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1 ZOOBOTIC AND VECTOR-BORNE DISEASES

a Plague antibodies in a rat in Johannesburg, Gauteng Province

In March 2016, one of 11 rodents collected from the Mayibuye informal settlement in Midrand on March 16 and submitted by City Of Johannesburg Region A environmental health officers, tested positive for plague IgM antibodies in serum. Testing was by a highly-specific competitive enzyme-linked immunosorbent assay (ELISA), and the result was verified by re-testing. The conclusion was that the juvenile female (approximately 2 months of age) *Rattus* sp. rodent had come into recent contact with *Yersinia pestis* and had produced antibodies to the organism. The spleen sample from this rodent was cultured appropriately, but no growth was observed on any of the culture media. Impression smears were also done from the spleen sample for staining and microscopy, and also for a direct immunofluorescence test. No organisms were seen and it was concluded that the rodent was not actively infected with *Y. pestis* despite recent exposure to the bacterium. The origin of infection is not known, but the most likely source was a flea from a wild rodent from the vicinity; alternatively the rat may have been accidentally introduced to Mayibuye by road or rail transport from elsewhere.

Plague is an acute bacterial infection transmitted by fleas. Plague mainly affects rodents, and endemic plague exists independent of human populations in wild rodent colonies. Under suitable conditions plague has the potential to spread into urban rodent populations, and potentially, from them to humans. The last reported outbreak of plague occurred in Coega, Eastern Cape Province, in 1982, with 13 cases and 1 death. Susceptible wild rodent foci probably exist in several areas of South Africa, namely parts of the Eastern Cape, Northern Cape, Free State, Mpumalanga and Gauteng Provinces. Decades may lapse between the occurrences of isolated cases or epidemics; only surveillance of rodents and their vector populations can warn of the presence of plague during periods when no human cases are reported.

Rodent surveillance in the City of Johannesburg

The City of Johannesburg (COJ), comprising 7 regions (Regions A-G), participates in a plague surveillance program run by the NICD, and thus

routinely traps, and submits rodent specimens to the Special Bacterial Pathogens Reference Laboratory, Centre for Emerging and Zoonotic Diseases, for plague testing. This surveillance programme has been in place since February 2010 and the coverage has grown from 78 samples collected in 2010 to 862 samples in 2015, and continues to improve (Figure 1).

Surveillance programmes alert public health authorities to increased human plague risks, thus allowing prevention and control programmes to be implemented before human plague cases occur. Control of plague transmission is directed at regulating the rodent reservoirs and flea vectors of the disease. The objective of this is to reduce the density of the rodent-flea vectors as quickly and as completely as possible, by area-wide insecticide application to houses and rodent habitats, followed by intensified rodent control by trapping and poisoning, and discouraging rodents by basic sanitary methods, e.g. clearing up garbage that provides food and shelter for rodents. Surveillance in the City of Johannesburg has been intensified, with increased numbers of rodents submitted for testing. To date no further rodents have tested positive, and no suspected human cases of plague have been reported. Domestic rodents pose a number of human health problems, of which plague is only one. While the acute garbage accumulation problem following the Pikitup strike has improved in parts of Johannesburg, it must be emphasised that many communities have a longstanding rodent problem that requires a multipronged approach to solve; trapping and poisoning of rodents will only have temporary effects.

Source: Special Bacterial Pathogens Reference Laboratory, Centre for Emerging and Zoonotic Diseases, NICD-NHLS (jfrean@nicd.ac.za); City of Johannesburg Environmental Health Department.

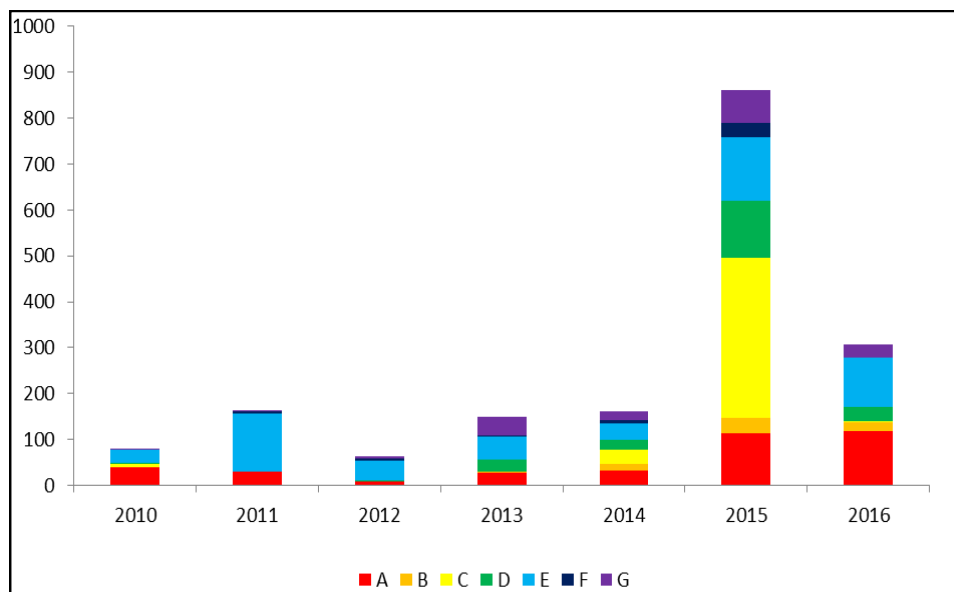


Figure 1. Number of rodents collected from the City of Johannesburg, February 2010-March 2016 (letters A-G signify the administrative regions of Johannesburg).

b Yellow fever prevention and diagnosis: An update for South African health care workers in the context of the ongoing yellow fever outbreak in Angola

The numbers of suspected and confirmed cases of yellow fever continue to rise in Angola, according to the WHO Situation Report (<http://www.afro.who.int/en/yellow-fever/sitreps/>). The WHO reports weekly on the epidemiological situation, response activities, support from partners and resources mobilisation. As of the 10 April 2014, a total of 1751 suspected and 582 confirmed cases have been reported. Twelve of the country's 18 provinces have reported yellow fever cases, but local transmission has been documented in 5 provinces. The epicentre of transmission remains in Luanda (Figure 2). Mass vaccination campaigns are ongoing and by 10 April almost 6 million people (90% of residents) in Luanda province have been vaccinated against yellow fever. A decline in the daily number of cases has been noted as a consequence. A number of cases have been imported to the Democratic Republic of Congo, Kenya and China, but local transmission in countries other than Angola is yet to be confirmed. The NICD continues to receive requests for yellow fever testing of returned travellers. Travellers to Angola and other yellow-fever endemic areas should receive yellow fever vaccine from accredited providers at least 10 days before arrival at their destination. The yellow fever vaccine is highly efficacious, and is licensed for administration to persons as young as 6 months. Persons who are not eligible for vaccination (age < 6 months, symptomatic HIV infection or CD4 <200 cells/mm³,

immunosuppression following transplantation or chemotherapy) should avoid visiting areas where yellow fever transmission has been documented. Persons over 65 years of age not eligible for vaccination.

