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FOREWORD

In this issue:

Two cases of Hepatitis A in a care facility for the elderly in Johannesburg led to the outbreak investigation described in this issue. Also presented are several surveillance reports, the first of which describes the histological subtypes, anatomical sites, and incidence trends of non-melanoma skin cancers (NMSCs) in South Africa for the period 1993-2014. This report shows that men and Caucasians are the most susceptible to NMSCs, and that the risk factors for NMSCs in Black populations may be unique.

The GERMS-SA annual surveillance report for laboratory-confirmed invasive meningococcal, *Haemophilus influenzae* and pneumococcal disease in South Africa during 2018 is reproduced in this issue. This surveillance system aims to describe the epidemiology of these diseases and monitor the impact of specific vaccines on invasive disease in South Africa.

Acute flaccid paralysis (AFP) surveillance is used as the standard indicator for the potential incidence of polio. The South African national non-polio AFP rate for 2018 by province is described in this issue, which also contains the cryptococcal antigen screening surveillance report for South Africa for the period February 2017 to July 2019. This is especially important given that thousands of South Africans with advanced HIV die each year from cryptococcal meningitis.

Lastly, this issue contains the first report of insecticide resistance in the arbovirus mosquito vector *Aedes aegypti* in the greater Johannesburg area. These data form part of a larger project designed to assess the risk of circulation of arbovirues, such as dengue and chikungunya, in South Africa.

We hope you enjoy this expanded issue and wish all our readers a safe and joyous holiday season.

Basil Brooke, Editor

AN OUTBREAK OF HEPATITIS A AT A RESIDENTIAL CARE FACILITY FOR SENIOR CITIZENS IN JOHANNESBURG, GAUTENG PROVINCE, SOUTH AFRICA

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Executive Summary

The hepatitis A virus (HAV) causes an acute infection that has a broad spectrum of clinical presentation with more severe disease and fatalities reported in the elderly. The infection is communicable, but vaccine preventable. On 16 April 2019, National Institute for Communicable Diseases (NICD) personnel were informed of laboratory-confirmed HAV cases from a care facility for the elderly involving two women with jaundice, aged 79 and 69 years. The 79-year-old developed fulminant HAV infection and subsequently died. The 69-year-old was hospitalized and later recovered. An investigation was conducted to assess the extent of the outbreak, to determine possible sources of infection, and to implement immediate public health prevention and control measures to contain the outbreak and prevent further spread. A HAV serological survey was carried out on close contacts of the confirmed cases. Blood samples were collected from 160 participants for IgM and IgG antibodies testing. A standardised questionnaire was administered and a walkthrough observational assessment was done at the facility. HAV IgM and IgG was tested in 159 and 160 participants respectively, of which 98.7% (157/159) were IgM negative, 1.3% (2/159) were IgM low-positive, 14.4% (23/160) were IgG negative and 85.6% (137/160) were IgG positive. Although no specific sources of HAV infection/exposure were identified, deficiencies in infection prevention and control (IPC) measures were noted. There was

no dedicated IPC focal person in the facility, and handwashing stations and hand sanitation dispensers were not available in the wards. Immunoglobulin post-exposure prophylaxis was recommended and administered to high-risk contacts aged ≥60 years. Vaccination was recommended for low-risk contacts aged <50 years. Strengthening and adherence to IPC practices was recommended to prevent horizontal spread of infectious diseases in this setting.

Introduction

Hepatitis A virus (HAV) is a small, non-enveloped, single stranded RNA virus that belongs to the Picornaviridae family and *Hepatovirus* genus.[1,2] HAV causes mild to severe viral liver disease.[2,3] There are high, medium and low HAV endemic regions globally.[4] In the high endemic areas, HAV is usually found in high quantities in sewage that has leaked into the general environment through agricultural activities (farms use sewage for fertilizing agricultural land).[1] HAV can then contaminate water sources and food.[4] HAV infection occurs as a result of either direct exposure to contaminated water or food, or by contact with an infected person.[5,6] Contact with a newly infected person (such as sharing living space, using the same facilities, caring for them, or via sexual contact) increases the risk of HAV spread.[7] The virus is shed in the stools of infected persons[1] and can spread via the fecal-oral route if good personal hygiene standards are not maintained.[8]

On 16 April 2019, the National Institute for Communicable Diseases (NICD) received a telephonic notification from a care facility for the elderly in Johannesburg, Gauteng Province, concerning two laboratory-confirmed HAV infection cases. This involved two elderly female residents aged 69 and 79 years. They were reported to have jaundice and were referred to hospital for further treatment. One of them subsequently died. Hepatitis A had been confirmed in the patient who died. Both patients had a number of co-morbidities and impaired mobility. On 17 April a site visit and investigation was initiated at the care facility to assess the extent of the outbreak, determine possible sources of infection, and to implement immediate public health prevention and control measures to contain the outbreak and prevent further spread.

Methods

Study setting: The care facility is a non-governmental organization (NGO) housing more than 450 retired residents and is staffed by more than 400 workers ((general workers, healthcare workers or caregivers and clinical staff (medical doctors)).

Study design: A cross-sectional study was conducted from 17 to 25 April 2019 to describe the characteristics and possible source(s) of HAV infection.

Case definitions

Clinical case presentation: an illness with acute onset of symptoms and jaundice with elevated serum aminotransferase levels upon testing.

S*uspected case:* One that meets the clinical case presentation, and who was a resident or staff member (healthcare worker/caregiver, clinician and kitchen staff) at the care facility from 22 March to 25 April 2019.

Probable case: One that meets the suspected case definition (as above) or a close contact with an epidemiological link to a laboratory-confirmed HAV case during the 15-50 day period prior to the onset of symptoms in the confirmed cases i.e. from 22 March to 25 April 2019.

Confirmed case: One that meets the suspected case definition and that is laboratory-confirmed by HAV IgM positive results for the period 22 March to 25 April 2019. Case investigation forms (CIF) were used to obtain information about prior illnesses (symptomatic/ laboratory confirmed cases) amongst the residents and staff. However, these were poorly completed as indicated in the Results and Limitations sections below. It was established that there were no symptomatic or laboratory-confirmed cases prior to the occurrence of the two that primed this investigation. There were no patient records to review and no previous laboratory data specific for this institution to analyse.

Contact/Close contact: Any person who shared the same living space, visited, cared or prepared food for the confirmed cases during the period 22 March to 15 April 2019.

Epidemiological investigation: A HAV outbreak is declared when there are two or more laboratory confirmed hepatitis A cases that are epidemiologically linked (have common exposure or direct contact with each other).[2] The care facility management provided clinical data for the two HAV-confirmed cases. Clinical test results obtained from the laboratory reports were extracted and captured on an excel line-list database. Case investigation forms (CIFs) were distributed amongst close contacts and the first two confirmed cases within the facility in order to collect information regarding HAV exposure risks factors, clinical presentation and demographic data of participants.

Laboratory investigation (serological survey): A HAV serological survey was conducted from 17 to 25 April 2019 on staff members and residents of the care facility who were identified as close contacts of the two confirmed cases. Blood samples were collected from 160 participants comprising kitchen staff, residents and healthcare workers/caregivers (including one clinician in charge). The blood samples were tested at Ampath private laboratory (N = 97) and at the Charlotte Maxeke Johannesburg Academic Hospital National Health Laboratory Service (NHLS) virology laboratory (N = 63). The serology tests were performed to detect the presence of anti-HAV IgM antibodies which would indicate a new/current infection, and to detect the presence of anti-HAV IgG to determine immunity or susceptibility to HAV.

Facility walk-through observational assessment: A walk-through observational assessment was conducted in the kitchen, water tank and in wards where the confirmed cases were accommodated. The observational assessment included daily operations of the kitchen such as food handling, cooking, delivering of food to wards, and serving to residents. An inspection was conducted with the on-site water technician to observe/assess the water storage tank within the facility. The team briefly interviewed the technician to obtain information on the water supply i.e. source, usage, and any information on water quality assessments and microbiological tests.

No water samples were collected for laboratory testing during this investigation. The daily activities, occupancy rates, hygiene practices and the IPC measures and practices in the affected wards were assessed.

Data management and analysis: Demographic information, clinical presentation, laboratory results and epidemiological data were captured and analyzed using Excel 2016 and Stata (MP Version 15).

Results

Epidemiological investigation

The two laboratory confirmed HAV cases were female residents of the care facility, aged 69 and 79 years old, both of whom were jaundiced. Case 1 (79 years old) had advanced dementia, epilepsy, rheumatoid arthritis and MRSA positive pressure sores. She had developed jaundice and was clinically ill from 11 April 2019, and was admitted to Rosebank Clinic on 12 April 2019 for further medical treatment. She tested positive for anti-HAV IgM, had fulminant hepatitis A infection and passed away on 13 April 2019. Case 2 (69 years old) had Parkinson's disease, previous colon cancer, dementia and impaired mobility. She developed jaundice on 14 April 2019 and was admitted to Linksfield Hospital on 15 April 2019 where she tested positive for anti-HAV IgM. The patient recovered and was discharged on 23 April 2019 (Figure 1). Both cases were on a soft meal diet.

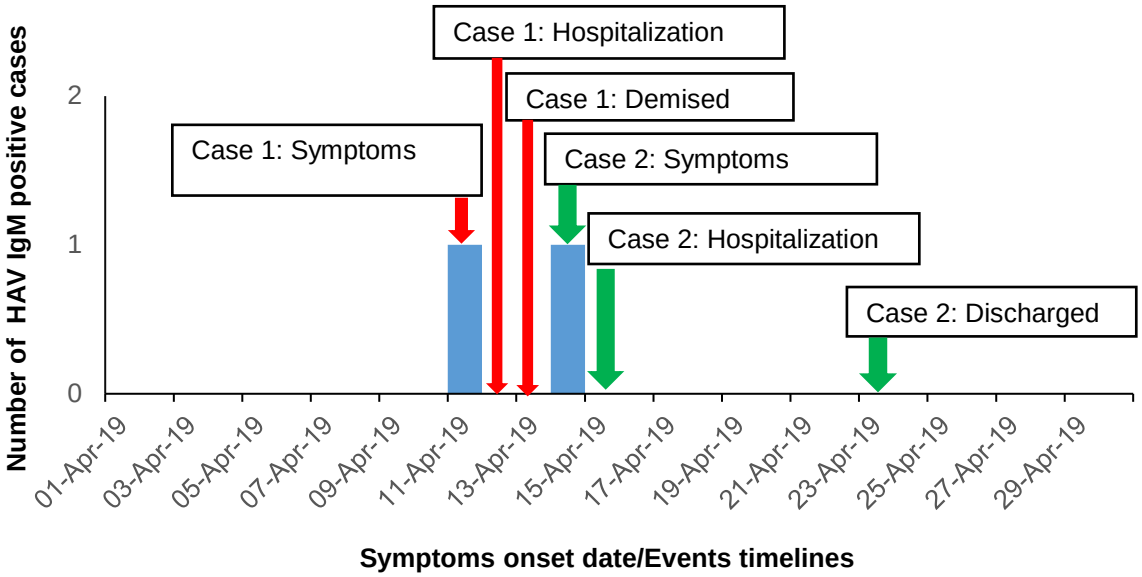

Figure 1. Epidemiologic curve of two hepatitis A virus (HAV) IgM positive cases from a care facility for the elderly in Johannesburg, Gauteng Province, April 2019.

No additional HAV cases were identified and no specific risk factors were evident from the case investigation forms (CIFs). The 45 CIFs from the kitchen staff were generally incomplete, with only their demographic information sections completed. The healthcare workers/caregivers, the two confirmed cases and the clinician in charge did not complete CIFs. All patients in the affected wards (2A and 2B) were female as were their caregivers and the clinician. The kitchen staff comprised male (n=34) and female (n=21) workers.

Laboratory investigation (serological survey)

The serological survey was carried out on 160 participants, of which 35 (22%) were residents of the care facility, 55 (34%) were kitchen staff, 64 (40%) were healthcare workers (caregivers and a clinician) and six (4%) had unspecified roles. The median ages of each group were: residents 85 (IQR: 55-99), kitchen staff 43 (IQR: 20-70), healthcare workers 63 (IQR: 20-65) and unspecified roles 37 (IQR: 32-76) (Table 1).

HAV IgM and IgG antibodies were tested for in 159 and 160 participants respectively. Of the 159 participants tested for HAV IgM, 99% (157/159) were IgM negative and 1% (2/159) were IgM low-positive. Of the 160 participants tested for HAV IgG, 14% (23/160) were IgG negative and 86% (137/160) were IgG positive. Of the thirty-five (35) residents screened for HAV IgM and IgG, 94% (33/35) tested IgM negative and 6% (2/35) were IgM low-positive, while 63% (22/35) were IgG positive and 37% (13/35) were IgG negative. Of the 55 kitchen staff members screened for HAV IgM and IgG, all tested IgM negative, while 87% (48/55) were IgG positive and 13% (7/55) were IgG negative. Sixty-four (64) healthcare workers (caregiver/nursing staff and the clinician) were screened for HAV IgG, of which 97% (62/64) were IgG positive and 3% (2/64) were IgG negative. IgM was screened in 63 healthcare workers and all tested negative. The clinician in charge was not tested for HAV IgM. All six participants with unspecified roles tested IgM negative, five (83%, 5/6) were IgG positive and one (17%, 1/6) was IgG negative (Table 1).

Table 1. Hepatitis A serological survey (IgM and IgG antibody screening) by participant category, 16 – 25 April 2019 (N =160). All participants are residents or workers at a care facility for the elderly in Johannesburg, Gauteng Province.

Description	Residents	Kitchen Staff	Healthcare workers	Unspecified Role	Total
Number of participants tested (n)	35	55	64	6	160
Testing Laboratory					
Ampath	35	55	1	6	97
NHLS	0	0	63	0	63
Total	35	55	64	6	160
Demographics					
Recorded age (n)	35	55	63	6	159
Age [median (IQR)]	85 (55-99)	43 (20-70)	35 (20-65)	37 (32-76)	49 (20-99)
Sex					
Females	35	21	64	6	127
Males	0	34	0	0	34
Total	35	55	64	6	160
Hepatitis A Antibodies					
IgM Positive	0	0	0	0	0
IgM Low Positive	2 (6%)	0	0	0	2
IgM Negative*	33 (94%)	55 (100%)	63 (98%)	6 (100%)	157
IgG Positive	22 (63%)	48 (87%)	62 (97%)	5 (83%)	137
IgG Negative	13 (37%)	7 (13%)	2 (3%)	1 (17%)	23

*One healthcare worker (the clinician) was not tested for HAV IgM.

Facility walk-through observational assessment

Kitchen: There were dedicated staff members for scrapping, cleaning, cooking (chefs) and preparing soft diet meals, and serving food in the wards. The kitchen staff had been trained in food handling and hygiene practices. The kitchen facility has received a certificate of compliance from the City of Johannesburg municipality and is audited regularly. Food prepared in the kitchen supplies five facilities (including another care facility, a lodge, a disabled person's facility and a children's home/crèche). No samples of old food were available, having been discarded in preparation for the upcoming religious festival of Passover.

Water source: The City of Johannesburg municipality supplies the water used in the facility. The water is kept in an alusteel storage tank, is treated on site and also supplies neighboring facilities. The water tank is above-ground, well maintained, and no water-associated problems have recently been reported at any of the facilities supplied by this source.

Wards: The two confirmed cases were/are residents of ward 2A and 2B (Figure 2). The first case-patient resided in ward 2B, room 201. Room 201 has eight beds of which the index case-patient occupied the first next to the room entrance. The second case-patient is a resident of ward 2A, room 202, and occupies the second bed from the room entrance. Neither of the rooms were fully occupied at the time of the investigation. Wards 2A and 2B were apart with separate entrances, and the two cases could not possibly have been in physical contact with each other since they both had impaired mobility and needed assistance. At the time of the investigation, there were no hand sanitizers in the main entrance and room entrances, and there was no dedicated IPC focal person for the facility. This facility accommodates trainee/student healthcare workers who also care for the residents (feeding, changing diapers, linen etc.). Each ward has designated cleaners and nursing staff (caregivers) who work in all the rooms of their allocated wards. The clinician in charge cares for all the residents of wards 2A and 2B.

