THE FEDERATION OF INFECTIOUS DISEASES SOCIETIES OF SOUTHERN AFRICA

FIDSSA Quarterly

Volume 6 Issue 3 1st September 2015

Points of interest

Update on international HIV conferences

What is needed to curb MERS-CoV

AMR maps for South Africa

Six good reasons to attend the 6th FIDSSA Conference 5-8 November 2015 Champagne Sports Resort

6th FIDSSA Congress 2015
Emerging Threats
5 - 8 November 2015
Champagne Sports Resort
Drakensberg • KwaZulu Natal • South Africa
fidssa www.fidssa.co.za
For further information contact Europa Organisation Africa
Tel: +27 (0)11 325 0020 | email: info@eafrica.co.za
www.ecafrica.co.za

1. Cutting edge plenaries & workshops on current issues in Infectious Diseases
2. Exposure to the ID problems affecting allied ID specialties
3. Networking with colleagues and international guests
4. CPD certification including Ethics Points
5. Have your say and direct policy at FIDSSA and individual society AGMs
6. Unwind for 3 days in the beautiful Drakensberg Mountains

Highlights from CROI / IAS 2015

Seattle's Space needle and the Haro Straits

CROI and the IAS conference were held across the Haro Straits in Seattle and Vancouver respectively during the course of this year. Results from the eagerly awaited TEMPANO and the START study were released, providing the evidence that immediate initiation of ART, results in significant benefits over delayed ART initiation. As a response to this data, the "Vancouver Consensus" was released (www.vancouverconsensus.org) following the IAS conference. The statement calls on world leaders, donors, governments and clinicians to support "immediate rights-based access to treatment for all" and ends with "Science has delivered solutions. The question for the world is: When will we put it into practice?"

How does the START and TEMPANO study impact paediatric practice?

The inclusion age for both studies were >18 years of age, with an average age of 35 years (29-44 years). In the TEMPANO study patients were randomized to one of 4 arms – deferred ART, deferred ART + IPT, early ART or early ART + IPT. The early ART arms fared better than the deferred ART arms (HR 0.56), with fewer serious AIDS related events (invasive bacterial infections and tuberculosis). In the START study, patients were randomized to immediate or delayed ART, with the composite endpoints favoring immediate ART (HR 0.43). Again the main driver of the endpoint was serious AIDS related events. Despite the positive results the lack of inclusion of children and adolescents in these studies does limit the generalizability of the results to the paediatric population. The only paediatric study comparing early ART to deferred ART (PREDICT Trial), did not demonstrate any difference between the early and the deferred ART groups in Thai children aged 1-12yrs (mean age 6.4yrs). These studies do create the urge to move towards a "test and treat" approach from both an individual patient basis and also from a societal basis with reduced transmission risk. From a paediatric perspective, the development of a safe, fixed dose once a day regimen and strategies to improve retention in care and adherence should be a prerequisite to moving to a test and treat strategy for all children and adolescents.

Renewed Hope of a functional HIV cure

Sáez-Cirión A, et al. described a perinatally infected child with sustained virological remission for more than 12 years after interruption of ART. The patient was initiated on AZT at birth, then changed to AZT/3TC/ddI/RTV at 6 weeks of age. Treatment was interrupted between 5.8 to 6.8 years, and on return to care remained <50 copies/ml for the last 12 years (except for one blip of 510 copies/ml). Viral stimulation has demonstrated ongoing low levels of viral replication. Following the disappointment of the "Mississippi Child", this case again demonstrates that early initiation of treatment soon after birth, although will not result in elimination of HIV, but can result in prolonged virological control by the patient's immune system.

Neonatal outcomes following the PROMISE trial

Previously released data from PROMISE trial demonstrated the benefit of Option B (HAART for all mothers) over Option A (HAART for mothers with CD4 count <500cells/ul or AZT in mothers with CD4 count over 500 cell/ul) for prevention of mother to child transmission. Neonatal outcomes from this study presented at CROI 2015, demonstrated a significantly higher risk of adverse neonatal events (neonatal deaths and prematurity) in the mothers on HAART, especially on TDF/FTC compared to AZT/3TC. These results highlight the need for continued pharmacovigilance in this high risk population by all treating clinicians.

