Issue 15- 23 December 2020

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

SCIENCE FOCUS

The Science Focus acknowledges NICD members of staff who have published in peer-reviewed journals. This publication is a compilation of scientific publications where an NICD staff member is either the first or last author.

Editor's Note

Notable research achievements of the National Institute of Communicable Diseases (NICD) are highlighted in The Science Focus Issue 15 December 2020. Outstanding statistical findings are featured, together with the number of peer-reviewed articles produced, the top three most published authors and high impact factor score articles.

The issue kicks off with an article written by Prof John Frean, where he shares an astute overview of scientific research publications in the time of COVID-19, stressing the necessity of distributing scientifically sound information.

Jackie Kleynhans delves into a PHIRST-C study, the COVID-19 version, which is a cohort study of Influenza, respiratory syncytial virus (RSV) and other respiratory pathogens. An interesting read, the objective of the study is to determine the burden of infection and transmission of these diseases within households.

A couple of featured research abstracts include Prof Nazir Ismail's Bedaquiline and clofazimine: successes and challenges, and Dr Villyen Motaze unpacking mathematical modelling in relation to the introduction of a rubella vaccine.

It is evident that NICD researchers continue to pave the way in publishing important public health papers and high-impact publications in, to name a few, the American Society for Microbiology, The European Journal of Clinical Microbiology and Infectious Diseases, and The Lancet Microbe.

NICD staff members are encouraged to continue to send their comments to the Communications Unit.

Happy reading!

On behalf of the team.

Sinenhlanhla Jimoh
Senior Communications Manager

Prof John Frean

Publishing scientific research in the time of COVID-19

Compared with the leisurely pace of evolution of previous pandemics, such as plague of the medieval period (which began in 1347 as the Black Death and persisted in Europe for more than 300 years), or the seventh cholera pandemic (still with us, since 1961), the COVID-19 pandemic struck with the suddenness of an earthquake, and the world is still experiencing the aftershocks. Even the 1918 influenza pandemic unfolded more slowly, if just as relentlessly, its geographic spread determined by the pace of ship and railway transport in an age before modern air travel. The seismic COVID-19 disease event precipitated an avalanche (or if you prefer, a tsunami) of publications. Understandably, when faced with a rapidly-spreading and apparently dangerous new disease, the scientific research community has a sense of urgency to get information into circulation as soon as possible to meet governments' and medical services' needs for guidance. The novelty of the pathogen and disease meant that the traditional process of peer review to assess the relevance and quality of submissions was often compromised or, in the case of articles posted on preprint servers such as medRxiv and bioRxiv, not applied at all. The combination of inadequately- or non-peer reviewed research of sometimes dubious quality and its ready public access and dissemination via social media, led to some at best ineffective, and at worst, dangerous treatment practices being irresponsibly promoted. Some prestigious medical journals like the New England Journal of Medicine and The Lancet retracted articles because of concerns over the quality of rapidly published data. The Editor-in-Chief of the Journal of the American Medical Association commented that there was a 53% increase in submissions in the first three months of 2020 compared with the same period in 2019, many of them about SARS-CoV-2, but most were of poor quality.

Now that the initial flood of publications has somewhat subsided, a number of commentaries about this unprecedented research publication environment have appeared. An editorial in the Chinese Medical Journal points out that both preprint servers and traditional academic journals have lessons to learn from each other; the former about the need for quality control measures like strict peer review and editorial oversight, and the latter about efficiency in speeding up the review process to allow rapid dissemination of research findings. A PLoS One survey of COVID-19-related publications, noting their huge increase, concluded that ' ... efforts and time should be devoted to scientifically sound information rather than rushing to publish results that may not be fit to print. Overproduction of research is another form of waste that undermines public trust in science.' The European Network of Research Integrity Offices has good advice for aspiring as well as established researchers; I recommend that you take a look at http://www.enrio.eu/enrio-statement-research-integrity-even-more-important-for-research-during-a-pandemic/

Jackie Kleynhans

The PHIRST-C study: A Prospective Household cohort study of Influenza, Respiratory Syncytial virus and other respiratory pathogens community burden and Transmission dynamics in South Africa – COVID version (PHIRST-C)

The study is conducted in Agincourt (Mpumalanga) and Klerksdorp (North West) and is a collaboration between the Centre for Respiratory Diseases and Meningitis (CRDM) at the National Institute for Communicable diseases (NICD), Wits Rural Public Health and Health Transitions Research Unit and the Perinatal HIV Research Unit.

This prospective cohort study started enrolling participants in July 2020. The main objective is to describe the burden of infection and transmission within households of SARS-CoV-2 the virus responsible for COVID-19, influenza and respiratory syncytial virus. In particular, we wanted to look at what proportion of people with COVID-19 have no symptoms and to understand transmission from people with no symptoms and people of different ages. It is important to understand this because we can use this information to help guide control measures to prevent and control COVID-19 such as limiting large gatherings and closing of schools. Should a vaccine become available, it will also provide important information to help guide who should receive a vaccine.

The Klerksdorp and Agincourt field teams worked hard to enrol 214 households, most of which had participated in the initial PHIRST study which was conducted between 2016 and 2018. Once all the households were enrolled the field teams started the intensive follow-up period. This means visiting the households twice a week to take nasal swabs and conduct questionnaires on symptoms of COVID-19; a blood draw was also done in the first few weeks of the study. The nasal swabs are tested for SARS-CoV-2 and the blood samples tested for antibodies to SARS-CoV-2 at NICD.