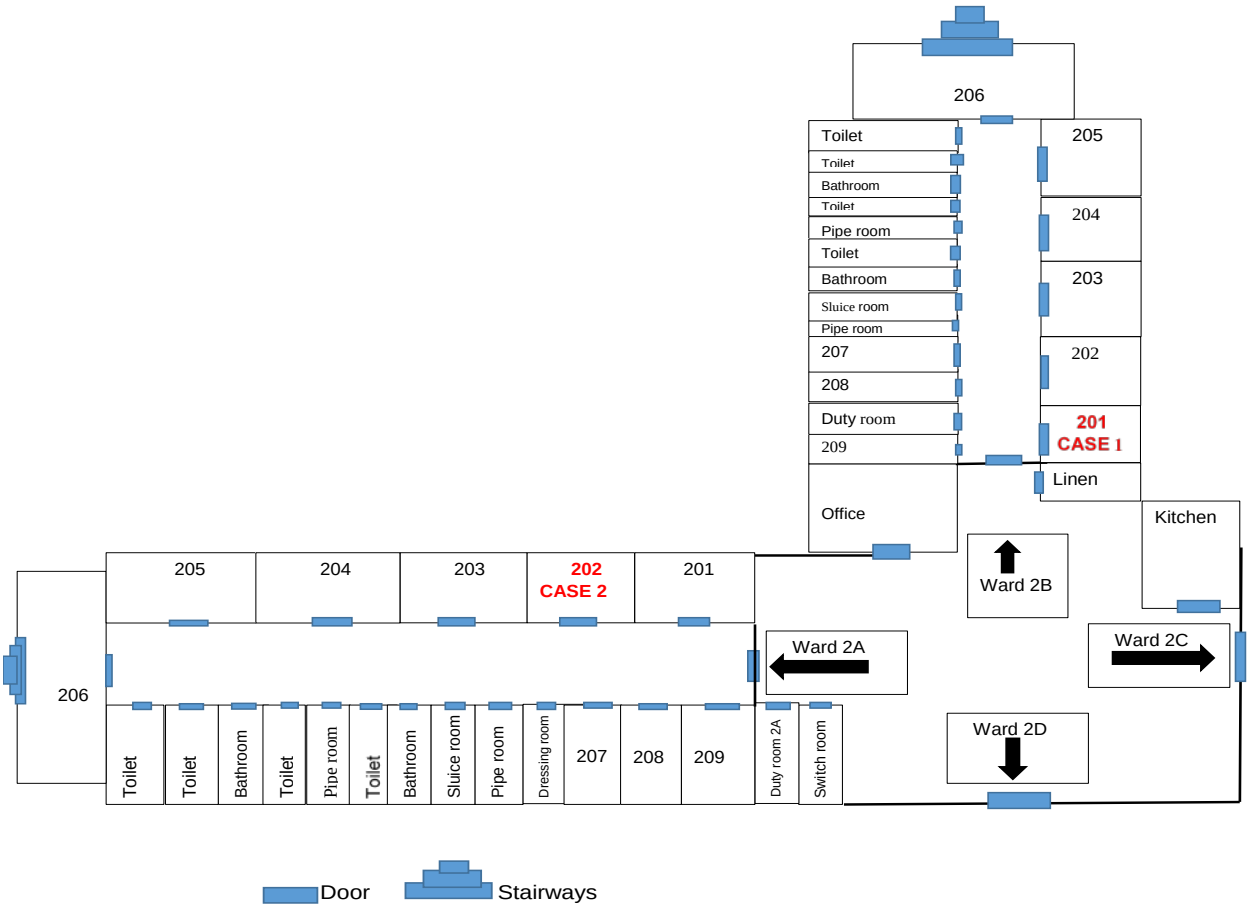

Figure 2. Map of wards 2A and 2B of a care facility for the elderly, Johannesburg, Gauteng Province, showing the rooms occupied by two hepatitis A virus (HAV) confirmed cases.

Discussion and conclusion

The two confirmed hepatitis A cases that prompted this investigation were elderly women who are/were permanent residents of the care facility. Their susceptibility to more severe disease may have been exacerbated by their weakened immune status due to old age and other underlying medical conditions. Morbidity from HAV infection generally increases with age, and mortality is more common in elderly people and those with other underlying medical conditions.[7] In developed countries or communities with access to good sanitation and clean water, a significant portion of the adult population is not immune to HAV.[7,10]

The residents of the care facility likely originate from higher-income communities, with better socio-economic conditions. It is therefore unlikely that they would have been exposed/infected with HAV during childhood, hence their lack of immunity against HAV (37% were IgG negative). Although the serological survey screening results for all participants did not detect new/additional cases (IgM positives), they did reveal that 14% (23/160) were not immune against HAV (being IgM and IgG negative). The negative IgM results suggests that none of the participants had acquired a recent HAV infection while the positive IgG results indicate immunity (protection) acquired from previous HAV infections or from immunization/vaccination. HAV outbreaks are usually associated with a common source such as contaminated food or water, horizontal transmission by direct person-to-person contact or by the oral-fecal route (contact with fecal contaminated surfaces/environment).[4,5,10] Transmission is therefore not always attributable to food or food handling practices, but can also occur as a result of poor sanitation leading to generalized environmental contamination.[8] As the serological survey did not detect any recent additional HAV infections, and the two infected patients are highly unlikely to have come into contact with each other, it is likely that they acquired their infections from outside of the wards they occupy.

HAV infection is preventable through vaccination or through acquired immunity from exposure during childhood. Infections acquired during childhood tend to be asymptomatic and confer life-long immunity.[6] The South African guidelines for the control of HAV identifies care-facility residents as an at-risk group.[2] The guideline however has no policy for immunization against HAV in this setting.[2] It is concluded that there was no clear epidemiological link (physical contact) between the two confirmed cases. Although their only commonalities include the same soft diet meal and care from the same clinician at the time of illness onset, other patients sharing these factors did not acquire HAV infections although many were immune. The source of HAV infection in the two confirmed cases in this facility was therefore not established and remains unknown. No irregularities or questionable hygiene standards were observed in the kitchen or from maintenance of the water source, and it is therefore highly unlikely that either of these is the source of infection.

Limitations of this investigation include the fact that the source of HAV infection was not established, not all contacts were surveyed (i.e. cleaners, visitors, volunteers and healthcare trainees who were not screened for anti-HAV IgM and IgG antibodies), the clinician who treated the two confirmed cases and the other residents in wards 2A and 2B was not tested for anti-HAV IgM to determine recent infection status, and only the IgG test was used to determine immunity. Due to limited finances at the care facility and lack of immunoglobulin supply from the Department of Health, only post-exposure prophylaxis (immunoglobulin) was administered to the 13 IgG negative residents. Immunoglobulin was not administered to the two IgG-negative nurses who cared for the two confirmed cases. Given a long incubation period of HAV, it is possible that some cases were missed by this investigation. However, the institution did not report any symptomatic cases after 25th of April 2019, suggesting that there were no further cases.

It is recommended that HAV vaccine be administered to the low-risk contacts (aged <50 years), such as the kitchen staff and healthcare workers/caregivers, who tested IgM and IgG negative. This is because institutions such as care facilities for the elderly are high-risk for HAV transmission and outbreaks. There is an urgent need to implement an IPC program that will prevent horizontal spread of infection in this setting.

Acknowledgements

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HISTOLOGICAL SUBTYPES, ANATOMICAL SITES, AND INCIDENCE TRENDS OF NON-MELANOMA SKIN CANCERS IN SOUTH AFRICA, 1993-2014

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Executive summary

Non-melanoma skin cancers (NMSCs) comprise of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and other rare skin cancers (RSC). The aim of this study was to describe NMSC trends in the South African (SA) population. NMSCs from the pathology-based National Cancer Registry (NCR), diagnosed from 1993 to 2014, were analyzed. Age-standardized incidence rates (ASIRs) were calculated using the country's mid-year population estimates and were standardized using Segi world standard population. Stata and Joinpoint software were used to statistically describe data and analyze trends. There were more males (58% of 330162) with NMSCs than females. The highest proportions of NMSCs were reported from the White population group (females 79%, n=106766 and males 81%, n=156058). The histological subtype proportions in non-Black populations (Asian, Coloured, White, n=291999) were as follows; BCC 73%, SCC 26% and RCS 1.5%. In the Black population (n=24141) SCC was 48%, BCC 37% and RSC 15%. The most susceptible site for NMSC in the non-Black population (n=162462) was the skin of head and neck (59.0%), followed by upper limbs (16.4%), trunk (13.5%), lower limbs (10.3%) and overlapping sites (0.9%). In the Black population (n=15429) the most susceptible site was the skin of head and neck (54%), followed by trunk (22%), lower limbs (13%), upper limbs (11%) and overlapping sites (<1%). ASIRs in White females significantly increased ($p<0.001$) by an annual percentage change (APC) of 1.32% (from 121 to 160 per 100 000 people) in the study period. Coloured female ASIRs significantly increased (p-value<0.01) from 1995 to 2000 by APC of 53.38%

(16 to 75 per 100 000 people) and has remained relatively unchanged since 2000. The Asian population showed lower ASIRs (less than 15 per 100 000 people) that have remained constant. The Black population's ASIRs increased significantly (p-value<0.001) from 1993 to 1999 by an APC of 12.21% (2 to 4 per 100 000 people). ASIR trends in males followed that of females. Men and Caucasians were more susceptible to NMSCs. In general, non-Black populations were more susceptible to BCC, which can be explained by lower levels of melanin in their skin. Blacks were more susceptible to SCC than BCC, which may be related to a higher human immunodeficiency virus (HIV) prevalence in Blacks. NMSCs frequently occurred on exposed skin areas such as head and neck, and upper limbs for non-Black populations. In Black populations however, NMSCs commonly occurred on the trunk in addition to head and neck. Risk factors for NMSCs in Black populations may be unique, requiring further exploration.

Introduction

Non-melanoma skin cancers (NMSCs) are the most frequently diagnosed cancers, and worldwide incidence continues to rise.[1] In general, mortality due to NMSCs is low because they are non-aggressive and their potential to spread is restricted, especially basal cell carcinoma.[2] The risk of developing NMSC varies markedly according to skin pigmentation and geographical location.[3] Caucasians are the most susceptible to NMSCs.[1] Dark-skinned individuals are less likely to develop NMSCs owing to abundant melanin in their skin.[4] However, most conclusions concerning NMSCs have been drawn from studies where the population is predominantly Caucasian. Population studies in which dark-skinned individuals predominate are therefore needed.[5]

The South African population is multiracial, comprising four categories: Black African (79.2%), White (8.9%), Coloured (8.9%) and Asian (2.5%).[6] A previous study on the incidence of skin cancers in South Africa's population groups for the period 2000 - 2004 showed that the White population was the most susceptible to skin cancer, followed by Coloureds, Asians and Blacks.[7] The age-standardized NMSC incidence rate for South Africa (SA) was reported to be 4.76 per 100,000 non-Whites and 19.2 per 100,000 Whites.[7]

Information on the burden, distribution and risk factors associated with NMSCs is critical for prevention, especially given that the management of skin cancer in SA in 2015 amounted to ZAR 92.4 million.[8] The aim of this study was to describe NMSC distribution by histological subtype, anatomical sites, and incidence trends by sex and population group in SA for the period 1993 - 2014.

Methods

This study was based on all laboratory-diagnosed NMSCs reported to the National Cancer Registry (NCR) over the 22-year period 1993 - 2014 in SA. The NCR is a pathology-based cancer registry that receives reports of laboratory-confirmed cancer cases from all pathology laboratories (public and private sectors) across SA. Each cancer case is assigned a code according to the International Classification of Diseases for Oncology Version 3 (ICD-O3).[9] Cases are coded to primary anatomical site of origin (topography) of the cancer and histological type (morphology). The registry reports cancer incidence annually. These reports are stratified by cancer type, sex, age and population group.

In this study records containing topography of skin (C44.0 – 44.9), and morphologies of basal cell carcinoma (BCC), squamous cell cancer (SCC) and other rare skin cancers (RSC) were analyzed. Proportion tests were conducted using Stata version 15 to quantify differences in proportional distributions of histological subtypes (BCC, SCC, and RSC) and anatomical sites (skin of head and neck, upper limbs, trunk, lower limbs and overlapping skin sites) by sex and population group.
Annual incidence rates were calculated using Statistics South Africa mid-year population estimates and were standardized using Segi world standard population.[6] The NMSC age-standardized incidence rate (ASIR) trends were stratified by sex and population group, and plotted using Joinpoint software. Trends for the years 2002 - 2009 were extrapolated as data for this period showed inconsistencies. These were attributed to poor compliance, which occurred when private laboratories withheld data due to their concerns regarding voluntary sharing of patient data with the NCR.[10]

Results

Demographic characteristics

Of 1 220 964 cancer cases diagnosed in SA during 1993 - 2014, 27% (n=330 162) were NMSCs (Table 1). The percentage of males diagnosed with NMSCs was significantly higher (58.4%, CI: 58.3 – 58.6) than that of females (41.1%, CI: 41.0-41.3) (sex was unrecorded in a small proportion of cases). Most NMSC cases occurred in the White population group (79.9%, CI: 79.8-80.1, n=263 887). The mean age at diagnosis of NMSC was 63.02±14.71 years (range: 0-104) and was significantly higher in females ((63.25±15.61 (0-104)) than males ((62.84±14.03 (0-103)) ($p<0.001$; CI: 0.307-0.514). The number of NMSC cases diagnosed increased with increasing age. The number of NMSC cases diagnosed in the private sector was substantially higher than those diagnosed in the public sector (Table 1).

Histological subtypes

The predominant NMSC histological subtype diagnosed in SA was BCC (70.3%, CI: 70.1-70.4), followed by SCC (27.1%, CI: 27.0-27.3) and RSC (2.6%, CI: 2.5-2.6). Comparative proportions in the Asian, Coloured and White populations mirrored these statistics, while subtype proportions in the Black population were SCC (48.0%, CI: 47.3-48.6), BCC (36.8%, CI: 36.2-37.4) and RSC (15.2%, CI: 14.8-15.7) (Figure 1).

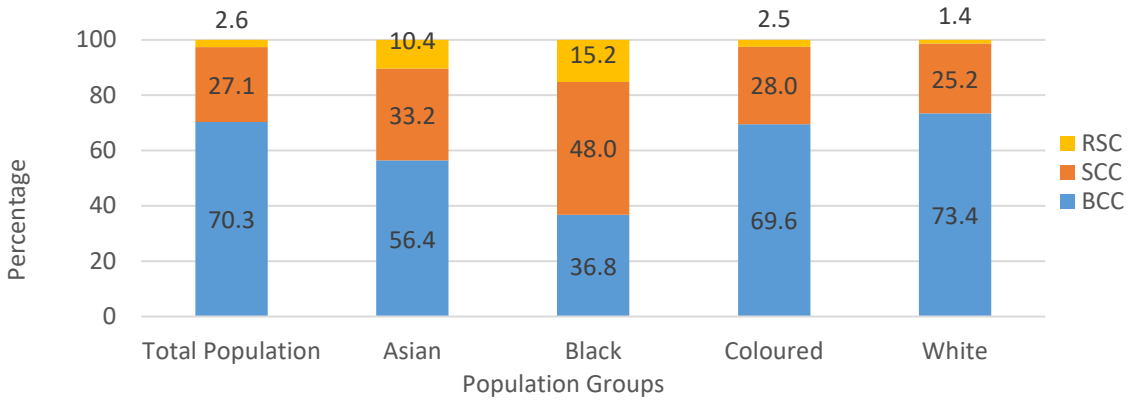

Figure 1. Proportional histological subtypes of non-melanoma skin cancer (NMSC) in South African population groups, 1993 - 2014. BCC = basal cell carcinoma, SCC = squamous cell carcinoma, RSC = rare skin cancers.

Table 1. Demographic characteristics of non-melanoma skin cancers (NMSC) in the South African population by group, sex, age and health sector source,1993-2014.

Variable	Total Population	Sex		
		Females	Males	Unrecorded Sex
Observations (n)	330162 (100%)	135815 (41.14%)	192915 (58.43%)	1432 (0.43%)
Population Group n (%)				
Asian	1927 (0.58%)	904	1011	12
Black	24141 (7.31%)	10993	12969	179
Coloured	26185 (7.93%)	11032	15072	81
White	263887 (79.93%)	106766	156058	1063
Unknown	14022 (4.25%)	6120	7805	97
Age mean±SD (min-max)	63.02±14.71 (0-104)	63.25±15.61 (0-104)	62.84±14.03 (0-103)	64.10±16.99 (1-94)
Mean difference (p-value; 95% CI UL-LL)		0.410 (0.00)		
Age Group (n)				
00-04	122	58	60	4
05-09	115	56	57	2
10-14	182	86	95	1
15-19	488	226	259	3
20-24	1366	714	640	12
25-29	3032	1566	1446	20
30-34	5946	2830	3097	19
35-39	10201	4735	5447	19
40-44	15863	6900	8930	33

	45-49	21965	9125	12785	55
	50-54	29106	11493	17544	69
	55-59	34602	13000	21532	70
	60-64	39197	14632	24482	83
	65-69	41003	15460	25446	97
	70-74	40115	15667	24325	123
	75+	76237	35043	40910	284
recorded age (n)		319540	131591	187055	894
Sector					
	Public	53198 (16.11%)	23200 (17.08%)	29196 (15.13%)	802 (56.01%)
	Private	276846 (83.85%)	112585 (82.90%)	163638 (84.82%)	623 (43.51%)
Unrecorded sector		118 (0.04%)	30 (0.02%)	81 (0.04%)	7 (0.49%)

Anatomical sites

Only 55.9% (n=184 560) of recorded NMSCs were coded to a specific skin site. In the total population the largest proportion occurred in the head and neck region (58.5%), followed by upper limbs (15.9%), trunk (14.3%), lower limbs (10.5%) and overlapping skin sites (0.8%). The anatomical site distributions of NMSCs in the Coloured (n=17 349) and White (n=143 884) population groups largely mirrored these statistics, while distributions in the Black (n=15 429) and Asian (n=1 229) groups differed slightly (Figure 2).

