the 2019 ANCHSS data that provided national estimates for HIV recent infection, unintended pregnancy and the VL cascade among pregnant women. These estimates are crucial for tracking trends in progress toward the UNAIDS 95-95-95 targets and the papers highlighted the contributing factors for delayed viral suppression among pregnant women on antiretroviral treatment (ARVs).

The routine surveillance for congenital syphilis (CS) continued in the fiscal year with the team embarking on online trainings for

CS surveillance and notification processes. Healthcare providers from Eastern Cape, Gauteng, KwaZulu-Natal and the Western Cape participated in the training sessions and quarterly data analysis and reporting continued throughout the reporting period. The most recent analysis from December 2021 registered and reported to the global AIDS monitoring programme 160 CS cases during the calendar year. The analyses uncovered no single factor associated with mother-to-child syphilis transmission, but there were multiple factors at various levels of the syphilis care and treatment cascade:

- 21.4% of mothers whose infants were notified as CS cases and for whom this information was available were unbooked;
- 12.8% of mothers whose infants were notified as cases, were tested during pregnancy and had results available were rapid plasma reagin (RPR) negative at the initial test suggesting transmission during pregnancy;
- 20.2% of mothers whose infants were notified as cases and had an RPR positive test result available were tested less than 28 days before delivery and
- 13.3% of mothers whose infants were notified as cases and were RPR positive had no evidence of treatment with Benzathine penicillin.

There was also a significant under-reporting of CS cases with 90% of cases notified from Gauteng, KwaZulu-Natal and the Western Cape. A new electronic case investigation form that can be completed and submitted in real time was developed to improve the timeliness and completeness of reporting.

HIV DRUG RESISTANCE

Surveillance of acquired HIV drug resistance in adult patients through routine ARV programme monitoring in South Africa continued in 2021. A nationally representative survey of HIV drug resistance (HIVDR) was implemented using remnant VL testing specimens from adult patients from 16 NHLS VL testing laboratories. Of the 7,008 VL test specimens collected, 859 had unsuppressed VL of which 621 were selected for further testing. HIVDR genotyping was performed using next-generation sequencing and drug level testing (DLT) using liquid chromatography mass spectrometry as a proxy for regimen. The survey showed 68% of patients with unsuppressed VL harbour resistance to antiretroviral therapy (ART). DLT confirmed 51% of specimens had detectable levels of ART.

HIVDR was lower in patients with undetectable levels of ART ($p < 0.0001$), presumably due to a lack of drug selection pressure. The use of residual specimens proved advantageous because it allowed for proportion to size sampling and reduced collection time and cost.

The sixth South African national HIV prevalence, incidence, behaviour and communication survey 2021 (SABSSM VI) was initiated in January 2021. Testing for HIVDR was introduced in the 2017 survey and addresses concerns regarding the development of drug-resistant HIV in South Africa. This will be the first household survey to include HIVDR since the advances in the available treatment regimens such as introducing Dolutegravir (DTG). Data will be used to inform practice and update treatment guidelines.

OUTBREAKS

SARS-CoV-2 has been a major focus and the centre's research has had an immediate and extensive impact on public health policy and response to the global Covid-19 pandemic. Professor Penny Moore advised the government on South Africa's vaccination rollout as a direct result the work concluded in her laboratory. She played a leadership role in defining the risk of emergent SARS-CoV-2 variants to compromise humoral immunity, as well as the design and testing of new vaccine candidates. As the Delta and Omicron variants emerged, the centre played a pivotal role in assessing viral escape and humoral immune responses in SARS-CoV-2 infected individuals and those who had been vaccinated had global implications for the design of second-generation vaccines.

POLICY CONTRIBUTIONS

CHIVSTI continues to make contributions to the following:

- WHO 2021 guidelines for managing symptomatic STIs launched in July 2021;
- Moore served as a member of the ministerial advisory board on vaccines in South Africa and associated Covid-19 associated technical working groups and serves as the Global Virus Network (GVN) director;
- the maternal syphilis testing and treatment guidelines were revised during the year. Syphilis data from the centre motivates for introducing rapid syphilis testing for mothers and
- the centre contributed to the Covid-19 testing guidelines and portfolio reviews of in vitro diagnostics tests submitted to the South African Health Products Regulatory Authority.

DIAGNOSTIC SERVICES

The centre provided the following diagnostic services:

- specialised reference testing (in-house and commercial PCR assays) for non-resolving STI syndromes, child abuse cases and complicated STI cases;

- verification of *Neisseria gonorrhoeae* culture identification and antimicrobial testing;
- *Mycoplasma genitalium* macrolide and fluoroquinolone resistance testing;
- HIV testing for the cross-sectional survey of healthcare use and seroprevalence during the Covid-19 pandemic (HUTS);
- HIV prevalence, incidence and drug resistance testing for the sixth South African National HIV prevalence, incidence, behaviour and communication survey 2021 (SABSSM VI);
- testing for the HSRC-led national COVID Seroprevalence study (NCAS);
- HIV vaccine trial diagnostic endpoint testing for the HIV vaccines trial network (HVTN);
- HIV rapid testing post-market surveillance (PMS) for the NDOH's HIV rapid testing at the facility level and
- HIV internal quality control panels were distributed to HIV rapid testing facilities.

PAEDIATRIC SURVEILLANCE

The centre offered individualised diagnostic support, including a range of serological and nucleic acid tests, for infants, children and adults for whom an HIV diagnosis is in doubt. The need arose on account of the decreased positive predictive value of both rapid diagnostic tests and early infant diagnostic assays; a consequence of a reduced positivity yield in the tested population within the context of potent antiretroviral agents that can cause loss of detection. Furthermore, alternative testing platforms and diagnostics algorithms are evaluated to assist diagnostic accuracy in the field.

RESEARCH ACTIVITIES

THE EVALUATION OF THE ALLPLEX™ BV MOLECULAR ASSAY FOR THE DIAGNOSIS OF BACTERIAL VAGINOSIS IN SYMPTOMATIC SOUTH AFRICAN FEMALES

NICD investigators: MC Mabugana, EE Müller, BDC Dias, T Kufa, L Gumede, MP Mahlangu, DV Maseko and RS Kularatne

Bacterial vaginosis (BV) is a dysbiosis of the vaginal microbiota characterised by colonisation by a predominantly heterogeneous mixture of anaerobic gram-negative and gram-variable bacteria instead of *Lactobacillus* spp. BV is a leading cause of vaginal discharge that, if untreated, can cause adverse obstetric outcomes for mother and infant and increase the risk of STI acquisition.

We compared the performance of the Seegene Allplex™ BV assay in diagnosing BV in symptomatic South African women with Nugent scoring as a gold standard. We tested vaginal swab specimens collected from sexually active women enrolled in the STI aetiological surveillance programme (2020-2021) from three South African provinces. In total 213 samples were assessed by both assays of which 99 (46.5%) and 132 (62.0%) BV samples were detected by Nugent scoring and Allplex™ respectively.

Using the Nugent scoring as reference method, the Allplex™ BV assay displayed a 94% sensitivity (95% CI, 92.0-97.9%) and a 62% specificity (95% CI, 55.2-68.3%) with a 79.8% agreement (95% CI, 73.8-84.7%) ($\kappa = 0.60$). In conclusion, due to the low specificity of the Seegene Allplex™ BV assay, it is currently unsuitable as an alternative diagnostic method in South African women presenting with vaginal discharge.

THE EMERGENCE OF HIGH-LEVEL AZITHROMYCIN-RESISTANT NEISSERIA GONORRHOEAE IN SYMPTOMATIC MALES FROM JOHANNESBURG, SOUTH AFRICA, 2021

NICD investigators: EE Müller, LYE Gumede, DV Maseko and RS Kularatne

In the period between 2008 and 2020 all Johannesburg gonococcal isolates were susceptible to ceftriaxone (<0.002 – 0.064 µg/mL) and azithromycin (0.032 – 1 µg/mL). In 2021 the drug susceptibility profiles of 240 N. gonorrhoeae isolates were determined either by agar dilution (azithromycin and spectinomycin) or E-test™ (ceftriaxone, cefixime and gentamycin). These isolates were susceptible to ceftriaxone, cefixime, spectinomycin and gentamycin. Four isolates (1.67%) demonstrated elevated MICs for azithromycin by agar dilution (>8 µg/mL). E-test™ results for these four isolates revealed azithromycin MICs ranging between 32 and >256 µg/mL. We used the web-based Neisseria gonorrhoeae sequence typing for antimicrobial resistance (NG-STAR) to identify antimicrobial resistance determinants in these isolates and Neisseria gonorrhoeae multi-antigen sequence typing (NG-MAST) to determine the antimicrobial resistant strain type.

Two isolates with azithromycin MICs of 32 and 48 µg/mL were identified as NG-STAR type 4323 with the C2611T resistance mutation in the 23S rRNA. Both isolates had NG-MAST 20367 strain profiles. The remaining two isolates had azithromycin MICs of >256 µg/mL; both belonged to the NG-STAR type 4322 with the characteristic A2059G 23S rRNA resistance mutation and had an identical NG-MAST 20366 strain type.

We identified the first cases of high-level azithromycin-resistant Neisseria gonorrhoeae in symptomatic males from Johannesburg in 2021. Continued surveillance is essential to monitor future trends in resistance to ceftriaxone and azithromycin to guide patient management and evaluate the effectiveness of the current STI syndromic management guidelines.

FACTORS ASSOCIATED WITH PARTNER NOTIFICATION INTENTIONS AMONG SYMPTOMATIC SEXUALLY TRANSMITTED INFECTION SERVICE ATTENDEES IN SOUTH AFRICA

NICD investigators: BDC Dias, T Kufa and R Kularatne

We explored gender-stratified factors (demographic, sexual behavioural and clinical) associated with an index case's willingness to notify their sexual partners of their STI diagnosis. In total 1,293 symptomatic adults were enrolled in Gauteng, KwaZulu-Natal and the Western Cape during the 2019/2020 period. Self-reported partner notification intentions were 83.5% and 64.4% among women and men respectively. In a multivariable model, recent non-regular sex partnerships and enrolment in KwaZulu-Natal were associated with lower partner notification intent among males. None of the factors investigated independently influenced partner notification intentions among females. The primary reasons for a lack of partner notification intent were:

- casual nature of sexual relationships;
- geographical distance between partners and
- fear of disclosure.

PREVALENCE OF SEXUALLY TRANSMITTED INFECTIONS AT EXTRA-GENITAL SITES AND AETIOLOGIES OF PERSISTENT URETHRITIS IN MSM: A PILOT SURVEILLANCE STUDY

NICD investigators: R Kularatne, BDC Dias and EE Müller

MSM and transgender women (TGW) are considered key populations in STI transmission networks due to their participation in high-risk sexual practices. Ceftriaxone (an extended-spectrum cephalosporin) was considered the last option for first-line monotherapy for Neisseria gonorrhoeae. However, ceftriaxone treatment failures for gonorrhoea have been described worldwide; most isolates were from pharyngeal specimens. Owing to the lack of STI surveillance data from the key South African populations, the STI reference centre conducted a pilot study in November 2021 to determine the feasibility of implementing an early warning surveillance system in an at-risk MSM to monitor for evolving resistance to extended-spectrum cephalosporins in Neisseria gonorrhoeae and emerging STI pathogens.