Clinicians attending to returned travellers from yellow fever-endemic areas who have acute febrile illnesses should be careful to exclude malaria, typhoid, viral haemorrhagic fever, dengue and non-travel associated infectious conditions, and to confirm date of receipt of the yellow fever vaccine. Yellow fever is highly unlikely in the presence of a history of vaccination. Clinicians should take a careful travel history, and correlate it with the latest distribution of confirmed and suspected cases. A history of being bitten by mosquitoes should be elicited. In the presence of a compatible clinical history, and where yellow fever vaccination cannot be confirmed, diagnostic testing for yellow fever is appropriate. Yellow fever has an incubation period of three to six days, followed by fever, muscle pain, prominent backache, headache, shivers, loss of appetite, nausea and vomiting. After a brief remission, about 15% of patients will progress to a more severe phase of illness presenting with jaundice, abdominal pain, vomiting, multiple organ failure, shock, renal failure and/or haemorrhage. The spectrum of illness ranges from asymptomatic or mild cases (the majority) to fatal (40% amongst persons with severe disease). Diagnostic testing is

complicated by prior administration of the vaccine, as IgM antibodies may be produced for up to a year following vaccination. Persons with previous dengue virus or other flavivirus infection may also produce non-specific (cross-reacting) antibodies to yellow fever. Persons with yellow fever are viraemic from approximately days 2-9, and PCR (available at the NICD) can identify cases if serum is taken early on in the course of illness. Presently the WHO case definitions are being used (Table 1). The NICD offers diagnostic testing for yellow fever

in consultation with a NICD pathologist, and following completion of the yellow fever case investigation form (available on the guidelines tab of the NICD webpage at www.nicd.ac.za). Please call Dr Jacqueline Weyer on 0113866376 or email jacquelinew@nicd.ac.za

Source: Division of Public Health, Surveillance and Response, (outbreak@nicd.ac.za) and Centre for Emerging and Zoonotic Diseases, NICD-NHLS (januszp@nicd.ac.za)

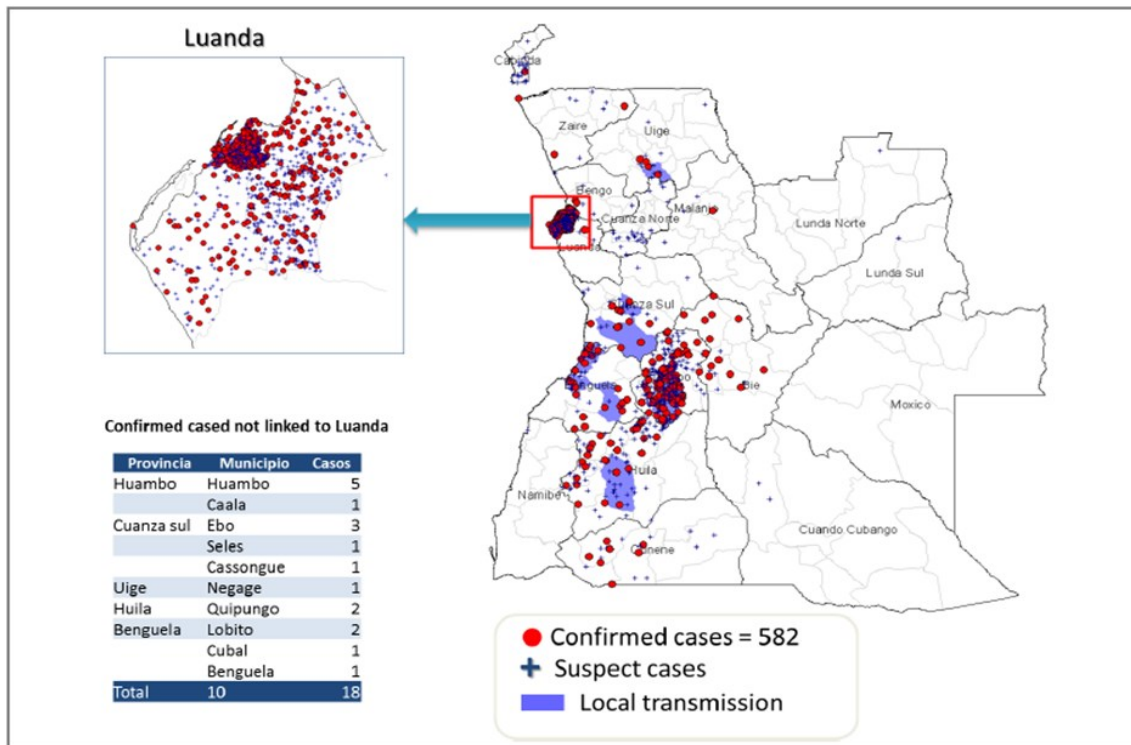


Figure 2. Geographic distribution of yellow fever cases, Angola December 2015-10th April 2015 (map courtesy WHO situation report)

Table 1. Current case definitions of yellow fever, according to WHO as per the revision published in Weekly Epidemiological Record, 19 November 2010

Suspected	Any person with acute onset of fever, with jaundice appearing within 14 days of onset of the first symptoms
Probable	A suspected case with one of the following: <ul style="list-style-type: none"> • presence of yellow fever IgM antibody in the absence of yellow fever immunization within 30 days before onset of illness • positive postmortem liver histopathology • epidemiological link to a confirmed case or an outbreak
Confirmed	A probable case with one of the following in the absence of yellow fever immunization within 30 days before onset of illness <ul style="list-style-type: none"> • detection of yellow fever-specific IgM • detection of fourfold increase in yellow-fever IgM, or IgG antibody titres between acute and convalescent serum samples, or both • detection of yellow fever-specific neutralizing antibodies OR A probable case with one of the following in the absence of yellow fever immunization within 14 days before onset of illness <ul style="list-style-type: none"> • detection of yellow fever virus genome in blood or other organs by PCR • detection of yellow fever antigen in blood, liver or other organs by immunoassay • isolation of yellow fever virus

c Microcephaly and neurological complications post-Zika virus infection: evaluating the evidence for causality

The WHO Strategic Response Framework and Joint Operations Plan includes research into 'the reported increase in incidence of microcephaly and neurological syndromes including their possible association with Zika virus infection'. The determination of a causal association of a micro-organism with a specific disease syndrome has been deliberated since the discovery of micro-organisms (1676, Van Leeuwenhoek) and the proposal of the 'germ-theory of disease' (in the 1700s). Robert Koch, who discovered the causative organisms of tuberculosis, anthrax and cholera, proposed criteria for causality, now known as 'Koch's postulates' in 1880 while he was a government advisor with the Imperial Department of Health in Prussia. Koch's postulates require that the implicated microorganisms should be present in every case of disease, should be grown in pure culture from an infected person, and when re-inoculated into a susceptible laboratory animal, the organisms should cause the same disease, and be isolated in pure culture from the same laboratory animal. While these criteria are sound, Koch's postulates are limited by the requirement for infection and isolation from susceptible laboratory animals: many, if not most human pathogens do not cause disease in animals.

In the 1950s, Austin Bradford Hill proposed a set of criteria by which to evaluate an apparently causal relationship between exposure and disease. These criteria (Table 2) are helpful today to examine the evidence for the hypothesized causal association of Zika virus with microcephaly or neurological complications such as Guillian-Barré syndrome. Evidence for the strength and consistency of the association between Zika and microcephaly is mounting. A Slovakian woman who had worked in northern Brazil and experienced a Zika-like illness in the week 13 of pregnancy, returned to Europe at week 28 and had a termination of pregnancy on account of severe fetal abnormalities including microcephaly. Zika virus was detected by RT-PCR, and flavivirus-like particles were visualized in brain tissue using electron microscopy. No other recognized cause of fetal abnormalities were identified (Mlakar *et al*, NEJM February 10 2016). In a prospective study in Brazil amongst 88 pregnant women with clinical symptoms compatible with Zika, 72 had laboratory-confirmed Zika virus infection; amongst the 42 who had a fetal ultrasound, 12 (29%) had abnormalities detected ranging from growth retardation to cerebral calcification and microcephaly. Of the 6 births that had occurred by the time of publication, all had

abnormalities (2 x stillbirth, 1 x microcephaly, and 3 x small for gestational age with ocular abnormalities) (Brasil *et al*, NEJM, March 4, 2016). In a retrospective study of the Zika outbreak in French Polynesia that occurred from October to April 2014, 8 of 4 100 infants born during the outbreak had microcephaly. The authors modeled the epidemic based on population serosurveys, and established that the incidence of microcephaly increased from 2 cases/10 000 women infected in the first trimester, to 95 cases/10 000 women infected in the first trimester, representing a risk ratio of approximately 50%.

The temporal association between the increase in cases of microcephaly and the Zika epidemic has been shown in a number of studies, but is nicely illustrated in Figure 3, showing the peak of the epidemic curve of microcephaly cases roughly 9 months after the peak of the outbreak in a province in Brazil (de Oliveira, MMWR, March 11, 2016). It is plausible, and biologically coherent that Zika virus may be teratogenic: other viral infections, notably rubella lead to similar clinical presentations, and there is evidence for neurotropism and interference by Zika with neural progenitor cells. By way of analogy, other flaviviruses may cause neurological sequelae in animals (Wesselsbron and Japanese encephalitis virus).