As we move towards the WHO goal of 90:90:90, results presented have highlighted the way forward and possible stumbling blocks along the way.

ICSSA
INFECTION CONTROL SOCIETY OF SOUTHERN AFRICA

Post Graduate Diploma in Infection Prevention and Control Nursing

A motivation together with core competencies for a Post Graduate Diploma in Infection Prevention and Control Nursing (IPC) was sent to the South African Nursing Council (SANC) in March, and again in July and August 2015. We are hoping that our request will be tabled and a decision reached so that we can start to develop the curriculum in order to address the skills shortage of qualified Infection Prevention and Control Specialists in South Africa.

In summary, the core competency framework consists of:
Domain 1: Professional, ethical and legal practice
Domain 2: Clinical and non-clinical practice – care provision and management
Domain 3: Personal development and quality of care
Domain 4: Management and Leadership
Domain 5: Research

Carbapenemase-producing Enterobacteriaceae (CPE) surveillance

There are currently differing opinions and a lack of consensus nationally which make decision making at hospital level difficult with regards to patient screening for CPE. Our thinking is largely based on what has happened globally in sporadic or isolated outbreaks and is not specific to current prevalence in South Africa. This lack of consensus causes confusion for healthcare workers and Infection Prevention and Control

There are presently 2 proposed point prevalence epidemiological studies of rectal carriage of CPE in intensive care unit patients in South Africa (that we are aware of). The broad objectives of the studies will be to determine the prevalence of rectal carriage as well as the potential risk factors associated with the carriage of CPE in ICU patients in South Africa.

Risk factors in the South African setting have not been formally studied but (based on the recommendations of the SASCM working group), will at least, include:

patients transferred from another healthcare or long-term care facility,
prior hospitalization;
admission to intensive care unit (ICU) or high care unit;
patients with an indwelling invasive device:
patients transferred from another country;
patients transferred from a facility with a known CPE problem;
patients receiving dialysis;
prior antibiotic use;
immune-compromised patients;
patients known to be previously colonized/ positive with CPE;
and contacts of patients known to be previously colonized/positive with CPE.

The Infection Prevention and Control community look forward to the results of both studies and welcome standardised guidelines for screening of patients for CPEs.

(Contributions from Joy Cleghorn, Briette du Toit and Lesley Devenish)

Lowman, W., Bamford, C., Govind, C., Han, K.S.S., Kularatne, R., Senekal, M., Brink, A., Moodley, P., Thomas, J., Smit, J., Perovic. 2014. The SASCM CRE-WG: consensus statement and working guidelines for the screening and laboratory detection of carbapenemase-producing Enterobacteriaceae South Afr J Infect Dis 2014;29(1):5-11

MERS-CoV: Surveillance required to curb spread

Dr Salim Parker – SASTM President

The Hajj, the world's largest annual Mass Gathering (MG), has been associated with the spread of infectious diseases. In 2000 and 2001 epidemics of serogroup W meningococcal meningitis occurred during the pilgrimage in Saudi Arabia and the bacteria were transported to fourteen different countries by returning pilgrims, causing localized outbreaks. Since Middle East Respiratory Syndrome (MERS), caused by a coronavirus (MERS-CoV), first surfaced in Saudi Arabia in June 2012 where the vast majority of the more than 1400 of confirmed cases were reported from, there has been the concern that the Hajj could be the catalyst for epidemics and the worldwide spread of this emerging disease, which has a mortality of over 40%. MERS-CoV was not detected during the Hajj of 2012, 2013 and 2014.