Among the 42 participants, 19% were positive for an extra-genital (rectal and/or pharyngeal) STI. The prevalence of pharyngeal and rectal STIs was 2.4% and 5% respectively. Serological data revealed 32% had prior exposure to syphilis with the prevalence of active syphilis at 23.7%. Our data reiterates the importance of STI screening in asymptomatic high-risk MSM and demonstrates the need for expanded and continued STI surveillance in this key South Africa population.

PAEDIATRIC HIV FUNCTIONAL CURE AND EARLY ARV TREATMENT

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Collaborators: L Kuhn, E Abrams, S Shiau, Y Shen (Columbia University, USA), A Coovadia (VIDA, RMMCH), K Technau (VIDA), R Strehlau, M Burke, A Coovadia (VIDA), F Patel (WHRI) on behalf of the LEOPARD study team

Early administration of ART is associated with many benefits for adults and children living with HIV-1 (LWH) that include reduced morbidity and mortality; limited HIV-1 diversity and virus escape; reduced immune activation; preserved immunity; smaller HIV-1 reservoirs and better virus control on ART.

Findings from the NIH-funded latency and early neonatal provision of ARV drugs clinical trial (LEOPARD) clinical trial of very early treatment (0-14 days of birth) showed higher pre-treatment VL associated with a poorer virologic response on ART. Furthermore, higher CD4+ T-cell percentage, pre-treatment VL <100 000 copies/mL; infection occurring in the absence of maternal antenatal ART and breastfeeding were associated with lower levels of HIV-1 DNA in the first 48 weeks of ART.

Longitudinal immunophenotyping by flow cytometry of HIV-exposed uninfected and HIV-infected infants revealed the normalisation of B cell subsets, but not of follicular T helper subsets by 72 weeks of age – highlighting that even with very early ART, immune reconstitution is not fully restored by 72 weeks in utero-infected infants. Studies are ongoing to explore clinical, viral, microbial and immune factors to determine mechanisms that associate with better viral control on ART to inform therapeutic interventions for improving viral control on ART and attaining remission in children LWH.

TWO RANDOMISED TRIALS OF NEUTRALISING ANTIBODIES TO PREVENT HIV-1 ACQUISITION

NICD investigators: Morris L

Collaborators: L Corey, PB Gilbert, M Juraska, DC Montefiori, ST Karuna, S Edupuganti, NM Mgodhi, AC de Camp, E Rudnicki, Y Huang, P Gonzales, R Cabello, C Orrell, JR Lama, F Laher, EM Lazarus, J Sanchez, I Frank, J Hinojosa, ME Sobieszczyk, KE Marshall, PG Mukwekwerere, J Makhema, LR Baden, JI Mullins, C Williamson, J Hural, MJ McElrath, C Bentley, S Takuva, MMG Lorenzo, DN Burns, N Espy, AK Randhawa, N Kochar, E Piwowar-Manning, DJ Donell, N Sista, P Andrew, JG Kublin, G Gray, JE Ledgerwood, JR Mascola and MS Cohen

Whether a broadly neutralising antibody (bnAb) can be used to prevent HIV type one (HIV-1) acquisition is unclear. At-risk cisgender men and transgender persons in the Americas and Europe in the HVTN 704/HPTN 085 trial and at-risk women in

sub-Saharan Africa in the HVTN 703/HPTN 081 trial were enrolled and received infusions of a bnAb (VRC01) (low-dose, high-dose or placebo). Participants received ten infusions at eight-week intervals. HIV-1 testing was performed every four weeks and VRC01 80% inhibitory concentration (IC80) of acquired isolates was measured with the TZM-bl assay. The prevention efficacy against sensitive isolates was similar for each VRC01 dose and trial; VRC01 did not prevent the acquisition of other HIV-1 isolates. VRC01 did not prevent overall HIV-1 acquisition more effectively than placebo, but analyses of VRC01-sensitive HIV-1 isolates provided proof of concept that bnAb prophylaxis can be effective.

SARS-COV-2 501Y.V2 ESCAPES NEUTRALISATION BY SOUTH AFRICAN COVID-19 DONOR PLASMA

NICD investigators: CK Wibmer, F Ayres, T Hermanus, M Madzivhandila, P Kgagudi, BE Lambson, von A Gottberg, C Cohen, L Morris, JN Bhiman and Moore PL

Collaborators: M Vermeulen, K van den Berg, T Rossouw, M Boswell, V Uckermann and S Meiring

SARS-CoV-2 501Y.V2 (B.1.351), a novel lineage of the Coronavirus causing Covid-19 contains substitutions in two immunodominant domains of the spike protein. We showed pseudovirus expressing 501Y.V2 spike protein completely escapes three classes of therapeutically relevant antibodies. This pseudovirus also exhibits substantial escape from neutralisation, but not binding, by convalescent plasma. This data highlighted the prospect of reinfection with anti-genically distinct variants and foreshadowed reduced efficacy of spike-based vaccines

CROSS-REACTIVE NEUTRALISING ANTIBODY RESPONSES ELICITED BY SARS-COV-2 501Y.V2 (B.1.351)

NICD investigators: T Moyo-Gwete, M Madzivhandila, Z Makhado, F Ayres, D Mhlanga, B Oosthuysen, BE Lambson, P Kgagudi, L Morris and PL Moore

Collaborators: H Tegally, A Iranzadeh, D Doolabh, L Tyers, LR Chinhoi, M Mennen, S Skelem, G Marais, JN Bhiman, V Ueckermann, T Rossouw, M Boswell, T de Oliveira, C Williamson, WA Burgers and N Ntusi

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) 501Y.V2 lineage (also known as B.1.351), first identified in South Africa in October 2020, has mutations that confer increased resistance to plasma from convalescent patients and vaccine recipients, as well as to some monoclonal antibodies. However, the immune response to 501Y.V2 is unknown. We characterised the SARS-CoV-2 infections in a cohort of patients with Covid-19 admitted to the Groote Schuur Hospital, Cape Town, after the emergence and dominance of 501Y.V2 in South Africa. Overall, we found 501Y.V2 elicits robust neutralising antibody responses against both the original variant and 501Y.

V3 (P.1), the variant first described in Brazil, that indicates high levels of cross-reactivity. Our data showed vaccines built on the spike protein 501Y.V2 may be promising candidates for the elicitation of cross-reactive neutralising antibody responses to SARS-CoV-2

PRIOR INFECTION WITH SARS-COV-2 BOOSTS AND BROADENS AD26.COV2.S IMMUNOGENICITY IN A VARIANT-DEPENDENT MANNER

NICD investigators: SI Richardson, T Moyo-Gwete, T Hermanus, NP Manamela, T Motlou and PL Moore

collaborators: R Keeton, MB Tincho, N Benede, R Baguma, Z Makhado, A Ngomti, M Mennen, L Chinhoyi, S Skelem, H Maboreke, D Doolabh, A Iranzadeh, A Otter, T Brooks, M Noursadeghi, J Moon, J Blackburn, N Hsiao, C Williamson, C Riou, A Gogo, N Garrett, L Bekker, G Gray, NAB Ntusi and WA Burgers

The Johnson and Johnson (J&J) Ad26.COV2.S single-dose vaccine represents an attractive option for Coronavirus disease 2019 (Covid-19) vaccination in countries with limited resources. We examined the effect of prior infection with different SARS-CoV-2 variants on Ad26.COV2.S immunogenicity and compared SARS-CoV-2 naive participants with those either infected with the ancestral D614G virus or infected in the second wave when Beta predominated. Prior infection significantly boosts spike-binding antibodies, antibody-dependent cellular cytotoxicity and neutralising antibodies against D614G, Beta and Delta; however, neutralisation cross-reactivity varied by wave. Robust CD4 and CD8 T-cell responses are induced after vaccination, regardless of prior infection. T-cell recognition of variants is largely preserved, apart from some reduction in CD8 recognition of Delta. Thus, Ad26.COV2.S vaccination after infection could result in enhanced protection against Covid-19. The impact of the infecting variant on neutralisation breadth after vaccination has implications for developing second-generation vaccines based on variants of concern.

EVALUATING THE ACCEPTABILITY OF PrEP AND YIELD OF DUAL SYPHILIS/HIV RAPID TEST KIT AMONG MEN ATTENDING HEALTH SERVICES

NICD investigators: T Kufa-Chakezha, E Cutler, R Kularatne, B Singh, Z Brukwe, V Maseko, C Mabugana, D Velashiya and A Puren

Collaborators: Philip Dorrell, Erushka Pillay and Ocean Tobaiwa (Clinton Health Access Initiative, CHAI) and Khumbulani Moyo (RTC)

This study evaluated the eligibility and acceptability of pre-exposure prophylaxis (PrEP) referral as well as acceptability and performance of dual HIV/syphilis testing among males attending voluntary male medical circumcision (VMMC) services at six

public sector facilities in two districts of Gauteng. Data collection involved completing the study-related questionnaire, on-site rapid HIV/syphilis testing and blood specimen collection for centralised laboratory testing. The study found a low knowledge of PrEP, high acceptability of PrEP referral, high eligibility for PrEP referral, high acceptability of dual HIV/syphilis testing, but sub-optimal sensitivity for active and current syphilis infection compared to laboratory testing.

TEACHING AND TRAINING

The centre contributed to the three-week training course for registrars covering STI management and laboratory methodologies, HIV-1 cure and HIV vaccines. During the reporting period, the section also participated in training medical scientists during their internship at the NICD.

- Dr Cathrine Scheepers taught a Fleming Fund-funded bioinformatics course for SEQAfrica on 21 May 2021 about analysing SARS-CoV-2 sequencing data.
- Dr Jinal Bhiman was a trainer on the NICD SARS-CoV-2 whole genome sequencing (WGS) in-person training course between 2 and 2 November 2021 where two Lesotho colleagues were trained on all aspects of SARS-CoV-2 WGS (including wet lab and bioinformatics techniques).
- Bhiman was also a course coordinator on the NICD respiratory syncytial virus (RSV) WGS virtual training course on 23 and 24 November 2021 where the Institute Pasteur Madagascar National Influenza Team were trained on bioinformatics and RSV sequence analysis

- a. Undergraduate level: eight
- b. Post-graduate level: eight

PROFESSIONAL DEVELOPMENT

- a. Post-graduate candidates enrolled:
 - MSc: seven
 - PhD: seven
 - BSc (Hons): two
- b. Post-graduate students graduated:
 - BSc (Hons): one
 - PhD: three
 - MSc: three

RESEARCH OUTPUTS

JOURNAL ARTICLES:

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PRESENTATIONS

International congresses: 29

National congresses: 21

Local congresses: one



CENTRE FOR RESPIRATORY DISEASES AND MENINGITIS (CRDM)



CENTRE FOR RESPIRATORY DISEASES AND MENINGITIS

PROF CHERYL COHEN

BACKGROUND

CRDM is a resource for surveillance, diagnostics, expertise and research in communicable respiratory diseases and meningitis for South Africa and Africa. The centre generates data and provides expertise to the national Department of Health (NDoH), healthcare providers and regional and international collaborators to assist in planning public health policies and programmes and respond to respiratory and meningitis disease outbreaks. CRDM is also a source of capacity building and formal training both within South Africa and Africa.

During the period of review, the centre continued its response activities to the COVID-19 pandemic, as well as its core function of surveillance through syndromic and laboratory-based surveillance programmes.