Certain of the Bradford-Hill criteria remain unfulfilled: studies of the association between maternal Zika viral load and risk of microcephaly will be difficult to establish (biological gradient). The neurological syndrome of microcephaly has multiple aetiologies, leaving the specificity of Zika virus infection for microcephaly difficult to establish. It may not be possible to demonstrate the association by experiment, as an animal model for Zika virus infection does not exist at the present moment. In conclusion, it appears increasingly likely that Zikavirus infection in pregnant women does cause fetal abnormalities.

Recommended reading:

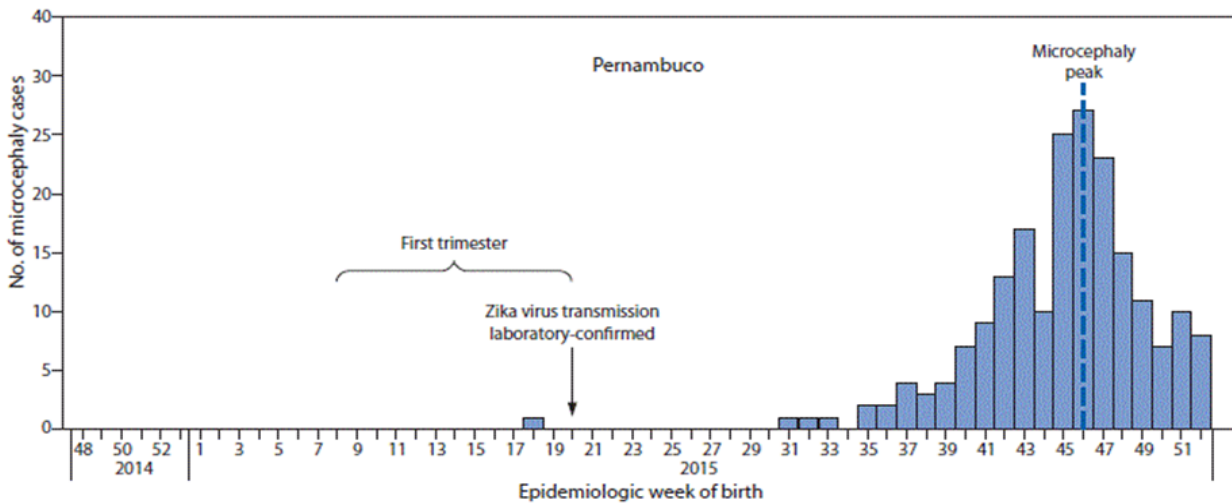
- Maestre AM, Caplivski D, Fernandez-Sesma A. Zika virus: More questions than answers. EBioMedicine. 2016 Mar 11;5:2-3.
 Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika Virus and birth defects - Reviewing the evidence for causality. N Engl J Med. 2016 Apr 13
 Frank C, Faber M, Stark K. Causal or not: applying the Bradford Hill aspects of evidence to the association between Zika virus and microcephaly. EMBO Mol Med. 2016 Mar 14.

Source: Division of Public Health, Surveillance and Response, NICD-NHLS, (outbreak@nicd.ac.za)

Strength of the association
Consistency
Specificity
Temporality
Biological gradient
Plausibility
Coherence
Experiment
Analogy

Table 2 (left). Bradford Hill criteria for assessment of a relationship between an exposure and disease

Figure 3 (below). An epidemic curve showing the number of cases of microcephaly by epidemiological week relative to the week when authorities confirmed the transmission of Zika virus in Pernambuco province, Brazil through laboratory testing. (de Oliveira, MMWR, March 11, 2016)



d A rabies update

The national shortage of rabies immunoglobulin (RIG) has become critical, with stock levels reaching zero in many facilities, particularly in KwaZulu-Natal Province. The National Bioproducts Institute has indicated that limited stocks will become available towards the end of April, but routine supply will only resume in 3-4 months time. The NICD and the Essential Drug committee are in the process of sourcing an international supplier. Most likely an equine RIG will be purchased, as human RIG is prohibitively expensive. Because of a small risk of allergic reaction to the equine product, equine RIG will need to be administered in a hospital or similar health setting. The National Department of Health will issue appropriate communications and provide clear instructions for administration in the coming weeks.

In 2016, to date, a single human death due to rabies has been reported (from KwaZulu-Natal Province, reported in the Communiqué, January 2016). Rabies is controllable and preventable through appropriate post-exposure prophylaxis (PEP). Despite this, rabies deaths continue to occur in South Africa with 8 confirmed, three probable and one suspected case occurring in 2015. A total of 424 human infec-

tions were confirmed in South Africa from 1983 until 2015. Nearly all human rabies cases are associated with injuries sustained by or contact with domestic rabid dogs. Enquiries are regularly received on the NICD (rabies) hotline regarding the need for PEP following bites from a variety of non-canine animals. All bites or scratches or mucous membrane exposures to bats require PEP. Bites from monkeys, rats, or field mice generally do not require PEP. Cane-rats and 'dassies' have been implicated in rabies transmission and exposure to these animals requires a risk assessment.

More information on rabies infection and treatment guidance in South Africa available on www.nicd.ac.za. The NICD Hotline for consultation about PEP is 082-883-9920

Source: Centre for Emerging and Zoonotic Diseases, NICD-NHLS (cezdn@nicd.ac.za); Division of Public Health Surveillance and Response, NICD-NHLS (outbreak@nicd.ac.za)

e Lassa fever — an update on the ongoing outbreak in Nigeria, and review of an imported case in Germany

There is an ongoing Lassa outbreak in West Africa since November 2015 with over 300 cases reported and over 160 deaths in Nigeria, Benin, Sierra Leone and Togo. Lassa fever virus is endemic in the area (Figure 4) but the number of cases and area of distribution has increased for 2016 compared with 2015. While Lassa fever virus is not found in South Africa, importation of cases may occur, as happened in 2007 when a Nigerian physician sought medical care for his presumed typhoid in a South African hospital. During the course of this current outbreak, a health care worker was evacuated to Cologne, Germany from Togo on 25 February 2016 for treatment of reported but unconfirmed complicated falciparum malaria. The patient passed away on 26 February 2016 following multi-organ failure. Autopsy findings were suggestive of haemorrhagic fever, and Lassa fever diagnosis was confirmed on 9 March at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany.

Unfortunately, prior to the diagnosis of Lassa fever in the health care worker, a funeral home employee handled the index patient's corpse on 2 March. He apparently wore gloves and did not recall being exposed to bodily fluids. On the day of exposure to the corpse, he reported pre-existing symptoms of an upper respiratory infection. His symptoms waxed and waned over the following days. When the diagnosis of Lassa fever was made in the index patient at autopsy, the funeral home employee was tested for Lassa fever on 10 March. His result was initially negative by polymerase chain reaction (PCR). How-

ever, when symptoms persisted, diagnostics were repeated and Lassa fever infection was confirmed by PCR on 15 March. The patient was transported to a special isolation unit in Frankfurt where he responded well to treatment, including ribavirin. He had no history of travel in the 21 days prior to the illness. Four of his family members voluntarily agreed to be quarantined in the same isolation unit.

Malaria is a common and important cause of severe illness in travelers to Africa, and must always be considered first in the differential diagnosis of persons with acute febrile illness. However, viral haemorrhagic fever, if missed, may have serious consequences for close contacts. Overlapping signs and symptoms between malaria and VHF mean that a cautious approach, especially in ill, potentially exposed health workers, is required. The diagnosis of malaria must be definitively confirmed through visualization of parasites in a peripheral blood smear, or PCR or antigen detection. When smears are negative, a malaria PCR should be done to detect current or recently treated malaria. If malaria tests are negative, consideration must be given to an alternative diagnosis, including a VHF. Appropriate infection control practices must be followed in the interim. Lassa fever may not be suspected as a definite exposure to rodent excreta is not easy to elicit.