The actual Hajj pilgrimage is from 22-27 September this year but the bulk of South Africans would have arrived in Saudi Arabia by the end of August already. It has to be noted that no current active transmission has been documented in the pilgrimage cities of Mecca and

Medina, nor in Jeddah, where the airport used by most international travellers is situated. However there is going to be an influx of pilgrims from the Saudi capital of Riyadh soon and the situation could change. As at 25 August there has been a total of 1162 cases of laboratory confirmed MERS---CoV infection, including 498 deaths, reported in Saudi Arabia since June 2012. The current outbreak in Riyadh, linked to the National Guard Hospital, has seen 101 newly confirmed cases and 30 fatalities since the beginning of August 2015.

This closely followed the South Korean May/June 2015 outbreak caused by a single traveller returning from the Middle East and resulting in 186 laboratory-confirmed cases of MERS-CoV infection, including36 deaths. A total of 16 693 contacts had to be quarantined before the outbreak was brought under control. Of 175 cases, nosocomial transmission was documented in 80 hospital patients and 33 staff members. Another 62 were visiting healthcare facilities with known MERS patients. The following factors were found to have aided the spread in the Asian country:

- A general lack of awareness of MERS-CoV.
- Inadequate infection control measures in the hospitals involved.
- Contact between MERS patients and other patients in overcrowded emergency rooms were frequently prolonged and close. There was also the custom of family members and visitors to infected patients staying in the hospital for long periods.
- 'Doctor shopping,' the practice of soliciting medical care at a number of hospitals.

Current data indicates that the virus is not easily transmitted from person to person and that prolonged close contact is needed in the endemic Middle Eastern countries. The Hajj is a period of intense congestion with pilgrims housed in crowded tents for prolonged periods with no significant barriers between sick and healthy pilgrims. Isolated cases of MERS-CoV infection has been reported from a number of countries, including France, Germany, Greece, Iran, Algeria, Austria, United Kingdom, USA, Malaysia and Egypt. All of these cases were associated with travel to the Middle East. Virological and serological studies point to bats and dromedary camels as being the most likely reservoir for MERS-CoV. Infected animals have been documented in sub-Saharan Africa (SSA) but no human cases. This could be due to non-recognition, a lack of reporting or surveillance, or a genuine absence of the disease. Close to 500 000 Hajj pilgrims are from SSA and it has been postulated that, before the current Riyadh outbreak, about 10 pilgrims will carry the virus back to their native country. That figure is likely to be revised upwards now.

The NICD in 2013 performed oropharyngeal swabbing surveillance in returning South African pilgrims. A total of 171 specimens were collected, all being negative for MERS-CoV. The exercise is going to be repeated for the 2015 Hajj season with pre and post Hajj surveillance being planned. In addition to MERS-CoV, other Hajj associated pathogens such as influenza, pneumococci, meningococci and pertussis will be screened. If successful this surveillance could be repeated in the future and form part of a global network of MG surveillance that can rapidly identify and curb the spread of pathogens such as MERS-CoV.

References:

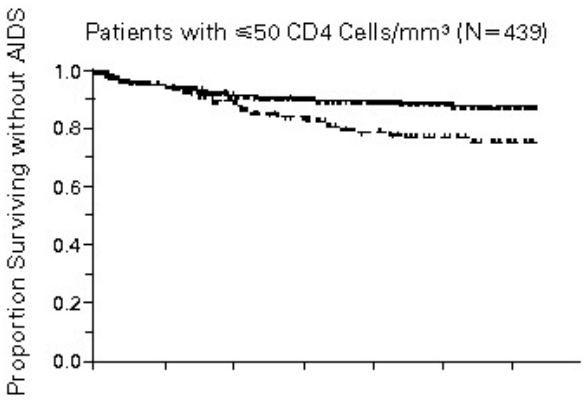
Zumla A et al: http://www.ijidonline.com/article/S1201-9712%2815%2900158-7/fulltext
http://www.who.int/emergencies/mers-cov/en/
http://www.promedmail.org/direct.php?id=20150826.3602455

The law of diminishing returns in 'When to Start' trails
Tom Boyles

This quarter saw the publication of a long awaited landmark HIV trial known as INSIGHT START which aimed to answer one of the most enduring questions in HIV research 'When should we start anti-retroviral therapy (ART)?' The clear answer is that patients benefit by starting ART at a CD4 count above 500 and probably as soon as HIV infection is confirmed. Studies like these always pose more questions than they answer such as What are the long-term effects of such a strategy? How will it affect adherence? How will it affect transmission? and How will we pay for it? There will no doubt now be a stream of follow-up papers aimed at these questions but it's likely that the WHO will soon adopt a policy of removing CD4 threshold as a criterion for starting ART.

