Science Focus acknowledges NICD members of staff who have published in peer-reviewed journals. The Science Focus is a compilation of scientific publications included in the quarterly reports submitted to the National Department of Health. It includes only publications where an NICD staff member is either the first or last author.
HIV superinfection drives de novo antibody responses and not neutralisation breadth


*Cell Host & Microbe*
**Impact Factor: 17.872**

Eliciting antibodies that neutralise a broad range of circulating HIV strains (broadly neutralising antibodies [bnAbs]) represents a key priority for vaccine development. HIV superinfection (re-infection with a second strain following an established infection) has been associated with neutralisation breadth, and can provide insights into how the immune system responds to sequential exposure to distinct HIV envelope glycoproteins (Env). Characterising the neutralising antibody (nAb) responses in four superinfected women revealed that superinfection does not boost memory nAb responses primed by the first infection or promote nAb responses to epitopes conserved in both infecting viruses. While one superinfected individual developed potent bnAbs, superinfection was likely not the driver as the nAb response did not target an epitope conserved in both viruses. Rather, sequential exposure led to nAbs specific to each Env but did not promote bnAb development. Thus, sequential immunisation with heterologous Envs may not be sufficient to focus the immune response onto conserved epitopes.

Common helical V1V2 conformations of HIV-1 Envelope exposes the α4β7 binding site on intact virions

*Wibmer CK, Richardson SI, Yolitz J, Cicala C, Arthos J, Moore PL, Morris L.*

*Nature Communications*
**Impact Factor: 12.353**

The α4β7 integrin is a non-essential HIV-1 adhesion receptor, bound by the gp120 V1V2 domain, facilitating rapid viral dissemination into gut-associated lymphoid tissues. Antibodies blocking this interaction early in infection can improve disease outcome, and V1V2-targeted antibodies were correlated with moderate efficacy reported from the RV144 HIV-1 vaccine trial. Monoclonal α4β7-blocking antibodies recognise two slightly different helical V2 conformations, and current structural data suggests their binding sites are occluded in prefusion envelope trimers. Here, we report cocrystal structures of two α4β7-blocking antibodies from an infected donor complexed with scaffolded V1V2 or V2 peptides. Both antibodies recognised the same helix-coil V2 conformation as RV144 antibody CH58, identifying a frequently sampled alternative conformation of full-length V1V2. In the context of Envelope, this α-helical form of V1V2 displays highly exposed α4β7-binding sites, potentially providing a functional role for non-native Envelope on virion or infected cell surfaces in HIV-1 dissemination, pathogenesis, and vaccine design.


Clinical Infectious Diseases
Impact Factor: 9.117

Invasive meningococcal disease (IMD) is endemic to South Africa, where vaccine use is negligible. We describe the epidemiology of IMD in South Africa. IMD cases were identified through a national laboratory-based surveillance programme, GERMS-SA, from 2003-2016. Clinical data on outcome and HIV status were available from 26 sentinel hospital sites. We conducted space-time analysis to detect clusters of serogroup-specific IMD. Over 14 years, 5,249 IMD cases were identified. Incidence was 0.97 cases per 100,000 persons in 2003, peaked at 1.4 in 2006 and declined to 0.23 in 2016. Serogroup was confirmed in 3,917 (75%) cases - serogroup A 5%, B 23%, C 9%, W 50%, Y 12%, X 0.3%, Z 0.1% and non-groupable 0.4%. Eight serogroup-specific geo-temporal clusters of disease were identified. Isolate susceptibility was 100% to ceftriaxone, 95% penicillin and 99.9% ciprofloxacin. In-hospital case-fatality was 17% (247/1479). Of those tested, 36% (337/947) were HIV-infected. IMD incidence in HIV-infected persons was higher for all age categories with age-adjusted relative risk ratio (aARR) of 2.5 (95% CI 2.2-2.8, P<0.001) from 2012-2016. No patients reported previous meningococcal vaccine exposure. Patients with serogroup W were 3 times more likely to present with severe disease than those with serogroup B (aARR 2.7 (95% CI 1.1-6.3); HIV coinfection was twice as common with W and Y disease (aARR W=1.8 (95% CI 1.1-2.9), Y=1.9 (95% CI 1.0-3.4)). In the absence of significant vaccine use, IMD in South Africa decreased by 76% from 2003-2016. HIV was associated with increased risk of IMD, especially serogroup W and Y disease.
**V2-directed vaccine-like antibodies from HIV-1 infection identify a novel K169-binding light chain motif with broad ADCC activity**