The field teams have maintained over 90% follow-up rates, visiting more than 1000 participants twice a week, which shows impressive commitment to the project. By October, we identified 205 SARS-CoV-2 infections in 131 households. The vast majority of these individuals did not have signs or symptoms. We were already able to identify clusters (transmission) within households. On average, SARS-CoV-2 could be detected from participants for 5.6 days (range 4-56 days). The average number of days for the first person testing positive, to the last person testing positive in the household was 10.2 days (range 4-58 days). Interestingly, at the time of analysis only 7% (15/205) of these infected participants had symptoms; however, 10% (3/29) of people older than 50 years had symptomatic infections. Although there is ongoing testing of the serology samples, at baseline (August 2020) 11% (71/625) of participants showed previous exposure to SARS-CoV-2.

The PHIRST-C investigators would like to thank all those who have contributed to the study, including staff at CRDM, Agincourt and Klerksdorp, the Bushbuckridge and Matlosana communities and most importantly the participants who have generously given of their time to support this important study.

EXCEPTIONAL RESEARCH STATISTICS

NUMBER OF PEER-REVIEWED ARTICLES PRODUCED

Q3

TOP 3

MOST PUBLISHED AUTHORS IN Q3 OF 2020/2021

1

PROF CHERYL COHEN

2

PROF LUCILLE BLUMBERG

3

PROF NICOLA PAGE

3

PROF NELESH GOVENDER

3

DR FARZANA ISMAIL

FEATURED RESEARCH ABSTRACTS FOR THE SECOND QUARTER OF 2020/2021

Prof Nazir Ismail

Bedaquiline and clofazimine: successes and challenges

Ismail N, *Ndjeka N*

The Lancet Microbe
Impact Factor: 60.39

Bedaquiline, a novel therapeutic drug, and clofazimine, a re-purposed drug, are front-line therapies recommended by WHO to treat rifampicin-resistant or multidrug-resistant tuberculosis. Both drugs have been in use in South Africa at least 10 years: bedaquiline since 2007 and clofazimine since 2010. The use of bedaquiline in programmatic settings in South Africa has reduced the risk of all-cause mortality threefold (hazard ratio 0·35, 95% CI 0·28–0·46)[1] and achieved treatment success in at least 70% of patients.[2] The inclusion of clofazimine in combination therapy has reduced treatment duration from 18–24 months to 9–12 months. South Africa has adopted both drugs extensively in the modified short and long regimens for rifampicin-resistant or multidrug-resistant tuberculosis. According to the electronic drug-resistant tuberculosis register, as of June 1, 2020, 29 193 individuals in South Africa have received bedaquiline, and 30 599 have received clofazimine. Emerging resistance and cross-resistance have been reported.[3, 4]

In *The Lancet Microbe,* Camus Nimmo and colleagues[5] used whole-genome sequencing of 676 *Mycobacterium tuberculosis* isolates from 391 patients with drug-resistant tuberculosis in KwaZulu-Natal, South Africa, to identify variants associated with resistance to bedaquiline and clofazimine.[5] Their study provides additional evidence of emerging resistance to these drugs. Among the cohorts analysed, 16 (4%) of 391 patients had genotypic resistance; of those who had a resistance pattern defined, 11 (79%) of 14 had pre-extensively drug-resistant or extensively drug-resistant tuberculosis and harboured unique *Rv0678* mutations. Interestingly, identical *Rv0678* mutations were only observed among patients who developed resistance during treatment, emerging between 2 and 20 months after exposure. Selection of these mutations could reflect adaptive responses requiring further investigation, although the authors noted that primary nosocomial transmission is the most likely reason.

Measuring resistance to bedaquiline and clofazimine is a challenge. Two multi-country quality studies showed poorer reproducibility[6] and false resistance[7] for the agar method used by Nimmo and colleagues (ie, the 1% proportion method on Middlebrook 7H11 agar).[5] Furthermore, clinical trial data did not show a substantial difference in culture conversion at 24 weeks between high and low minimum inhibitory concentrations (MICs) using this method.[8] Determination of genetic resistance is also problematic

as not all mutations in the *Rv0678* gene confer large increases in MIC, with some mutations having the opposite effect.[9] Population-level analysis of these data is useful, although for individual patient management the evidence base for specific mutations, levels of resistance, and final treatment outcomes is sparse and requires further research.

The number of patients with rifampicin-resistant or multidrug-resistant tuberculosis in sub-Saharan Africa was estimated to be 77 000 in 2018 while only 19 730 were reported to have started treatment, and of these patients 9558 (48%) were treated in South Africa. The bold decision in South Africa to use these new and repurposed drugs in shortened treatment regimens was based on operational research data and the ethical need for effective, patient-friendly, injection-free regimens. The introduction of bedaquiline was accompanied by a national surveillance programme to monitor the emergence of drug resistance. Data generated led to the criteria for resistance adopted by WHO in 2018.[4] Additionally, two crucial changes in South African policy occurred in 2018: the modified short regimen was strengthened with linezolid, and a standardised laboratory testing protocol to detect resistance to bedaquiline, clofazimine, and linezolid was introduced. These interventions overlap in time with the study by Nimmo and colleagues,[5] pre-emptively addressing the concerns raised. The approach applied by South Africa should be used as an example for other countries when adopting these new regimens at scale. A rapid assay that can screen for resistance to either bedaquiline or clofazimine at treatment initiation is still urgently needed.