Source: Division of Public Health, Surveillance and Response, NICD-NHLS; (outbreak@nicd.ac.za)

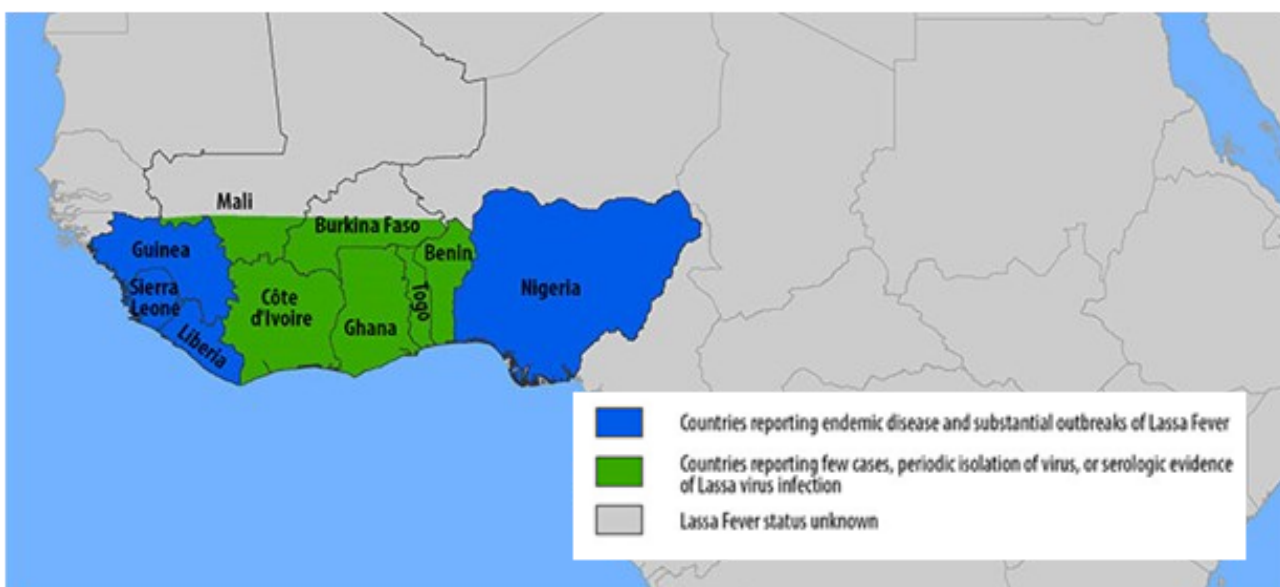


Figure 4. Lassa fever distribution map ([www. http://www.cdc.gov/vhf/lassa/outbreaks/index.html](http://www.cdc.gov/vhf/lassa/outbreaks/index.html))

f WHO rescinds the Ebola virus disease (EVD) global emergency

In March 2016, Ebola virus disease (EVD) re-emerged in Guinea and Liberia after the two countries were declared Ebola free on 29 December 2015 and 14 January 2016 respectively. Since the re-emergence, 12 EVD cases (9 confirmed, 3 probable) have been reported in Guinea and Liberia. In Guinea, as at 5 April 2016, nine EVD cases have been reported (six confirmed, three probable), eight of whom died. More than 1 400 associated contacts have been vaccinated with the Ebola vaccine. In Liberia, as at 7 April 2016, three confirmed EVD cases including one death have been reported. All three cases are epidemiologically linked to the current flare-up in Guinea. To date, more than 100 contacts linked to the cluster have been identified. Plans to vaccinate associated contacts with the Ebola vaccine are underway. Sierra Leone was declared free of Ebola transmission for the second time on 17 March 2016 and has since entered a 90-day period of heightened surveillance.

Although work in progress, systems are in place to ensure that all three countries have the capacity to detect and respond rapidly when need arises. To

date, the affected countries have demonstrated the ability to respond rapidly to new clusters of cases, interrupt transmission and prevent further spread. As such, the EVD outbreak in West Africa is no longer considered a Public Health Emergency of International Concern. The emergency status was rescinded by the WHO Director-General at a meeting held on 29 March 2016 in recognition that the risk of Ebola being introduced into other communities internationally remains low. Furthermore, temporary recommendations that were adopted in response were also ended, signalling that any restrictions on travel and trade with Guinea, Liberia and Sierra Leone should be lifted with immediate effect.

More information is available at:

<http://www.who.int/csr/disease/ebola/Liberia-guinea-flareups-update/en/>

<http://www.who.int/mediacentre/news/statements/2016/end-of-ebola-pheic/en/>

Source: Division of Public Health, Surveillance and Response, NICD-NHLS (outbreak@nicd.ac.za)

g Probable odyssean malaria in Gauteng Province

Three cases of malaria have been identified in Fochville near Carletonville on the border between Gauteng and North West. A young female with no travel history tested positive for *Plasmodium falciparum* on 25 March 2016. Though she presented to the health system soon after symptoms began, malaria was not initially suspected given the absence of a history of travel to a malaria transmission area. Malaria parasites were detected after a peripheral blood smear was examined to elucidate the possible cause of a profound thrombocytopenia. Unfortunately the patient sadly demised from severe malaria. Two additional cases from the same area that also have no travel history are possibly linked. Both these patients responded to malaria treatment. Entomological and epidemiological investigations are ongoing and will be reported in the next edition of the Communiqué.

Clinicians are urged to remember that April is the height of the malaria season, and persons are at risk in traditionally endemic areas of the country,

particularly because of the late rains. Clinicians are advised to keep a high index of suspicion for malaria in any patient who presents with unexplained fever and thrombocytopenia with multiple organ system involvement, as well as with returning travellers presenting with flu-like symptoms. Treatment for uncomplicated cases is with artemether-lumefantrine (Coartem®); while for complicated cases treatment is with quinine, following an intravenous loading dose of quinine 20 mg/kg, plus doxycycline or clindamycin, or IV artesunate.

South African malaria treatment guidelines are available at <http://www.gov.za/documents/>

Source: Division of Public Health, Surveillance and Response, NICD-NHLS (outbreak@nicd.ac.za)

[guidelines-treatment-malaria-south-africa](#)

2 ENTERIC DISEASES

a Typhoid fever cases in South Africa: January-March 2016

As of 14 April 2016, a total of 52 laboratory-confirmed typhoid fever case-patients including two deaths have been reported in six provinces across South Africa, with 21 cases reported in January, 19 cases in February, eight cases in March and four cases in April (Figure 5). Where age was reported (n=51), age range is 9 months to 68 years (mean 19 years; median 14 years) and 31% (16/51) are children aged <10 years. Females account for 56% (n=29) of cases reported. Amongst the contacts in which stool specimens were collected and tested, *S. Typhi* has been isolated from the stool of a single contact of a case-patient in Gauteng Province. Amongst the 43 case investigation forms (CIFs) received by NICD, travel history is available for 41 case-patients. Amongst the 41 case-patients, 21 (51%) reported a history

of travel outside their hometown/city within 1 month before the onset of illness. Travel history was to Limpopo Province (n=2), Eastern Cape Province (n=1), KwaZulu-Natal Province (n=2), Zimbabwe (n=10), Malawi (n=1, deceased), India (n=2), India/Seychelles (n=1), Bangladesh (n=1) and USA (n=1). Of the 20 case-patients without travel history, four had visitors who had travelled from the Eastern Cape Province (n=1), Gauteng Province (n=2), and Tanzania (n=1) respectively. Data on the monthly numbers of typhoid cases in South Africa for 2013-15 is shown in Figure 6.

Source: Division of Public Health, Surveillance and Response, NICD-NHLS (outbreak@nicd.ac.za); Centre for Enteric Disease, NICD-NHLS (karenk@nicd.ac.za)

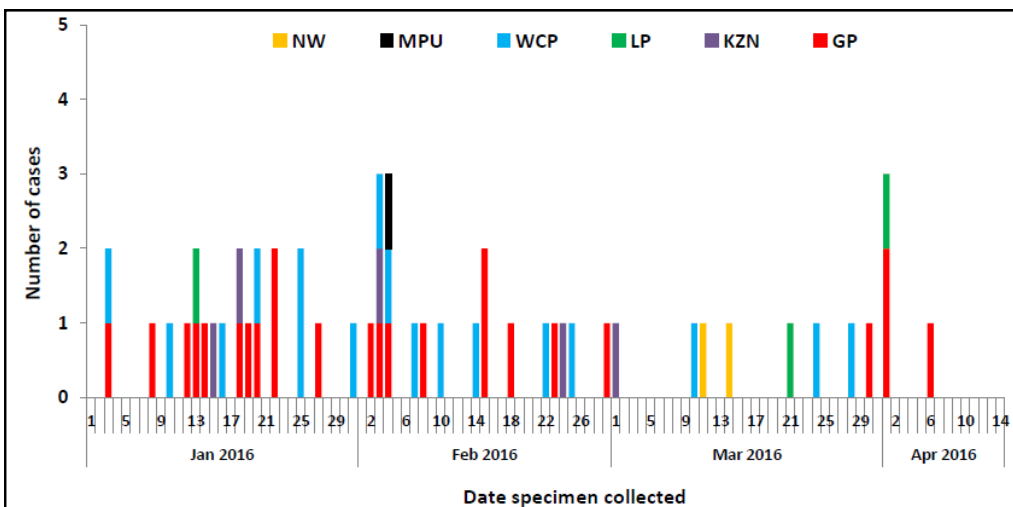


Figure 5. Epidemiological curve showing number of cases of typhoid identified in South Africa by province, and date of specimen collection.