CRDM is responsible for six category one notifiable medical conditions (NMC), namely acute rheumatic fever, COVID-19, diphtheria, meningococcal disease, pertussis and respiratory disease caused by a novel respiratory pathogen, as well as the category two NMCs *Haemophilus influenzae* type b (Hib) disease and legionellosis.

The centre provides ongoing laboratory and epidemiology support to the NDoH for suspected diphtheria, pertussis, legionella and meningococcal disease cases.

SURVEILLANCE

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

This programme conducts national, laboratory and population-based active surveillance for invasive pneumococcal (IPD), meningococcal, Hib, group A and B streptococcal disease to evaluate the ongoing impact of the pneumococcal and Hib conjugate vaccines, assist in assessing appropriateness of new vaccines in development, and the impact of the COVID-19 pandemic on these pathogens. GERMS-SA surveillance data from our centre were submitted to the global pneumococcal serotype replacement and distribution estimation (PSERENADE) project and the invasive respiratory infections surveillance initiative (IRIS) to contextualise GERMS data relative to global statistics in the COVID-19 context.

The centre also contributed data on *Neisseria meningitidis* and supported diagnostic testing and outbreak response for suspected cases of meningococcal disease. Surveillance for group A and group B Streptococcus continued, aiming to generate evidence to contribute to vaccine development and decision-making for introducing future vaccines or other control interventions.

SYNDROMIC SURVEILLANCE FOR RESPIRATORY ILLNESS

National pneumonia surveillance operates in six provinces, with Tembisa Hospital (Gauteng) and Livingstone Hospital (Eastern Cape) added in March 2022. Systematic surveillance for outpatient influenza-like illness (ILI) and suspected pertussis is ongoing at outpatient public sector clinics in four provinces. The Viral Watch ILI surveillance network of general practitioners operates in eight provinces, while the pneumonia and systematic ILI programmes have been expanded to include systematic tuberculosis testing as well as COVID-19 vaccine effectiveness evaluation.

In addition, all syndromic programmes provide information on the timing of influenza and RSV seasons and COVID-19 waves, and provide data on influenza virus circulation and strains for decision-making around annual influenza vaccine composition and annual estimates of influenza vaccine effectiveness.

The programmes aim to describe the burden, risk groups, seasonality and characteristics of COVID-19, influenza, RSV and *Bordetella pertussis*. Additional studies investigate factors associated with severity of illness. Similar to data from other Southern Hemisphere countries, surveillance data showed a decline in influenza circulation during the 2021 winter season and a decrease in circulation of RSV and *B. pertussis*, partly due to the widespread measures to mitigate transmission of SARS-CoV-2.

Increased influenza activity was reported outside the usual winter season in 2021 and in 2021-2022, the programmes described risk factors for severe COVID-19; provided vaccine effectiveness estimates for COVID-19 vaccines and provided a platform for SARS-CoV-2 genomic surveillance to monitor circulating and emerging variants.

OUTBREAKS

COVID-19

CRDM played a leading role in responding to South Africa's COVID-19 pandemic. It supported the national COVID-19 incident management team, particularly in the epidemiology and laboratory streams and produced regular COVID-19 surveillance reports, including but not limited to the weekly epidemiological brief, weekly testing summary, weekly sequencing report and COVID-19 reproductive number reports. Various detailed epidemiologic reports were published in the Communicable Diseases Surveillance Bulletin.

CRDM is a WHO COVID-19 international regional reference laboratory and provides technical support and training to a number of African countries. In collaboration with other NICD centres, CRDM conducted expanded SARS-CoV-2 testing including PCR, sequencing, serology and viral culture. Staff were consulted on numerous expert committees and WHO working groups as well as Africa Centres for Disease Control (Africa CDC) and the WHO African Region (AFRO). The centre was a founding member of the Network for Genomic Surveillance in South Africa (NGS-SA), using routine genomic surveillance of SARS-CoV-2 to detect new SARS-CoV-2 variants as the pandemic progressed in South Africa and regionally, including discovering Omicron in November 2021.

CRDM obtained funding to conduct a range of COVID-19-related research activities, mainly focused on the burden of disease, transmission, sero-epidemiology and viral sequencing. CRDM staff participated in numerous media engagements informing the public about COVID-19 risks and how to reduce transmission and provided updates on the epidemic progression. Cheryl Cohen was appointed to the Ministerial Advisory Committee on COVID-19 vaccines and was a member of the WHO technical advisory group on COVID-19 vaccine composition (TAG-CO-VAC).

Anne von Gottberg was appointed vice-chairperson of the WHO technical advisory group on SARS-CoV-2 evolution and CRDM staff contributed to the emergency operations centre and national incident management team by providing data, epidemiology, laboratory and clinical expertise nationally and for Africa.

POLICY CONTRIBUTIONS

COVID-19 pandemic data advised several policy recommendations to the ministerial advisory committee and NDoH on topics including health system planning for emerging SARS-CoV-2 variants, implementing non-pharmaceutical interventions and policies around controlling COVID-19 in schools. Influenza vaccination guidelines were updated in light



of new data on effectiveness and safety when these vaccines are co-administered. In 2021, Anne von Gottberg was appointed as the NAGI chair. CRDM data and staff have contributed to a NAGI pertussis vaccine advisory group since 2019; this advisory has been finalised and submitted to NAGI.

DIAGNOSTIC SERVICES

CRDM routinely offers advanced molecular testing for several respiratory and meningitis-causing pathogens using various in-house and commercial platforms including meningitis/encephalitis, bacterial and viral respiratory and pneumonia multi-pathogen panels. The centre offers serotyping/grouping of vaccine-preventable bacterial pathogens and sub-typing for influenza and RSV.

RESEARCH ACTIVITIES

ASYMPTOMATIC TRANSMISSION AND HIGH COMMUNITY BURDEN OF SEASONAL INFLUENZA IN AN URBAN AND A RURAL COMMUNITY IN SOUTH AFRICA, 2017-18 (PHIRST): A POPULATION COHORT STUDY.

NICD investigators: Cohen C, Kleynhans J, Moyes J, et al.

Nasopharyngeal swabs were collected from 1,116 individuals in a rural and an urban community, twice weekly for an average 10 months each in 2017 and 2018, and tested for influenza virus. The incidence of influenza was 43.6 per 100 person-seasons (95% CI 39.8–47.7) and 69/408 (17%) individuals who had one influenza infection had a repeat influenza infection during the same season. Incidence and reinfections were highest in

children under the age of five years; 56% of infections were symptomatic and 10% of household members were infected following another case in the household. Transmission was highest from individuals aged 1-4 years and those with two or more symptoms. However asymptomatic individuals still transmitted influenza to 6% of contacts.

HIV INFECTION IS ASSOCIATED WITH INCREASED MENINGOCOCCAL CARRIAGE ACQUISITION AMONG FIRST-YEAR STUDENTS IN TWO SOUTH AFRICAN UNIVERSITIES.

NICD investigators: Meiring S, Cohen C, de Gouveia L, et al.

Meningococcal carriage prevalence among first-year South African university students increased over time, peaking at 8%. HIV infection was associated with carriage acquisition, while social-behavioural risk factors were associated with carriage and acquisition. These data advocate for targeted meningococcal vaccination of students.

EPIDEMIOLOGY OF PERTUSSIS IN INDIVIDUALS OF ALL AGES HOSPITALISED WITH RESPIRATORY ILLNESS IN SOUTH AFRICA, JANUARY 2013 TO DECEMBER 2018.

NICD investigators: Wolter N, Cohen C, Tempia S, et al.

Mean annual incidence was 17 cases per 100,000 population with the highest incidence in children under the age of one year (228 per 100,000). Age-adjusted incidence was 65.9 per 100,000 in HIV-infected individuals compared to 8.5 per 100,000 in HIV-uninfected individuals (risk ratio 30.4; 95% confidence interval (CI) 23.0-40.2). Ten individuals (4.2%) died, of whom seven were infants less than six months old, and three were immune-compromised adults.



DIFFERENCE IN MORTALITY AMONG INDIVIDUALS ADMITTED TO HOSPITAL WITH COVID-19 DURING THE FIRST AND SECOND WAVES IN SOUTH AFRICA: A COHORT STUDY.

NICD investigators: Jassat W, Mudara C, Ozougwu L, et al.

Data were analysed from national active surveillance for COVID-19 admissions in South Africa and characteristics were compared between the first and second SARS-CoV-2 waves. Peak admission and death rates were higher in the second wave as was the growth rate. There was a 31% increase in in-hospital mortalities and mortality was higher in weeks of high admissions.

SARS-COV-2 SEROPREVALENCE IN A RURAL AND URBAN HOUSEHOLD COHORT DURING FIRST AND SECOND WAVES OF INFECTIONS, SOUTH AFRICA, JULY 2020 TO MARCH 2021.

NICD investigators: Kleynhans J, Tempia S, Wolter N, et al.

Post-second wave seroprevalence ranged from 18% (95% CI 10-26%) in the rural community children (under the age of five years) to 59% (95% CI 49-68%) in adults (35-59 years) in the urban community.

The second wave was associated with a shift in age distribution of cases from individuals aged 35-59 years to individuals at the extremes of age; higher attack rates in the rural community and a higher infection fatality ratio in the urban community. Approximately 95% of SARS-CoV-2 infections were not reported to national surveillance.

EARLY ASSESSMENT OF THE CLINICAL SEVERITY OF THE SARS-COV-2 OMICRON VARIANT IN SOUTH AFRICA: A DATA LINKAGE STUDY.

NICD investigators: Wolter N, Jassat W, Walaza S, et al.

Clinical severity of individuals infected with Omicron was assessed using S-gene target failure (SGTF) on the ThermoFisher Scientific TaqPath COVID-19 PCR test as a proxy, using national case and admission data, laboratory testing data and genomic sequence data. Compared to non-SGTF infections, individuals with SGTF infection had an 80% lower odds of being admitted to hospital (adjusted odds ratio (aOR) 0.2, 95% c CI 0.1-0.3). Compared to Delta infections from the third wave, SGTF infections were associated with 70% lower odds of severe disease among hospitalised individuals (aOR 0.3, 95% CI 0.2-0.5).

RAPID EPIDEMIC EXPANSION OF THE SARS-COV-2 OMICRON VARIANT IN SOUTHERN AFRICA.

NICD investigators: Amoako DG, Wolter N, von Gottberg A et al.

This study describes the genomic profile and early transmission dynamics of Omicron, highlighting the rapid spread in regions with high levels of population immunity. Genotypic and phenotypic data suggest Omicron has the capacity for

substantial evasion of neutralising antibody responses, and modelling suggests immune evasion could be a major driver for the observed transmission dynamics. Closely monitoring Omicron's spread outside southern Africa is necessary to better understand its transmissibility and the capacity of this variant to evade post-infection and vaccine-elicited immunity.

TEACHING AND TRAINING

- Ongoing training at various sites for surveillance and COVID-19 special studies
- Ongoing training workshops for SARS-CoV-2, influenza and RSV detection and further characterisation and sequencing national and international
- Ongoing advisory, technical and epidemiological support in-country and in Africa for SARS-CoV-2, influenza, RSV and bacterial meningitis
- Ongoing training and MSc and PhD supervising efforts as part of an international research training grant (D43) from the US National Institutes of Health (NIH) and Fogarty International Centre (FIC) sub-award through the University of Pittsburgh. The grant provides young South African public health and academic investigators from historically-disadvantaged backgrounds with multidisciplinary tools to conduct cutting-edge research in public health genomic and metagenomic epidemiology of respiratory and invasive bacterial and fungal diseases. Six students (three each PhD and MSc) are currently enrolled in the programme.