Of interest is the phylogenetic analysis by Nimmo and colleagues[5]—which included the genome sequences from their study, publicly available sequences from previously published studies in southern Africa, and sequences indexed in the National Center for Biotechnology Information Sequencing Read Archive originating from samples collected in southern African countries—showing emergence of *Rv067*8 mutations preceding the introduction of bedaquiline, which was also reported in a previous study.[10] The current study highlights the propensity of these mutations to occur in specific strain lineages, and the need for further investigation into the nature of these occurrences. Are these sporadic mutations unrelated to selection pressure and well established among mycobacteria? Alternatively, selection pressure could be due to the azole group of antifungal agents, which would have different implications for control, especially in sub-Saharan Africa, where they are commonly used.

The excellent successes achieved with bedaquiline and clofazimine require scale-up if the poor global outcomes for rifampicin-resistant or multidrug-resistant tuberculosis are to be addressed. However, upscaling the use of these drugs comes at the cost of resistance emergence, which needs to be mitigated. Early detection of resistance is essential, requiring development of new rapid technologies combined with strengthening of laboratory capacity to support the introduction of new regimens. Additionally, effective combination therapies and adherence to these regimens are crucial factors in curbing emergence of resistance. Unfortunately, the pipeline for new drug classes for tuberculosis is running at a trickle when compared with HIV, and if not addressed urgently, we will find ourselves in a pre-antibiotic era, which we cannot afford as we set our sights on ending tuberculosis by 2035.

We declare no competing interests.

Prof Nazir Ismail

Dr Shaheed Vally Omar

A Multimethod, Multicountry Evaluation of Breakpoints for Bedaquiline Resistance Determination

Ismail N, *Aono A, Borroni E, Cirillo DM, Desmaretz C, Hasan R, Mitarai S, Shakoor S, Torrea G, Kaniga K,* ***Omar SV***

Antimicrob Agents Chemother
Impact Factor: 4.904

Criteria defining bedaquiline resistance for tuberculosis have been proposed addressing an emerging concern. We evaluated bedaquiline phenotypic drug susceptibility testing (pDST) criteria using drug-resistant tuberculosis clinical isolates tested at five reference laboratories. Isolates were tested at the proposed bedaquiline MGIT960 and 7H11 agar proportion (AP) critical concentrations and also at higher dilutions. The epidemiological cutoff value for the broth microdilution (BMD) plates (frozen and dry) was investigated. Sanger sequencing was performed *(atpE and Rv0678 genes)* for any isolate testing resistant. The composite reference standard (CRS) defined susceptibility or resistance as is if all pDST methods agreed. If the pDST result was discordant, sequencing results were used for final classification. Geographically diverse and bedaquiline-unexposed isolates were tested *(n = 495)*. The epidemiological cutoff value for BMD was confirmed to be 0.12 µg/ml. The majority of isolates were determined to be susceptible by all methods (467/495; 94.3%), and 28 were determined to be resistant by at least one method; 4 of these were determined to be resistant by all methods. Of the 28 resistant isolates, 12 harbored Rv0678 mutations exclusively. Isolates with insertions/deletions were more likely to be determined to be resistant by more than one method (5/7) compared to isolates with a single nucleotide polymorphism (1/5). Applying the CRS to 24 discordant pDST, BMD dry correctly detected most (15/24; 63%), followed by MGIT960 and BMD frozen (13/24; 61%) and lastly AP (12/24; 50%). Applying the CRS, the prevalence of bedaquiline resistance was 2.2% and ranged from 1.4 to 3.4%, depending on the method used. All methods performed well for bedaquiline susceptibility determination; however, resistance detected should be investigated by a second, alternative method.

AMERICAN SOCIETY FOR MICROBIOLOGY

Dr Villyen Motaze

Rubella Vaccine Introduction in the South African Public Vaccination Schedule: Mathematical Modelling for Decision Making

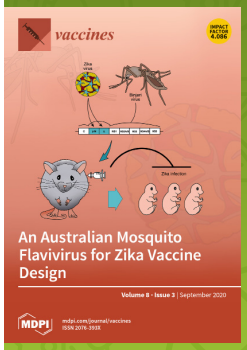
Motaze NV, *Edoka I, Charles S, Jessica C, Metcalf E, Winter AK*

Vaccines (Basel)
Impact Factor: 4.086

Background: age structured mathematical models have been used to evaluate the impact of rubella-containing vaccine (RCV) introduction into existing measles vaccination programs in several countries. South Africa has a well-established measles vaccination program and is considering RCV introduction. This study aimed to provide a comparison of different scenarios and their relative costs within the context of congenital rubella syndrome (CRS) reduction or elimination. Methods: we used a previously published age-structured deterministic discrete time rubella transmission model. We obtained estimates of vaccine costs from the South African medicines price registry and the World Health Organization. We simulated RCV introduction and extracted estimates of rubella incidence, CRS incidence and effective reproductive number over 30 years.

Results: compared to scenarios without mass campaigns, scenarios including mass campaigns resulted in more rapid elimination of rubella and congenital rubella syndrome (CRS). Routine vaccination at 12 months of age coupled with vaccination of nine-year-old children was associated with the lowest RCV cost per CRS case averted for a similar percentage CRS reduction.