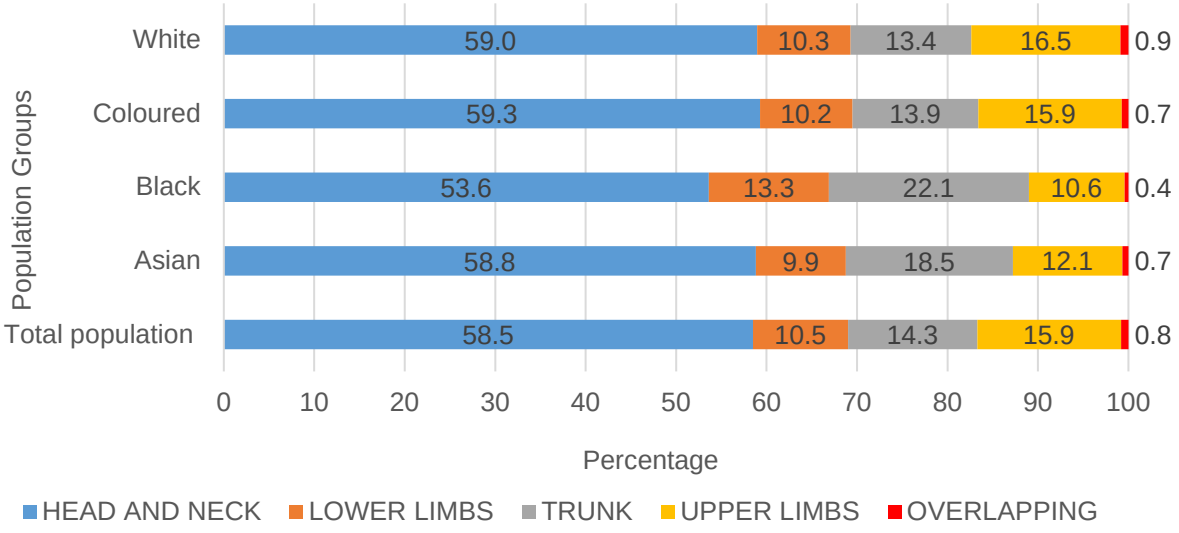

Figure 2. Proportional distributions of non-melanoma skin cancer (NMSC) anatomical sites in South African population groups; 1993 to 2014.

Age-standardized incidence rate trends for non-melanoma skin cancers

Total Population: While female NMSC incidence rates remained relatively constant over the 22-year period, incidence in males increased from 56 per 100 000 in 1993 to 80 per 100 000 in 2014 ($p<0.001$), with an annual percentage change (APC) of 1.66% (Figure 3A).

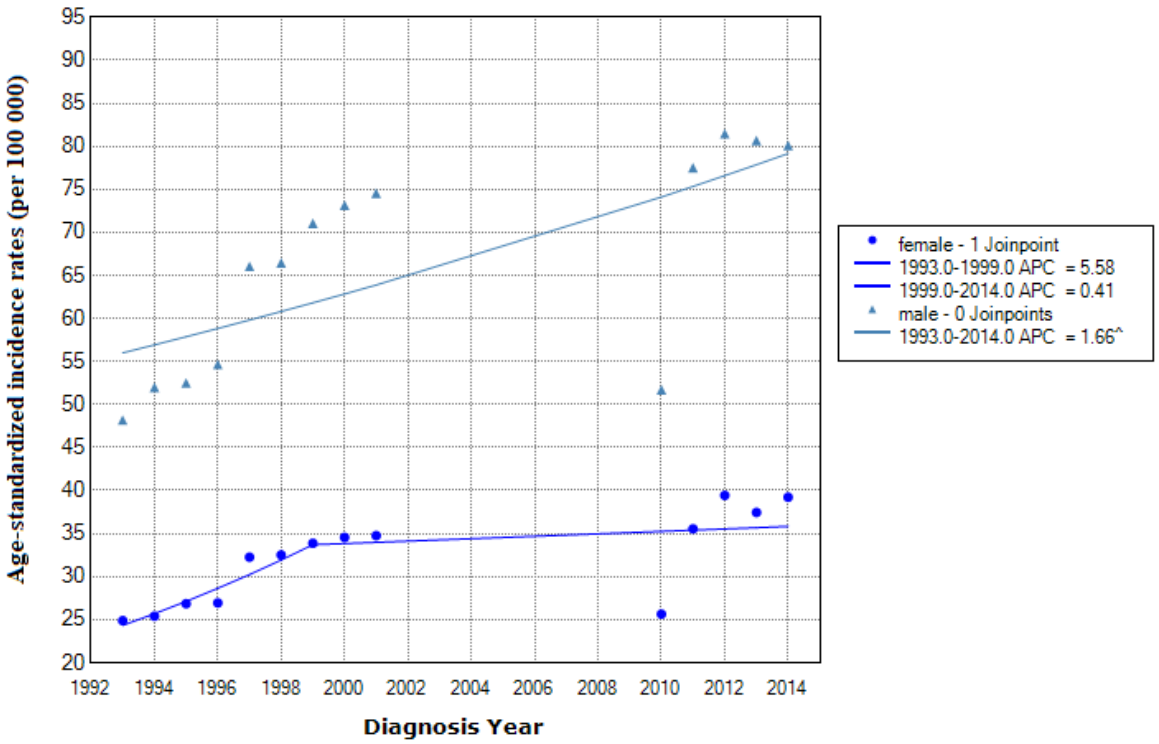

Figure 3A. Age-standardized incidence rate trends and annual percentage change (APC) for non-melanoma skin cancers in the South African population by sex, 1993-2014. (^ = p<0.05).

Females: NMSC incidence in White females was substantially higher than that of the Coloured, Asian and Black female populations (Figure 3B). During the review period, incidence in White females increased significantly from 121 to 160 per 100 000 (p<0.001), with an APC of 1.32%. NMSC incidence in Coloured females increased significantly from 16 to 75 per 100 000 (p<0.001), with an APC of 53.38%, but remained unchanged from 2000 onwards. The Asian and Black populations showed substantially lower incidence rates of less than 15 per 100 000, which remained constant in Asians throughout the review period. Incidence in Black females increased significantly from 2 to 4 per 100 000 (p<0.001), with an APC of 12.21%.

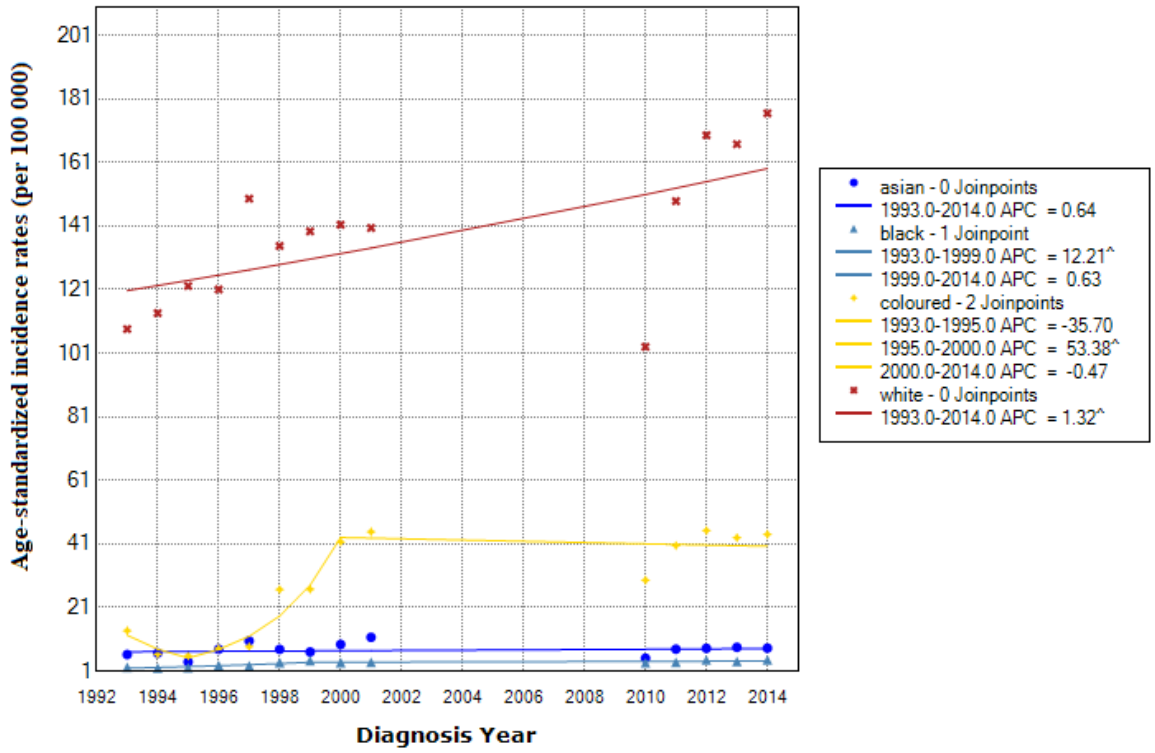

Figure 3B. Age-standardized incidence rate trends and annual percentage change (APC) for non-melanoma skin cancers in the female South African population by group, 1993-2014. (^ = p<0.05).

Males

NMSC incidence rate trends in the male population groups were similar to those of the females, with the highest incidence recorded in Whites followed by Coloured, Asian and Black males. During the review period, incidence in the Black male population showed a significant increase from 4 to 8 per 100 000 (p<0.001), with an APC of 10.82%, and remained constant from 1999 onwards (Figure 3C).

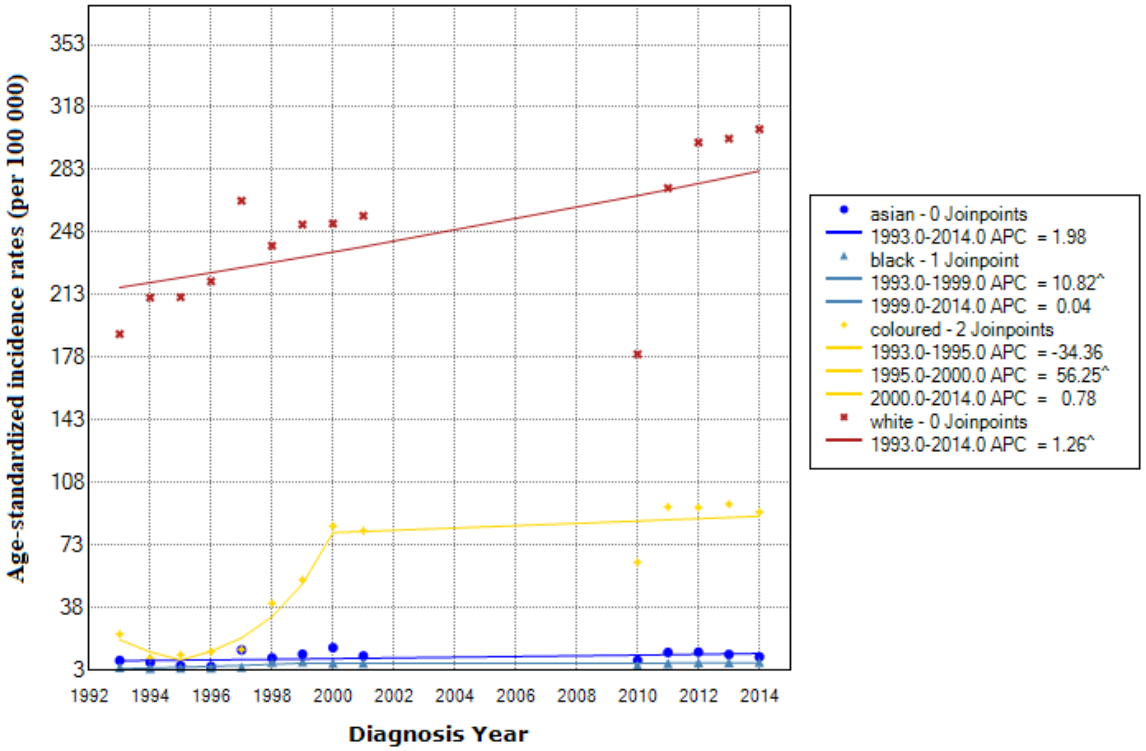

Figure 3C. Age-standardized incidence rate trends and annual percentage change (APC) for non-melanoma skin cancers in the male South African population by group, 1993-2014. (^ = p<0.05).

Discussion

During the period 1993 to 2014, non-melanoma skin cancers accounted for a substantial proportion of cancer diagnoses in South Africa annually, and were more prevalent in males. Incidence was highest in the White population, followed by the Coloured, Asian and Black populations. Basal cell carcinoma was the commonest subtype in the non-Black population (Asian, Coloured, and White), followed by SCC and RCS. Squamous cell carcinoma was the commonest subtype in the Black population, followed by BCC and RCS. In the non-Black population groups, the most susceptible skin sites for NMSCs were the head and neck, followed by the upper limbs, the trunk, lower limbs, and overlapping skin sites. In the Black population, the order of susceptibility regarding skin sites was: head and neck, trunk, lower limbs, upper limbs, and overlapping skin sites. The ASIRs showed that males were twice more likely to be diagnosed with NMSCs than females. The female ASIR trends remained relatively constant over the study period, whereas the male ASIR trends increased. NMSC ASIR trends were higher in the White and Coloured populations than in the Asian and Black populations, and increased significantly during the review period.

Trends for the review period showed that males were at higher risk of developing NMSCs than females. A 2-fold higher NMSC incidence in males is consistent with studies from other countries also showing that males are more susceptible to NMSCs than females.[11] Given that sun exposure is a primary risk factor for NMSCs, the higher incidence seen in males may be explained by a greater amount of time spent outdoors during work and leisure activities, and by a greater amount of outdoor activity during childhhood.[11]

White people are at increased risk of NMSC due to a lack of melanin in the skin that protects from the sun's ultraviolet (UV) light.[1] The distribution of NMSC histological subtypes in the South African population corresponds with other databases, showing that BCC is generally most abundant, followed by SCC and RSC.[2] There are however population group differences. Data from this review show that in South Africa's Black population SCC is most abundant, followed by BCC and RSC. This suggests that risk factors vary in importance between population groups. Hence, exposure to UV light is an important risk factor for light-skinned population groups, corresponding to a high incidence of BCC[12], whereas SCC is more common in pigmented-skin population groups, and the preponderance of this subtype in South Africa's Black population may also be linked to a high prevalence of HIV.[13]

Regardless of histological subtype, most NMSC lesions occur on the head and neck (in more than 50% of cases) and, more generally, on uncovered parts of the body most likely to be exposed to the sun.[14] Sunbed use has been shown to cause skin cancer in young and fair-skinned individuals.[15] The use of sunbeds before age 35 increases the risk of SCC and BCC by 102% and 40% respectively.[15] Unlike the White and Coloured populations in which upper limb lesions occur less frequently than head and neck lesions, the Asian and Black populations show higher proportions of NMSC lesions on the trunk, followed by head and neck lesions.[14] This suggests risk factors other than or in addition to sun exposure in these groups. These risk factors require further investigation, which was also a limitation of this study i.e. risk factor information was not coupled to these cases, enabling a risk factor analysis. The significant differences observed in these results were partly explained using findings from other studies.

Conclusion and recommendations

All population groups are at a risk of developing NMSCs. Males and the White population group are most at risk owing to increased sun exposure and lack of melanin protection respectively. The non-Black population groups are more susceptible to BCC, while the Black population is more susceptible to SCC, which may be linked to a high HIV prevalence in this group. Anatomical sites most susceptible to NMSCs are the head and neck, and upper limbs for the non-Black populations, and head and neck, trunk and lower limbs in the Black population. Detailed risk factor studies are needed to explain differences in NMSC susceptibilities between population groups.

It is recommended that:

- Persons should minimize time spent in direct sunlight and protect their heads by wearing hats or using umbrellas when outdoors.
- Persons apply sunscreen lotion on all body sites exposed to the sun, including the scalp in individuals with hair loss.

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GERMS-SA ANNUAL SURVEILLANCE REPORT FOR LABORATORY-CONFIRMED INVASIVE MENINGOCOCCAL, *HAEMOPHILUS INFLUENZAE* AND PNEUMOCOCCAL DISEASE, SOUTH AFRICA, 2018

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Executive summary

The National Institute for Communicable Diseases (NICD), in collaboration with GERMS-SA, performs national laboratory-based surveillance for *Neisseria meningitidis, Haemophilus influenzae* and *Streptococcus pneumoniae*. The surveillance aims to describe the epidemiology of these diseases and monitor the impact of the pneumococcal and *H. influenzae* serotype b conjugate vaccines on invasive disease in South Africa. This report summarises the findings for 2018.