POSTGRADUATE STUDENTS

There are currently 14 staff enrolled for post-graduate studies, namely MSc (six) and PhD (eight).

RESEARCH OUTPUTS

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Conferences: Seven



CENTRE FOR TUBERCULOSIS (CTB)



CENTRE FOR TUBERCULOSIS

DR SHAHEED VALLY OMAR

BACKGROUND

The core functions of the CTB are to execute tuberculosis (TB) surveys and population research, conduct laboratory-based public health surveillance of TB and contribute to advance TB epidemiology, diagnostics and treatment, thus guiding South African policy. In addition, the centre houses the National TB Reference Laboratory and is a member of the World Health Organisation (WHO) TB Supranational Reference Laboratory network. The centre works closely with both National and International stakeholders in an effort to direct and support policies and guidelines.

For this year, the Centre focussed assessing the impact of Covid-19 on TB diagnosis nationally, continued analysis of the first National TB Prevalence Survey, evaluation and introduction of new diagnostic assays for the National TB programme and provide support to the NDoH with developing the National TB Recovery Plan.

THE IMPACT OF THE COVID-19 EPIDEMIC ON THE LABORATORY INVESTIGATIONS FOR TB

The CTB provided the national TB programme with bi-weekly analysis of Xpert MTB/RIF (Xpert) TB testing volumes, positive tests, positivity rate and rifampicin-resistant rate to support the TB Covid-19 recovery plan. Xpert TB testing volumes recovered during 2021 and have exceeded upper confidence bounds since November 2021 (figure 1).

SURVEILLANCE

FIRST NATIONAL TB SURVEY

The national TB prevalence survey was a collaboration between the South African Medical Research Council (MRC), Human Sciences Research Council (HSRC), CTB and the NDoH. The survey planned to establish the true burden of pulmonary TB disease in the country and was conducted according to the international recommendations of the WHO Global Task Force on TB Impact Measurement.

The survey began in mid-August 2017 and over 35,000 people participated with 15,268 sputum samples processed at NICD. The findings were presented on 27 January 2021 and the overall TB prevalence was 852 per 100,000 (95% CI 679-1,026), with a higher prevalence in males (1,094 per 100,000) versus females 675 per 100,000. The majority of the survey cases were HIV-negative and 57.8% did not report any symptoms at the time of the specimen submission.

ROUTINE SURVEILLANCE REPORTING AND REQUEST FOR ACTION ALERTING

Surveillance findings are regularly analysed and reported to the national and provincial TB programmes. The weekly results for action (RfA) reports cover both drug-susceptible and drug-resistant TB. Quarterly reporting about the number of TB cases (drug-susceptible and drug-resistant), nationally and further stratified by province and sub-district are ongoing, with automated reports regularly emailed to the relevant

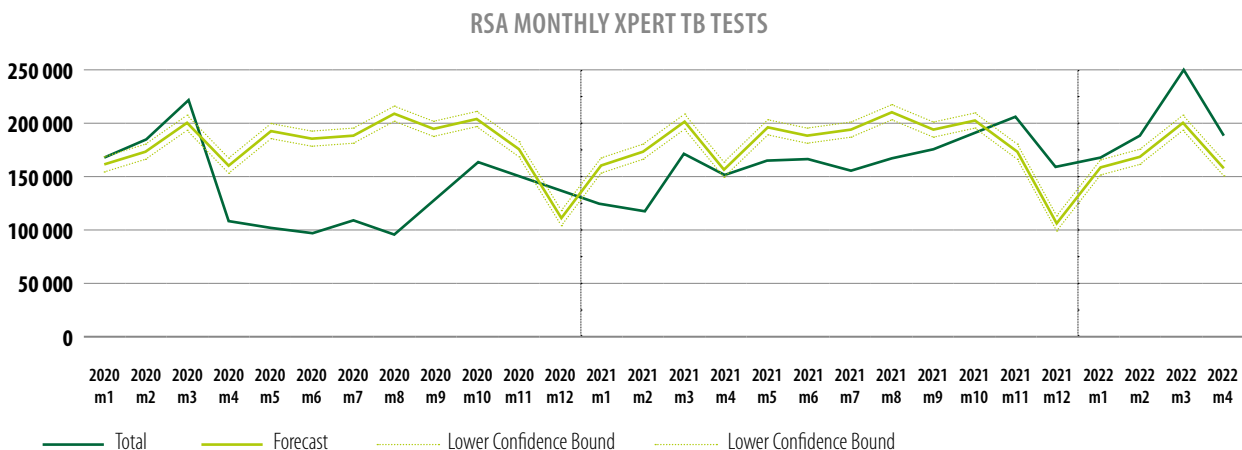


Figure 1: Monthly Xpert tests and projection bounds, South Africa January 2020 – April 2022

stakeholders. The updated 2021 definition for pre-XDR and XDR was incorporated into the quarterly reports and will be applied in future reports. Integration of the NHLS laboratory data and the electronic drug-resistant TB registration www.edrweb.net were developed, enabling improved estimates of the country's total drug-resistant TB burden.

GLOBAL FUND REPORTS

Support from the Global Fund, meant enhanced TB surveillance reports were developed for nine priority TB districts to support targeting local interventions to improve the TB programme. The enhanced reports include detailed facility level epidemiological, geospatial and trajectory analyses. Reports for the 2021 year were distributed to stakeholders and discussions are ongoing for supporting and expanding the enhanced TB surveillance reports in every district.

GERMS SURVEILLANCE

The GERMS surveillance TB section focuses on participants with rifampicin-susceptible TB diagnosed at hospitals to detect isoniazid (INH) mono-resistance and monitor the relative contribution of HIV/ART, TB preventative therapy (TPT) and pathways to care in reducing incidence and achieving the NDoH strategic plan's expectations. Hospitals in five provinces are included in the surveillance. The global pandemic severely hampered the surveillance programme with only 267 samples received; only 184 were culture positive and 14 (7.6%) INH resistant.

MODERNISING TB SURVEILLANCE

Developing the Notifiable Medical Conditions (NMC) TB module system was an important advancement in the public health surveillance and response front. The module allows user

to capture cases electronically to be viewed in near real-time by public health responders. This eliminates the need for paper-based notification and reduces notification time and capturing errors. It will reduce the initial loss to follow up on TB patients and integrate clinical and laboratory notifications to provide a more accurate measure of the country's TB burden. The internal pilot has been completed with the next phase to expand the pilot to several healthcare facilities.

DIAGNOSTIC SERVICES

SPECIALISED REFERENCE MYCOBACTERIOLOGY – NATIONAL AND SUPRANATIONAL REFERENCE LABORATORY ACTIVITIES

The centre prepared proficiency testing panels for second-line drugs-susceptibility testing (including Bedaquiline (BDQ)). These were sent to the NHLS laboratories performing DR-TB Reflex testing. As no formal BDQ testing kit is yet available, the centre provides prepared BDQ drug aliquots to enable routine testing within the NHLS. Second-line LPA EQA was handed over to NHLS QA division to be included in the TB EQA scheme. Pilot panels were distributed in the third quarter with the centre assisting with sample preparation and analysis. Regionally, CTB supported Namibia in terms of performing drug-susceptibility testing for patients who have a poor response to a drug-resistant TB regimen.

ADVANCING DIAGNOSTICS, EPIDEMIOLOGY AND TREATMENT

As part of the centre's function to advance diagnostics, epidemiology and treatment, several cutting-edge diagnostic technologies were evaluated including next-generation target sequencing technologies for predicting drug resistance. The centre was instrumental in advising on the GeneXpert MTB/XDR assay adoption and is currently playing a pivotal role in its



implementation. Implementing this technology will significantly improve turnaround times to detect drug-resistant TB, thus providing comprehensive information to adequately manage clinical patients. The centre also leads a multi-country collaboration to assess backward compatibility with the Xpert MTB/RIF assays on the new GeneXpert 10 colour platform. This data was shared with the WHO for review and used for the WHO policy statement. CTB also participated in advisory roles in several WHO reviews of diagnostic technologies resulting in policy guidance.

RESEARCH ACTIVITIES

MICROBIOLOGICAL AND EPIDEMIOLOGICAL SURVEILLANCE OF TB IN SOUTH AFRICA: APPLICATION OF WHOLE GENOME SEQUENCING (WGS) TO ENHANCE MICROBIOLOGICAL AND EPIDEMIOLOGICAL SURVEILLANCE OF DRUG-RESISTANT TB (DR-TB) IN SOUTH AFRICA

NICD investigators: Farzana Ismail, Shaheed V Omar, Halima Said, Lavania Joseph, Harry Moultrie, Judith Mwansa, Elizabeth Kachingwe

Collaborator: Centre for Disease Control, South Africa/USA

This research aims to assess WGS as the primary phylogenetic investigation tool for:

- longitudinal surveillance of transmission in selected regions with relatively high burdens of MDR-TB;
- improving the detection of high-risk cluster transmissions with outbreak potential and
- demonstrating the effective use of WGS to improve surveillance by comprehensively detecting drug resistance to guide national policy.

It also aims to validate the diagnostic performance of target next-generation sequencing (tNGS) assays in predicting drug-resistance to first-line, second-line and new anti-TB drugs and diagnostic performance among smear positive and negative samples.

Currently in its second year, the study has more than 1,200 sequential MDR-TB isolates from the Johannesburg and Cape Town metropolitan areas to investigate WGS utility. Another 267 samples have been processed to evaluate the tNGS assay for predicting drug resistance. Analysis is on-going and primary findings are expected in the next reporting year.

MULTI-CENTRE CLINICAL TRIAL TO ASSESS THE PERFORMANCE OF CULTURE-FREE, END-TO-END tNGS SOLUTIONS FOR DIAGNOSIS OF DR-TB

NICD investigators: Shaheed V Omar and Farzana Ismail

Collaborator: Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland

This FIND-sponsored multi-site study includes India, Georgia

and South Africa and aims to determine the diagnostic accuracy of culture-free, end-to-end tNGS solutions for diagnosing DR-TB. This would offer higher throughput and greater accuracy across more TB drugs than current WHO-endorsed molecular assays and a significantly faster time-to-result than phenotypic drug susceptibility testing (DST). The findings will be critical to inform global and national policy.

To date 260 TB patients have been screened and 147 (of an expected 250) participants have been enrolled. An additional site has been activated to improve the enrolment rate.

INVESTIGATING THE USEFULNESS OF THE NEW QUANTIFERON-TB PLUS ASSAY IN DIAGNOSING LATENT TB INFECTION AND PROGRESSION TO ACTIVE TB DISEASE AMONG HEALTHCARE WORKERS IN HIGH-INCIDENCE SETTINGS

NICD investigators: Shaheed V Omar, Farzana Ismail and Judith Mwansa

Collaborator: TB Directorate – National Department of Health and Aurum Institute

This collaborated project is designed to understand and provide a baseline of the prevalence of latent TB infection (LTBI) and the progression from latent to active TB among healthcare workers. Additionally, it will assess the feasibility of using QuantiFERON-TB Plus among healthcare workers in a routine South African healthcare setting. However, Covid-19 meant study sites were revised and activities reinitiated in the fourth quarter. There are currently three activated sites namely Pretoria West Hospital and Edenvale Hospital (both Gauteng) and Dora Ngiza Hospital (Eastern Cape).