Conclusion: At 80% RCV coverage, all vaccine introduction scenarios would achieve rubella and CRS elimination in South Africa. Any RCV introduction strategy should consider a combination of routine vaccination in the primary immunization series and additional vaccination of older children.



Dr Farzana Ismail

Outbreak of *Ralstonia mannitolilytica* bacteraemia in patients undergoing haemodialysis at a tertiary hospital in Pretoria, South Africa

Said M, van Hougenhouck-Tulleken W, Mbelle N, Naidoo R, ***Ismail F***

Antimicrobial Resistance & Infection Control
Impact Factor: 3.594

Background: *Ralstonia* species are Gram-negative bacilli of low virulence. These organisms are capable of causing healthcare associated infections through contaminated solutions. In this study, we aimed to determine the source of *Ralstonia mannitolilytica* bacteraemia in affected patients in a haemodialysis unit.

Methods: Our laboratory noted an increase in cases of bacteraemia caused by *Ralstonia mannitolilytica* between May and June 2016. All affected patients underwent haemodialysis at the haemodialysis unit of an academic hospital. The reverse osmosis filter of the haemodialysis water system was found to be dysfunctional. We collected water for culture at various points of the dialysis system to determine the source of the organism implicated. ERIC-PCR was used to determine relatedness of patient and environmental isolates.

Results: Sixteen patients were found to have *Ralstonia mannitolilytica* bacteraemia during the outbreak period. We cultured *Ralstonia* spp. from water collected in the dialysis system. This isolate and patient isolates were found to have the identical molecular banding pattern.

Conclusions: All patients were septic and received directed antibiotic therapy. There was one deat. The source of the *R. mannitolilytica* infection in these patients was most likely the dialysis water as the identical organism was cultured from the dialysis water and the patients. The hospital management intervened and repaired the dialysis water system following which no further cases of *R. mannitolilytca* infections were detected. A multidisciplinary approach is required to control healthcare associated infections such as these. Routine maintenance of water systems in the hospital is essential to prevent clinical infections with *R. mannitolilytica*.

Ms Jaime MacDonald

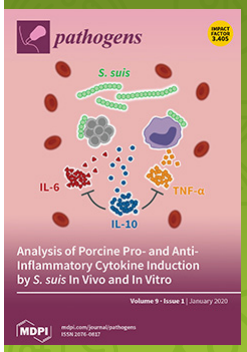
Prof Nicola Page

FUT2 Secretor Status Influences Susceptibility to VP4 Strain-Specific Rotavirus Infections in South African Children

MacDonald J, *Groome MJ, Mans J,* ***Page N.***

Pathogens
Impact Factor: 3.018

Gastroenteritis is a preventable cause of morbidity and mortality worldwide. Rotavirus vaccination has significantly reduced the disease burden, but the sub-optimal vaccine efficacy observed in low-income regions needs improvement. Rotavirus VP4 'spike' proteins interact with FUT2-defined, human histo-blood group antigens on mucosal surfaces, potentially influencing strain circulation and the efficacy of P[8]-based rotavirus vaccines. Secretor status was investigated in 500 children <5 years-old hospitalised with diarrhoea, including 250 previously genotyped rotavirus-positive cases (P[8] = 124, P[4] = 86, and P[6] = 40), and 250 rotavirus-negative controls. Secretor status genotyping detected the globally prevalent G428A single nucleotide polymorphism (SNP) and was confirmed by Sanger sequencing in 10% of participants. The proportions of secretors in rotavirus-positive cases (74%) were significantly higher than in the rotavirus-negative controls (58%; $p < 0.001$). The rotavirus genotypes P[8] and P[4] were observed at significantly higher proportions in secretors (78%) than in non-secretors (22%), contrasting with P[6] genotypes with similar proportions amongst secretors (53%) and non-secretors (47%; $p = 0.001$). This suggests that rotavirus interacts with secretors and non-secretors in a VP4 strain-specific manner; thus, secretor status may partially influence rotavirus VP4 wild-type circulation and P[8] rotavirus vaccine efficacy. The study detected a mutation (rs1800025) ~50 bp downstream of the G428A SNP that would overestimate non-secretors in African populations when using the TaqMan® SNP Genotyping Assay.



Prof Olga Perovic

Carbapenem-resistant Enterobacteriaceae in patients with bacteraemia at tertiary hospitals in South Africa, 2015 to 2018

Perovic O, *Ismail H, Quan V, Bamford C, Nana T, Chibabhai V, Bhola P, Ramjathan P, Swe Swe-Han K, Wadula J, Whitelaw A, Smith M, Mbelle N, Singh-Moodley A; for GERMS-SA.*

European Journal of Clinical Microbiology & Infectious Diseases
Impact Factor: 2.837