*Cell Reports*

Impacts Factor: 8.032

Antibodies that bind residue K169 in the V2 region of the HIV-1 envelope correlated with reduced risk of infection in the RV144 vaccine trial but were restricted to two ED-motif-encoding light chain genes. Here, we identify an HIV-infected donor with high-titer V2 peptide-binding antibodies and isolate two antibody lineages (CAP228-16H/19F and CAP228-3D) that mediate potent antibody-dependent cell-mediated cytotoxicity (ADCC). Both lineages use the IGHV5-51 heavy chain germline gene, similar to the RV144 antibody CH58, but one lineage (CAP228-16H/19F) uses a light chain without the ED motif. A cocrystal structure of CAP228-16H bound to a V2 peptide identified a IGLV3-21 gene-encoded DDxD motif that is used to bind K169, with a mechanism that allows CAP228-16H to recognise more globally relevant V2 immunotypes. Overall, these data further our understanding of the development of cross-reactive, V2-binding, antiviral antibodies and effectively expand the human light chain repertoire able to respond to RV144-like immunogens.

**Candida auris in South Africa, 2012-2016**


*Emerging Infectious Diseases*

Impact Factor: 7.422

To determine the epidemiology of *Candida auris* in South Africa, we reviewed data from public- and private-sector diagnostic laboratories that reported confirmed and probable cases of invasive disease and colonisation for October 2012–November 2016. We defined a case as a first isolation of *C. auris* from any specimen from a person of any age admitted to any healthcare facility in South Africa. We defined probable cases as cases where the diagnostic laboratory had used a nonconfirmatory biochemical identification method and *C. haemulonii* was cultured. We analysed 1,692 cases; 93% were from private-sector healthcare facilities, and 92% of cases from known locations were from Gauteng Province. Of cases with available data, 29% were invasive infections. The number of cases increased from 18 (October 2012–November 2013) to 861 (October 2015–November 2016). Our results show a large increase in *C. auris* cases during the study period, centred on private hospitals in Gauteng Province.
Living donor liver transplant from an HIV-positive mother to her HIV-negative child: Opening up new therapeutic options


AIDS
Impact Factor: 4.914

A unique case of living donor liver transplantation from an HIV-positive mother to her HIV-negative child in South Africa. Two aspects of this case are ground-breaking. First, it involves living donation by someone who is HIV-positive and second it involves controlled transplant of an organ from an HIV-positive donor into an HIV-negative recipient, with the potential to prevent infection in the recipient. Standard surgical procedure for living donor liver transplantation at our centre was followed. HIV-prophylaxis was administered preoperatively. Extensive, ultrasensitive HIV testing, over and above standard diagnostic assays, was undertaken to investigate recipient serostatus and is ongoing. Both mother and child are well, over 1 year post-transplantation. HIV seroconversion in our recipient was detected with serological testing at day 43 post-transplant. However, a decline in HIV antibody titres approaching undetectable levels is now being observed. No plasma or cell-associated HIV-1 DNA has been detected in the recipient at any time-point since transplant. This case potentially opens up a new living liver donor pool which might have clinical relevance in countries where there is a high burden of HIV and a limited number of deceased donor organs or limited access to transplantation. However, our recipient’s HIV status is equivocal at present and additional investigation regarding seroconversion events in this unique profile is ongoing.
Due to competing health priorities, low- and middle-income countries (LMIC) may need to prioritise between different influenza vaccine risk groups. Risk group prioritisation may differ in LMIC based upon programmatic feasibility, country-specific prevalence of risk conditions and influenza-associated morbidity and mortality. In South Africa, we collected local disease burden data (both published and unpublished) and published vaccine efficacy data in risk groups and healthy adults. We used these data to aid policy makers with risk group prioritisation for influenza vaccination. We used the following formula to assess potential vaccine averted disease in each risk group: rate of influenza-associated hospitalisation (or death) per 100 000 population influenza vaccine efficacy (VE). We further estimated the cost per hospital day averted and the cost per year of life saved by influenza vaccination. Pregnant women, HIV-infected adults, and adults and children with tuberculosis (TB) disease had among the highest estimates of hospitalisations averted per 100 000 vaccinated and adults aged 65 years and older had the highest estimated deaths averted per 100 000 vaccinated. However, when assessing both the cost per hospital day averted (range: USD148 - 1 344) and the cost per year of life saved (range: USD112 - 1 230); adults and children with TB disease, HIV-infected adults and pregnant women had the lowest cost per outcome averted. An assessment of the potential disease outcomes averted and associated costs may aid policymakers in risk group prioritisation for influenza vaccination.
A review on the progress of sex-separation techniques for sterile insect technique applications against *Anopheles arabiensis*