INVENTORY STUDY MEASURING THE LEVEL OF UNDER-REPORTING AND ESTIMATING INCIDENCE FOR TB IN SOUTH AFRICA: AN INVENTORY STUDY AND CAPTURE-RECAPTURE ANALYSIS

NICD investigators: Harry Moultrie

Collaborators: TB Directorate (NDoH) and WHO

The study aims to determine the extent of under-reporting of TB cases to the national TB control programme (NTCP) and entails linking data from the NHLS, private sector labs and the electronic TB and drug-resistant TB registers to quantify under-reporting and generate a more accurate measure of TB incidence. Linking has been completed and the final analysis is in progress.

TARGETED SEQUENCING TO ENHANCE, LIBERATE AND OPTIMISE TREATMENT OF DR-TB: A PRAGMATIC, IMPLEMENTATION EVALUATION (TS ELIOT)

NICD investigators: Farzana Ismail and Shaheed V Omar

Collaborators: University of California and University of Stellenbosch

TSELIOT is a pragmatic, stepped-wedge programme evaluation of a sequencing-based strategy to provide comprehensive drug susceptibility data to inform RR-TB management in the Western Cape. All Xpert-identified RR-TB specimens collected in the nine administrative units under study will be included.

PREVALENCE OF SARS-COV-2 AND MYCOBACTERIUM TB CO-INFECTION AND THE IMPACT OF CO-INFECTION ON CLINICAL PRESENTATION AND OUTCOME AMONG PATIENTS PRESENTING WITH INFLUENZA-LIKE ILLNESS OR HOSPITALISED WITH SEVERE RESPIRATORY ILLNESS OR SUSPECTED COVID-19 AT SENTINEL SITES IN SOUTH AFRICA

NICD CTB investigators: Farzana Ismail and Harry Moultrie

Collaborators: Centre for Respiratory Diseases - NICD

This study aims to describe the prevalence of MTB-SARS-CoV-2 co-infection and the impact of co-infection on clinical presentation and short-term outcomes in:

- patients presenting with influenza-like illness (ILI);
- suspected Covid-19 at ILI surveillance sites or
- patients admitted with severe respiratory illness (SRI) at pneumonia surveillance sites in South Africa.

Existing hospital surveillance included in the SRI and clinic-based surveillance for ILI will be included. Conducting systematic testing for TB among outpatients and hospitalised individuals with respiratory illness as part of the surveillance will allow for more complete data on the TB status, thus allowing for a better evaluation of the prevalence of SARS-CoV-2 and TB co-infection and their interaction. Acute TB cases will also be identified that may have been missed when using the current testing guidelines.

PRETOMANID RESISTANCE SURVEILLANCE PROGRAMME

NICD investigators: Shaheed V Omar and Farzana Ismail

Collaborator: TB Alliance

Pretomanid is a new nitroimidazooxazine antimycobacterial drug. One of the US Food and Drug Administration (FDA) post-marketing requirements (PMRs) specifies a five-year resistance surveillance study be conducted after introducing pretomanid to monitor changes in Mycobacterium TB susceptibility to pretomanid.

The primary goal is to conduct a five-year study to determine pretomanid minimum inhibitory concentrations (MICs) of a sample of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Mycobacterium TB complex isolates. In addition to MIC data for pretomanid, the programme will collect susceptibility data for other anti-TB drugs available for the MTB isolates included in the study.

CALIBRATION OF ANTIMICROBIAL SUSCEPTIBILITY TESTING METHODS AND BREAKPOINTS AGAINST THE EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING (EUCAST) REFERENCE STANDARDS FOR BEDAQUILINE, CLOFAZIMINE, LEVOFLOXACIN AND LINEZOLID

NICD investigators: Shaheed V Omar

Collaborator: University of Cambridge

The purpose of the calibration is to propose quality control ranges/targets and epidemiological cut-offs (ECOFFs) for the EUCAST Middlebrook 7H9 broth (7H9) microdilution (BMD) reference method and calibrate surrogate methods, the results of which will be submitted to the EUCAST sub-committee on Antimycobacterial Susceptibility Testing (EUCAST-AMST) for review.

All quality control isolate runs will be included in the calculations for essential agreement between BMD and mycobacteria growth indicator tube (MGIT).

POLICY CONTRIBUTIONS

NATIONAL POLICY

- TB recovery plan: standard operating procedures for systematic screening and investigation for TB in South Africa
- South African national TB THINK tank guidelines and advisories
- Ministerial advisory committee on Covid-19 advisory on monitoring Covid-19 between acute outbreaks and deciding on appropriate and timely responses
- Ministerial advisory committee on Covid-19 position paper on mitigating Covid-19 in South Africa going forward
- Ministerial advisory committee on Covid-19 advisory on quarantining and contact tracing
- South African Covid-19 modelling consortium (SACMC) analyses, projections and dashboards

INTERNATIONAL POLICY

- WHO operational handbook on TB: module three rapid diagnostics for TB detection 2021 update
- WHO rapid communication: TB antigen-based skin tests for the diagnosis of TB infection
- WHO target product profile for next-generation TB drug-susceptibility testing at peripheral centres
- WHO policy statement: use of alternative interferon-gamma release assays for the diagnosis of TB infection
- WHO policy statement: use of Xpert MTB/RIF and Xpert MTB/RIF Ultra on GeneXpert 10-colour instruments

- WHO policy statement: Optimised broth microdilution plate methodology for drug susceptibility testing of Mycobacterium TB complex
- WHO catalogue of mutations in Mycobacterium TB complex and their association with drug resistance
- WHO rapid communication: update on the use of nucleic acid amplification tests to detect TB and DR-TB
- WHO technical report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine)

TEACHING AND TRAINING

Training was provided on both reference mycobacteriology testing and public health aspects of TB to rotating registrars and intern medical scientists from university-based medical microbiology and public health departments. Due to Covid-19, training was conducted on a virtual platform. CTB staff also provided formal lectures to undergraduate medical students and medical microbiology registrars at the University of Pretoria and post-graduate students at the University of Witwatersrand. The centre trained and performed advanced testing for several post-graduate students to support their research.

PROFESSIONAL DEVELOPMENT

There is currently one PhD and two MSc post-graduates under supervision. One intern medical scientist passed the national assessment and another two are in training.

RESEARCH OUTPUT

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World TB Day outreach in the Northern Cape



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WORLD TB DAY ACTIVITIES AND TB AWARENESS MONTH OUTREACH IN THE NORTHERN CAPE

CTB activities marking the annual World TB Day on 24 March included a World TB Day awareness campaign and a World TB Day competition. Staff were requested to design a slogan for

increased TB awareness with the winning slogan being: "TB or not TB? No longer a choice. End TB".

In addition, the centre coordinated and supported the NDoH's TB awareness month and World TB Day activities in the Northern Cape by coordinating mobile TB testing together with the CEO's office, National Priority Programme and NHLS Northern Cape (Figure 2).

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CENTRE FOR VACCINES AND IMMUNOLOGY (CVI)



CENTRE FOR VACCINES AND IMMUNOLOGY

DR NISHI PRABDIAL-SING

BACKGROUND

The CVI provides epidemiological, virological and immunological support to the National Department of Health (NDOH) for vaccine-preventable diseases. The centre conducts testing and/or surveillance for poliovirus, measles, rubella, tetanus and viral hepatitis, all targeted for either eradication or elimination in the next few years. Target indicators for polio and measles, set by the World Health Organisation (WHO) and NDOH, guides the centre to improve our surveillance detection and sensitivity. In addition, the centre performs testing on wastewater samples for poliovirus and SARS-CoV2 detection. Research projects include next generation sequencing on poliovirus and viral hepatitis.

SURVEILLANCE

POLIO SURVEILLANCE

Wild poliovirus type 1 and vaccine-derived polioviruses (VDPV) circulate in many countries, despite extensive global efforts. Immunisation and surveillance must be strengthened to fulfil the polio endgame strategy by 2023. The poliovirus isolation laboratory serves eight southern African countries, namely Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, Swaziland and South Africa, for acute flaccid paralysis (AFP) surveillance and Angola, Botswana, Malawi, Mozambique, Namibia, and South Africa for environmental surveillance. The poliovirus regional reference laboratory is only one of three in Africa.

During the period under review, 3,452 samples were processed for poliovirus isolation; South Africa (696) and 2,756 from the other seven countries. Between January and March 2022, the AFP detection rate in children under the age of 15 years in the country was 3.2 per 100,000 population, meeting the WHO indicator of 2/100,000 but below the national target indicator of 4/100,000. In September 2021, a case of immunodeficiency related vaccine-derived poliovirus type 3 (iVDPV3) in a 6 month old female with severe combined immunodeficiency was detected, in Ekurhuleni, Gauteng.

A wild poliovirus type 1 was detected in a sample from a Malawian AFP case, but community and household contact sampling and testing plus local environmental samples showed no new cases. Heightened surveillance continues in an attempt to detect any circulation.

VDPV type 1 (VDPV1) was identified in 53 samples received from Madagascar and VDPV2 in 149 samples from Burkina Faso, Democratic Republic of Congo (DRC), Ivory Coast, Liberia, Mali, Niger, Republic of the Congo (Congo Brazzaville), South Sudan and Sierra Leone including two cases in Mozambique. Type 2 Sabin polioviruses were detected in 96 samples, most from countries using monovalent oral polio vaccine type 2 to halt VDPV2 transmission (Burkina Faso, Ivory Coast, Mali, DRC, South Sudan, Congo Brazzaville and Uganda).

The NICD applied to the Global Certification Commission for Polio Eradication to host a polio essential facility to work with poliovirus type 2 culture material under high containment, and type 3 culture material following cessation of oral polio vaccine type 3. The national authority for containment conducted a pre-audit visit in March 2022.

ENVIRONMENTAL SURVEILLANCE

POLIOVIRUS

The NICD offers ongoing support to the WHO for environmental polio surveillance from African sewerage sites. The regional reference laboratory identified VDPV1 in 91 environmental samples from Madagascar, while VDPV2 was found in 55 environmental samples from the DRC, Ivory Coast, Liberia, Niger and Congo Brazzaville.

Locally, an environmental sample from the Eastern Cape contained a type 2 Sabin poliovirus. No AFP cases were reported. While neighbouring laboratories, medical facilities and vaccine depots were investigated for an accidental release of Sabin 2, the source was not determined and heightened surveillance showed no more detections in the community or environment. Other South African environmental sites revealed two Sabin poliovirus samples, a type 3 and a type 1. These isolates are to be expected as the Sabin strain is excreted in the stool following a receipt of oral polio vaccine and may be transmitted to unvaccinated contacts.

SARS-COV-2 ENVIRONMENTAL SURVEILLANCE

The NICD partnered with the National Institute for Occupational Health (NIOH), Lumegen Laboratories, GreenHill Laboratories, Praecautio, Waterlab, Durban University of Technology (DUT),

South African Medical Research Council-Tuberculosis (SAMRC-TB) platform and the Council for Scientific and Industrial Research (CSIR) in the South African Collaborative COVID-19 Environmental Surveillance (SACCESS) network to detect and geographically locate SARS-CoV-2 distribution in sewage.