Enhanced surveillance for CREs was established at national sentinel sites in South Africa. We aimed to apply an epidemiological and microbiological approach to characterise CREs and to assess trends in antimicrobial resistance from patients admitted to tertiary academic hospitals. A retrospective analysis was conducted on patients of all ages with CRE bacteraemia admitted at any one of 12 tertiary academic hospitals in four provinces (Gauteng, KwaZulu-Natal, Western Cape and Free State) in South Africa. The study period was from July 2015 to December 2018. A case of CRE bacteraemia was defined as a patient admitted to one of the selected tertiary hospitals where any of the Enterobacteriaceae was isolated from a blood culture, and was resistant to the carbapenems (ertapenem, meropenem, imipenem and/or doripenem) or had a positive result for the Modified Hodge Test (MHT) according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. A positive blood culture result obtained after 21 days of the last blood culture result was regarded as a new case. To distinguish hospital-acquired (HA) from the community-acquired (CA) bacteraemia, the following definitions were applied: the HA CRE bacteraemia was defined as a patient with CRE isolated from blood culture ≥ 72 h of hospital admission or with any prior healthcare contact, within 1 year prior to the current episode or referral from a healthcare facility where the patient was admitted before the current hospital. A case of the CA CRE bacteraemia was defined as a patient with CRE isolated from blood culture < 72 h of hospital admission and with no prior healthcare contact. The majority of carbapenem-resistant Enterobacteriaceae (CRE) (70%) were hospital-acquired (HA) with *Klebsiella pneumoniae* being the predominant species (78%). In-hospital mortality rate was 38%. The commonest carbapenemase genes were *bla-*$_{OXA-48}$ (52%) and *bla-*$_{NDM}$ (34%). The high mortality rate related to bacteraemia with CRE and the fact that most were hospital-acquired infections highlights the need to control the spread of these drug-resistant bacteria. Replacement with OXA-48 is the striking finding from this surveillance analysis. Infection control and antibiotic stewardship play important roles in decreasing the spread of resistance.

Dr Husna Ismail

Prof Olga Perovic

An outbreak of cutaneous abscesses caused by Panton-Valentine leukocidin-producing methicillin-susceptible *Staphylococcus aureus* among gold mine workers, South Africa, November 2017 to March 2018

Ismail H, *Govender NP, Singh-Moodley A, Van Schalkwyk E, Shuping L, Moema I, Feller G, Mogokotleng R, Strasheim W, Lowe M, Mpembe R, Naicker S, Maphanga TG, De Abreu C, Ismail F, Ismail N, Allam M, Ismail A, Singh T, Matuka O, Duba T &* ***Perovic O***

BMC Infectious Diseases
Impact Factor: 2.688

Background: We aimed to describe an outbreak of cutaneous abscesses caused by Panton-Valentine leukocidin (PVL)-producing methicillin-susceptible *Staphylococcus aureus* (MSSA) among gold mine workers.

Methods: In February 2018, we retrospectively reviewed a random sample of 50 medical records from 243 cases and conducted face-to-face interviews using a structured questionnaire. Pus aspirates were sent to the National Institute for Communicable Diseases from prospectively-identified cases (November 2017–March 2018). Nasopharyngeal swabs were collected during a colonisation survey in February 2018. *Staphylococcus aureus* isolates were screened with a conventional PCR for *lukS/F-PV*. Pulsed-field gel electrophoresis (PFGE) was performed to determine the genetic relatedness among the isolates. A sample of isolates were selected for whole genome sequencing (WGS). We conducted an assessment on biological risks associated with mining activities.

Results: From January 2017 to February 2018, 10% (350/3582) of mine workers sought care for cutaneous abscesses. Forty-seven medical files were available for review, 96% were male (n = 45) with a mean age of 43 years (SD = 7). About 52% (24/46) were involved in stoping and 28% (13/47) worked on a particular level. We cultured *S. aureus* from 79% (30/38) of cases with a submitted specimen and 14% (12/83) from colonisation swabs. All isolates were susceptible to cloxacillin. Seventy-one percent of *S. aureus* isolates (30/42) were PVL-PCR-positive. Six PFGE clusters were identified, 57% (21/37) were closely related. WGS analysis found nine different sequence types. PFGE and WGS analysis showed more than one cluster of *S. aureus* infections involving closely related isolates. Test reports for feed and product water of the mine showed that total plate counts were above the limits of 1000 cfu/ml, coliform counts > 10 cfu/100 ml and presence of faecal coliforms. Best practices were poorly implemented as some mine workers washed protective clothing with untreated water and hung them for drying at the underground surface.

Conclusions: PVL-producing MSSA caused an outbreak of cutaneous abscesses among underground workers at a gold mining company. To our knowledge, no other outbreaks of PVL-producing *S. aureus* involving skin and soft tissue infections have been reported in mining facilities in South Africa. We recommend that worker awareness of infection prevention and control practices be strengthened.

Mr Rembuluwani Netshikweta

Prof Nicola Page

Molecular epidemiology of human bocavirus infection in hospitalized children with acute gastroenteritis in South Africa, 2009-2015

Netshikweta R, *Chidamba L, Nadan S, Taylor MB,* ***Page NA.***

Journal of Medical Virology
Impact Factor: 2.021

Human bocavirus (HBoV) is known to be associated with a variety of clinical manifestation including acute gastroenteritis (AGE). Despite their global prevalence, no data are available on the epidemiology of HBoV associated with AGE in South Africa (SA). Between April 2009 and April 2015, 3765 stool specimens were collected from children less than 5 years of age hospitalized with diarrhea. Specimens were screened for selected enteric viruses by enzyme immunoassay and quantitative polymerase chain reaction, bacteria by culture and parasites by staining and microscopy. HBoV was detected in 5.63% (212 of 3765) of cases, the majority of which were children ≤2 years (92%, 195 of 212), and were common in the summer and autumn months (60%; 128 of 212). Further investigations of coinfections showed that bacteria (adjusted odds ratio [aOR] = 2.20; 95% confidence interval [CI], 1.41-3.45; *P* = .001) and sapovirus (aOR = 2.05; 95% CI, 1.08-3.86; *P* = .027) were significantly associated with HBoV in multivariate analysis. HBoV genotyping was successful in 191 of the 212 samples with HBoV-1 being the most prevalent genotype observed (79.6%; 152 of 191) followed by HBoV-3 (13.6%; 26 of 191), HBoV-2 (5.2%; 10 of 191), and HBoV-4 (1.6%; 3 of 191). The high prevalence of HBoV-1, a virus known to be associated with respiratory infections, and the association between HBoV-positive specimens and already established AGE agents, suggests that HBoV may play a limited role in the observed AGE cases in SA.