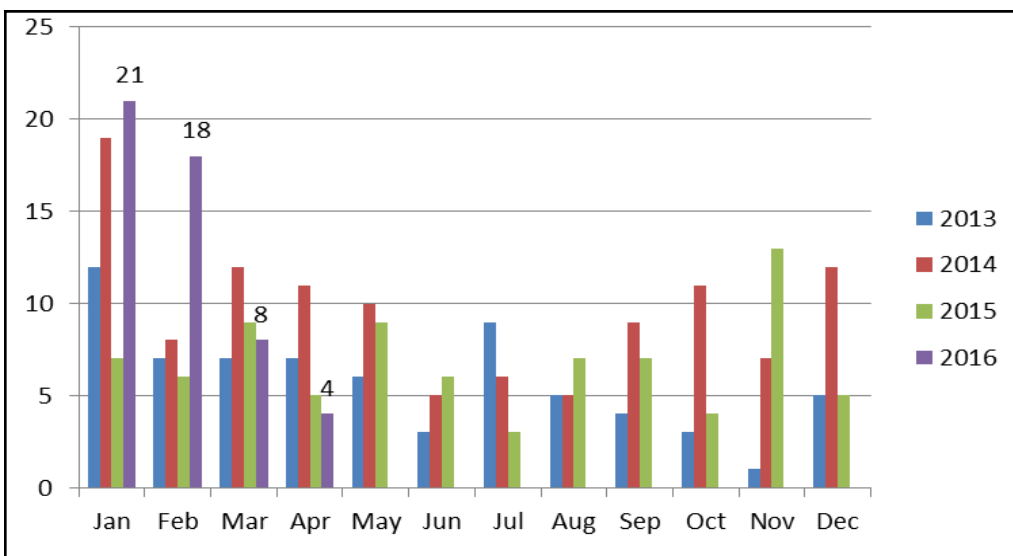


Figure 6. Number of *Salmonella Typhi* cases by month in South Africa, 2013-2016.

3 SEASONAL DISEASES

a Influenza — awaiting the 2016 season

The influenza season is considered to have started when the detection rate of surveillance specimens tested at the NICD has risen above 10% and is sustained for ≥ 2 weeks. This criterion has not yet been met, and therefore the season has not commenced. There have been sporadic detections of influenza reported from the influenza surveillance programmes: influenza-like illness surveillance (ILI) (systematic ILI at public health clinics and viral watch) and pneumonia surveillance for severe disease in hospitalized patients: In the first 13 weeks of 2016, 63 specimens were received from Viral Watch sites. Of these, one was positive for influenza A(H1N1)pdm09 and five were positive for influenza B. During the same period, 234 specimens were received from two ILI sites, one was positive for influenza A(H3N2) and one for influenza B. In this time period, specimens from 669 patients with severe respiratory illness were received from the 6 sentinel sites. Influenza B was detected in the specimens of four patients.

Influenza vaccination

Influenza vaccination, which provides protection against at least three strains of influenza each

season, remains the most effective measure to prevent illness and possibly fatal outcomes. Protecting those who are at increased risk of severe influenza outcomes plays an important role in management and prevention of respiratory illnesses. Individuals at risk of influenza and severe disease include, among others pregnant women, and those vulnerable due to pre-existing illnesses or risk factors. The influenza vaccine for the 2016 season is available at public health facilities and private pharmacies. Clinicians are encouraged to vaccinate individuals in the groups that are targeted for influenza vaccination. Vaccines should be given sufficiently early to provide protection for the influenza season, though it is never too late to vaccinate. A protective antibody response takes about 2 weeks to develop. Detailed recommendations on target groups, dosages and contraindications for the vaccine during the 2016 influenza season can be accessed in the February issue of the South African Medical Journal: available at <http://www.samj.org.za/index.php/samj/article/>

Sources: Centre for Respiratory Diseases and Meningitis, NICD-NHLS (cherylc@nicd.ac.za)

4 SEXUALLY TRANSMITTED INFECTIONS

a Disseminated gonococcal infection with meningitis: a rare presentation

A 46-year-old male was admitted to a tertiary care hospital in KwaZulu-Natal Province on 30 January 2016 with a one-day history of confusion, inability to communicate and urinary incontinence. He had no history of seizures or head trauma. He was HIV-positive and had been recommenced on first-line ARVs two weeks prior to admission, following a prolonged period of non-adherence. He had completed treatment for pulmonary tuberculosis in 2013. On examination he was cachectic and afebrile. His vital signs were normal. He had no skin lesions or evidence of arthritis. Cardiovascular and respiratory system examination revealed no abnormalities. There was no neck stiffness. Salient findings on central nervous system examination included a GCS of 13/15, and a right-sided hemiparesis (left upper motor neurone pattern). Preliminary laboratory investigations revealed a neutrophilia, mild anaemia, and a raised CRP (152 mg/dl) and ESR (81 mm/hr). His CD4 count was 154 cells/ μ l. Syphilis serology was negative. His chest radiograph was normal. Due to the presence of focal neurological signs, lumbar puncture was deferred. CT brain scan re-

vealed features consistent with a meningitis and vasculitis of the left middle cerebral artery with resultant cerebral infarction. Blood cultures taken on admission grew an oxidase-positive Gram-negative coccus. A panel of biochemical tests (Vitek 2 bio-Mérieux) identified the organism as *Neisseria gonorrhoeae*. The patient was commenced on high-dose intravenous ceftriaxone, but his condition deteriorated and he died approximately two weeks later. The isolate was referred to the STI Laboratory at the Centre for HIV & STIs, NICD, for confirmatory identification. Molecular testing using an in-house multiplex PCR, as well as a real time *N. gonorrhoeae* specific PCR, verified the phenotypic identification.

In South Africa, periodic aetiological surveillance of STI syndromes conducted by the NICD has revealed that *N. gonorrhoeae* is the cause of 70-80% of male urethritis syndrome (MUS) and approximately 10% of vaginal discharge syndrome (VDS). Disseminated gonococcal infection (DGI), which results from bloodstream invasion of the organism, typically de-

velops 2-3 weeks after primary mucosal infection. Although most patients will not give a history of recent urogenital disease, the majority (up to 80%) have evidence of asymptomatic mucosal (urogenital, rectal, pharyngeal) infection. Patients usually present with one of two syndromes, with some overlap between the two forms: (1) a triad of tenosynovitis, dermatitis and polyarthralgias; or (2) purulent asymmetrical oligo/mono-arthritis without associated skin lesions. Fever is usually (but not invariably) present during the acute bacteraemic stage of infection.¹ However, central nervous system (CNS) infection with *N. gonorrhoeae* is a rare manifestation of DGI. Disease onset is acute, and includes features of meningism and confusion. Infection may be complicated by cerebral vasculitis and the development of focal neurological signs. In immunocompromised patients, the prognosis may be worsened by the development of overwhelming sepsis and disseminated intravascular coagulation. Laboratory investigations for extra-genital infection should include, where applicable, synovial fluid analysis and at least two sets of blood cultures. Suspected meningitis necessitates lumbar puncture and cerebrospinal fluid analysis. Additionally, mucosal sites (urethral, cervical, rectal, pharyngeal) should be sampled both for bacterial culture and validated molecular testing.

In 2015, the National Department of Health STI management guidelines for primary healthcare centres were formally revised with respect to the syndromic management of MUS and VDS.² In response to the increase in *N. gonorrhoeae* antimicrobial resistance observed worldwide, a pre-emptive strategy of dual antimicrobial therapy was incorporated to curb the emergence of resistance to extended-spectrum cephalosporins. Specifically, oral cefixime was replaced with single doses of injectable ceftriaxone and oral azithromycin. Recommended antimicrobial treatment of DGI consists of dual therapy: intravenous ceftriaxone for 7-14 days and a 1 g stat dose of oral azithromycin. The public health response involves tracing and treating direct sexual contacts with stat doses of intramuscular ceftriaxone and oral azithromycin.