In total 548 wastewater samples were processed for SARS-CoV-2 surveillance from sites in Gauteng, the Western Cape, the Free State, KwaZulu-Natal, the Eastern Cape and the Northern Cape. SARS-CoV-2 was identified in 498 samples (91%). This was quantitated using optimised methodology to obtain copies of SARS-CoV-2 RNA/ml of wastewater.

Quantitative PCR has documented increases and subsequent decreases in viral load in wastewater correlating with clinical caseloads in each metropolitan area. In addition to testing, NICD collates and reports results from 73 additional sites from SACCESS partners. Reports are compiled and shared with stakeholders every Friday and published online (<https://wastewater.nicd.ac.za/>). Mutations of the SARS-CoV-2 variants Beta, Delta, Omicron and C.1.2 have been successfully detected in wastewater using next-generation sequencing. SARS-CoV-2 is considered non-infectious from sewage samples, but the viral RNA remains detectable in raw sewerage. Sewage monitoring may provide accessory information to the NDOH for planning geographically localised interventions.

MEASLES AND RUBELLA SURVEILLANCE

The centre is the national and WHO regional reference laboratory for measles and rubella testing and surveillance. CVI provides serological testing for these diseases and molecular testing for measles in support of the measles and rubella strategic framework 2021-2030.

Laboratory results (detection of measles-specific IgM antibodies, avidity of anti-measles IgG antibodies, RT-PCR and genotyping) are used in conjunction with epidemiologic case investigations in diagnosing acute measles infections. A total of 960 South African febrile rash samples were tested during the period under review with five confirmed measles cases, two classified as compatible and eight cases still requiring classification (case notes required). Measles genotype B3 was detected in a patient who had recently returned from the DRC, but no clusters of cases were detected.

Only 20 rubella cases were identified via febrile rash surveillance. This is considerably lower than previous years, but likely reflects lower health-seeking behaviour resulting from the COVID-19 pandemic and lower transmission because of social distancing and lockdown measures. Between January and March 2022 South Africa met the WHO indicator of a non-measles non-rubella discard rate of $\geq 2/100,000$ population.



Zambia and Mozambique experienced measles outbreaks and throat swabs were sent to NICD for genotyping. Measles genotype B3 was detected in the Zambian outbreak samples (linked to the DRC) and genotype D8 detected in the Mozambican outbreak samples.

As part of the WHO regional quality assurance programme, the centre should retest approximately 10% of serum samples from 11 southern and eastern African countries, namely Botswana, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, eSwatini, Zambia and Zimbabwe. Although only six countries sent samples and 180 samples were tested, there was good concordance for the measles IgM and rubella IgM results.

TETANUS

The centre collates and classifies tetanus cases reported through the NMC system. In the reporting period, two tetanus cases were notified and confirmed. No neonatal tetanus cases were reported. The WHO declared South Africa had eliminated maternal and neonatal tetanus in 2002 with the country's rate of neonatal tetanus below the threshold of less than one case per 1,000 live births in every district annually.

VIRAL HEPATITIS

The centre remains committed to achieving the viral hepatitis elimination goals by 2030. CVI performs passive laboratory-based surveillance for hepatitis A, B and C using data from the NHLS corporate data warehouse (CDW) and NMC.

HEPATITIS A

During the year 121,281 cases were tested for hepatitis A IgM antibodies through NHLS laboratories nationally with 1,437 cases testing positive; an overall detection rate of 1.2%. The centre has used Cusum2 and mean +3SD (standard deviation) thresholds to detect any increase in hepatitis A IgM. In this way provincial epidemiologists can be contacted to investigate any potential regional outbreak. During the reporting period, positive numbers remained below the thresholds for all districts.

HEPATITIS B

Between 1 April 2021 and 31 March 2022, national NHLS laboratories tested 537,846 cases for HBsAg of which 24,503 (4.6%) tested positive. Of these the majority (18,155/74%) were among the age group of 25 to 49 years and 70 cases (0.3%) were in children under 12 months old. The number of incident cases (defined by a positive IgM result against hepatitis B core antigen) was 389. Hepatitis B data was shared with the NDOH (joint reporting format) and the national advisory group on immunisation meetings held during this period.

HEPATITIS C

From 1 April 2021 to 31 March 2022, there were 129,583 patients tested for hepatitis C virus exposure with a hepatitis C antibody test. Of the 2.63% (3,317) positive results, only 427 patients had a hepatitis C viral load test of which 69% (295) were positive. The gaps in patient care and testing algorithm must be addressed to achieve eliminating viral hepatitis by 2030. Hepatitis C genotyping information showed circulation of genotypes 1 to 5 in South Africa.

RESEARCH ACTIVITIES

PHYLOGENETIC TRANSMISSION CLUSTERS OF HEPATITIS C VIRUS AMONG KEY SOUTH AFRICAN POPULATIONS

NICD investigators: Ndlovu N and Prabdial-Sing N

Collaborators: Blackard J (University of Cincinnati), Scheibe A (TB/HIV care association), Young K (TB/HIV care association), Hausler H (TB/HIV care association), Medeiros N (OUT LGBT Well-being), Nel D (OUT LGBT Well-being), Rebe K (Anova Health Institute), Sonderup M (University of Cape Town) and Spearman W (University of Cape Town).

People who inject drugs are disproportionately infected with HCV. A three-city cross-sectional survey revealed about half tested positive for HCV viremia with participant sequences forming a phylogenetic clade (or cluster) being highly related. Phylogenetic clustering is associated with a network of people who inject drugs, inferring the epidemic structure, particularly when partner-tracing data is unavailable. The study analysed genetic sequence data in the core-envelope2 regions with demographic data to map transmission networks for targeted intervention.



Members of the successful SACCESS team at CVI, NICD, a leading partner of the South African Collaborative COVID-19 Environmental Surveillance (SACCESS) network.

From left: Chinwe Juliana Jaja; Melinda Suchard; Mukhlid Yousif; Kerrigan McCarthy; Nkosenhle Ndlovu and Said Rachida.

AMPLIFICATION AND SEQUENCING OF WHOLE GENOME OF POLIOVIRUS

NICD investigators: Koketso Makua, Emmanuel Phalane, Wayne Howard, Lerato Seakamela, Kerrigan McCarthy, Shelina Moonsamy and Mukhlid Yousif

Collaborators: Alex Shaw and Nicholas Grassly (Imperial College London, UK)

The Sanger sequencing method has been widely used for targeted sequencing the viral protein 1 (VP1) of the poliovirus in AFP surveillance. In some cases, polioviruses can have unusual mutation patterns making it difficult to classify them into serotypes, sabins and VDPVs. Hence, whole genome sequencing (WGS) has been used as an alternative method. CVI aims to optimise amplification and sequencing of the whole genome of poliovirus by using paired primers to generate approximately 7.5 kb amplicon with Nextera-flex and Illumina NextSeq550 and MinION nanopore technology. This method can support poliovirus WGS surveillance in the WHO/AFRO region.

TEACHING AND TRAINING

UNDERGRADUATE LEVEL

GEMPII and PHII (viral hepatitis), medicine (medical immunology, vaccinology)

POST-GRADUATE LEVEL

Registrar rotation, MSc, MMed, PhD, MPH

PROFESSIONAL DEVELOPMENT

POST-GRADUATE STUDENTS ENROLLED

There were five MSc, four PhD, four intern scientists and one FETP students enrolled during the year under review.

POST-GRADUATE STUDENTS GRADUATED

Three PhD, two intern scientists and one FETP graduated during the review period.

OTHER ACTIVITIES

The centre provided key support to NICD COVID-19 activities in the following ways:

- Drs M Suchard, K McCarthy and M Yousif gave multiple media interviews related to the pandemic;
- Dr S Malfeld supported daily reporting duties for COVID-19 and
- CVI hosted a World Polio Day webinar on 22 October 2021.

RESEARCH OUTPUT

JOURNAL ARTICLES

- [1] Moonsamy S, Suchard MS, Pillay P and Prabdi-Sing N. Prevalence and Incidence rates of laboratory-confirmed hepatitis B infection in South Africa, 2015-2019. BMC Public Health. 2022; 22:29. DOI: 10.1186/s12889-021-12391-3.
- [2] Opperman CJ, Moodley C, Lennard K, Smith M, Ncayiyana J, Vulindlu M, et al. A citywide, clonal outbreak of *Pseudomonas aeruginosa*. Int J Infect Dis. 2022; 117:74-86. DOI: 10.1016/j.ijid.2022.01.039.
- [3] McCarthy K, Howard W, Yousif M, Moonsamy S and Suchard M. The show is not over – wild-type polio in Malawi is a wake-up call and an opportunity for elimination efforts. International Journal of Infectious Diseases. 2022; 4:1. DOI: <https://doi.org/10.1016/j.ijid.2022.03.004>.
- [4] Suchard, MS., Martinson, N., Malfeld, S., De Assis Rosa, D., Mackelprang, RD., Lingappa, J, et al. Alloimmunity to class 2 human leucocyte antigens may reduce HIV-1 acquisition-a nested case-control study in HIV-1 serodiscordant couples. Frontiers in Immunology. 2022; 24:13. DOI: <https://doi.org/10.3389/fimmu.2022>.
- [5] Morifi M, Malevu N, Odayan S, McCarthy K and Kufa T Congenital Syphilis Case Surveillance in South Africa 2017-19: Experience, Challenges and Opportunities. J Trop Pediatr. 2021; 27:67. DOI: 10.1093/tropej/fmab079.
- [6] Howard W, Moonsamy S, Seakamela L, Jallow S, Modiko F, du Plessis H et al. Sensitivity of the acute flaccid paralysis surveillance system for poliovirus in South Africa, 2016–2019. Journal of Medical Microbiology. 2021; 70:001441. DOI 10.1099/jmm.0.001441.

- [7] Prabdial-Sing N, Motaze V, Manamela JM, McCarthy K and Suchard MS Establishment of outbreak thresholds for Hepatitis A in South Africa using laboratory surveillance 2017-2020. *Viruses*. 2021; 13:2470. DOI: 10.3390/v13122470.
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- [9] Morifi M, Malevu N, Odayan S, McCarthy K, Kufa T. Congenital Syphilis Case Surveillance in South Africa 2017-19: Experience, Challenges and Opportunities. *J Trop Pediatr.* 2021 Aug 27;67(4):fmab079. doi: 10.1093/tropej/fmab079. PMID: 34490454.
- [10] McCarthy KM, Tempia S, Kufa T, Kleynhans J, Wolter N, Jassat W, Ebonwu J, von Gottberg A, Erasmus L, Muchengeti M, Walaza S, Ntshoe G, Shonhiwa AM, Manana PN, Pillay Y, Moonasar D, Muthivhi T, Mngemane S, Mlisana K, Chetty K, Blumberg LH, Cohen C, Govender NP; South African COVID-19 Surveillance Team. The importation and establishment of community transmission of SARS-CoV-2 during the first eight weeks of the South African COVID-19 epidemic. *EClinicalMedicine*. 2021 Sep;39:101072. doi: 10.1016/j.eclinm.2021.101072. Epub 2021 Aug 12. PMID: 34405139; PMCID: PMC8360332.
- [11] Paleker M, Tembo YA, Davies MA, Mahomed H, Pienaar D, Madhi SA, McCarthy K. Asymptomatic COVID-19 in South Africa - implications for the control of transmission. *Public Health Action*. 2021 Jun 21;11(2):58-60. doi: 10.5588/pha.20.0069. PMID: 34159063; PMCID: PMC8202632.
- [12] Foster N, Cunnama L, McCarthy K, Ramma L, Siapka M, Sinanovic E, Churchyard G, Fielding K, Grant AD, Cleary S. Strengthening health systems to improve the value of tuberculosis diagnostics in South Africa: A cost and cost-effectiveness analysis. *PLoS One*. 2021 May 14;16(5):e0251547. doi: 10.1371/journal.pone.0251547. PMID: 33989317; PMCID: PMC8121360.
- [13] Nkosi N, Preiser W, van Zyl G, Claassen M, Cronje N, Maritz J, Newman H, McCarthy K, Ntshoe G, Essel V, Korsman S, Hardie D, Smuts H. Molecular characterisation and epidemiology of enterovirus-associated aseptic meningitis in the Western and Eastern Cape Provinces, South Africa 2018-2019. *J Clin Virol*. 2021 Jun;139:104845. doi: 10.1016/j.jcv.2021.104845. Epub 2021 Apr 24. PMID: 33962182.