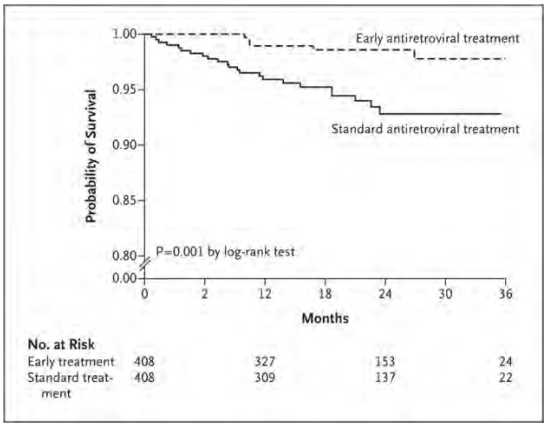
It's interesting at this point to look back at the history of HIV trials to put this new knowledge in perspective. The landmark study of AZT, published in 1987, randomised 282 patients to AZT or placebo and was stopped early when only 27 patients had completed the planned 24 weeks of treatment[1]. At this point there were 19 deaths in the placebo group and only 1 in the AZT group. As the trial was halted with patients at various time points it's difficult to provide an accurate number needed to treat (NNT) to save a life but it's fair to say that it would be in single figures. Although the effects turned out to be short-term, at that time they were enormous by any measure.

By the mid 1990's the drug arsenal was beginning to build and dual NRTI therapy had become standard of care but mortality remained high. At this point a trial of triple therapy including 2 NRTI's plus indinavir vs 2 NRTI's showed the powerful effect of protease inhibitors[2]. Patients with CD4 >200 were excluded and results showed that for patients with CD4<50 there was a clear survival benefit with a NNT to prevent 1 death after 1 year of 10. For patients with CD4 50-200 the NNT was around 25. The figure below shows AIDS free survival in those with CD4<50 over 48 weeks. Clearly these were impressive figures but the early benefits at least, were less than had been seen with the introduction of AZT.

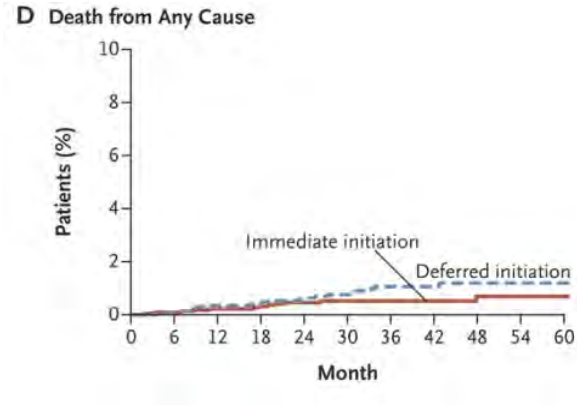


The question of when to start is as old as ART itself. A systematic review published in 2000 showed that when given to asymptomatic or mildly symptomatic patients, although AZT monotherapy halved disease progression, the effects were short lived and there was no effect on long-term survival[3]. Although by then triple therapy was considered standard of care, guidelines recommended therapy only when CD4 dropped below 200 and the quest for the optimal time to start began.

A landmark 'when to start trial', published in 2010 randomised patients in Haiti to receive ART at CD4 count around 350 or to wait until it had dropped to around 200[4]. The figure below shows the Kaplan-Meyer survival analysis with a clear benefit for early therapy. The estimated absolute reduction in mortality after 3 years was 5% giving an NNT of 20 to prevent 1 death. Over a 1 year period the NNT was therefore around 60. Once again the benefits are impressive but much less than the first trials of triple therapy.