Mrs Antoinette A. Grobbelaar

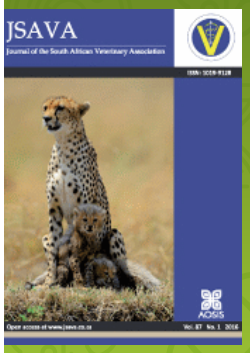
Dr Jacqueline Weyer

Human rabies associated with domestic cat exposures in South Africa, 1983–2018

Grobbelaar AA, *Blumberg LH, Dermaux-Msimang V, Le Roux CA, Moolla N, Paweska JT,* ***Weyer J***

Journal of the South African Veterinary Association
Impact Factor: 1.16

Rabies is a fatal, neurological viral zoonosis endemic in South Africa, caused by lyssaviruses. Laboratory confirmed human rabies cases in South Africa from 1983-2018, were investigated to determine the frequency of exposure to domestic cats. In addition, partial nucleoprotein sequences were generated from available archived patient clinical material or virus isolates and analyzed in order to type the lyssavirus or rabies virus variant involved in these cases. From 458 confirmed human rabies cases reported for the 35 year period, 13 (2.84%) were linked to domestic cat exposures. Rabies in domestic cats was linked to different cycles of rabies in South Africa, including both canid and mongoose variants of the rabies virus. No cases of rabies associated with rabies-related lyssavirus infection were identified.



Ms Veronica Mathebula

Dr Tendesayi Kufa

Factors associated with repeat genital symptoms among sexually transmitted infection service attendees in South Africa

Mathebula RC, *Kuonza LR, Musekiwa A, Kularatne R, Maseko V,* ***Kufa T***

South African Medical Journal
Impact Factor: n/a

Background: South African guidelines recommend a syndromic approach for the management of sexually transmitted infections (STIs), based on the presence of genital symptoms. However, the guidelines do not prescribe specific indications for microbiology testing for patients presenting with or without repeat genital symptoms.
Objectives. To describe the prevalence of and factors associated with repeat genital symptoms among STI service attendees at primary care facilities.

Methods: This was a cross-sectional study at 7 STI primary care facilities participating in the aetiological surveillance of STIs between January 2015 and December 2016. Demographic and clinical information and appropriate genital specimens were collected from participants presenting with vaginal discharge syndrome (VDS), male urethral syndrome (MUS) and/or genital ulcer syndrome (GUS). Repeat genital symptoms were defined as self-reported history of the same STI-related genital symptoms in the preceding 12 months. Multivariable logistic regression identified factors associated with repeat genital symptoms.

Results: Of 1 822 eligible participants, 480 (30%) had repeat genital symptoms (25% and 75% in the preceding 3 months and 12 months, respectively). Of those with repeat genital symptoms, the median age was 28 (interquartile range (IQR) 24 - 32) years, and 54% were females. The most common aetiological agents among participants with VDS, MUS and GUS were bacterial vaginosis (*n*=132; 55%), *Neisseria gonorrhoeae* (*n*=172; 81%) and ulcers (*n*=67; 63%), respectively. One hundred and seven (20%) participants had no detectable common STI aetiology. In the multivariable analysis, repeat genital symptoms were associated with HIV co-infection (adjusted odds ratio (aOR) 1.43; 95% confidence interval (CI) 1.14 - 1.78), VDS diagnosis (aOR 1.39; 95% CI 1.10 - 1.76), self-reported condom use (aOR 1.56; 95% CI 1.20 - 2.03) and age 25 - 34 years (aOR 1.33; 95% CI 1.03 - 1.71).

Conclusions: Our study found a high prevalence of repeat genital symptoms - a significant proportion without STI aetiology. Identified factors of repeat genital symptoms highlight the need for improved integration of HIV and STI prevention and management. Further research is needed to determine the aetiology of repeat genital symptoms and the contribution of non-STI causes.

Dr Vivien Essel

Prof Nelesh Govender

A multisectoral investigation of a neonatal unit outbreak of *Klebsiella pneumoniae* bacteraemia at a regional hospital in Gauteng Province, South Africa

Essel V, *Tshabalala K, Ntshoe G, Mphaphuli E, Feller G, Shonhiwa AM, McCarthy K, Ismail H, Strasheim W, Lowe M, Perovic O, Hlonipho M,* ***Govender NP***

South African Medical Journal 2020
Impact Factor: n/a

Background: Rates of healthcare-associated infections (HAIs) among babies born in developing countries are higher than among those born in resource-rich countries, as a result of suboptimal infection prevention and control (IPC) practices. Following two reported deaths of neonates with carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections (BSIs), we conducted an outbreak investigation in a neonatal unit of a regional hospital in Gauteng Province, South Africa.