OTHER PUBLICATIONS

- [1] McCarthy K, Rachida S, Yousif M, Ndlovu N, Howard W, Moosamy S, Pocock G, Coetzee L, Mans J, Schaefer L, Le Roux W, Gomba A, Jambo D, de Villiers DM, Lepart NL, Johnson RL, Muller C, Berkowitz N, Bhagwan J and Suchard MS for the SACCESS network. Monitoring for the third wave: detection and sequencing of SARS-CoV-2 at sentinel wastewater treatment sites (National SARS-CoV-2 Wastewater-based Epidemiology Surveillance Initiative). Science Brief, Water Research Commission, June 2021.
- [2] McCarthy et al, Monitoring the third wave: detection of SARS-CoV-2 at sentinel wastewater treatment sites by the South African Collaborative COVID-19 Environmental Surveillance System (SACCESS) network, 2020-2021. COVID-19 Special Public Health Bulletin of the NICD, July 2021
- [3] Howard W and Suchard MS. It's been a year since Africa was declared polio free. But a threat remains. *The Conversation*, August 2021. <https://theconversation.com/its-been-a-year-since-africa-was-declared-polio-free-but-a-threat-remains-166625>

PRESENTATIONS

CVI presented at two international and nine national conferences during the period under review.



DIVISION OF PUBLIC HEALTH SURVEILLANCE AND RESPONSE (DPHSR)



DIVISION OF PUBLIC HEALTH SURVEILLANCE AND RESPONSE

DR MICHELLE GROOME

BACKGROUND

The DPHSR facilitates communication and data sharing between the national and provincial health departments and the NICD and provides epidemiological input to other NICD centres through collaborative projects. It provides support for surveillance, epidemiological and research activities, as well as outbreak responses. DPHSR incorporates the GERMS-SA surveillance programme, Provincial Epidemiology Team (PET), Notifiable Medical Conditions (NMC) Surveillance Unit and Outbreak Response Unit (ORU) that works closely with the Emergency Operations Centre (EOC). Together, these teams contribute significantly to national communicable disease surveillance and response efforts by providing systems for the rapid alert and notification of diseases of public health importance, as well as technical expertise to provinces, districts and healthcare workers nationally.

GERMS-SA collaborates with NICD centres to provide a national active surveillance programme for laboratory-confirmed bacterial and fungal infections, complemented by enhanced surveillance at sentinel hospital sites. Clinical syndromic surveillance for pneumonia and diarrhoea at sentinel sites has been integrated into the programme. GERMS-SA provides a robust platform for determining trends and data inform and guide public health policy decisions. The PET comprises epidemiologists based in eight South African provinces who support provincial health departments with epidemiological interpretation of TB, HIV and NMC data and support outbreak investigation and management activities. The NMC Unit provides a coordinated approach to South Africa's collection, collation, analysis, interpretation and dissemination of public and private sector NMC data through a real-time surveillance system and provides information for targeted public health response, decision-making and resource allocation. The ORU and EOC provide technical support to national, provincial and district health departments for every aspect of communicable disease outbreaks and control and facilitate the coordination of outbreak detection, investigation and response activities, together with the appropriate NICD centres. The DATCOV COVID-19 hospital surveillance system allows public and private sector hospitals to submit data on admissions for COVID-19 patients and provides real-time analysis and reporting.

In the past year, the DPHSR was integral to the national and provincial COVID-19 pandemic response, providing valuable epidemiological expertise and maintaining data platforms to monitor trends in the disease, including positive cases, tests, hospitalisations and deaths. DPHSR representatives attend the national COVID-19 incident management team meetings with the NDOH and, during the pandemic, epidemiological support from EOC, ORU and PET brought about better-coordinated and structured data flow, management and analysis processes to the national and provincial response teams. PET also worked with stakeholders to improve data collection and reporting of COVID-19-related deaths including post-mortem testing on natural deaths outside of hospitals. Since March 2021, accessibility of the NMC application (app) has become available on all device platforms. The DATCOV hospital surveillance system has informed understanding of the SARS-CoV-2 epidemic evolution and was an important alert mechanism for COVID-19 resurgences. The data informed hospital resource needs and provided vital insights into the severity and mortality during each wave.

SURVEILLANCE

The GERMS-SA laboratory surveillance includes pathogens of public health importance. Approximately 250 microbiology laboratories in both the public and private sectors send specimens to NICD centres for further characterisation. The GERMS-SA databases reflect over 18,000 cases of communicable diseases meeting its case definitions. Within this network, an enhanced surveillance arm operates at 25 sentinel public sector sites nationally where nurse surveillance officers collect clinical information and outcome data on patients relating to specific pathogens. The GERMS-SA core team also supports the operational side of syndromic surveillance programmes including pneumonia and influenza-like illnesses (with CRDM), diarrhoea (with CED), brucellosis (with CEZPD) and neonatal sepsis (with CHARM). Antimicrobial resistance data is shared annually with the World Health Organization (WHO). The impact of the Streptococcal and *Haemophilus influenzae* Type B vaccines used in the Expanded Programme on Immunisation were evaluated and NICD collaborated with other surveillance programmes globally to monitor the impact of various COVID-19 containment measures on invasive pneumococcal, *Haemophilus influenzae* and meningococcal infections.

NMC are reported through the NMC app, initially rolled-out in 2018 to facilitate real-time notifications of NMC and thus strengthening the NMC surveillance system (NMCSS) as required by the International Health Regulations (2005). The app has been improved and since March 2021 has been available on all device platforms. Paper-based forms can still be used if necessary but use of the electronic system is encouraged. By March 2022 there were 7,440 active users with the average user's monthly engagement increasing to 214 in March 2022 (April 2021: 86). In the year under review, the NMCSS received 30,486 notifications of which 14% (n=4,275) were Category 1 NMC and 86% (n=26,211) Category 2. The most common Category 1 notifications were clinical and laboratory notifications of malaria cases (46%, n=3 804) followed by enteric fever cases (2%, n=169). Common Category 2 notifications included bilharzia (23%, n=12 187) followed by hepatitis B (17%, n=8 804).

The critical role of the NICD provincial epidemiologists became more evident and established during the COVID-19 pandemic. Epidemiological support brought about better-coordinated and structured data flow and management and analysis processes within the provincial response teams. In collaboration with the NDoH, sentinel surveillance was implemented in Nelson Mandela Bay, Mangaung and Thabo Mofutsanyane to strengthen post-mortem COVID-19 testing on natural deaths outside of hospitals. In response to the higher proportion of community than in-facility COVID-19-related deaths in Thabo Mofutsanyana, a knowledge, attitude and practice (KAP) survey was conducted to better understand the knowledge gaps, perceptions and behaviour toward COVID-19 in the community, specifically those which influence health-seeking behaviour.

The DATCOV system has informed understanding of the SARS-CoV-2 epidemic evolution in different provinces and served as an important alert mechanism for COVID-19 resurgences. The data informed hospital resource needs and identified hospitals with higher case fatality rates that required additional support. DATCOV provided insight during each COVID-19 wave when new variants emerged; demonstrating the increased severity and mortality in the Beta and Delta waves and decreased severity and mortality during Omicron. DATCOV demonstrated the value of hospital-based surveillance and offers lessons for monitoring future epidemics.

OUTBREAKS

The EOC and ORU supported the NDoH and the provinces in the country's continued response to the COVID-19 pandemic during 2021/2022. This included essential COVID-19 laboratory-based surveillance and multiple cluster investigations. There were 1,094 calls to the NICD clinician hotline.

Other notable outbreak investigations included *Corynebacterium diphtheriae* outbreak (Western Cape, June/July 2021) and the West Rand rabies outbreak investigation and response (August 2021).

POLICY CONTRIBUTIONS

Pneumococcal surveillance data from the GERMS-SA programme were used to draft guidelines for advocating for adult pneumococcal vaccinations. Outcome and treatment data from cryptococcal meningitis surveillance supported liposomal Amphotericin B and 5 flucytosine use in South African public sector facilities. DATCOV data were used for reproductive rate modelling and to describe Long COVID-19 sequelae. COVID-19 analysis in special groups like paediatrics, care homes and pregnant women has informed guidelines and best practices for prevention, early alerts and care. DATCOV also shared data with local research organisations, namely the National Institute for Occupational Health for analysis of healthcare worker admissions; South African COVID Modelling Consortium for projections of resurgences; South African Medical Research Council for streamlining COVID-19 death reporting and international organisations, for example WHO and the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC). South African data constituted over 50% of global data submitted.

DATCOV data were used in modelling and guided the Ministerial Advisory Committee (MAC) and IMT recommendations regarding the national restriction levels. Analysis of age and co-morbidities data was used in decisions around vaccine prioritisation, while data on the disease severity and mortality during Omicron were shared globally to inform other countries' preparedness and response. The Long COVID study informed our understanding of the long-term sequelae of COVID-19 and the team have participated in the clinical technical working group, contributing to guidelines, training HCWs on Long COVID and informing on the health services required for Long COVID sufferers. The DATCOV lead Dr Waasila Jassat was also asked to join the COVID-19 vaccine MAC on paediatric vaccinations.

RESEARCH ACTIVITIES

The DPHSR conducted several research activities in collaboration with NICD centres and national and international partners including:

ACUTE FEBRILE ILLNESS SURVEILLANCE FOR ZOOSE (WITH CEZPD)

NICD investigators: V Quan, J Freaan, J Weyer, J Rossouw, L Blumberg

Collaborators: M Oosthuizen, N Collins, I van Wyk, J Wentzel.

The Acute Febrile Illness Surveillance Project continues at one clinic site in rural Mpumalanga. This surveillance is a One-Health project, the aim of which is to describe the prevalence of zoonotic infections in adult patients presenting with acute febrile illness. Study data published showed a high seroprevalence of tick bite fever, Q-fever and leptospirosis in parallel with significant exposures at the human/animal interface.