Five years later the INSIGHT START trial was published[5]. The design was similar to that in Haiti but with higher CD4 thresholds. Patients started either at CD4 >500 or waited until CD4 was 350. Unlike earlier trials the primary outcome wasn't mortality but a composite of mortality and serious AIDS or serious non-AIDS events. The study showed a clear benefit of early ART in terms of the primary outcomes. However, to put this trial in perspective and compare with earlier trials we should look at the mortality benefits. Although there was a trend in favour of early therapy, despite the trial lasting 5 years and including more than 4,600 patients the difference was not statistically significant (see below). Were this benefit to be confirmed the NNT to save a life would be measured in the 1000's.



The INSIGHT START trial is an important contribution to our understanding of HIV treatment but it is interesting to see it in the context of previous trials. The benefits are real and may extend beyond those measured in the trial itself if wider ART coverage has a significant impact on HIV prevention. However, there is a law of diminishing returns at work here. The absolute benefits in terms of mortality which were enormous when the first effective drugs arrived are now tiny by comparison. Future trials are unlikely ever to have mortality as a primary endpoint and focus will shift towards reducing morbidity, side-effects and transmission.

References
(1) Fischl MA. N.Engl.J.Med. 1987 Jul 23;317(4):185-191.
(2) Hammer SM. N.Engl.J.Med. 1997 Sep 11;337(11):725-733.
(3) Darbyshire J. Cochrane Database Syst.Rev. 2000;(3)(3):CD002039.
(4) Severe P. N.Engl.J.Med. 2010 Jul 15;363(3):257-265.
(5) INSIGHT START Study Group. N.Engl.J.Med. 2015 Jul 20.

Key populations and their role in STI & HIV transmission. Is S. Africa ready for the 'storm' ahead

Sexually Transmitted Diseases Society of Southern Africa

Frans Radebe - Centre for HIV and STIs. NHLS/NICD

Every day nearly a million people acquire a sexually transmitted infection (STI), and each year 340 million people aged 15 – 49 are infected with a curable STI. Syphilis epidemics are especially tragic because syphilis causes great harm, poses the largest risk for HIV transmission and is preventable. Individuals who engage in illegal or stigmatized behaviors – injecting drugs, exchanging sex for money, or having multiple same-sex partners, comprise a small percentage of the population but have a disproportionate role in the transmission of infection and a greater need for health services.These groups of core transmitters are widely accepted as critical actors in generating endemic and epidemic rates of STIs, including HIV.

Recently, it has been proven that the re-emergence of certain STIs such as syphilis, LGV and antibiotic resistant gonorrhea, which were under control to the extent of elimination, have surfaced among the hard-to-reach subset of the population, namely, men who sleep with men (MSM),mainly in developing countries. While the global prevalence of HIV has stabilized, there seems to be a trend of increasing HIV prevalence among MSM with new, newly identified and resurging HIV epidemics among MSM being documented in different parts of the world. In South Africa, we have recently seen treatment failure for *Neisseria gonorrhea*among the same key population. The importance of this subset of the population, who have higher rates of partner change and concurrent sexual partnerships, have been ignored. There is a substantial gap in knowledge relating to how different populations' sexual structures and networks relate to epidemic potential of the different STI pathogens, such as HIV, syphilis, *Chlamydia*, gonorrhea, trichomoniasis and bacterial vaginosis.

Sex work as a commercial industry, which exists as an open secret, is still considered a forbidden culture and is illegal in a number of countries. The general theory is that poverty and lack of economic opportunities are the major drivers for women entering sex trade (female sex workers, FSW), but there is an uncertainty in terms of MSM and their operations. Little is known about FSW/MSM and their clients, who are considered members of a core group that sustains endemic, or fuels epidemic, transmission of STIs. Other FSWs may have an income source other than sex work and may not consider themselves as sex workers, thus are unable to utilize the services available to FSWs, if any. Generally in South Africa, the coverage, scale, quality and impact of HIV prevention interventions in FSW and MSM remain low or nonexistent. Knowledge is also lacking in terms of bisexual partnerships, which have the potential to sustain STI transmission, through bridges to other sexual networks.