References

1. Suzaki A, Hayashi K, Kosuge K *et al.* Disseminated gonococcal infection in Japan: a case report and literature review. *Intern Med* 2011; 50: 2039-2043.
2. Sexually Transmitted Infections Management Guidelines 2015. National Department of Health. Adapted from the Standard Treatment Guidelines and Essential Drugs List, PHC.

Source: Attending nd pathologist. Centre for HIV & STIs, NICD-NHLS (ranminik@nicd.ac.za).

5 VACCINE-PREVENTABLE DISEASES

a A global change in the oral poliomyelitis vaccination: the switch from trivalent to bivalent

A milestone in the progress towards poliovirus elimination will be achieved during the last two weeks of April 2016. Worldwide, poliovirus type 2 has been removed from the oral polio vaccine (OPV), which is a live attenuated vaccine. This is due to type 2 poliovirus being declared eradicated from the planet in September 2015. Vaccination against type 2 poliovirus will be done through the type 2 component of the inactivated polio vaccine (IPV) which was included in the Expanded Program on Immunization (EPI) schedule of South Africa since 2009.

The date earmarked for the switch from trivalent OPV (containing types 1, 2 and 3) to bivalent OPV (only containing types 1 and 3) is 20 April 2016. Throughout the country all trivalent OPV was removed from health facility fridges, depots and distribution points, and bivalent OPV replaced it. No trivalent OPV should be in use from 20 April 2016. The National Department of Health (NDoH), the National Task Force (NTF) for polio containment

and National Certification Committee (NCC) for polio eradication are involved in conducting, monitoring and validating the vaccine switch. The Centre for Vaccines and Immunology at NICD, specifically staff members of the polio isolation and polio molecular laboratories are providing technical expertise to these bodies.

Certain sites of OPV use will be selected by the NTF and visited to ensure the switch has proceeded as planned. These will include all national and provincial depots and distribution warehouses, as well as a select number of health facilities that use OPV. Once removed from the cold chain, all trivalent OPV, will be destroyed over the next 3 months, and will no longer be produced. This event mark the beginning of the final endgame of poliovirus eradication from all areas of the globe, envisioned by the World Health Organization (WHO) and its partners.

Source: Centre for Vaccines and Immunology, NICD-NHLS (villyenm@nicd.ac.za)

6 MYCOLOGY**a Outbreaks of neonatal candidaemia detected through NICD surveillance at a single tertiary healthcare institution, 2014-2016**

Cases of candidaemia are monitored through NICD/GERMS-SA active, laboratory-based surveillance at a number of sentinel sites across South Africa. Candidaemia is defined as a blood specimen from which *Candida* species is cultured; multiple isolates cultured within 30 days of the first positive specimen are included within a single case. Confirmation of isolate identification to species-level and antifungal susceptibility is performed at NICD's Centre for Opportunistic, Tropical and Hospital Infections.

Over the past two years (January 2014 through February 2016), a total of 255 cases of candidaemia was detected at Hospital A, a sentinel surveillance site in the GERMS-SA programme. Amongst these 255 cases, 180 cases (71%) occurred in the neonatal intensive care unit (NICU). Seven different species of *Candida* were identified; the most common species was *Candida krusei* (90/180; 50%), followed by *Candida albicans* (44/180; 24.4%) and *Candida glabrata* (20/180; 11.1%) (Figure 7).

At least three outbreaks of candidaemia were detected in Hospital A's NICU since July 2014. The first of these was due to *C. krusei*. A total of 48 cases of candidaemia was detected over a four-month period, July through October 2014. A formal outbreak investigation, including an infection prevention and control (IPC) audit, was performed. Hand hygiene practices, knowledge and perceptions were assessed using a standardised World Health Organization tool¹. Targeted environmental sampling was also performed; however, *C. krusei* was not isolated from the environment. Staff shortages, overcrowding of the ward, poor ventilation and periods of interrupted water supply were among the main problems identified in the observational audit. Healthcare workers had 76% compliance with hand hygiene practices. Although the source of the outbreak could not definitively be established, we hypothesised that person-to-person transmission likely occurred, influenced by sub-optimal IPC practices in the NICU.

From April 2015 through July 2015, another outbreak due to *C. krusei* occurred, with 41 identified cases. Focus on IPC was re-emphasised and measures to improve the staff-to-patient ratio and to minimise overcrowding were instituted.

In February 2016, seven cases of candidaemia due to *Candida (Cyberlindnera) fabianii*, an uncommon species detected for the first time since the start of surveillance at Hospital A, were detected. As these seven cases were caused by a rare pathogen clustered in the NICU of Hospital A over a short time period, this again constitutes an outbreak. IPC practices have been intensified to prevent further cases and the NICD is currently working with the hospital and provincial department of health to initiate a formal outbreak investigation.

Candida bloodstream infections result in long-term morbidity and mortality among hospitalised patients. *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. krusei* are the most common species implicated in bloodstream infections. Known risk factors for candidaemia include very low birth weight, gestational age of less than 30 weeks, necrotizing enterocolitis (NEC), central venous catheter use, parenteral nutrition, prior antibiotic use and mechanical ventilation. In several outbreaks of neonatal candidaemia, often caused by *C. parapsilosis*, the outbreak was presumed to be propagated person-to-person owing to inadequate IPC measures. Healthcare associated infections (HAIs) such as candidaemia are largely preventable and affect vulnerable populations already compromised by underlying illness. Outbreaks of HAIs should be promptly investigated to identify the cause, mode of transmission and propagating factors, in order to reduce unnecessary morbidity, mortality and costs.

Well-functioning disease surveillance systems have the ability to detect outbreaks and set in motion the necessary steps to contain outbreaks and perform formal outbreak investigations. Continued focus on hand hygiene and innovative measures to encourage compliance with IPC should be emphasised to prevent and control HAIs.

Reference

1. World Health Organization (WHO) hand hygiene observation tool (Available from <http://www.who.int/gpsc/5may/tools/>)

Source: Centre for Opportunistic, Tropical and Hospital Infections, NICD-NHLS (neleshg@nicd.ac.za)

[evaluation feedback/en/](#)