Neisseria meningitidis: In 2018, 125 cases of laboratory-confirmed invasive meningococcal disease (IMD) were identified. Incidence was highest in the Western Cape Province (0.59/100 000) followed by Eastern Cape (0.40/100 000), Gauteng (0.25/100 000) and North West provinces (0.15/100 000). Disease peaked in winter, from May to September, with a further peak in December. Serogroup B (42/98, 43%) was the most common serogroup, followed by W (24/98, 24%) and Y (21/98, 21%). IMD occurred equally in females and males, and incidence was highest in children <1 year. All isolates were susceptible to 3rd generation cephalosporin and ciprofloxacin, but 12% were non-susceptible to penicillin. In 2018, IMD incidence was low with no outbreaks detected. High-dose penicillin is still recommended as first-line therapy for confirmed IMD, along with provision of ciprofloxacin as chemoprophylaxis for close contacts.

Haemophilus influenzae: In 2018, 327 cases of invasive *H. influenzae* (HI) disease were identified. Western Cape Province (101/327, 31%) had the highest number of cases, followed by Gauteng

Province (93/327, 28%). Seventeen percent of cases (34/201) were serotype b (Hib), and non-typeable (HNT) disease was found in 64% (129/201). Children <1 year had the highest numbers of all types of invasive HI, followed by the 25-44 years age group. Thirty-five percent (9/26) of Hib isolates and 13% (11/86) of HNT isolates were non-susceptible to ampicillin. Case fatality was 27% (36/133) with no statistically significant difference between those with Hib or HNT disease ((13% (2/15) vs. 36% (21/59), p=0.2)). Amongst those with known HIV status, 52% (47/91) were HIV infected. Conditions other than HIV predisposing to HI disease were history of smoking (17), chronic lung disease (12) and prematurity (10). The overall incidence of HI remained low and HNT accounted for the majority of cases. Although many of the children with Hib disease had been fully vaccinated, only few vaccine histories were attainable. It is extremely important for clinicians and infection control nurses in hospitals to make a thorough note of vaccine histories when encountering children with this illness, and to ensure appropriate use of vaccinations offered in the infant immunization programme.

Streptococcus pneumoniae: The incidence of invasive pneumococcal disease (IPD) in 2018 was 4 per 100 000 population. The highest incidence occurred in the Western Cape Province (9.5 per 100 000 population) followed by Gauteng Province (5.1 per 100 000 population). The highest incidence was in infants (21 per 100 000 population), dropping to 3 per 100 000 population in 1-4 year olds and then increasing from 25 years and above to 5-6 per 100 000 population in the older age categories. Penicillin non-susceptibility was detected in 30% (402/1335) and ceftriaxone non-susceptibility (MIC >0.5µg/ml) in 8% (96/1238) of isolates. Serogroups 8, 19F, 16F, 19A and 12F were the most predominant in children <5 years-of-age, whilst serogroups 8, 3, 19A, 12F and 4 caused the majority of disease in persons ≥5 years. Overall case fatality was 32% (244/758). HIV infection was present in 70% (397/567) of IPD patients, and 45% (38/85) of infants were HIV exposed (7 HIV infected, 20 HIV uninfected and 11 HIV-status unknown). Forty-five percent (341/758) of patients had a condition/risk factor (excluding HIV infection) predisposing them to IPD including history of smoking (98 patients), chronic lung disease (45 patients) and chronic renal disease (41 patients). Residual disease in children <5 years is largely due to non-vaccine serotypes, and the majority of vaccine-type disease occurs in children who have not received adequate doses of PCV13. Serotypes causing IPD in those ≥ 5 years remain diverse including both vaccine and non-vaccine serotypes. Clinicians should ensure that all children (and adults with risk factors for IPD) receive adequate PCV doses. The small number of viable isolates submitted to the NICD for serotyping is concerning, and laboratories

are urged to remember to forward pneumococci from normally sterile sites to the NICD to ensure ongoing reporting of IPD serotype data.

Introduction

The Centre for Respiratory Diseases and Meningitis (CRDM) of the National Institute for Communicable Diseases (NICD), in collaboration with GERMS-SA, performs national laboratory-based surveillance for *Neisseria meningitidis, Haemophilus influenzae* and *Streptococcus pneumoniae*. The surveillance aims to describe the epidemiology of these diseases and monitor the impact of the pneumococcal and *H. influenzae* serotype b conjugate vaccines on invasive disease in South Africa. This report summarises the findings for 2018.

Methods

Approximately 181 South African clinical microbiology laboratories participated in the GERMS-SA surveillance programme in 2018, including 30 enhanced surveillance sites (ESS) (Table 1).[1] The population under surveillance in 2018 was estimated at 57.7 million.[2] Diagnostic laboratories reported case patients to the NICD using laboratory case report forms according to a standard case definition: the detection of the organism under surveillance from any normally sterile site. If available, isolates from case patients were preserved on Dorset transport media and were submitted to the NICD for further phenotypic and genotypic characterisation. Culture-negative cases with a positive supplementary test e.g. Gram stain and/or antigen detection were also reported, and samples were submitted for molecular detection of the three pathogens. At ESS surveillance officers completed clinical case report forms electronically using the Mobenzi application on mobile phones for patients with laboratory-confirmed invasive meningococcal disease, invasive *H. influenzae* disease and invasive pneumococcal disease, by case-patient interview or hospital medical record review, to obtain additional clinical details, including antimicrobial use, vaccination history, HIV status, and patient outcome. Case patients were followed up for the duration of the hospital admission. Data management was centralised at the NICD. Laboratory, clinical and demographic data from case-patients were recorded on a Microsoft Access database. A surveillance audit was performed for NHLS laboratories in all provinces using the NHLS Central Data Warehouse (CDW). The audit was designed to obtain basic demographic and laboratory data from additional case-patients with laboratory-confirmed disease not already reported to GERMS-SA by participating laboratories; these cases are included in this report. Incidence was

calculated using mid-year population estimates for 2017 and 2018 from Statistics South Africa.[2] Ethics approval for the on-going activities of the surveillance programme was obtained from the Human Research Ethics Committee (Medical), University of Witwatersrand (clearance number M08-11-17) and from relevant University and Provincial Ethics Committees for other enhanced surveillance sites. Surveillance activities were funded by the NICD/NHLS.

Table 1. Number of laboratory-confirmed cases of invasive meningococcal, *Haemophilus influenzae* and pneumococcal disease presenting to GERMS-SA enhance surveillance sites, South Africa, 2018.

Enhanced surveillance site hospitals	Case patients, n		Completed case report forms, n (%)	Case report forms completed by interview, n (%)	
Addington	23	21	(91)	16	(76)
Charlotte Maxeke Johannesburg Academic	101	100	(99)	75	(75)
Chris Hani Baragwanath	119	91	(76)	49	(54)
Dr George Mukhari	24	24	(100)	18	(75)
Edendale/ Greys'/ Northdale	25	25	(100)	23	(92)
Groote Schuur/ Red Cross	121	109	(90)	64	(59)
Helen Joseph/ Rahima Moosa Mother & Child	116	99	(85)	75	(76)
Kimberley	47	29	(62)	11	(38)
King Edward VIII/ Inkosi Albert Luthuli Central Hospital	21	21	(100)	17	(81)
Klerksdorp/ Tshepong	41	36	(88)	19	(53)
Mankweng/ Polokwane/ Seshego	43	21	(49)	3	(14)
Pelonomi/ Universitas	38	32	(84)	13	(41)
Port Elizabeth/ Dora Nginza/ Livingstone	129	113	(88)	60	(53)
RK Khan	40	38	(95)	27	(71)
Rob Ferreira/ Themba	53	50	(94)	38	(76)
Steve Biko Pretoria Academic/ Tshwane District	58	52	(90)	33	(63)
Tygerberg	79	74	(84)	42	(57)
TOTAL	1078	935	(87)	583	(62)

The percentage (in brackets) in each cell was calculated using the numerator from that cell and the corresponding denominator from the cell to the left.

Neisseria meningitidis

Results

In 2018, 125 cases of laboratory-confirmed invasive meningococcal disease (IMD) were identified through the surveillance system, of which 49 (39%) viable isolates were received and 23 (18%) cases were detected on audit. The overall disease incidence was 0.22 cases per 100 000 population, similar to that in 2017 (0.24/100 000). Incidence was highest in the Western Cape Province (0.59/100 000) followed by Eastern Cape (0.40/100 000), Gauteng (0.25/100 000) and North West provinces (0.15/100 000) (Table 2). Disease peaked in winter, from May to September, with a further peak in December (Figure 1). Once again, no outbreaks of meningococcal disease were detected in 2018. Cerebrospinal fluid was the most common specimen from which meningococci were identified (82/125, 66%) (Table 3). Serogroup B (42/98, 43%) was the most common serogroup causing disease, followed by W (24/98, 24%) and Y (21/98, 21%) (Table 4). IMD occurred equally in females (63/124, 51%) and males. Incidence of IMD was highest in children <1 year for all serogroups (Figure 2). Of the viable isolates tested for antimicrobial susceptibility, 12% (6/49) were non-susceptible to penicillin with minimum inhibitory concentrations (MICs) between 0.094µg/ml and 0.25µg/ml, and all were susceptible to 3rd generation cephalosporin and ciprofloxacin.

Fifty-one (41%) IMD patients presented to the enhanced surveillance sites and 44/51 (86%) had additional clinical information available (Table 1). The median time for each admission was 8 days (interquartile range 6-11 days). The case-fatality ratio was 12% (5/43); three patients died on the day of admission. Seventeen percent of patients with HIV status available were HIV infected (6/36). For those who survived to discharge from hospital, 3/23 (13%) suffered sequelae following IMD. All three had skin scarring from necrotic lesions and two of these patients required reconstructive surgery to correct the deformity.

Table 2. Number of cases and incidence rates of meningococcal disease reported to GERMS-SA by province, South Africa, 2017 and 2018, n=261 (including audit cases).

Province	2017		2018	
	n	Incidence rate*	N	Incidence rate*
Eastern Cape	18	0.28	26	0.40
Free State	8	0.28	2	0.07
Gauteng	42	0.29	37	0.25
KwaZulu-Natal	8	0.07	8	0.07
Limpopo	4	0.07	4	0.07
Mpumalanga	4	0.09	2	0.04
Northern Cape	0	0.00	1	0.08
North West	5	0.13	6	0.15
Western Cape	47	0.72	39	0.59
South Africa	**136**	**0.24**	**125**	**0.22**

*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100 000 population.

Table 3. Number and percentage of cases of meningococcal disease reported to GERMS-SA by specimen type, South Africa, 2017 and 2018, n=261.

Site of specimen	2017		2018	
	n	%	n	%
Cerebrospinal fluid	93	68	82	66
Blood	42	31	43	34
Other	1	1	0	0
Total	**136**		**125**	

Table 4. Number of cases of invasive meningococcal disease reported to GERMS-SA by serogroup and province, South Africa, 2018, n=125*.

Province	Serogroup							
	Serogroup not available	A	B	C	W	Y	Z	NG**	Total
Eastern Cape	2	0	7	4	4	9	0	0	26
Free State	1	0	0	0	0	1	0	0	2
Gauteng	10	0	12	3	8	4	0	0	37
KwaZulu-Natal	4	0	2	0	1	1	0	0	8
Limpopo	2	0	1	0	1	0	0	0	4
Mpumalanga	0	0	2	0	0	0	0	0	2
Northern Cape	1	0	0	0	0	0	0	0	1
North West	4	0	1	0	0	1	0	0	6
Western Cape	3	0	17	4	10	5	0	0	39
South Africa	**27**	**0**	**42**	**11**	**24**	**21**	**0**	**0**	**125**

*98 (78%) with viable isolates or specimens available for serogrouping/genogrouping; ** NG: Non-groupable

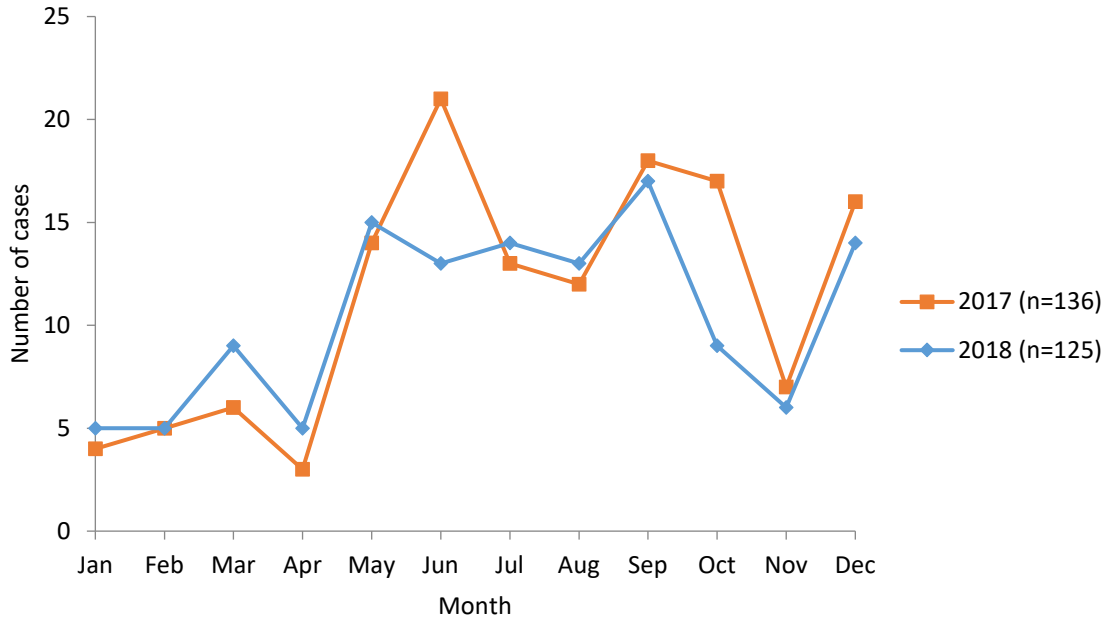

Figure 1. Number of laboratory-confirmed, invasive, meningococcal cases, reported to GERMS-SA, by month and year, South Africa, 2017-2018, n=261.

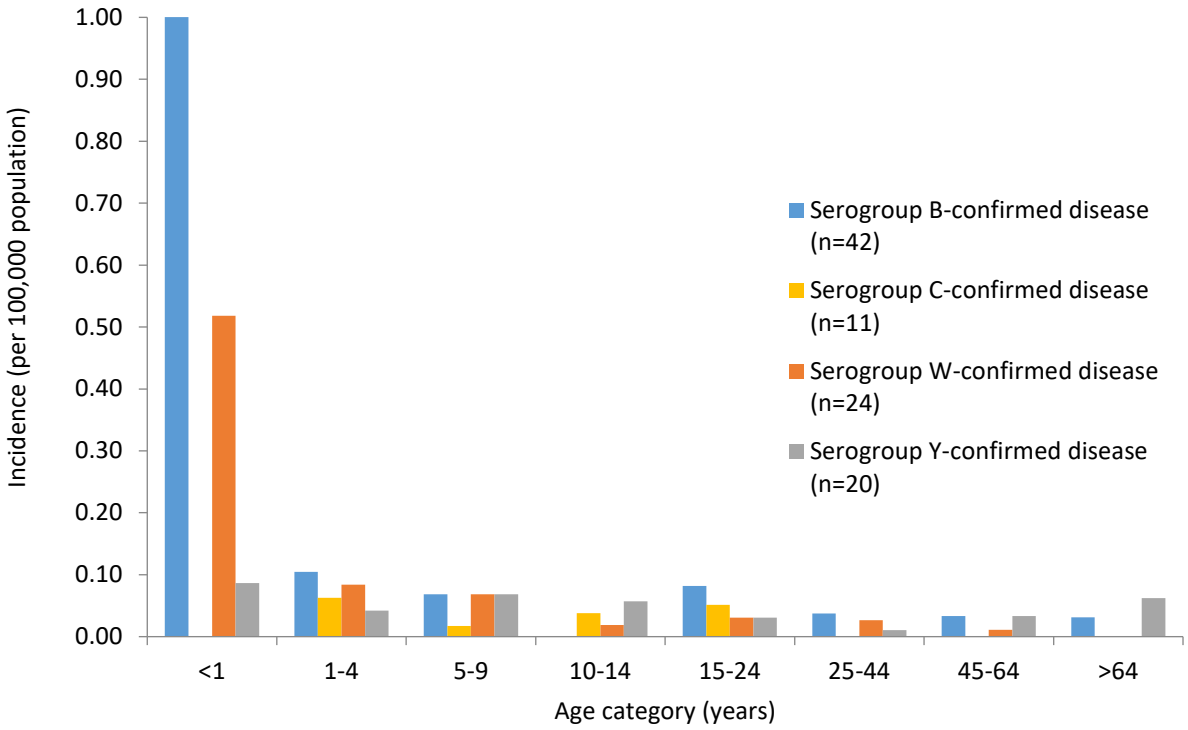

Figure 2. Age-specific incidence rates* for laboratory-confirmed, invasive, meningococcal cases, by serogroup B, C, W and Y, South Africa, 2018, n=125** (**age unknown for n=1; specimens or viable isolates unavailable for serogrouping n=27).