BABY GERMS-SA (WITH CHARM)

NICD investigators: S Meiring, R Mathebula, O Perovic, M Smith, R Mpembe, V Quan, A von Gottberg, L de Gouveia, S Walaza, C Cohen, E van Schalkwyk, NP Govender

Collaborators: C Mackay, R Phayane, T Mailula, O Mekgoe, C Kapongo, N Maphosa, A Dramowski

Funder: Bill and Melinda Gates Foundation

Baby GERMS provides a baseline description of the aetiology, antimicrobial susceptibility profile and clinical characteristics of culture-confirmed neonatal bloodstream infections and meningitis in South Africa. Results show a high burden of antimicrobial-resistant Gram-negative sepsis in this vulnerable population.

SENTINEL SURVEILLANCE FOR NON-COMMUNICABLE DISEASES (NCD) AND LONG COVID

NICD investigators: W Jassat, L Blumberg

Collaborators: ISARIC

Funder: Bill and Melinda Gates Foundation

NCD, HIV and TB sentinel surveillance was implemented in 18 public hospitals nationally to collect more detailed data on COVID-19 admissions using trained surveillance officers to collect data. The study demonstrated a large proportion of patients with diabetes and HIV to have poorly-controlled disease. This shows the importance of considering multi-morbidity in the South African context and confirmed other studies reflecting high levels of undiagnosed and poorly-controlled co-morbidities in the country.

NATIONAL COVID-19 MORTALITY AUDIT

NICD investigators: W Jassat, C Vika, T Arendse

Collaborators: NDoH, Clinton Health Access Initiative

Funder: Clinton Health Access Initiative (operational costs)

The national mortality audit was implemented in 33 public hospitals with high COVID-19-related mortalities during the first and second waves across the nine provinces. It involved a qualitative key informant interview with clinical managers and quantitative retrospective record review of patients who died during the study period. The study revealed important patient level and health system factors that contributed to COVID-19 mortality.

TEACHING AND TRAINING

DPHSR staff provided and contributed to teaching, training and supervising intern scientists, SAFETP residents, public health medicine registrars and microbiology registrars from various South African universities. Staff provided lectures for undergraduates and post-graduates in the Wits Faculty of Health Sciences and other South African universities, while the EOC collaborated with Georgetown University to deliver Using EOCs for Epidemic Response: Virtual Public Health Emergency Management Training. A staff member is an active member of the WHO GOARN Online Gaming for Enhanced Outbreak Response Working Group.

PROFESSIONAL DEVELOPMENT

GRADUATION

Andronica Moipone Shonhiwa graduated on 29 July 2021 from the Wits University School of Governance: post-graduate diploma in management in public and development sector monitoring and evaluation

CURRENT STUDENTS

- Joy Ebonwu (Wits School of Public Health) - PhD
- Dr Susan Meiring (Wits School of Public Health) - PhD
- Genevie Ntshoe (University of Pretoria) - PhD
- Neo Legare (University of Pretoria) – MPH
- Kate Bishop (University of Cape Town) – MPH
- Molly Morapeli (University of the Free State) - MPH
- Sunnieboy Njikho (University of Johannesburg) - MPH

RESEARCH OUTPUT

JOURNAL ARTICLES

- Aavitsland P, Aguilera X, Al-Abri SS, Amani V, Aramburu CC, Attia TA, Blumberg LH, Chittaganpitch M, et al. Functioning of the International Health Regulations during the COVID-19 pandemic. *Lancet*. 2021 Oct 9; 398 (10308):1283-1287. doi: 10.1016/S0140-6736(21) 01911-5.
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NATIONAL CANCER REGISTRY(NCR)



NATIONAL CANCER REGISTRY

DR MAZVITA MUCHENGETI

BACKGROUND

The National Cancer Registry (NCR) is responsible for cancer surveillance including the systematic collection, storage, analysis, interpretation and reporting of cancer cases. National pathology-based cancer surveillance and implementation of population-based cancer registration are the NCR's primary roles. During the year under review, the NCR also undertook childhood cancer surveillance as one of its primary roles. Within NHLS/NICD, the NCR is the only unit specialised for non-communicable disease surveillance. The information provided from the national pathology-based cancer registry provides important insight into South Africa's cancer landscape and affirms the important role NCR plays in cancer surveillance; an important growing non-communicable disease in the country.

The NCR faced the devastating loss of the head of department Dr Elvira Singh in February 2022. Dr Singh was a respected public health medicine specialist with extensive experience in cancer surveillance and cancer epidemiology. She was determined to enhance the pathology-based cancer surveillance system; implement a pilot population-based cancer registration and extend this initiative to three other sentinel surveillance sites nationally. The Ekurhuleni Population-Based Cancer Registry (EPBCR) is the country's first urban population-based cancer registry and Dr Singh passionately led a team that produced three years' worth of data from that source. It was an honour to work with her and we will miss her warmth, enthusiasm, beautiful smile and commitment to strengthening cancer surveillance in Africa.

Despite extenuating circumstances, the NCR met its key performance indicators including publishing two national cancer incidence reports. The population-based surveillance team pushed hard to catch up on data collection despite the difficulties in 2020 posed by the global COVID-19 pandemic. With hospital wards closed, outpatient clinics suspended and restrictions on movement of surveillance officers, high quality and complete cancer data collection was hindered. The overall case finding and data collection for 2020 decreased by 33.3% compared to 2018.

The newly established National Childhood Cancer Registry published its first report on childhood cancer incidence (0-14 years old) for 2018. There is a need for accurate childhood cancer

estimates globally, but this is particularly difficult and scarce in sub-Saharan Africa. Annual reports of childhood cancers are the first step toward improving reporting of childhood cancers and raising awareness about these cancers.

SURVEILLANCE:

PATHOLOGY-BASED CANCER REGISTRY

In the year under review the NCR published the 2018 and 2019 cancer incidence reports on the NCR website (<https://www.nicd.ac.za/centres/national-cancer-registry/>). In 2019 there was a 5.58% increase in the number of cancer cases compared to 2018 and data on cancers diagnosed in 2020 and 2021 are currently being coded and cleaned.

A decade-long cancer trend analysis (2010-2019) report was produced providing a comprehensive and up-to-date overview of the trends in South Africa's cancer incidence. Regulation 380's success that made cancer reporting obligatory in 2011 is reflected in the increase in cancer incidence between 2010 and 2012 as illustrated in this report. The key finding was that breast cancer incidence among South African women increased between 2010 and 2019 and is still the leading cancer diagnosed among women. There was also a significant increase in prostate cancer among men between 2010 and 2019.

EPBCR

This report details the fourth year of population-based cancer registration in the Ekurhuleni metropolitan municipality, Gauteng, South Africa and includes cancers diagnosed during the 2020 calendar year. Data was collected during 2020 and 2021 as the pandemic posed challenges to public health programmes globally, EPBCR included. The case finding and data collection for 2020 decreased by 33.31% to 3,131 (2018: 4,695) with challenges including:

- restricted access for EPBCR surveillance officers to collect cancer data in health facilities during national lockdown;
- misinterpretation of the Protection of Personal Information Act (POPIA) resulting in facilities being less willing to report cancer data and
- closure of the Charlotte Maxeke Johannesburg Academic Hospital (a major data source for EPBCR) due to the fire in 2021.

Despite these challenges, the report provides valuable information for key stakeholders to guide decision making, planning of cancer initiatives and intervention programmes and important data for evaluating health interventions.

CHILDHOOD CANCER REGISTRY

This is the first time the NCR is publishing a standalone report on childhood cancer using the International Classification of Childhood Cancers Third Edition (ICCC-3). A total of 975 cancers were diagnosed in children aged 0-14 years old in South Africa in 2018. This equated to an overall age standardised rate of 59.8 cases per million (95%CI: 48.6-73.2). The most common diagnoses followed global trends with leukaemias, after which were lymphomas that aligned with previous South African childhood cancer reports. Almost half (n=441) were diagnosed in children aged 0-4 years old and most of the results were comparable to regional and global trends.

POLICY CONTRIBUTIONS

Dr Singh represented the NCR on the ministerial advisory committee on cancer, while Dr Mazvita Muchengeti contributed to the World Health Organisation (WHO) publication Cervical cancer elimination in Africa: where are we now and where do we need to be? that provides strategies for cervical cancer elimination on the continent.

RESEARCH ACTIVITIES

SOUTH AFRICAN HIV CANCER MATCH STUDY (SAM)

The SAM study is a national cohort of HIV-positive people created from NHLS HIV data (HIV tests, CD4 count and HIV viral load tests) and linked probabilistically to the NCR to determine the spectrum and risk of cancer in the HIV population. In the year under review, NIH funding for the SAM study through the (International epidemiologic Databases to Evaluate AIDS) leDEA-Southern Africa was renewed for another five years to June 2026. A new server was procured for greater computational capacity and efficiency of linkage. The HIV data has been updated to include records obtained between 2015 and 2019, while de-duplication of the full 2004 to 2019 HIV data was completed and the linkage to cancer data is in progress. There was one publication from the SAM study in the period under review; several others are in the pipeline.

JOHANNESBURG CANCER CASE-CONTROL STUDY (JCS) AND EVOLVING RISK FACTORS FOR CANCER IN AFRICAN POPULATIONS (ERICA-SA)

The JCS is a case-control study of newly (under six months) diagnosed black cancer patients enrolled between 1995 and 2016 with over 26,000 patients interviewed over 20,000 blood samples were stored to examine genetic and emerging and/or novel risk factors.

The two PhD students, Melitah Motlhale and Gideon Singini continued working on the ERICA study and had ongoing online meetings and supervisor consultations with their external supervisor Prof Freddy Sitas.

TEACHING AND TRAINING

Dr Singh gave lectures to Wits School of Medicine undergraduate students. NCR epidemiologists Lactatia Motsuku and Natasha Abraham supervised Sizeka Mashele, who is an SAFETP resident. Dr Muchengeti and Victor Olago were trainers of the virtual ESTHER record linkage course held in August/September 2021. This course was offered to NCR staff, leDEA-SA collaborators in Switzerland and Zambia and the NICD provincial epidemiology team to strengthen their record linkage skills. Abraham completed all activities of the virtual paediatric Global Initiative for Cancer Registry Development Masterclass (ChildGICR Masterclass) from April to July 2022, while Motsuku was invited to review two Union for International Cancer Control (UICC) fellowship applications. Dr Singh and Abraham attended the South African National Stakeholder Prioritisation Workshop on Childhood Cancers in August-September 2021.

Dr Muchengeti and Dr Max Parkin (African Cancer Registry Network AFCRN) were jointly awarded the one-year Africa Oxford Development Grant (<http://www.afox.ox.ac.uk/2020/12/11/afox-research-development-awards-accelerating-progress-towards-the-sdgs/>) worth £49,992 to strengthen childhood cancer registration in Southern Africa (South Africa, Zimbabwe, Zambia, Eswatini and Mozambique). Abraham is leading this work and was a trainer for AFCRN-hosted childhood cancer staging course attended by 65 participants from various African countries.

COLLABORATING CENTRE FOR SUB-SAHARAN AFRICA

The Global Initiative for Cancer Registry (GICR) Development nominated South Africa as a regional collaborating centre for sub-Saharan Africa for childhood cancers and record linkage and talks are underway with the International Agency for Research on Cancer (IARC) and AFCRN to the define roles and responsibilities including mentorship, training and research assistance.

PROFESSIONAL DEVELOPMENT

There were 12 post-graduate students (six PhD and six MSc) in the period under review and had a further two MSc students who graduated.

RESEARCH OUTPUT:

PUBLICATIONS

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CONFERENCES

NCR staff undertook 13 presentations at international conferences and one at a local congress.



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