*Parasites & Vectors*  
*Impact Factor: 3.163*

The feasibility of the sterile insect technique (SIT) as a malaria vector control strategy against *Anopheles arabiensis* has been under investigation over the past decade. One of the critical steps required for the application of this technique to mosquito control is the availability of an efficient and effective sex-separation system. Sex-separation systems eliminate female mosquitoes from the production line prior to irradiation and field release of sterile males. This is necessary because female mosquitoes can transmit pathogens such as malaria and, therefore, their release must be prevented. Sex separation also increases the efficiency of an SIT programme. Various sex-separation strategies have been explored including the exploitation of developmental and behavioural differences between male and female mosquitoes, and genetic approaches. Most of these are, however, species-specific and are not indicated for the major African malaria vectors such as *An. arabiensis*. There is currently no reliable sex-separation method for *An. arabiensis*, various strategies were explored in an attempt to develop a robust system that can be applied on a mass-rearing scale. The progress and challenges faced during the development of a sexing system for future pilot and/or large-scale SIT release programmes against *An. arabiensis* are reviewed here. Three methods of sex separation were examined. The first is the use of pupal size for gender prediction. The second is the elimination of blood-feeding adult females through the addition of an endectocide to a blood meal source. The third is the establishment of a genetic sexing strain (GSS) carrying an insecticide resistance selectable marker (dieldrin-resistance rdl gene and/or other GABA receptor antagonists that can be used as alternative insecticides to dieldrin) or a temperature-sensitive lethal marker.
The FCGR2C allele that modulated risk of HIV-1 infection in the Thai RV144 vaccine trial is implicated in HIV-1 disease progression


Genes & Immunity
Impact Factor: 2.339

In the HIV-1 Thai RV144 vaccine trial—the only trial to demonstrate any vaccine efficacy to date—a three-variant haplotype within the Fc gamma receptor 2C gene (FCGR2C) modified the risk of HIV-1 acquisition. A similar vaccine regimen is currently being evaluated in South Africa in the HVTN702 trial, where the predominant population is polymorphic for only a single variant in the haplotype, c.134-96C>T. To investigate the significance of c.134-96C>T in HIV-specific immunity in South Africans, this study assessed its role in HIV-1 disease progression. In a cohort of HIV-1-infected South African controllers (n = 71) and progressors (n = 73), the c.134-96C>T minor allele significantly associated with increased odds of HIV-1 disease progression (odds ratio 3.80, 95% confidence interval 1.90–7.62; P = 2.0 × 10–4, PBonf = 2.4 × 10–3). It is unlikely that the underlying mechanism involves wild-type FcγRIIC function, since only a single study participant was predicted to express wild-type FcγRIIC as determined by the FCGR2C c.798+1A>G splice-site variant. Conversely, in silico analysis revealed a potential role for c.134-96C>T in modulating mRNA transcription. In conclusion, these data provide additional evidence towards a role for FCGR2C c.134-96C>T in the context of HIV-1 and underscore the need to investigate its significance in the HVTN702 efficacy trial in South Africa.