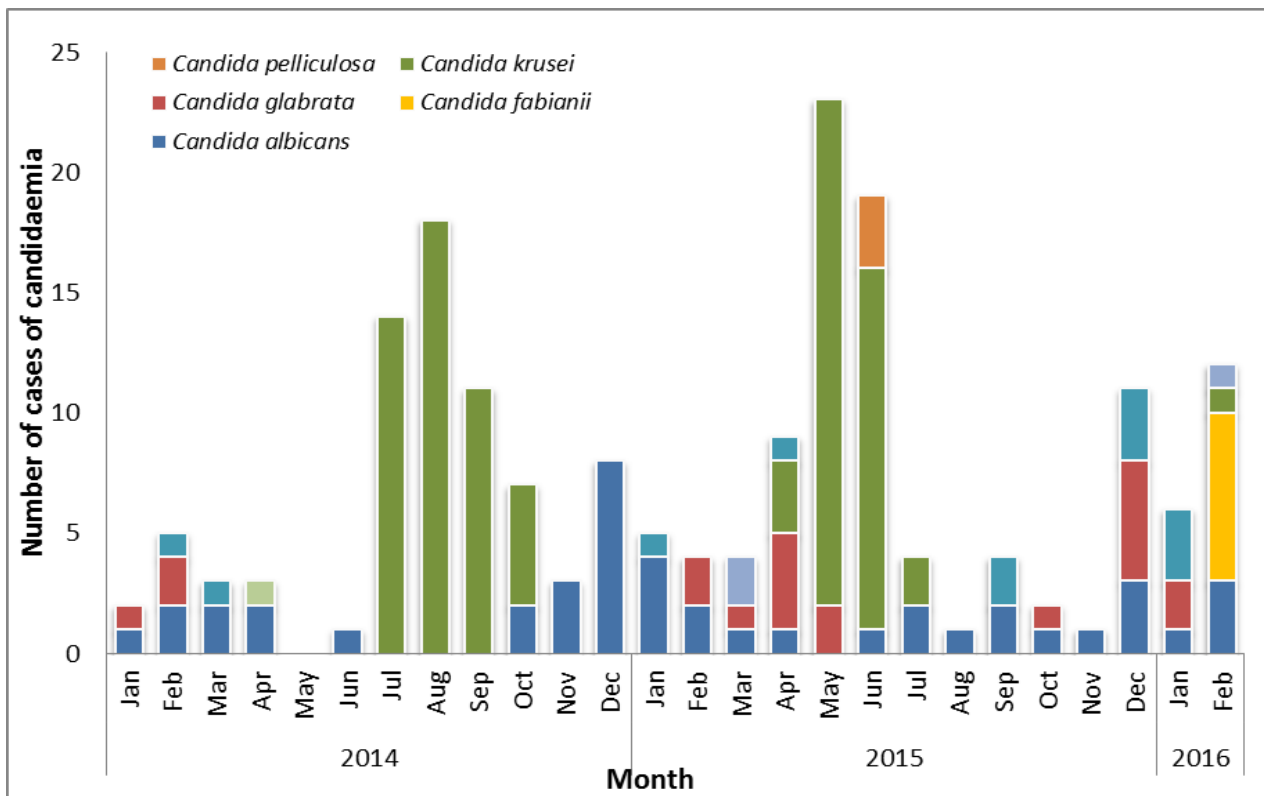


Figure 7: Number of cases of candidaemia (n=180) by *Candida* species at a local tertiary hospital Neonatal Intensive Care Unit, January 2014 to February 2016.

7 ENVENOMATIONS

a Envenomation due to black widow spider

A 38-year-old male patient presented to a tertiary hospital following a spider bite. The patient gave a history of experiencing a sharp pain at a particular spot on his right lower abdominal quadrant and on further inspection, noticed a large (15 mm) black spider which he was able to catch alive. Within minutes, he experienced intense local pain at the bite site. Over the next few hours he became progressively symptomatic, with intense muscle pain which spread gradually upwards to his trunk, arms and neck, severe flushing, sweating, and headache. Finally, he presented to a local tertiary hospital. On examination, he had a red, macular lesion at the presumed bite site which showed no puncture marks. He had a mild tachycardia and rigors. His blood pressure, temperature and neurological state were normal. He experienced no

GIT symptoms. Bloods were normal apart from an elevated creatine kinase (1000 IU/l). The muscle pain and rigors were extremely difficult to control and the patient was treated using calcium gluconate infusions (providing only very short term relief), opiate and NSAID analgesia. In addition, corticosteroids and antihistamines were administered.

Fortunately the patient had retained the spider, which was identified as a mature female adult black button or black widow spider (*Latrodectus indistinctus*) (Figure 8). This spider typically has a distinguishing short red stripe down the back, along the midline and above the spinnerets. With age, however, the spider undergoes multiple moults and the red stripe disappears, resulting in an indistinct

brownish-orange patch, and hence the name black button (for the 4 'button holes' on the dorsal aspect). The name 'black widow' derives from the cannibalistic behaviour of the female, who consumes the male after mating, a practice not uncommon with spiders.

The venom of the black widow is a complex collection of toxic agents containing latrotoxin. In large volumes latrotoxin may cause latrotoxicism – a syndrome of intense muscle pain, nausea and vomiting, flushing, rigors and sweating, headache and weakness. Latrotoxin acts on the presynaptic neural membrane and causes the release of massive amounts of the neurotransmitters norepinephrine, GABA and acetylcholine. This results in stimulation of the sympathetic nervous system and symptoms of latrotoxicism. The symptoms usually wax and wane over the next 1-4 days. In children, injection of large volumes of latrotoxin may result in neurological symptoms – decreased level of consciousness and seizures, and antivenom administration is required. In adults, because the volume of injected venom is small relative to the adult body volume, it is seldom necessary to use antivenom. In addition, a bite from *Latrodectus* may be 'dry' – no venom

injected, while 75% of 'wet' bites will result in only localised pain.

While antivenom was sourced for this patient (it is produced by South African Vaccine Producers based at the NICD/NHLS campus), it was never administered. The antivenom is of equine extraction and has a high potential for anaphylactic and allergic type reactions. Further, the patient had a history of penicillin and sulphur allergies, suggesting he was at risk for anaphylaxis. If clinically indicated (deranged level of consciousness or haemodynamic instability), antivenom should only be administered in a high care/ ICU setting with appropriate life support equipment close at hand.

After 48 hours of intense latrotoxicism symptoms, most disabling of which were severe muscle cramps, the patient made a rapid recovery and he was discharged home.

Source: Attending physician (kimroberg@yahoo.com), Division of Public Health, Surveillance and Response, NICD-NHLS (outbreak@nicd.ac.za); Centre for Opportunistic, Tropical and Hospital Infections (johnf@nicd.ac.za)

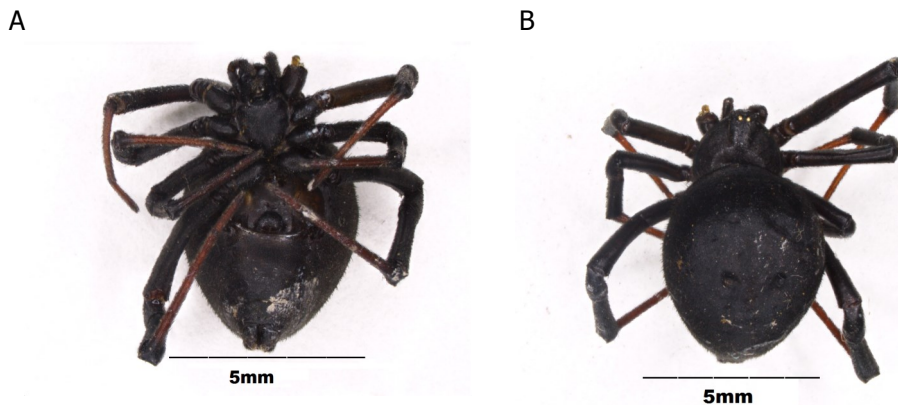


Figure 7. A photomicrograph of ventral (A) and dorsal view (B) of the black widow spider (*Latrodectus indistinctus*) implicated in the case described above.

8 SURVEILLANCE FOR ANTIMICROBIAL RESISTANCE

a Update on carbapenemase-producing Enterobacteriaceae

The Johannesburg Antimicrobial Resistance Laboratory and Culture Collection (AMRL-CC) of the Centre for Opportunistic, Tropical and Hospital Infections (COTHI) at the NICD have been testing referred isolates of suspected carbapenemase-producing Enterobacteriaceae (CPE) for the

presence of selected carbapenemase genes. CPE have become a threat to healthcare and patient safety worldwide by compromising empiric antibiotic therapeutic choices and increasing morbidity, hospital costs and the risk of death. CPE surveillance is required to determine the extent of

the problem as a first step in order to restrain the emergence and spread of CPE. For March 2016, a total of 165 Enterobacteriaceae isolates was received. Of 138 isolates screened, 111 of which expressed carbapenemases (Table 3). The majority of these CPE isolates were *Klebsiella pneumoniae* (93) followed by *Enterobacter cloacae* (13).

It is important to note that these figures do not represent the current burden of CPEs in South Africa. Given that CPE infections are currently not reportable or notifiable in South Africa, there is no platform for appropriate surveillance reports and consequently no locally representative data is

available. This is of major concern, since meaningful data can inform public health policy and highlight priorities for action. Controlling the spread and limiting the impact of CPEs in South Africa will require intensive efforts in both the public and private healthcare sectors going forward. NHLS and private laboratories are encouraged to submit suspected CPE isolates based on antimicrobial susceptibility testing (AST) criteria to AMRL-CC, NICD/NHLS. Please telephone (011) 555 0342/44 or email: olgap@nicd.ac.za; for queries or further information.