Objectives: To confirm an outbreak of *K. pneumoniae* BSIs and assess the IPC programme in the neonatal unit.

Methods: We calculated total and organism-specific BSI incidence risks for culture-confirmed cases in the neonatal unit for baseline and outbreak periods. We conducted a clinical record review for a subset of cases with *K. pneumoniae* BSI that had been reported to the investigating team by the neonatal unit. An IPC audit was performed in different areas of the neonatal unit. We confirmed species identification and antimicrobial susceptibility, and used polymerase chain reaction for confirmation of carbapenemase genes and pulsed-field gel electrophoresis (PFGE) for typing of submitted clinical isolates.

Results: From January 2017 to August 2018, 5 262 blood cultures were submitted, of which 11% (560/5 262) were positive. Of 560 positive blood cultures, 52% (n=292) were positive for pathogenic organisms associated with healthcare-associated BSIs. *K. pneumoniae* comprised the largest proportion of these cases (32%; 93/292). The total incidence risk of healthcare-associated BSI for the baseline period (January 2017 - March 2018) was 6.8 cases per 100 admissions, and that for the outbreak period (April - September 2018) was 10.1 cases per 100 admissions. The incidence risk of *K. pneumoniae* BSI for the baseline period was 1.6 cases per 100 admissions, compared with 5.0 cases per 100 admissions during the outbreak period. Average bed occupancy for the entire period was 118% (range 101 - 133%), that for the baseline period was 117%, and that for the outbreak period was 121%. In a subset of 12 neonates with *K. pneumoniae* bacteraemia, the median (interquartile range (IQR)) gestational age at birth was 27 (26 - 29) weeks, and the median (IQR) birth weight was 1 100 (880 -1 425) g. Twelve bloodstream and 31 colonising *K. pneumoniae* isolates were OXA-48-positive. All isolates were genetically related by PFGE analysis (89% similarity). Inadequate IPC practices were noted, including suboptimal adherence to aseptic technique and hand hygiene (57% overall score in the neonatal intensive care unit), with poor monitoring and reporting of antimicrobial use (pharmacy score 55%).

Conclusions: Overcrowding and inadequate IPC and antimicrobial stewardship contributed to a large outbreak of BSIs caused by genetically related carbapenemase-producing *K. pneumoniae* isolates in the neonatal unit.

Dr Mushal Allam

Dr Jinal N. Bhiman

Genome sequencing of a severe acute respiratory syndrome coronavirus 2 isolate obtained from a South African patient with coronavirus disease 2019

Allam M, *Ismail A, Khumalo ZTH, Kwenda S, Van Heusden P, Cloete R, Wibmer CK, Mtshali PS, Mnyameni F, Mohale T, Subramoney K, Walaza S, Ngubane W, Govender N, Motaze NV,* ***Bhiman JN***

Microbiology Resource Announcements
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As a contribution to the global efforts to track and trace the ongoing coronavirus pandemic, here we present the sequence, phylogenetic analysis, and modeling of nonsynonymous mutations for a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome that was detected in a South African patient with coronavirus disease 2019 (COVID-19).

Dr Jacqueline Weyer

Prof Lucille Blumberg

Epidemiology of human rabies in South Africa, 2008 - 2018

Weyer J, *Dermaux-Msimang V, Grobbelaar A, Le Roux C, Moolla N, Paweska J,* ***Blumberg L***

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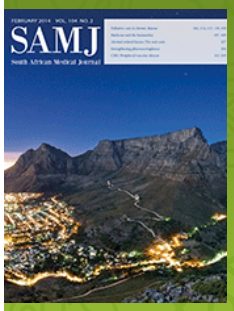
Background: Human rabies cases continue to be reported annually in South Africa (SA). Previous investigations have shown the association between the occurrence of human rabies cases and dog rabies cases in the country.
Objectives. To describe the epidemiology of laboratory-confirmed human rabies cases in SA for the period 2008 - 2018.

Methods: A retrospective document review of laboratory-confirmed human rabies cases for the period 2008 - 2018 was performed using a case register and related documentation available from the National Institute for Communicable Diseases.

Results: A total of 105 human rabies cases was laboratory confirmed from 2008 to 2018, with cases reported from all the provinces of SA except the Western Cape. Children and adolescents were most affected by the disease during the study period. In almost half of the cases, medical intervention was not sought after exposure. When victims did seek healthcare, deviations from post-exposure prophylaxis protocols were reported in some cases.

Conclusions: The epidemiological trends of human rabies cases reported in SA for the period 2008 - 2018 remained largely the same as in previous reports. Dog-mediated rabies remains the main source of human rabies in SA.

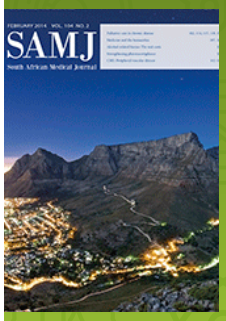


Dr Farzana Ismail

Antimicrobial susceptibility and serotype distribution of *Streptococcus agalactiae* rectovaginal colonising isolates from pregnant women at a tertiary hospital in Pretoria, South Africa: An observational descriptive study

Said M, Dangor Y, Mbelle N, Madhi SA, Kwatra G, ***Ismail F***

South African Medical Journal 2020
Impact Factor: n/a



Introduction: *Streptococcus agalactiae* or group B streptococcus (GBS) is a significant cause of neonatal sepsis. Intrapartum antibiotic prophylaxis is recommended for pregnant women identified to be recto-vaginally colonised between 34-37 weeks gestational age to decrease the risk of invasive disease in their newborns. The aim of this study was to investigate serotype distribution and antimicrobial susceptibility patterns of GBS isolates cultured from recto-vaginal specimens during pregnancy.