Measuring the ability of HIV-specific antibodies to mediate trogocytosis

Richardson SI, Crowther C, Mkhize NN, Morris L.

Journal of Immunological Methods
Impact Factor: 2.19

Antibody Fc effector functions contribute to HIV control and have been implicated in the partial efficacy seen in the RV144 vaccine trial. Fc-mediated trogocytosis has been previously described for anti-cancer antibodies and results in the removal of membrane fragments from target cells. Here we developed a flow cytometry-based assay which measures the transfer of membrane fragments from a gp120-coated CD4+ lymphocytic cell line (CEM.NKR-CCR5 cells stained with a membrane dye PKH26) to monocytic cells (THP-1 cells stained with CFSE). We showed that this transfer occurred rapidly, within 1 h, and was mediated through engagement of the FcγRIIa/b receptors on the THP-1 cells. HIV-specific IgG as well as gp120 and CD4 could be detected on the surface of THP-1 cells in a process that we demonstrated was distinct from phagocytosis. Furthermore, while the THP-1 effector cells remained intact following the receipt of new membrane proteins, the viability of the target CEM.NKR-CCR5 cells decreased over time. Analysis of HIV-specific plasma revealed that antibodies with trogocytic activity were common in acute and chronic HIV infection but were higher in individuals with broadly neutralising antibody responses. We also examined trogocytosis mediated by broadly neutralising antibodies (bNAbs) targeting multiple epitopes on the BG505.SOSIP.664 trimer and show that levels of binding correlated with the trogocytosis score. Overall, our data describe a new antiviral Fc effector function mediated by HIV-specific antibodies that could be harnessed for vaccination and cure strategies.
Data on viral hepatitis in South Africa is scarce. Although viral hepatitis A, B, and C are notifiable conditions in South Africa, discrepancies have been noted in the number of viral hepatitis cases notified by the National Department of Health compared with laboratory confirmed cases from the National Institute for Communicable Diseases. The aim of the study was to assess the knowledge, attitudes, and practices of health care professionals on the notification of viral hepatitis A, B, and C. A descriptive, cross-sectional study on 385 health care professionals was conducted at Charlotte Maxeke Johannesburg Academic and Tshwane District hospitals in Gauteng province, South Africa, between March and May 2015. A pre-tested, structured questionnaire with 21 (6 demographic and 15 knowledge, attitudes, and practice (KAP)) questions was used to collect information from invited participants. A score was assigned to each KAP question and a mean (SD) score was calculated for each section. Data were analysed using descriptive statistics in STATA version 13. Of the total 385 respondents, 65% (n = 250) were nurses and 35% (n = 135) were doctors. The overall mean knowledge score for health care professionals was 2.0 ± 1.6 (mean ± SD) out of a score of 6 regarding viral hepatitis notification. Overall mean scores of practice and attitude towards notification were higher at 2.9 ± 0.4 and 3.3 ± 0.7, out of a score of 4 and 5, respectively. Lack of training, poor knowledge, a complex process and excessive workload were some of the reasons for poor notification of viral hepatitis. Overall, knowledge on notification of viral hepatitis was poor among health care professionals. Adequate training on viral hepatitis, notification process, roles and responsibilities of health care professionals to notify and the implication of viral hepatitis notifications is recommended to improve reporting rate of notifiable diseases and referrals to increase linkage to care.
The demographic and clinical profiles of women presenting with vaginal discharge syndrome at primary care facilities in South Africa: Associations with age and implications for management

Kufa T, Gumede L, Maseko DV, Radebe F, Kularatne R.