Discussion

IMD epidemiology in 2018 remained largely unchanged from previous years: IMD incidence was low with serogroup B disease causing the majority of episodes. A small increase in the proportion of serogroup Y cases was recorded, particularly in the Eastern Cape Province where it now predominates. High-dose penicillin is still recommended as first-line therapy for confirmed IMD, along with provision of ciprofloxacin as chemoprophylaxis for close contacts. Although uncommon, meningococcal disease in South Africa is a devastating illness affecting all age groups. In 2018, in-hospital case fatality was 12%, with 13% of survivors suffering sequelae post discharge from hospital.

Haemophilus influenzae

Results

There were 327 cases of invasive *Haemophilus influenzae* (HI) disease identified through the surveillance programme in 2018, 35% (126) of which were detected on audit, and 61% (201) had either viable isolates (142) or specimens (59) available for serotyping (Table 5). Four cases were co-infected with invasive *S. pneumoniae*. Western Cape Province (101/327, 31%) had the highest number of cases reported, followed by Gauteng Province (93/327, 28%) (Table 5). Seventeen percent of cases (34/201) were serotype b (Hib) and non-typeable (HNT) disease was found in 64% (129/201) (Table 5). Most HI cases were isolated from blood (200/327, 61%), however Hib isolates were more likely to be found in CSF than HNT isolates (8/34, 24% versus 15/129, 12%, p=0.01) (Table 6). Children <1 year had the highest numbers of all types of invasive HI, followed by the 25-44 years age group (Figure 3). Hib incidence was still highest in infants even though significant declines have been noted since 2010 (5.2 cases per 100 000 in 2010 to 0.8 cases per 100 000 in 2018 (p<0.001)) (Figures 4 and 5). Hib has remained below 0.2 per 100 000 in 1-4 year olds, since 2013 (Figure 5). HNT incidence was highest in infants (2.9 per 100 000), dropping substantially throughout the rest of the childhood age groups before increasing again in the older groups with a moderate peak in the >64 years category (0.3 per 100 000) (Figure 4). Thirty-five percent (9/26) of Hib isolates and 13% (11/86) of HNT isolates were non-susceptible to ampicillin (MIC>1mg/L). Seventeen cases of Hib disease occurred in children <15 years of age and vaccine history was available for 29% (5/17). Eighty percent (4/5) of those children with invasive Hib had received at least 3 doses of Hib vaccine, and were possible vaccine failures (including one fully vaccinated child who had underlying congenital cardiac disease). One 4-month-old child had only received one dose of Hib vaccine.

Clinical information was available for 88% (133/152) of cases presenting to the enhanced surveillance sites (ESS) (Table 1). Patients were admitted for a median of 7 days (interquartile range (IQR) 2-13). Case fatality was 27% (36/133) and median time to death was within one day of admission (IQR 0-4). There was no statistically significant difference between case fatalities of those with Hib or HNT disease ((13% (2/15) vs. 36% (21/59), p=0.2)). Amongst those with known HIV status, 52% (47/91) were HIV infected. Conditions other than HIV predisposing to HI disease were reported in 71/133 (53%) patients – the most common conditions included history of smoking (17), chronic lung disease (12) and prematurity (10). Of the 19 patients at ESS with HI on CSF: one patient

died during their hospitalization, and 22% (4/18) of those who survived to discharge suffered sequelae – these included three with hearing loss and one with hydrocephalus.

Table 5. Number of cases of invasive *Haemophilus influenzae* disease reported to GERMS-SA by serotype and province, South Africa, 2018, n=327*.

Province	Serotype								
	Serotype not available	a	b	c	d	e	f	Non-typeable	Total
Eastern Cape	14	1	4	0	0	0	2	24	45
Free State	4	0	0	0	0	0	0	3	7
Gauteng	42	5	9	1	1	1	5	29	93
KwaZulu-Natal	30	3	4	1	1	1	0	8	48
Limpopo	5	0	0	0	0	0	0	0	5
Mpumalanga	6	1	1	0	0	0	1	5	14
Northern Cape	1	0	0	0	0	0	0	3	4
North West	7	1	0	0	0	0	0	2	10
Western Cape	17	8	16	0	2	0	3	55	101
South Africa	**126**	**19**	**34**	**2**	**4**	**2**	**11**	**129**	**327**

*201 (61%) with specimens or viable isolates available for serotyping

Table 6. Number and percentage of cases of invasive *Haemophilus influenzae* disease reported to GERMS-SA by specimen type, South Africa, 2018, n=327

Site of specimen	No serotype available		Serotype b		Serotypes a, c, d, e, f		Non-typeable	
	n	%	n	%	n	%	n	%
Cerebrospinal fluid	26	21	8	24	12	32	15	12
Blood	64	51	24	70	24	63	88	68
Other	36	28	2	6	2	5	26	20
Total	**126**		**34**		**38**		**129**	

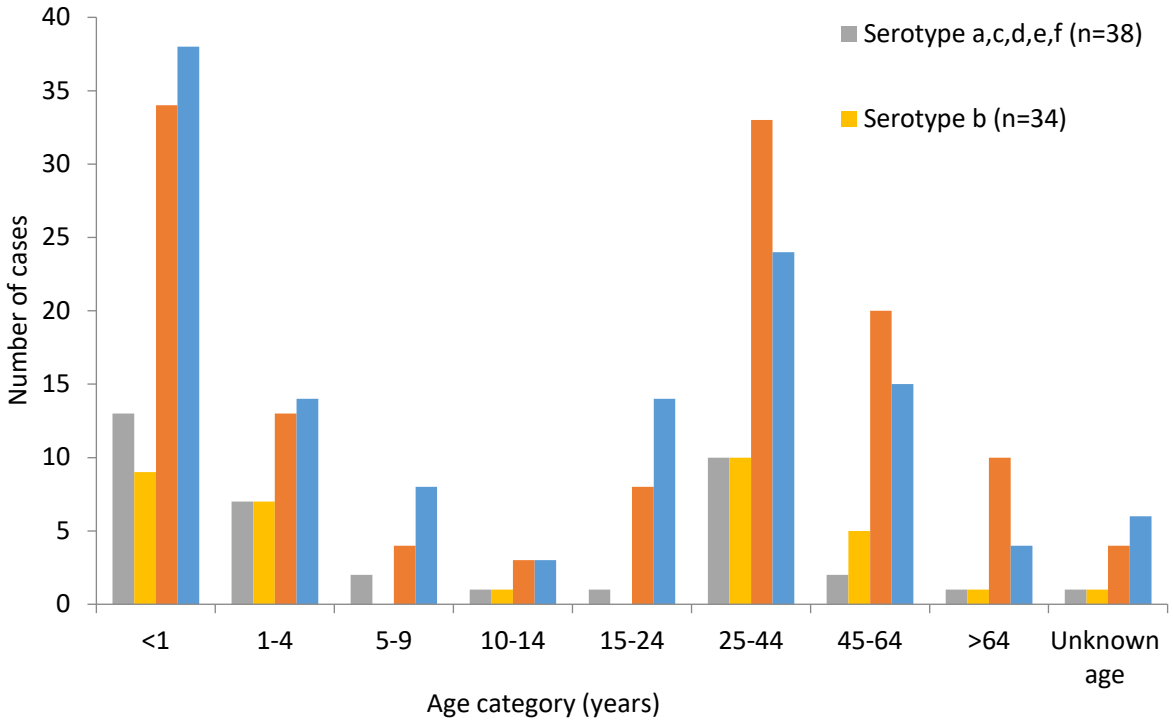

Figure 3. Number of laboratory-confirmed, invasive, *Haemophilus influenzae* cases, reported to GERMS-SA, by serotype and age group, South Africa, 2018, n=327 (age unknown for n=12; specimens or viable isolates unavailable for serotyping for n=126).

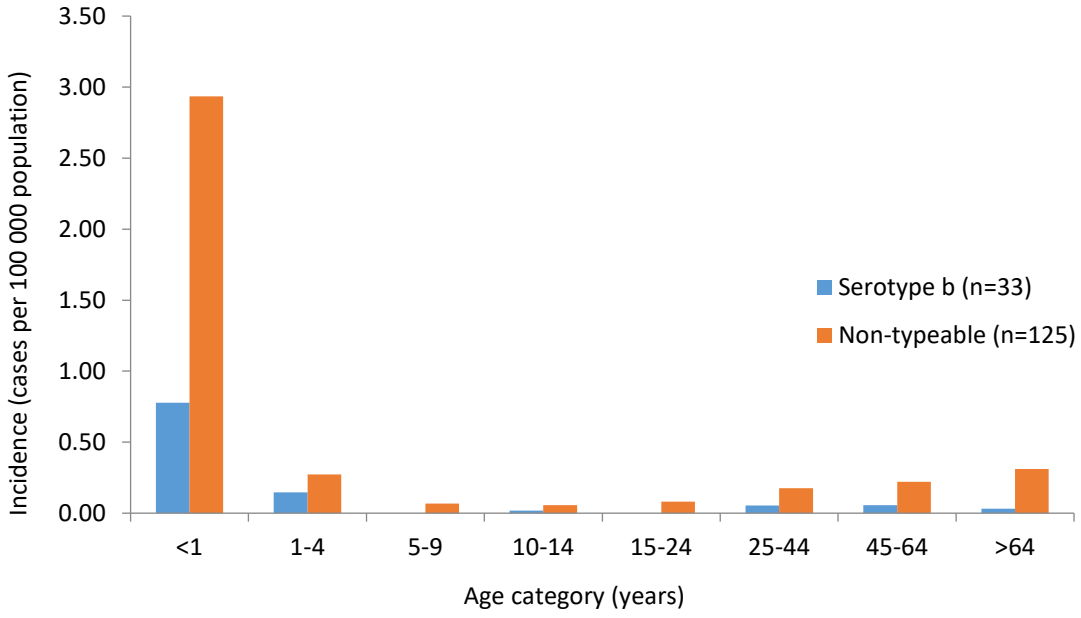

Figure 4. Age-specific incidence rates* for laboratory-confirmed, invasive *Haemophilus influenzae* disease, reported to GERMS-SA, by serotype b and non-typeable, South Africa, 2018, n=327 (age unknown, n=5; viable isolates unavailable for serotyping, n=126; other serotypes from cases with known age, n=38

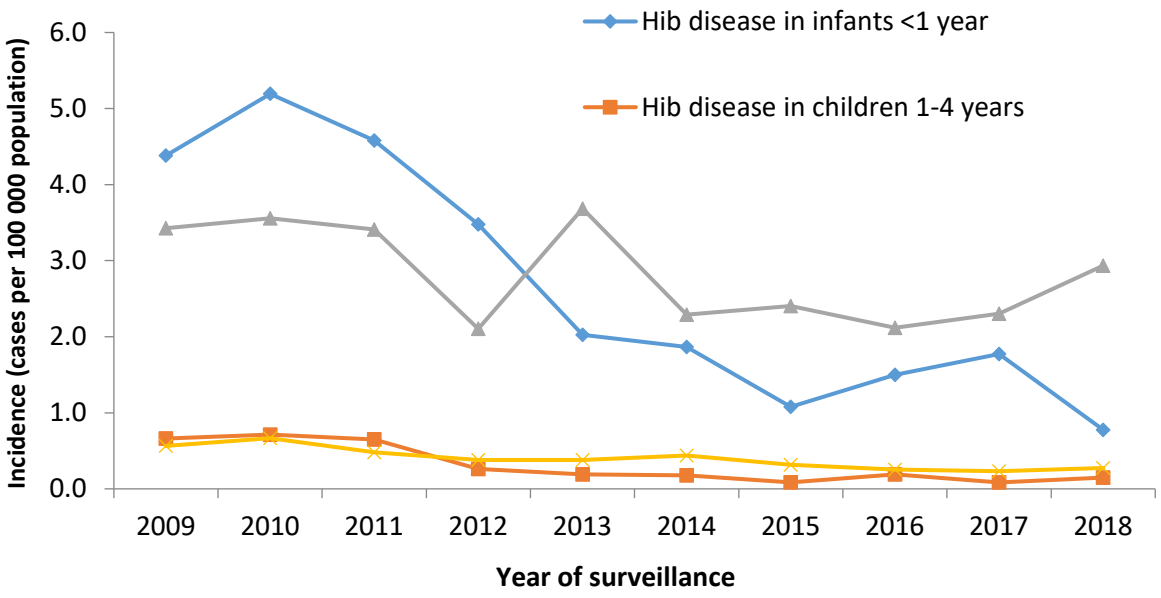

Figure 5. Incidence rates* of laboratory-confirmed *Haemophilus influenzae* serotype b and non-typeable disease, reported to GERMS-SA, in children <5 years old, South Africa, 2009-2018. *Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100 000 population.

Discussion

Overall incidence of HI remained low and HNT accounted for the majority of cases. The highest rates of disease were seen in infants for both Hib and HNT, with HNT incidence increasing in the elderly. Case-fatality ratios were high (27%) and long-term sequelae following meningitis occurred in 22% of cases. Although many of the children with Hib disease had been fully vaccinated, only few vaccine histories were attainable. It is extremely important for clinicians and infection control nurses in hospitals to make a thorough note of vaccine histories when encountering children with this devastating vaccine-preventable illness, and to ensure appropriate use of vaccinations offered in the infant immunization programme.

Streptococcus pneumoniae

Results

The incidence of invasive pneumococcal disease (IPD) in 2018 was 4 per 100 000 population, similar to that of 2017 (Table 7). IPD incidence varied greatly by province with the highest incidence in the Western Cape Province (9.5 per 100 000 population) followed by Gauteng Province (5.1 per 100 000

population) (Table 7). Pneumococcal conjugate vaccine (PCV7) was introduced into the Expanded Programme on Immunisation (EPI) in 2009, and subsequently replaced by PCV13 in 2011. Between 2009 and 2013 there were substantial reductions in IPD in all age categories and this reduction has been sustained over recent years. In 2018, the highest incidence of IPD was in infants (21 per 100 000 population), dropping to 3 per 100 000 population in 1-4 year olds and then increasing from 25 years and above to 5-6 per 100 000 population in the older age-categories (Figure 6). Four patients with IPD were co-infected with invasive *Haemophilus influenzae*. The majority of IPD cases were isolated from blood culture specimens (59%, 1362/2314) (Table 8). Penicillin non-susceptibility (minimum inhibitory concentration (MIC) >0.06µg/ml) was detected in 30% (402/1335) of IPD isolates, the highest proportion being in children 1-4 years of age (56%, 36/64) (Table 9 and Figure 7). Ceftriaxone non-susceptibility (MIC >0.5µg/ml) was detected amongst 8% (96/1238) of isolates from all specimens, and amongst 7% (25/365) of IPD isolated from CSF. In 2018, serogroups 8, 19F, 16F, 19A and 12F were the most predominant serogroups causing IPD in children <5 years-of-age, whilst serogroups 8, 3, 19A, 12F and 4 caused the majority of disease in persons ≥5 years (Figures 8a and 8b). Only 45% (170/375) of IPD isolates from children <5 years-of-age were sent to the NICD for serotyping (Figure 9). Of these, 26% (44/170) were serotypes contained in PCV13 (Table 10).

Eighty-seven percent (758/875) of IPD patients presenting to the enhanced surveillance sites (ESS) had clinical information available (Table 1). Patients were admitted for a median hospital stay of 7 days (interquartile range (IQR) 2-14) and most deaths occurred within 2 days of admission (IQR 0-5). Overall case fatality was 32% (244/758). HIV infection was present in 70% (397/567) of IPD patients, and 45% (38/85) of infants with maternal HIV status available were HIV exposed (7 HIV infected, 20 HIV uninfected and 11 HIV-status unknown). Forty-five percent (341/758) of patients had a condition/risk factor (excluding HIV infection) predisposing them to IPD. The top three factors included: history of smoking (98 patients), chronic lung disease (45 patients) and chronic renal disease (41 patients).

Of 206 patients at ESS with pneumococcus on CSF: 35% (73/206) died during their hospitalisation, and 23% (30/133) who survived to discharge suffered at least one sequelae – these included new onset seizures (13), limb weakness/paralysis (9), hearing loss (7), necrotic skin lesions (4) and hydrocephalus (1). Of 115 IPD cases from children <10 years of age at ESS with serotype data available, 24 episodes were caused by serotypes present in the PCV13 vaccine. Vaccine history was

available for 79% (19/24) of these children. Twenty-six percent (5/19) were too young to receive vaccine; 16% (3/19) of children eligible to receive vaccine had not received any PCV doses; 26% (5/19) had received all 3 doses of PCV; and 32% (6/19) had only received one dose of PCV at 6 weeks of age. The vaccine serotypes responsible for disease in those who had received PCV13 included serotypes 19F, 19A, 23F, 6A and 14.

Table 7. Number of cases and incidence rates of invasive pneumococcal disease reported to GERMS-SA by province, South Africa, 2017 and 2018, n=4754 (including audit cases).