Methods: Sixty-nine archived maternal colonizing isolates were tested against penicillin, erythromycin, clindamycin, vancomycin and levofloxacin. Minimum inhibitory concentration (MIC) testing was performed using the E-test method. Serotyping was performed by latex agglutination method.

Results: The most common serotypes detected were Ia (54%), III (20%), V (16%), II (6%), IV (2%) and Ib (1%), respectively. All isolates were fully susceptible to penicillin, vancomycin and levofloxacin. Eight (11%) and 50 (56%) isolates showed intermediate resistance to erythromycin and clindamycin respectively, and one isolate was resistant to erythromycin. MLSB phenomenon was noted in 3 (4%) of the isolates.

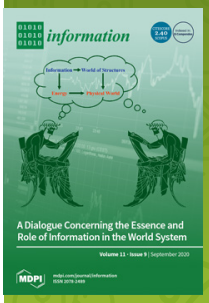
Conclusion: GBS colonizing isolates remain susceptible to penicillin and this remains the drug of choice for intrapartum antibiotic prophylaxis and treatment of invasive disease in newborns. Macrolides should only be used if clinically indicated due to the high prevalence of intermediate resistance. A hexavalent GBS vaccine currently under development would provide coverage for 100% of the isolates identified in this study.

Mr Wenlong Chen

Identification of Malignancies from Free-Text Histopathology Reports Using a Multi-Model Supervised Machine Learning Approach

Olago V, Muchengeti M, Singh E, ***Chen WC***

Information 2020
Impact Factor: n/a



We explored various machine learning (ML) models to evaluate how each model performs in the task of classifying histopathology reports. We trained, optimized, and performed classification with stochastic gradient descent (SGD), support vector machine (SVM), random forest (RF), K-nearest neighbor (KNN), adaptive boosting (AB), decision trees (DT), gaussian naïve bayes (GNB), logistic regression (LR), and dummy classifier. We started with 60,083 histopathology reports, which reduced to 60,069 after pre-processing. The F1-scores for SVM, SGD KNN, RF, DT, LR, AB, and GNB were 97%, 96%, 96%, 96%, 92%, 96%, 84%, and 88%, respectively, while the misclassification rates were 3.31%, 5.25%, 4.39%, 1.75%, 3.5%, 4.26%, 23.9%, and 19.94%, respectively. The approximate run times were 2 h, 20 min, 40 min, 8 h, 40 min, 10 min, 50 min, and 4 min, respectively. RF had the longest run time but the lowest misclassification rate on the labeled data. Our study demonstrated the possibility of applying ML techniques in the processing of free-text pathology reports for cancer registries for cancer incidence reporting in a sub-Saharan Africa setting. This is an important consideration for the resource-constrained environments to leverage ML techniques to reduce workloads and improve the timeliness of reporting of cancer statistics.

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Ms. Andronica Moipone Shonhiwa

Prof Nicola Page

Investigation of two suspected diarrhoeal-illness outbreaks in Northern Cape and KwaZulu-Natal provinces, South Africa, April–July 2013: The role of rotavirus

Andronica M. Shonhiwa, *Genevie Ntshoe, Noreen Crisp, Ayo J. Olowolagba, Vusi Mbuthu, Maureen B. Taylor, Juno Thomas,* ***Nicole A. Page***

Southern African Journal of Infectious Diseases
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Introduction: Suspected diarrhoeal-illness outbreaks affecting mostly children < 5 years were investigated between May and July 2013 in Northern Cape province (NCP) and KwaZulu-Natal (KZN) province. This study describes the epidemiological, environmental and clinical characteristics and diarrhoeal-illnesses causative agent(s).

Methods: A descriptive cross-sectional study was conducted. Cases were patients presenting at healthcare facilities with diarrhoeal-illness between 09 April and 09 July 2013 in NCP and 01 May and 31 July 2013 in KZN. Laboratory investigations were performed on stools and water samples using microscopy, culture and sensitivity screening and molecular assays.

Results: A total of 953 cases including six deaths (case fatality rate [CFR]: 0.6%) were recorded in the Northern Cape province outbreak. Children < 5 years accounted for 58% of cases. Enteric viruses were detected in 51% of stools, with rotavirus detected in 43%. The predominant rotavirus strains were G3P[8] (45%) and G9P[8] (42%). Other enteric viruses were detected, with rotavirus co-infections (63%). No enteric pathogens detected in water specimens. *KwaZulu-Natal outbreak:* A total of 1749 cases including 26 deaths (CFR: 1.5%) were recorded. Children < 5 years accounted for 95% of cases. Rotavirus was detected in 55% of stools; other enteric viruses were detected, mostly as rotavirus co-infections. The predominant rotavirus strains were G2P[4] (54%) and G9P[8] (38%).

Conclusion: Although source(s) of the outbreaks were not identified, the diarrhoeal-illnesses were community-acquired. It is difficult to attribute the outbreaks to one causative agent(s) because of rotavirus co-infections with other enteric pathogens. While rotavirus was predominant, the outbreaks coincided with the annual rotavirus season.

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