*South African Medical Journal*

**Impact Factor:** 2.163

Current South African guidelines for the management of vaginal discharge syndrome (VDS) do not recommend treatment for sexually transmitted infection (STI) pathogens for women aged ≥35 years whose partners do not have male urethritis syndrome. The guideline assumes that older women are unlikely to have an STI and that their partners do not have asymptomatic infections. To describe the demographic, behavioural and clinical characteristics of women with VDS, comparing older women (≥35 years) with younger women, and to determine the performance of age alone as a criterion for predicting the presence of STI. This was a cross-sectional study at seven primary healthcare centres taking part in the aetiological surveillance of STIs between January 2015 and December 2016. Eligible women presenting with VDS were enrolled and completed a nurse-administered questionnaire. Genital swabs and blood specimens were collected for laboratory testing. Data were entered into surveillance-specific databases and exported into Stata 14 for analysis. Descriptive statistics were used to compare demographic and clinical profiles of older with younger women. A receiver operator curve (ROC) was used to determine the age cut-off that would best differentiate between women who had infection with STI pathogens and those without. Of 757 women enrolled, 157 (20.7%) were aged ≥35 years. HIV positivity was 46.6%, and higher in older than younger women (54.9% v. 44.5%; p=0.02). Of those enrolled, 283 (37.4%) had BV and/or *Candida* infection only, 232 (30.7%) had BV or *Candida* with STI pathogens detected, 98 (13%) were infected with STI pathogens only, and 144 (19.0%) did not have any detectable STI or non-STI causes. Although older women were less likely than younger women to have *Neisseria gonorrhoeae, Chlamydia trachomatis* or *Mycoplasma genitalium* infection (23.6% v. 38.2%; p<0.01), the burden in older women was not negligible. The area under the ROC for age was 57.5% (95% confidence interval 53.2 - 61.8%), which implies suboptimal performance. Although older women with VDS were less likely than younger women to have STIs, a significant proportion of them did have an infection with STI pathogens. Age alone was not a good criterion for discriminating between women with and without infection with STI pathogens. Other ways of improving the VDS algorithm performance are needed, as it is better integration of HIV and STI prevention and treatment.
Malaria control is not simply a matter of killing mosquitoes

Brooke, BD.

Southern African Journal of Infectious Diseases

Impact Factor: 0.39

South Africa has a particularly long history of controlling malaria in its affected provinces – KwaZulu-Natal, Mpumalanga and Limpopo. Suppressing malaria vector mosquitoes with insecticides, accurate and timely diagnosis of infected persons, and subsequent case management with appropriate treatment regimens have reduced the incidence of malaria by at least 95% over the past seven decades. This level of success has placed South Africa in a particularly strong position to eliminate malaria within its borders in the near future (the current target is 2023). There is of course a ‘however’ to this statement. Malaria elimination does not mean business as usual. Stabilising and maintaining the baseline level of control whilst scaling up current interventions, and adding new elements, is costly, logistically challenging and a tough project to sell in the face of competing public health priorities. The necessary stakeholder commitments have nevertheless been made, a revised elimination strategy for the period 2019 to 2023 has been developed and a detailed business case for eliminating malaria in South Africa is in the final stages of preparation.
Antimicrobial resistance surveillance in the South African private sector report for 2016


Southern African Journal of Infectious Diseases
Impact Factor: 0.39

Aim: The relevance of surveillance for antimicrobial resistance is increasingly recognised in the light of a global action plan to combat resistance. This report presents antimicrobial susceptibility testing on ESKAPE pathogens from private sector laboratories in South Africa for 2016.

Methods: Antimicrobial susceptibility testing (AST) performed on ESKAPE organisms (Enterococcus faecium, Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter cloacae and Escherichia coli) isolated from blood cultures at four private pathology laboratories in 2016 were analysed. Analysis and reporting of data were done via a uniform platform created by the National Institute for Communicable Diseases for national AST data.

Results: AST were reported on 9 029 ESKAPE organisms including 58% Enterobacteriaceae, 28% Gram-positive bacteria and 14% Gram-negative bacteria and drug-bug combination was performed following the Global Antimicrobial Surveillance System guidelines by the World Health Organization.