Province	2017		2018	
	n	Incidence rate*	n	Incidence rate*
Eastern Cape	208	3.20	258	3.96
Free State	109	3.80	106	3.59
Gauteng	891	6.24	757	5.14
KwaZulu-Natal	269	2.43	242	2.13
Limpopo	66	1.14	84	1.45
Mpumalanga	99	2.23	116	2.56
Northern Cape	53	4.37	52	4.24
North West	70	1.82	71	1.78
Western Cape	675	10.37	628	9.48
South Africa	**2440**	**4.32**	**2314**	**4.01**

*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100 000 population.

Table 8. Number and percentage of cases of invasive pneumococcal disease reported to GERMS-SA by specimen type, South Africa, 2017 and 2018, n=4754.

Site of specimen	2017		2018	
	n	%	n	%
Cerebrospinal fluid	792	32	794	34
Blood	1480	61	1362	59
Other	168	7	158	7
Total	**2440**		**2314**	

Table 9. Number and percentage of penicillin susceptible and non-susceptible isolates from invasive pneumococcal disease cases reported to GERMS-SA by province, South Africa, 2018, n=2314.

Province	Isolate not available	Susceptible*		Intermediate*		Resistant*	
	n	n	%	n	%	n	%
Eastern Cape	122	101	74	30	22	5	4
Free State	55	38	75	11	22	2	4
Gauteng	372	258	67	92	24	35	9
KwaZulu-Natal	135	71	66	28	26	8	7
Limpopo	72	7	58	5	42	0	0
Mpumalanga	41	51	68	19	25	5	7
Northern Cape	15	26	70	10	27	1	3
North West	53	13	72	5	28	0	0
Western Cape	114	368	72	108	21	38	7
South Africa	**979**	**933**	**70**	**308**	**23**	**94**	**7**

*2016 CLSI breakpoints for penicillin (oral penicillin V) were used: susceptible, ≤0.06mg/L; intermediately resistant, 0.12-1mg/L; resistant, ≥2mg/L

Table 10. Number and percentage of invasive pneumococcal cases reported amongst children less than 5 years of age caused by the serotypes contained in the 7-valent, 10-valent and 13-valent pneumococcal conjugate vaccines, South Africa, 2018, n=375 (n=170 with viable isolates).

Province	Total isolates available for serotyping	7-valent serotypes*		Serotype 6A#		10-valent serotypes**		13-valent serotypes***	
		n	%	n	%	n	%	n	%
Eastern Cape	11	0	0	0	0	0	0	2	18
Free State	6	3	50	0	0	3	50	3	50
Gauteng	72	15	21	0	0	16	22	22	31
KwaZulu-Natal	18	4	22	0	0	4	22	6	33
Limpopo	1	0	0	1	100	0	0	1	100
Mpumalanga	7	0	0	0	0	0	0	1	14
Northern Cape	1	0	0	0	0	0	0	0	0
North West	2	0	0	0	0	0	0	0	0
Western Cape	52	7	13	1	2	7	13	9	17
South Africa	**170**	**29**	**17**	**2**	**1**	**30**	**18**	**44**	**26**

All serotypes included in each of the categories: 7-valent serotypes*: 4, 6B, 9V, 14, 18C, 19F, 23F

10-valent serotypes**: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F

13-valent serotypes***: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 19A, 3, 6A

Cross-protection with 6B has been demonstrated

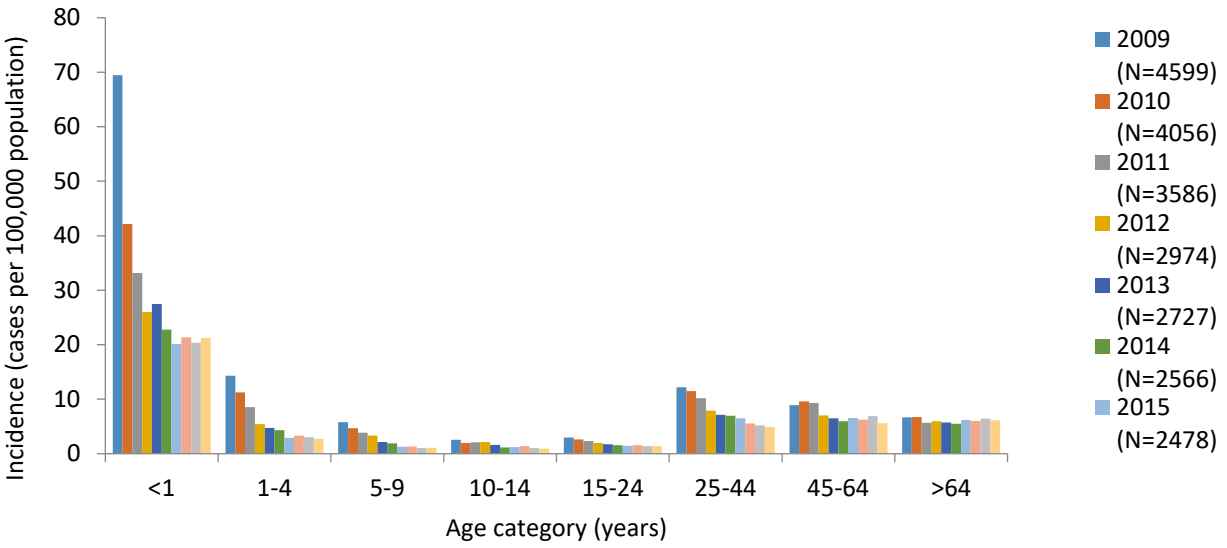

Figure 6. Age-specific incidence rates* for laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, South Africa, 2009 through 2018, n=31 401. *Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100 000 population.

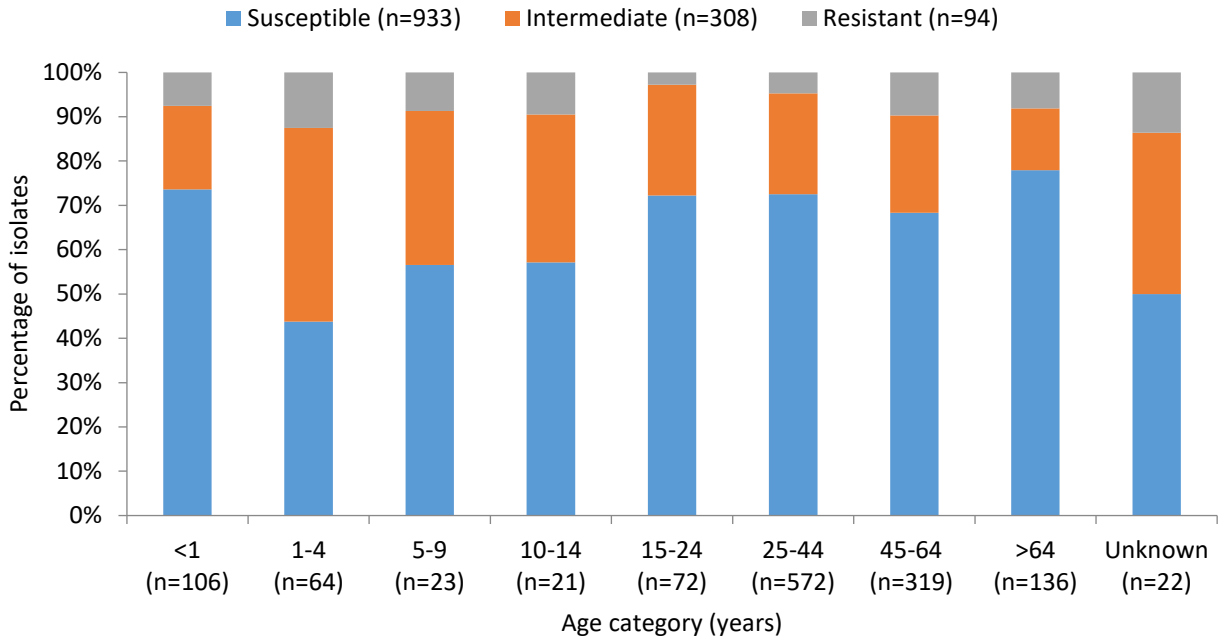

Figure 7. Number of laboratory-confirmed, invasive pneumococcal disease cases, reported to GERMS-SA, by age group and penicillin susceptibility, South Africa, 2018, n=2314 (n=1335 with viable isolates). 2016 CLSI breakpoints for penicillin (oral penicillin V) were used: susceptible, ≤0.06mg/L; intermediately resistant, 0.12-1mg/L; resistant, ≥2mg/L.

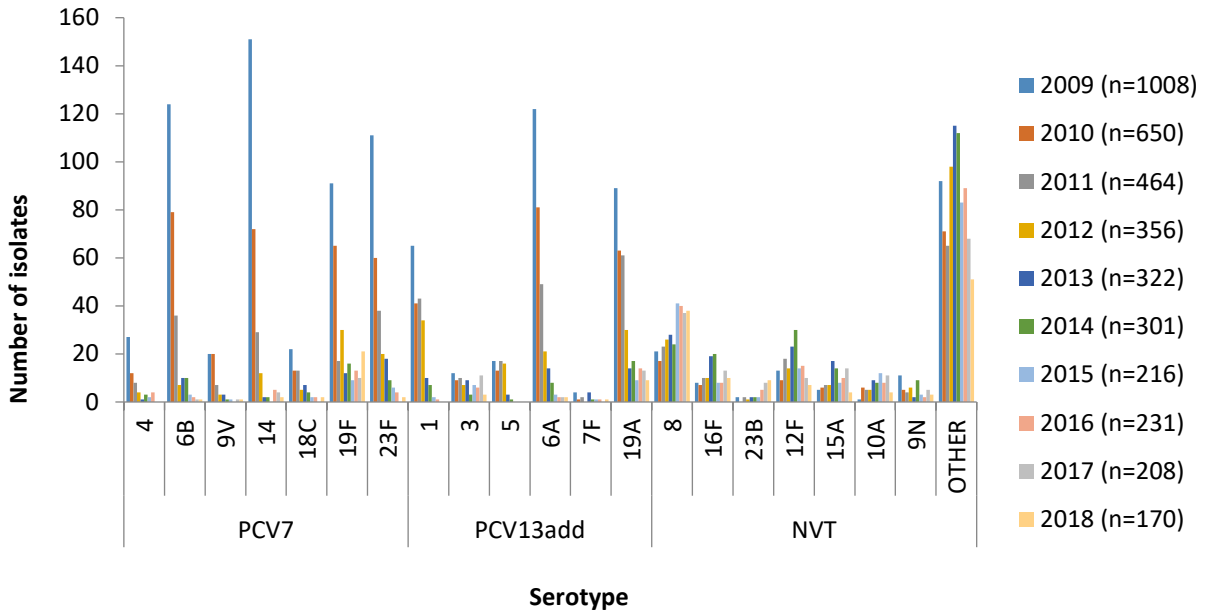

Figure 8a. Most common pneumococcal serotypes causing laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, in children <5 years, South Africa, 2009-2017. PCV7: seven-valent pneumococcal conjugate vaccine; PCV13add: additional serotypes in the thirteen-valent pneumococcal conjugate vaccine; NVT: non-vaccine serotypes.

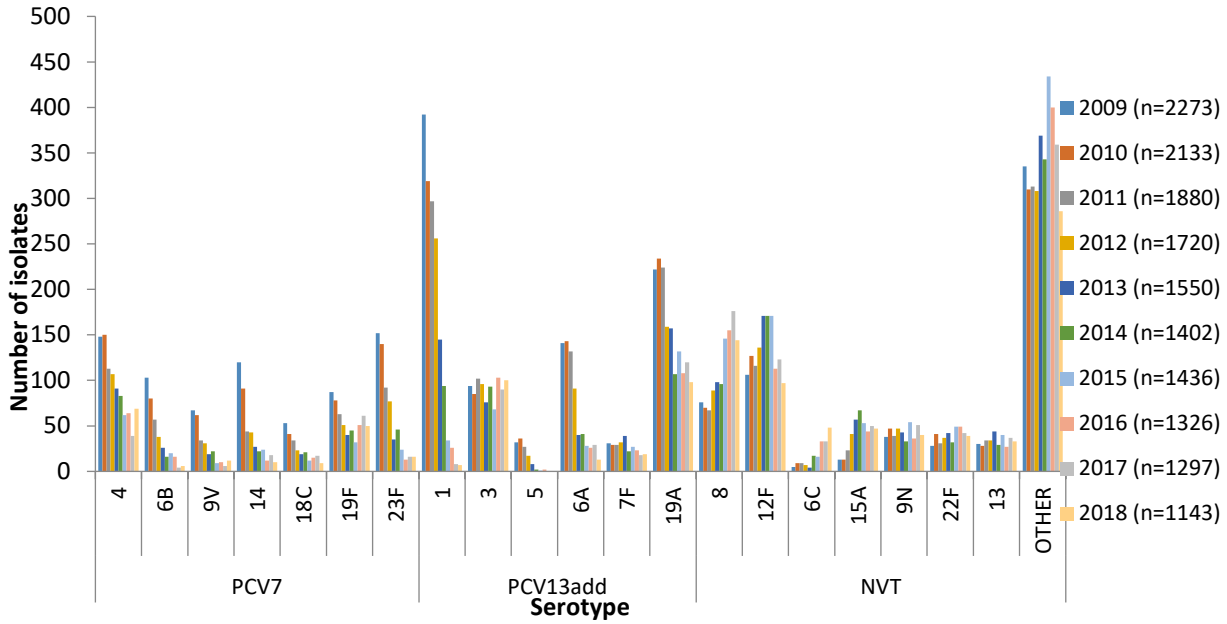

Figure 8b. Most common pneumococcal serotypes causing laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, in adults and children ≥5 years, South Africa, 2009-2018. PCV7: seven-valent pneumococcal conjugate vaccine; PCV13add: additional serotypes in the thirteen-valent pneumococcal conjugate vaccine; NVT: non-vaccine serotypes.

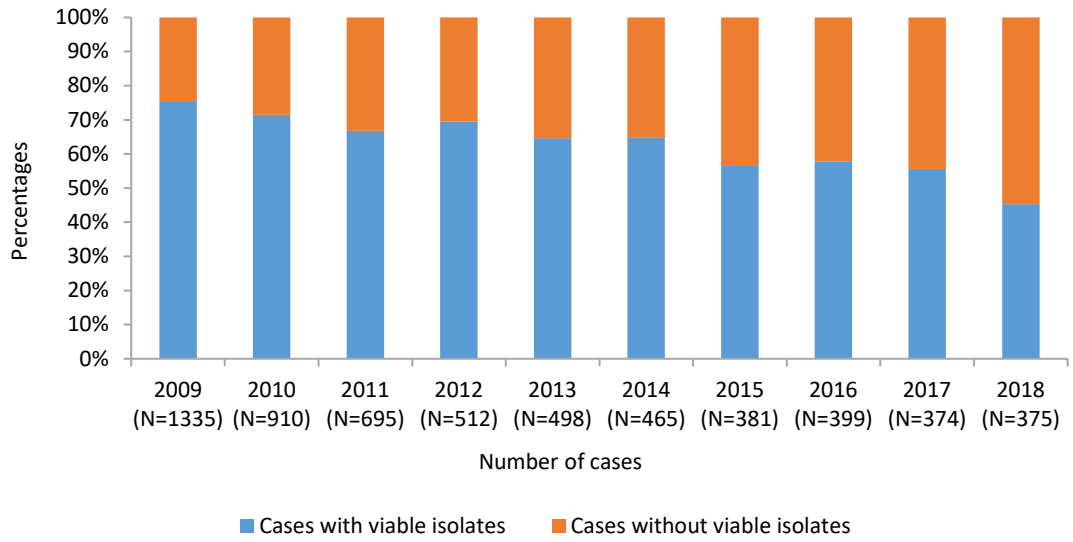

Figure 9. Percentages of invasive pneumococcal disease cases with viable isolates reported to GERMS-SA, in children <5 years, South Africa, 2009-2018.

Discussion

IPD incidence remained low in 2018, with sustained reductions seen amongst all age categories post PCV introduction. Infants still have the highest disease incidence, peaking again after age 25 years. Penicillin and ceftriaxone susceptibility of IPD isolates remained unchanged. HIV infection and infant HIV exposure remain risk factors for IPD. Pneumococcal disease has a high mortality and morbidity. Residual disease in children <5 years is largely due to non-vaccine serotypes, and the majority of vaccine-type disease occurs in children who have not received adequate doses of PCV13. Serotypes causing IPD in those ≥ 5 years remain diverse including both vaccine and non-vaccine serotypes. Clinicians should ensure that all children (and adults with risk factors for IPD) receive adequate PCV doses to protect them from this serious illness. The small number of viable isolates submitted to the NICD for serotyping is concerning, and laboratories are urged to remember to forward pneumococci from normally sterile sites to the NICD to ensure ongoing reporting of IPD serotype data.