Source: Centre for Opportunistic, Tropical, and Hospital Infections, NICD-NHLS; (olgap@nicd.za.za)

Table 3: Enterobacteriaceae by CPE enzyme type, AMRL-CC, CO THI, NICD, March 2016 and January-February 2016

Organism	OXA-48 & Variants		NDM		GES		VIM	
	Jan-Feb 2016	Mar 2016	Jan-Feb 2016	Mar 2016	Jan-Feb 2016	Mar 2016	Jan-Feb 2016	Mar 2016
<i>Citrobacter amalonaticus</i>	1	1	-	-	-	-	-	-
<i>Citrobacter freundii</i>	-	1	2	2	-	-	-	-
<i>Enterobacter cloacae</i>	4	6	6	1	-	-	-	-
<i>Escherichia coli</i>	6	10		1	-	-	-	-
<i>Klebsiella pneumoniae</i>	66	50	42	25	-	2	-	1
<i>Morganella morganii</i>	-	-	-	2	-	-	-	-
<i>Proteus mirabilis</i>	1	-	-	-	-	-	-	-
<i>Proteus penneri</i>	-	-	-	-	-	-	-	-
<i>Providencia rettgeri</i>	-	-	4	2	-	-	-	-
<i>Serratia marcescens</i>	2	1	7	5	-	1	-	-
Total	80	69	61	38	-	3	-	1

NDM: New Delhi metallo-beta-lactamase; **OXA:** oxacillinase; **GES:** Guiana extended beta-lactamase; **VIM:** Verona integron-encoded metallo-beta-lactamase.

9 GENERAL INTEREST

a Implications of drought for public health: how the government and NICD are responding

The 2015-2016 El Niño cycle is currently affecting rainfall patterns and temperatures, and consequently, the health of millions of vulnerable people in the Horn of Africa, southern and eastern Africa, South Pacific, Central America and South Asia. Although it is understood that El Niño-induced climatic conditions peaked in January 2016, the health consequences arising from these changes will be sustained throughout 2016. Drought leading to water shortages, diarrhoeal disease, famine and malnutrition will place additional burdens on already constrained health services.

In East Africa, the devastating drought has been followed by unusually heavy rains causing a high risk of vector-borne disease and other communicable disease outbreaks, such as Rift Valley fever, especially among displaced populations and those with high levels of malnutrition. It is feared that the on-going cholera outbreak in Tanzania will spread to adjacent countries. In southern Africa, below-average rainfall was experienced during the main growing season (December-April). Many regions are experiencing a 'green drought', a period of limited rainfall causing new, but insubstantial plant growth after a long dry period. Grazing animals in particular are left with inadequate food supplies until the next rainfall season. In Malawi, Madagascar, Zimbabwe and Lesotho, it is expected that more than 5 million people will experience food insecurity as a consequence during 2016. In addition to food insecurity and malnutrition, the region is expected to experience outbreaks of communicable disease and disruption of health services. Presently up to 15% of persons in Lesotho are experiencing acute water shortages. Outbreaks of watery and bloody diarrhoea are already reported and will likely increase in the coming months. Persons living with HIV and AIDS and children under the age of five are increasingly at risk of diarrhoea and pneumonia. There have been reports of suspension of certain critical services in health facilities due to lack of water.

Although the WHO has not highlighted South

Africa's potential health concerns as a result of the extreme weather patterns, South Africa's current water storage across the country is at critical levels. Several metropolitan districts have announced water restrictions in order to curb the increased demand and over-usage of water by households and industries. The South African government (SAG) under the Ministry of Cooperative Governance and Traditional Affairs, has called together key stakeholders including the National Disaster Management Centre and the Multi-sectoral National Outbreak Response Team (MNORT) to mitigate the effects of the drought. The Emergency Medicine Directorate of the National Department of Health (NDoH) has drafted a Strategic Preparedness and Response to the Effects of the Drought Action Plan to assist in reducing the effects of the drought, especially amongst at risk communities. The impact of the drought on health in South Africa will call on nearly every cluster within the NDoH, that is, health promotion, communication, surveillance, communicable disease control, malaria, food control, environmental health services, port health services, child health, hospital management services, National Health Operations Centre (NatHOC) and mental health. The National Institute for Communicable Diseases (NICD) has been identified as one of the key stakeholders in responding to communicable diseases brought about by the effects of the drought. The anticipated role of the NICD is to support and intensify surveillance of disease, support outbreak response and maintain outbreak response capacity, support malaria vector control activities, support food control activities by responding to food- and water-borne outbreaks, and to support MNORT as it provides oversight of all activities related to the management of the drought response.

Reference: El Niño-related health risks <http://www.who.int/globalchange/publications/factsheets/el-nino-and-health/en/>

Source: Division of Public Health Surveillance and Response, NICD-NHLS (outbreak@nicd.ac.za)

10 BEYOND OUR BORDERS

The 'Beyond our Borders' column focuses on selected and current international diseases that may affect South Africans travelling abroad. Numbers correspond to Figure 9 on page 18.

1. Avian influenza, Egypt

The WHO reported on four recent H5N1 patients in Egypt- all female and 3 of them children. Most A (H5) influenza human cases have a history of exposure through contact with infected poultry or contaminated environments, including live poultry markets. The virus does not infect humans easily, and spread from person to person appears to be unusual. Travellers should avoid contact with poultry while staying in Egypt.

2. MERS-CoV, Saudi Arabia

The Saudi Arabia Ministry of Health confirmed 4 new cases for the time period between 12 and 16 April 2016 from Riyadh (2 cases), Khaiber and Buraidah. All were non-health care workers, of which 3 were primary cases, two of these having contact with camels. A single case was nosocomially acquired. This brings the total of laboratory confirmed cases of MERS-CoV in Saudi Arabia to 1375, with 587 deaths (case fatality rate 42.7%) and 12 currently active cases. Of the new cases, two were primary cases with known contact with camels. These animals should be avoided when travelling to Saudi Arabia.

3. Cholera, Congo DR (Katanga Province)

There are 60 people who have reportedly been diagnosed with cholera in Lubumbashi (Katanga Province) in the last 10 days. Lubumbashi is the 2nd largest city of the Democratic Republic of Congo where many of the country's biggest mining companies are based. The outbreak has been linked to poor hygiene in some municipalities.

4. Yellow Fever See page 3

5. Zika Virus, Saint Lucia

Local mosquito transmission of Zika virus infection has now also been reported in Saint Lucia. The CDC has issued a level 2 alert to practice enhanced precautions and recommends that travellers to Saint Lucia protect themselves from mosquito bites.

6. Chikungunya, South America

As of February 23, 2015, local transmission of chikungunya is being reported in the following South American countries: Argentina, Bolivia, Brasil, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Venezuela. Travellers to South America should protect themselves from mosquito bites

7. Measles, West Africa

Measles has been reported in high numbers from several West and Central African countries, with case numbers as on 31 March 2016 as follows: South Sudan (350 cases), Liberia (1341 cases), Chad (5832 cases), Benin (85 cases), Burkina Faso (1258 cases), Central African Republic (31 cases) Cote d'Ivoire (491 cases) and Cameroon (1338 cases), DR Congo (3976 cases), Guinea (1013 cases, 2 deaths), Mauritania (863 cases), Mali (774 cases, 1 death), Niger (352 cases), Senegal (560 cases), Sierra Leone (351 cases) and Togo (295 cases). Measles is one of the leading causes of death among children worldwide, especially those who are malnourished. Travellers to West Africa should ensure their measles vaccinations are up to date.

Source: Division of Public Health, Surveillance and Response, NICD-NHLS (outbreak@nicd.ac.za)



Figure 9. Current outbreaks that may have implications for travellers. Number correspond to text above. The red dot is the approximate location of the outbreak or event

11 PHOTOQUIZ



April Photoquiz (left): This person developed swelling and suppuration of their inguinal lymph nodes, accompanied by systemic symptoms of fever, malaise and diarrhoea. What is your differential diagnosis?

Please submit your answers in an email to kerriganm@nicd.ac.za with 'April Photoquiz' in the subject line. Correct and incorrect responses will receive a free subscription to the NICD Communiqué

March Photoquiz (right): The correct response was 'encrusted scabies', and the offending organism is the mite, *Sarcoptes scabiei*. Despite the extent and degree of crusting, the patient's condition responded well to benzyl benzoate lotion (Ascabiol®) applied daily for two weeks. In addition, the patient recommenced anti-retroviral therapy, which most likely contributed to his improvement. Encrusted scabies was formerly called 'Norwegian encrusted scabies' and is a form of scabies occurring predominantly in immunocompromised patients. Photograph courtesy K McCarthy.