Conclusions: The most important resistance to address is a high level of ESBL in Enterobacteriaceae, which necessitates the use of carbapenems for treatment. Resistance to carbapenems is recorded in this report but not confirmation of genes by genotypic methods. During this period, no increase in vancomycin-resistant Enterococci was observed.
Drug resistant tuberculosis in Africa: Current status, gaps and opportunities

Ismail N, Ismail F, Omar SV, Blows L, Gardee Y, Koornhof H, Onyebujoh PC.

African Journal of Laboratory Medicine
Impact Factor: Score unavailable

We sought to review the current status of drug resistant tuberculosis in Africa and highlight key areas requiring improvement. Available data from 2016 World Health Organization global tuberculosis database were extracted and analysed using descriptive statistics. The true burden of drug resistant tuberculosis on the continent is poorly described with only 51% of countries having a formal survey completed. In the absence of this data, modelled estimates were used and reported 92 629 drug resistant tuberculosis cases with 42% of these occurring in just two countries: Nigeria and South Africa. Of the cases estimated, the majority of patients (70%) were not notified, representing ‘missed cases.’ Mortality among patients with multi-drug resistant tuberculosis was 21%, and was 43% among those with extensively drug resistant tuberculosis. Policies on the adoption of new diagnostic tools was poor and implementation was lacking. A rifampicin result was available for less than 10% of tuberculosis cases in 23 of 47 countries. Second-line drug resistance testing was available in only 60% of countries. The introduction of the short multi-drug resistant tuberculosis regimen was a welcome development, with 40% of countries having implemented it in 2016. Bedaquiline has also been introduced in several countries. Drug resistant tuberculosis is largely missed in Africa and this threatens prospects to achieve the 2035 targets. Urgent efforts are required to confirm the true burden of drug resistant tuberculosis in Africa. Adoption of new tools and drugs is essential if the 2035 targets are to be met.
An overview of antimicrobial resistance surveillance among healthcare-associated pathogens in South Africa

Singh-Moodley A, Ismail H, Perovic O.

African Journal of Laboratory Medicine
Impact Factor: Score unavailable

Healthcare-associated infections are a serious public health concern, resulting in morbidity and mortality particularly in developing countries. The lack of information from Africa, the increasing rates of antimicrobial resistance and the emergence of new resistance mechanisms intensifies this concern, warranting the need for vigorous standardised surveillance platforms that produce reliable and accurate data which can be used for addressing these concerns. The implementation of national treatment guidelines, policies, antimicrobial stewardship programmes and infection prevention, and control practices within healthcare institutions require a platform from which it can draw information and direct its approach. In this review, the importance of standardised surveillance systems, the challenges faced in the application of a surveillance system and the condition (existence and nonexistence) of such systems in African countries is discussed. This review also reports on some South African data.

Cryptococcus neoformans: Diagnostic dilemmas, electron microscopy and capsular variants

Birkhead M, Naicker SD, Blasich NP, Rukasha I, Thomas J, Sirutatan C, Abrahams S, Mavuso GS, Govender NP.

Tropical Medicine and Infectious Disease
Impact Factor: Score unavailable

Two cases of cryptococcal meningitis went undetected by a cryptococcal antigen (CrAg) lateral flow assay on blood in a reflex CrAg screen-and-treat programme in South Africa, although Cryptococcus neoformans was identified by culturing the cerebrospinal fluid specimens. Further investigations into these discordant diagnostic results included multilocus sequence typing (which showed no mutations in the CAP59 gene) and transmission electron microscopy using a capsule-staining protocol (which revealed a >50% reduction in capsular material in both cases, relative to a control culture). A multi-disciplinary approach for resolving discordant diagnostic test results is recommended.
Complete genome sequences of Spondweni viruses isolated between 1958 and 1960

Jansen van Vuren P, Kgaladi J, Patharoo V, Paweska JT.

Microbiology Resource Announcements
Impact Factor: Score unavailable

Here, we report the complete genome sequences of 14 Spondweni viruses isolated in South Africa and Mozambique between 1958 and 1960. The sequences comprise 13 mosquito isolates and 1 human isolate following a documented laboratory infection. This study expands the publicly available data for this neglected virus from four to 18 sequences.
Thank you for your contributions!
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