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ACUTE FLACCID PARALYSIS SURVEILLANCE FOR POLIO, SOUTH AFRICA AND OTHER AFRICAN COUNTRIES, 2018

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Summary

Acute flaccid paralysis (AFP) surveillance is used as the standard indicator for the potential incidence of polio. For January to December 2018, the South African national non-polio AFP rate was 2.9/100 000 in children under 15 years, compared to 2.3/100 00 children in 2017. The detection rate reached the World Health Organization's (WHO) target of 2.0/100 000 but did not reach the country's target of 4.0/100 000. Surveillance still needs to be strengthened because two of South Africa's provinces (North West and Western Cape) and seven districts did not reach 2.0/100 000. Stool adequacy of less than 80% was reported in six of South Africa's nine provinces. An immunodeficiency-associated vaccine-derived poliovirus (VDPV) was detected in October 2018. This prompted a co-ordinated response from all stakeholders, showing that despite its shortcomings, the surveillance network can identify and respond to poliovirus events.

Introduction

The National Institute for Communicable Diseases (NICD) serves as the national polio reference laboratory for acute flaccid paralysis (AFP) surveillance in South Africa and other southern African countries including Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia and Swaziland. The NICD additionally serves as the regional reference centre for the polio laboratory network of the

African region, and conducts molecular characterization of poliovirus isolates from the national laboratories of the Democratic Republic of Congo (DRC), Ethiopia, Niger, Uganda and Zambia.

The Global Polio Eradication Initiative uses two types of vaccines; inactivated polio vaccine (IPV) to prevent symptomatic polio, and oral polio vaccine (OPV) to prevent both symptomatic polio and polio transmission. IPV is an injectable vaccine consisting of all three poliovirus serotypes. OPV is composed of live attenuated polioviruses and can be monovalent (mOPV, type specific) or bivalent (bOPV, types 1 and 3). The polio vaccination schedule for South Africa comprises bivalent OPV at birth and 6 weeks, and IPV as part of hexavalent vaccine at 6, 10, and 14 weeks, followed by a booster at 18 months. It should be noted that if OPV circulates in the environment for many months in areas of low vaccine coverage, it can mutate resulting in the circulation of vaccine-derived poliovirus (cVDPV).

Since the establishment of the Global Polio Eradication Initiative in 1988, the global incidence of wild poliovirus has decreased to 33 reported cases in 2018, from an estimated 350 000 cases in more than 125 endemic countries. The lowest number of cases ever reported was 21 in 2017, thus showing that incidence increased in 2018. This increase highlights the need to enhance effective surveillance and immunization programmes. The three countries that remain endemic for the transmission of wild poliovirus type 1 are Afghanistan, Pakistan and Nigeria. The last case of wild poliovirus type 2 was reported in 1999, and this type was declared eradicated in 2015. Wild poliovirus type 3 has not been detected since November 2012. In South Africa, the last wild poliovirus case occurred in 1989.

Within the WHO African (AFRO) region in 2018, there were 71 AFP cases caused by circulating vaccine-derived poliovirus type 2 (cVDPV2). These were from Nigeria, DRC, Niger, Somalia and Mozambique. This is likely because mOPV2 vaccine was used as part of their mop-up campaigns to end polio transmission. In Somalia, seven cases of vaccine-derived poliovirus type 3 (cVDPV3) were detected in 2018. Outside of the African region, Indonesia and Papua New Guinea reported cVDPV1 outbreaks in late 2018 (www.polioeradication.org).[1]

Methods

Nationwide, case-based surveillance for AFP with laboratory confirmation of poliovirus from stool specimens was conducted in South Africa in 2018.

Field Surveillance

Cases of AFP from all health facilities were notified to the Provincial and National Departments of Health, together with samples for investigation and associated case investigation forms. (An adequately investigated case requires the collection of two stool specimens from the suspected AFP case within 14 days of onset of paralysis. The stool samples should be collected 24-48 hours apart. Stool samples are to be transported on ice and should arrive at the NICD laboratory within 72 hours of collection). Field surveillance was also conducted through active case detection, targeting children under 15 years. In 2018, the South African operational AFP target detection rate was 4.0/100 000 (double the 2015 target of 2.0/100 000), while the WHO target detection rate was 2.0/100 000. The National Polio Expert Committee (NPEC) performed the final classification for all inadequately investigated AFP cases quarterly (Table 1).

Laboratory methods

Viral isolation was performed by inoculation of faecal material into cell culture, followed by microscopic examination of the cells for cytopathic effect, which indicates the presence of suspected poliovirus. Intratypic differentiation by polymerase chain reaction (PCR) was conducted on suspected poliovirus isolates. Polioviruses were then sequenced to classify them as either wild poliovirus (WPV), Sabin or VDPV. Sequencing helps to monitor poliovirus transmission pathways and transmission links. All South African polioviruses were sequenced at the VP1 region and 5' untranslated region (UTR).

Table 1. Polio case classification system used by South Africa's National Polio Expert Committee (NPEC).

Status	Classification	Code	Reason
Final	Confirmed (wild type)	A1	Wild-type poliovirus found in stool sample of case or one of the contacts.
	Confirmed (vaccine-associated)	B1	Vaccine-type poliovirus found in stool sample of case, which has residual paralysis at 60-day follow-up; and is confirmed clinically.
	Compatible	C1	AFP case lost to follow-up at 60 days.
		C2	Death related to the illness within 60 days.
		C3	Residual paralysis for which other no medical reason is evident.
	Discarded	D1	No residual paralysis and no wild polio found in stool samples.
		D2	Confirmed alternative diagnosis
		D3	Non-polio enterovirus isolated.
		D4	No virological investigation and a clinical picture incompatible with polio.
		D5	Two adequate negative stool specimens with 14 days of onset of paralysis
	Denotified	E1	Not an AFP case
Pending	Inadequate Information	F1	PEC is unable to make a decision due to the lack of information. The investigating team is given 30 days from the committee meeting to find further details. The final decision is taken at the next NPEC meeting.
	60-day follow-up not yet done	F2	Final decision is referred to the next NPEC meeting for final decision.

Results

South Africa

A total of 1026 faecal samples was received from 505 AFP cases with dates of onset of paralysis between 1 January and 31 December 2018. No wild-type strains were detected. Sabin poliovirus type 1 was detected in two cases (Gauteng & Mpumalanga provinces). Sabin poliovirus type 3 was

detected in two cases from Gauteng. Detection of Sabin virus from stool is usually a coincidental finding in countries using OPV; no case was classified by the NPEC as vaccine-associated paralytic poliomyelitis (VAPP). The 2018 NPEC final classification of 2018 AFP cases is listed in Table 2.

Table 2. Final classifications of acute flaccid paralysis (AFP) cases in South Africa, 2018, as at 30 September 2019 (courtesy of the National Department of Health).

Classification	Number	Percentage
Compatible	7	1.25
Discarded	516	91.81
Denotified (not an AFP)	20	3.56
iVDPV (immune deficient vaccine-derived Poliovirus)	1	0.18
Pending	18	3.2
Total	562	100

In October 2018, VDPV type 3 was detected in a 10-month-old child who presented with AFP in Johannesburg. Following recognition of the case, several activities were conducted as part of a multi-stakeholder public health response. These activities included 1) case investigation; 2) household and community contact investigation; 3) a vaccine coverage survey; and 4) active case finding. Case investigation revealed a rare immunodeficiency disorder, MHC class II deficiency (known as bare lymphocyte syndrome), with complete absence of HLA-DR expression on lymphocytes. The child completed the course of pocapavir treatment but with no improvement. The child subsequently died in March 2019.[2]

Of the 112 contacts tested, Sabin 1 and Sabin 3 polioviruses were isolated from two. Non-polio enteroviruses were isolated from seven of the contacts. Preliminary findings of the vaccination coverage survey revealed that 43% (67/156) of households had at least one child aged <5 years. Within these 67 households, 97 children were surveyed and Road to Health Booklets were available for review by healthcare workers in 69% of cases (n=67). Of these, 93% (62/67) had received age-appropriate vaccines as per their Road to Health Booklets.

Active case detection identified 14 missed AFP cases from 33 hospitals visited, which were reported to NPEC. For those without Road to Health Booklets, it was difficult to accurately determine their vaccination status.

Surveillance indicators:

The AFP detection rate measures the sensitivity of the surveillance program and is calculated on a district, provincial and country level (Table 3). The 2018 AFP detection rate for South Africa was 2.9/100 000 children under the age of 15 years, an improvement compared to the 2017 rate of 2.6/100 000. While the rate was below the country's target of 4.0/100 000, it exceeded the World Health Organization's target rate of 2.0/100 000. Mpumalanga, Free State and Limpopo provinces exceeded the 4.0/100 000 target; Eastern Cape, Gauteng, KwaZulu-Natal, Northern Cape and Western Cape provinces reached the WHO target but not the country target; North West and Western Cape provinces had a detection rate below 2.0/100 000. The North West provincial government was a site of political instability in 2018, with various departments under administration, including the North West Department of Health. Western Cape Province experienced challenges as a result of drought, devastating fires and financial constraints. There were two silent districts in Northern Cape Province, Namakwa DM and ZF Mgcawu DM, that should have reported at least one and five AFP cases respectively as per the WHO target rate of 2.0/100 000. These districts have small populations and low targets, which may explain why no cases were identified.

The national stool adequacy rate was 59% in 2018, below the required target of at least 80%. Table 4 indicates reasons for low stool adequacy.

Table 3. Field surveillance adequacy for acute flaccid paralysis (AFP) by district, South Africa, January – December 2018 (case-based data, courtesy of National Department of Health).

2018 AFP Summary

Province	District	Year	Total_population	Under15_years	Target_AFP_Case	Total NP AFP Cases in DB	Adequately_investigated_cases	Not_Adequately_investigated_cases	NP_Detection_Rate	Stool_Adequacy
Eastern Cape	A Nzo DM	2018	866,646	335,787	13	7	4	3	2.1	57.1
Eastern Cape	Amathole DM	2018	972,188	355,095	14	9	0	9	2.5	0.0
Eastern Cape	Buffalo City MM	2018	874,199	279,545	11	4	3	1	1.4	75.0
Eastern Cape	C Hani DM	2018	818,915	276,284	11	11	6	5	4.0	54.5
Eastern Cape	Joe Gqabi DM	2018	371,240	123,699	5	4	1	3	3.2	25.0
Eastern Cape	N Mandela Bay MM	2018	1,298,412	395,779	16	6	1	5	1.5	16.7
Eastern Cape	O Tambo DM	2018	1,492,014	564,261	23	21	7	14	3.7	33.3
Eastern Cape	Sarah Baartman DM	2018	522,720	164,358	7	1	1	0	0.6	100.0
Eastern Cape		**2018**	**7,216,334**	**2,494,808**	**100**	**63**	**23**	**40**	**2.5**	**36.5**
Free State	Fezile Dabi DM	2018	504,058	137,694	6	6	0	6	4.4	0.0
Free State	Lejweleputswa DM	2018	668,413	185,399	7	6	4	2	3.2	66.7
Free State	Mangaung MM	2018	808,251	217,613	9	7	4	3	3.2	57.1
Free State	T Mofutsanyana DM	2018	791,490	238,268	10	12	9	3	5.0	75.0
Free State	Xhariep DM	2018	129,309	33,828	1	2	1	1	5.9	50.0
Free State		**2018**	**2,901,521**	**812,802**	**33**	**33**	**18**	**15**	**4.1**	**54.5**
Gauteng	Ekurhuleni MM	2018	3,550,039	879,044	35	24	16	8	2.7	66.7
Gauteng	Johannesburg MM	2018	5,172,937	1,285,502	51	37	18	19	2.9	48.6
Gauteng	Sedibeng DM	2018	982,061	261,456	10	17	14	3	6.5	82.4
Gauteng	Tshwane MM	2018	3,454,751	890,907	36	18	11	7	2.0	61.1
Gauteng	West Rand DM	2018	879,799	229,236	9	13	6	7	5.7	46.2
Gauteng		**2018**	**14,039,587**	**3,546,145**	**142**	**109**	**65**	**44**	**3.1**	**59.6**
KwaZulu-Natal	Amajuba DM	2018	575,265	215,673	9	7	5	2	3.2	71.4
KwaZulu-Natal	eThekwini MM	2018	3,760,409	1,110,278	44	23	12	11	2.1	52.2
KwaZulu-Natal	Harry Gwala DM	2018	513,362	201,474	8	5	2	3	2.5	40.0
KwaZulu-Natal	iLembe DM	2018	702,222	234,902	9	6	6	0	2.6	100.0
KwaZulu-Natal	King Cetshwayo DM	2018	995,462	393,024	16	8	3	5	2.0	37.5
KwaZulu-Natal	Ugu DM	2018	780,676	281,537	11	12	7	5	4.3	58.3
KwaZulu-Natal	uMgungundlovu DM	2018	1,153,896	383,596	15	10	9	1	2.6	90.0
KwaZulu-Natal	Umkhanyakude DM	2018	693,899	272,439	11	7	3	4	2.6	42.9
KwaZulu-Natal	Umzinyathi DM	2018	571,650	217,031	9	6	1	5	2.8	16.7
KwaZulu-Natal	Uthukela DM	2018	755,749	301,890	12	10	8	2	3.3	80.0
KwaZulu-Natal	Zululand DM	2018	877,285	327,254	13	2	0	2	0.6	0.0
KwaZulu-Natal		**2018**	**11,379,875**	**3,939,098**	**158**	**96**	**56**	**40**	**2.4**	**58.3**
Limpopo	Capricorn DM	2018	1,335,951	412,584	17	20	13	7	4.8	65.0
Limpopo	Mopani DM	2018	1,222,202	388,636	16	19	13	6	4.9	68.4
Limpopo	Sekhukhune DM	2018	1,229,286	419,277	17	16	16	0	3.8	100.0
Limpopo	Vhembe DM	2018	1,451,836	493,193	20	20	19	1	4.1	95.0
Limpopo	Waterberg DM	2018	712,724	211,839	8	5	4	1	2.4	80.0
Limpopo		**2018**	**5,951,999**	**1,925,529**	**77**	**80**	**65**	**15**	**4.2**	**81.3**
Mpumalanga	Ehlanzeni DM	2018	1,732,249	575,055	23	32	28	4	5.6	87.5
Mpumalanga	G Sibande DM	2018	1,191,707	345,627	14	13	11	2	3.8	84.6
Mpumalanga	Nkangala DM	2018	1,523,787	404,108	16	20	14	6	4.9	70.0
Mpumalanga		**2018**	**4,447,743**	**1,324,790**	**53**	**65**	**53**	**12**	**4.9**	**81.5**
North West	Bojanala Platinum DM	2018	1,712,216	484,894	19	9	0	9	1.9	0.0
North West	Dr K Kaunda DM	2018	758,963	222,701	9	3	2	1	1.3	66.7
North West	Ngaka Modiri Molema DM	2018	954,615	294,050	12	3	2	1	1.0	66.7
North West	Ruth Segomotsi Mompati DM	2018	478,895	176,182	7	5	2	3	2.8	40.0
North West		**2018**	**3,904,689**	**1,177,827**	**47**	**20**	**6**	**14**	**1.7**	**30.0**
Northern Cape	Frances Baard DM	2018	381,046	102,053	4	3	1	2	2.9	33.3
Northern Cape	J T Gaetsewe DM	2018	243,123	77,817	3	2	2	0	2.6	100.0
Northern Cape	Pixley ka Seme DM	2018	209,241	56,412	2	5	5	0	8.9	100.0
Northern Cape	Namakwa DM	2018	113,585	28,508	1	0	0	0		
Northern Cape	ZF Mgcawu DM	2018	262,574	63,528	3	0	0	0		
Northern Cape		**2018**	**1,209,569**	**328,318**	**13**	**10**	**8**	**2**	**3.0**	**80.0**
Western Cape	Cape Town MM	2018	4,127,040	988,323	40	37	26	11	3.7	70.3
Western Cape	Cape Winelands DM	2018	912,107	238,105	10	7	4	3	2.9	57.1
Western Cape	Central Karoo DM	2018	76,634	21,252	1	1	0	1	4.7	0.0
Western Cape	Eden DM	2018	626,685	155,773	6	9	5	4	5.8	55.6
Western Cape	Overberg DM	2018	292,077	70,312	3	2	2	0	2.8	100.0
Western Cape	West Coast DM	2018	457,068	117,873	5	3	2	1	2.5	66.7
Western Cape		**2018**	**6,491,611**	**1,591,638**	**24**	**22**	**13**	**9**	**1.4**	**59.1**
South Africa		**2018**	**57,542,928**	**17,140,955**	**646**	**498**	**307**	**191**	**2.9**	**61.6**

Legend colour	Non-Polio AFP detection rate	Stool adequacy (%)
	1-1.99/100 000	<80
	2.00-3.99/100 000	
	>=4.0/100 000	>=80
	Silent district/zero-reporting	Silent district/zero-reporting

DM = district municipality, MM = metropolitan municipality, NP = Non-polio, DB = Database

Table 4. Reasons for low stool adequacy by province, acute flaccid paralysis (AFP) surveillance, South Africa, 2018 (courtesy of the WHO, South Africa).