MSM bear a disproportionately higher burden of HIV infection than the general population. Because of real and perceived barriers to health care, MSM may be less likely to be aware of new HIV infection and other STIs, leading to longer periods of increased susceptibility and infectiousness. The MSM population may still endure pervasive stigma, harassment and discrimination at the social and political levels in most countries, thus limiting the ability to assess infection transmission patterns among them. MSM risk behaviors overlap considerably with other high risk groups, e.g. injecting drug users (IDUs) and FSWs – a key factor facilitating bridging of the infection between different high risk groups, contributing further to HIV transmission among the MSM.

There is an urgent need to undertake active outreach work in order to reach certain high-risk groups of FSWs and MSMs. The pattern of sex work has evolved and is more complex than previously. A number of STI outbreaks have been attributed to group sex activities in certain countries. There is emerging evidence that group sex participation is quite common in youth and teenagers including age mixing where drug use is common at those events. Heterosexual group sex events have been documented in media, where people have sex with those whom they cannot describe or identify in a network. Sex practices are common, where bodily fluids on condoms, fingers, toys, genitals, mouth or anuses may transmit HIV and STI indirectly between people who never have sex together. **Messages that focus only on using condoms would not be relevant anymore in the future among the general population as they are not among group sex participants**. Consistent condom use of 50% or less in all categories of sex workers and group sex attendees may not prevent third-party transmission. Effective interventions need to engage the networks of partners regarding testing and care seeking. There is an urgent need to expand STI/HIV surveillance and access to STI/HIV testing, prevention and treatment services in a rapidly narrowing window of opportunity to prevent the worst STI/HIV transmission among this population. These new "strange" sex practices are quite numerous and behavioural patterns and mixing patterns at group sex events make them important for both research and interventions which should be a high priority for public health and for STI and HIV prevention.

World Health Organization, *Global Strategy for the Prevention and Control of Sexually Transmission Infection: 2006-2015: breaking the chain of transmission*. 2007: World Health Organization.
Weir et al. Aids,2003. **17**(6): p. 895-903. and Weir et al. *Sex Transm Infect*, 2004. **80 Suppl 2**: p. ii63-8.

South African Antimicrobial Resistance update

The South African Society of Clinical Microbiology (SASCM) has endeavoured to address Antimicrobial Resistance (AMR) in line with the World Health Organization's Global Action Plan for AMR adopted by the 68th World Health Assembly in May 2015. AMR is a grave threat to public health and modern medicine and has the potential to adversely impact South Africa's national security and economic stability. The development and implementation of a national AMR strategy that complements international efforts is a major step towards the containment of the threat of AMR.

SASCM, together with the South African Antimicrobial Stewardship Programme (SAASP) and the National Department of Health (NDoH), has undertaken to optimize AMR reporting, in an effort to meet this challenge. SASCM has also partnered with The Centre for Disease Dynamics, Economics & Policy (CDDEP) and together aim to launch the Global Resistance Map and *The State of the World's Antibiotics, 2015,* two new sources of antibiotic resistance research and policy, in the near future.

Colleagues in South Africa have been early contributors to a web-based AMR map ("Resistance Maps") that allows users to explore interactive graphics and charts of antibiotic consumption and resistance data from 39 countries. South Africa is represented by laboratory-based surveillance data from both the public and private sectors for the ESKAPE organisms (*Enterococcus, S. aureus, Klebsiella* spp.*, Acinetobacter* spp.*, Pseudomonas* spp., and ESBL-producing *Enterobacteriaceae*). In the public sector, laboratory data are reported by the National Institute for Communicable Diseases (NICD) and public sentinel hospitals through the NICD's GERMS-SA surveillance. Surveillance is conducted in 31 hospitals and more than 200 laboratories on 12 pathogens. Data from private sector laboratories have been contributed by SASCM, which collates private laboratory data from five laboratory groups for 13 pathogens. The two data sets are now being consolidated through the South African Antibiotic Resistance Partnership and GARP.

CDDEP is also releasing *The State of the World's Antibiotics, 2015*, a global report on antibiotic use and resistance in humans and animals. This report highlights the work of the Global Antibiotic Resistance Partnership (GARP), including the GARP-South Africa Working Group. Policy recommendations are based on the global experience of all eight GARP working groups.

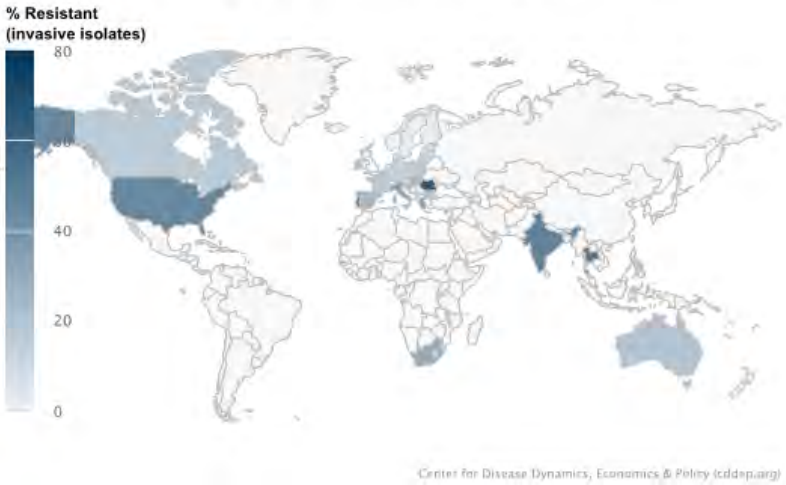
Thus far, significant findings relating to three key organisms are:

All three organism-antibiotic combinations show statistically significant change over time:

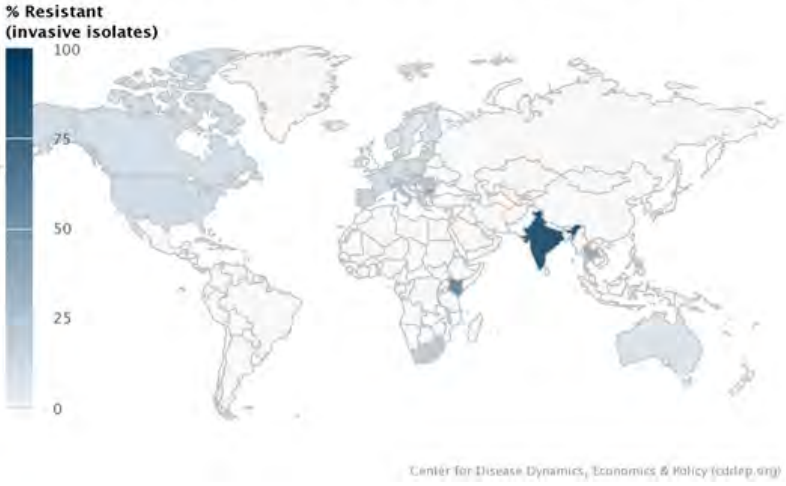
- *Staphylococcus aureus* and cloxacillin – significant decrease in resistance over 3 years ($p<0.001$) - currently resistance is at 30%.
- *Klebsiella pneumoniae* and carbapenems – significant increase in resistance over 3 years ($p<0.001$) - currently resistance is at 3.2%.
- *Escherichia coli* and ciprofloxacin – no change in resistance over the 3 years ($p=0.83$) - currently resistance is at 27%.

Below, are examples of informatics that will be available on Resistance Maps.

Resistance of *Staphylococcus aureus* to oxacillin (MRSA)



Resistance of *Escherichia coli* to cephalosporins (3rd gen)



Resistance of *Pseudomonas aeruginosa* to carbapenems

SAVE THE DATE!