	Reasons for Inadequately investigated cases						
Province	2nd stool not collected	Interval between stool is 0 days	Interval between stool is more than 48hrs	No Stool collected	Specimen not collected within 14 days of onset	Stool not on ice	**Total (Percentages shown represent totals)**
Eastern Cape	11	0	10	13	4	2	**40**
	(22.4%)	(0.0%)	(16.4%)	(41.9%)	(8.7%)	(18.2%)	**(19.1%)**
Free State	4	1	6	0	0	4	**15**
	(8.2%)	(9.1%)	(9.8%)	(0.0%)	(0.0%)	(36.4 %)	**(7.2%)**
Gauteng	14	3	16	9	5	0	**47**
	(28.6%)	(27.3%)	(26.2%)	(29.0%)	(10.9%)	(0.0%)	**(22.5%)**
KwaZulu-Natal	5	2	11	4	19	3	**44**
	(10.2%)	(18.2%)	(18.0%)	(12.9%)	(41.3%)	(27.3%)	**(21.1%)**
Limpopo	2	3	2	0	8	1	**16**
	(4.1%)	(27.3%)	(3.3%)	(0.0%)	(17.4%)	(9.1%)	**(7.7%)**
Mpumalanga	4	1	1	1	3	0	**10**
	(8.2%)	(9.1%)	(1.6%)	(3.2%)	(6.5%)	(0.0%)	**(4.8%)**
North West	7	1	3	2	1	0	**14**
	(14.3%)	(9.1%)	(4.9%)	(6.5%)	(2.2%)	(0.0%)	**(6.7%)**
Northern Cape	1	0	2	0	1	0	**4**
	(2.0%)	(0.0%)	(3.3%)	(0.0%)	(2.2%)	(0.0%)	**(1.9%)**
Western Cape	1	0	10	2	5	1	**19**
	(2.0%)	(0.0%)	(16.4%)	(6.5%)	(10.9%)	(9.1%)	**(9.1%)**
Total	49	11	61	31	46	11	**209**

Laboratory indicators: Reverse cold-chain should be observed in the transport of stool specimens to the laboratory. On arrival at the laboratory, 98.3% of the samples were received on ice. The interval between stool collection and arrival at the laboratory should be within 72 hours. In 2018, only 47.2% were received within three days or had two samples collected adequately. The stipulated target is that >80% of stool samples should reach the laboratory within three days of collection. Improvements are needed in terms of transport logistics to ensure samples reach the laboratory within the required timeframe. Continued training of healthcare workers is needed to ensure that the correct samples are collected.

Laboratory surveillance indicators showed that 96.5% of samples were reported within fourteen days of receipt, above the target of 80%. The non-polio enterovirus isolation rate was 12.3%, (target 10%), showing that laboratory systems are adequate to detect enterovirus.

Southern African countries supported by NICD

A total of 1858 stool samples was sent to the NICD's Polio Reference Laboratory from other southern African countries in 2018. Of these, 1856 were received in good condition and 95% were processed within 14 days of receipt. The non-polio isolation rate was 17%, implying that the sensitivity of the testing was adequate to detect polioviruses. No wild polioviruses were detected. One case of circulating VDPV type 2 (cVDPV2) was detected from Mozambique.

The broader African region

In 2018, 329 samples from cases and contacts of cases in Ethiopia, Niger and Democratic Republic of Congo were sent to the NICD for molecular analysis. VDPV type 2 was detected in 35 samples from Niger and Democratic Republic of Congo, owing to the circulating VDPV type 2 outbreak in these two countries. One case from Niger was Sabin 1. 288 samples were Sabin 2, with cases and contacts of cases from Ethiopia, Niger and Democratic Republic of Congo. The Sabin 2 polioviruses detected were most likely due to mop-up campaigns using monovalent OPV type 2 to restrict VDPV type 2 circulation in those countries where it had been detected. Updated data is available on the Global Polio Eradication Initiative website: www.polioeradication.org.[1]

Environmental surveillance for the African Region

The Polio Reference Laboratory supported the WHO by testing environmental samples as a supplement to AFP surveillance. From January to December 2018, the NICD received 98 samples from eight sites in Angola, 82 samples from four sites in Mozambique, 24 samples from four sites in Republic of South Sudan and 120 samples from eight sites in Zambia, with 44%, 56.1%, 33.3% and 52.5% of samples with non-polio enteroviruses detected respectively. Furthermore, 1.6% non-enteroviruses were detected from Zambia.

Molecular testing involved environmental samples from Uganda, Ethiopia and DRC. VDPV type 2 and Sabin 2 were detected from DRC. Sabin 3 was detected from Uganda and Ethiopia. Sabin 1, Sabin 2 and Sabin 3 were detected in samples from Mozambique and Zambia.

Conclusion

The global effort to eradicate polio is one of the largest public health initiatives in history. The AFP surveillance network needs to be highly sensitive, enabling the immediate detection of polioviruses and ensuring that the polio eradication mission is successful. In South Africa, North West and Western Cape provinces did not reach the WHO non-polio AFP detection rate target of 2.0 cases per 100 000, most likely due to a range of challenges experienced in 2018. Additionally, seven districts fell short of the target of 2.0 cases per 100 000. Also of concern is low overall stool sample adequacy. The surveillance system, however, was effective as it was able to detect and respond to a poliovirus event i.e. detection of a case of immune-deficiency associated VDPV in South Africa.

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CRYPTOCOCCAL ANTIGEN SCREENING SURVEILLANCE REPORT, SOUTH AFRICA, FEBRUARY 2017 – JULY 2019

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Executive summary

Thousands of South Africans with advanced HIV die each year from cryptococcal meningitis. Even with ideal antifungal treatment, mortality from this disease remains high. However, screening for cryptococcal antigenaemia among persons with CD4 counts below 100 cells/µL offers an opportunity to detect cryptococcal disease early and pre-emptively treat patients to prevent progression from antigenaemia to meningitis. Following a recommendation by the World Health Organization in 2011, South Africa piloted reflex laboratory-based cryptococcal antigen (CrAg) screening in 2012 and scaled this up to a national screening programme in 2016. During the period February 2017 to July 2019, over 600 000 patients were screened of which almost 35 000 (5.8%) were identified with cryptococcal antigenaemia, most of whom are working-age men with CD4 counts below 50 cells/µL. CrAg screening numbers remained steady over the reporting period, although a slight decrease in CrAg-positive cases was observed. Case burden was highest in urban areas, although prevalence nearing 10% has been observed in several rural areas of KwaZulu-Natal, Western Cape, and Eastern Cape provinces. Reflex testing has achieved a coverage of 99%, but questions remain as to the proportion of patients who receive adequate care following positive test results. Programmatic data collected by the CAST-NET study are expected to fill this knowledge gap and guide future screening programme improvements. This will hopefully ensure that South Africa's CrAg screening programme will prevent deaths caused by this HIV-related disease.

Introduction

Cryptococcal meningitis (CM) is the second leading cause of AIDS-related deaths worldwide and is responsible for nearly 200,000 deaths per year, the majority of which occur within sub-Saharan Africa.[1] Persons with very advanced HIV disease (CD4 count <100 cells/µL) are at highest risk for development of CM and, if left untreated, face certain death.[2]

Cryptococcal meningitis is caused by the ubiquitous environmental fungi *Cryptococcus neoformans* and *Cryptococcus gattii*. Infection can be diagnosed by lumbar puncture and antigen testing or by culturing of cerebrospinal fluid. Subsequent treatment requires hospitalisation, therapeutic lumbar punctures, and combination therapy with amphotericin B and either fluconazole or flucytosine. Even with optimal combination antifungal treatment, mortality is still nearly 40%. With fluconazole monotherapy, the only available treatment in much of sub-Saharan Africa, mortality can be in excess of 80%.[3–5] A recent clinical trial showed that 1-week combination therapy with amphotericin B and flucytosine for the induction phase of treatment can reduce mortality by 38%.[6]

An increase in antiretroviral treatment (ART coverage) was associated with a decline in CM incidence in resource-rich settings.[7] However, late presentation to care still persists in resource-limited countries, and a growing number of people identified with advanced HIV are now ART-experienced.[8] In South Africa, reductions in the numbers of people with CD4 counts <100 or <200 cells/µL (reductions that were previously realised following the expansion of ART coverage) have recently stalled, with over 30% of people seeking care having advanced HIV disease (CD4 < 200 cells/µL), and over 15% having very advanced disease (CD4 <100 cells/µL).[9]

Early detection of cryptococcal disease in persons with CD4 counts <100 cells/µL offers the opportunity to pre-emptively treat antigenaemia and possibly prevent progression to CM. Cryptococcal antigen (CrAg), a highly-specific biomarker of cryptococcal disease, can be found in the blood weeks to months prior to the development of CM, and is strongly associated with CM and CM-related mortality.[10,11] Previously detected by cryptococcal latex agglutination tests (CLAT), the development of inexpensive and highly accurate (>99% sensitivity and specificity) CrAg lateral flow assays (LFA) have made routine screening for early detection simpler.[12] A randomised-controlled trial conducted among outpatients in Tanzania and Zambia found that, along with ART adherence support, screening for CrAg and pre-emptively treating antigenaemia with fluconazole reduced

all-cause mortality by 28%.[13] CrAg screening is also cost-effective, and the World Health Organization (WHO) has recommended routine CrAg screening for all individuals with CD4 <100 cells/µL since 2011. This recommendation has recently expanded to include those with a CD4 count <200 cells/µL.[14]

Cryptococcal antigen screening in South Africa

Following the WHO's recommendation for routine CrAg screening, laboratory-based reflexive screening was first piloted in South Africa in 2012. In this reflex approach, all CD4 samples with results below 100 cells/µL were automatically, or *reflexively*, tested for CrAg using remnant plasma, allowing for CD4 count and CrAg test results to be returned to clinicians simultaneously. A subsequent cost-effectiveness analysis found this approach to be superior in terms of coverage and the potential for saving lives as compared to traditional provider-initiated CrAg screening.[15] These findings led to the inclusion of CrAg screening in South Africa's national ART guideline in 2015.[16] The programme was later scaled up to cover all provinces in 2016, making South Africa the first country in the world to implement a national routine screening programme for cryptococcal disease. Currently, a network of 45 National Health Laboratory Service (NHLS) CD4 laboratories reflexively screen all samples with CD4 <100 cells/µL nationwide.

Cryptococcal antigenaemia in South Africa, 2017 - 2019

Data extraction

CrAg test results are stored along with CD4 results in the NHLS laboratory information system, TrakCare. The NICD Surveillance Data Warehouse (SDW) routinely extracts and processes data stored in the TrakCare system for use in NICD surveillance. To obtain surveillance results for this report, epidemiologists from the NICD's Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses (CHARM) extracted all CD4 tests and accompanying CrAg results for all NHLS laboratories from 1 February 2017 through to 31 July 2019. February 2017 was chosen as the beginning of the reporting period due to a CrAg LFA kit recall that was in effect from October 2016 through to January 2017. The dataset obtained was subsequently restricted to the above-mentioned period and to include only tests coded as reflex CrAg tests performed by CD4 laboratories, excluding provider-ordered tests processed by NHLS microbiology laboratories. For reporting of patient-level data, deduplication was performed using a NHLS-developed algorithm and unique identifier based

on names and birth dates. Although not providing perfect deduplication, this algorithm has demonstrated >80% matching accuracy.[17]

Summary of the CrAg screening programme

From 1 February 2017 through to 31 July 2019, 721 323 CrAg tests were performed through the NHLS reflex screening programme. As these tests were performed automatically on eligible samples, patients with multiple CD4 tests below 100 cells/µL were retested for CrAg. Deduplication of test data revealed that 604 558 patients were screened through the programme, achieving 99% coverage of eligible patients. Of these, 34 534 were found to be CrAg-positive, giving a prevalence of 5.8%.

Demographics of people with cryptococcal antigenaemia

CrAg-positive patients were predominately men of working age, although more women in the late teens to late 20s age range ($p<0.001$) tested positive (Figure 1). The largest difference in the number of CrAg-positive test results between men and women occurred between the ages of 35 and 54 years. Across all age categories, the odds ratio of a CrAg-positive test for men to women was 1.26, adjusted for CD4 count (95% confidence interval (CI) = 1.23-1.29).

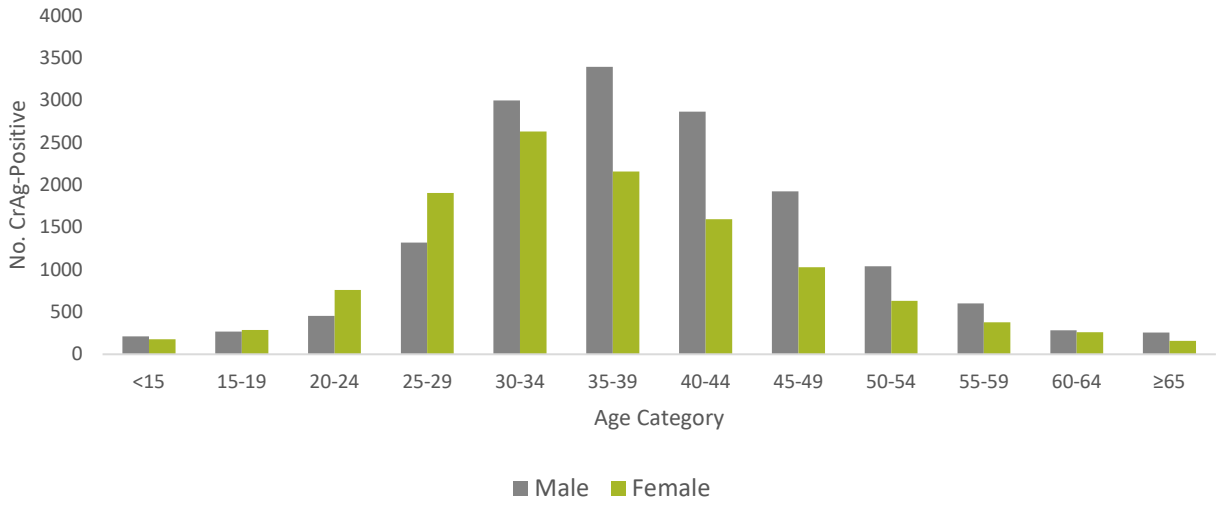

Figure1. Age and sex of cryptococcal antigen (CrAg)-positive patients, February 2017 – July 2019, South Africa.

CrAg and CD4 count

The number of CrAg-positive test results was inversely correlated to CD4 count, with most antigenaemia-positive persons detected in the lower CD4 count ranges. Almost half of the CrAg-positive patients had a CD4 count <30 cells/µL, and over 20% had a CD4 count <10 cells/µL at time of screening (Figure 2). Although most cases fell within the lower CD4 strata, over 8 800 CrAg-positive patients had CD4 counts between 50 and 99 cells/µL. Persons with CD4 counts ≤50 cells/µL were 1.95 (95% CI = 1.91-1.99) times more likely to be CrAg-positive, and were classified as *very* advanced HIV disease.

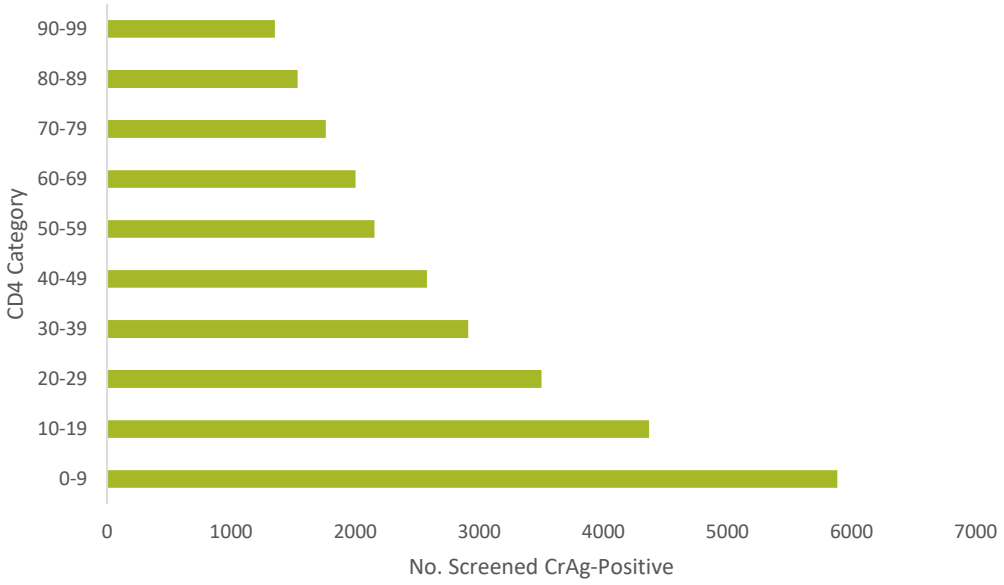

Figure 2. Distribution of CD4 count (cells/µL) categories (amongst cryptococcal antigen (CrAg)-positive patients, February 2017 – July 2019, South Africa.

CrAg screening and prevalence over time

On average, almost 24 000 tests were performed per month across South Africa. Yearly CrAg prevalence remained relatively constant across the survey period, ranging from 5.6% in 2017 to 5.8% in 2019. There was no significant trend in CrAg positivity over the 30-month surveillance period (p=0.11).

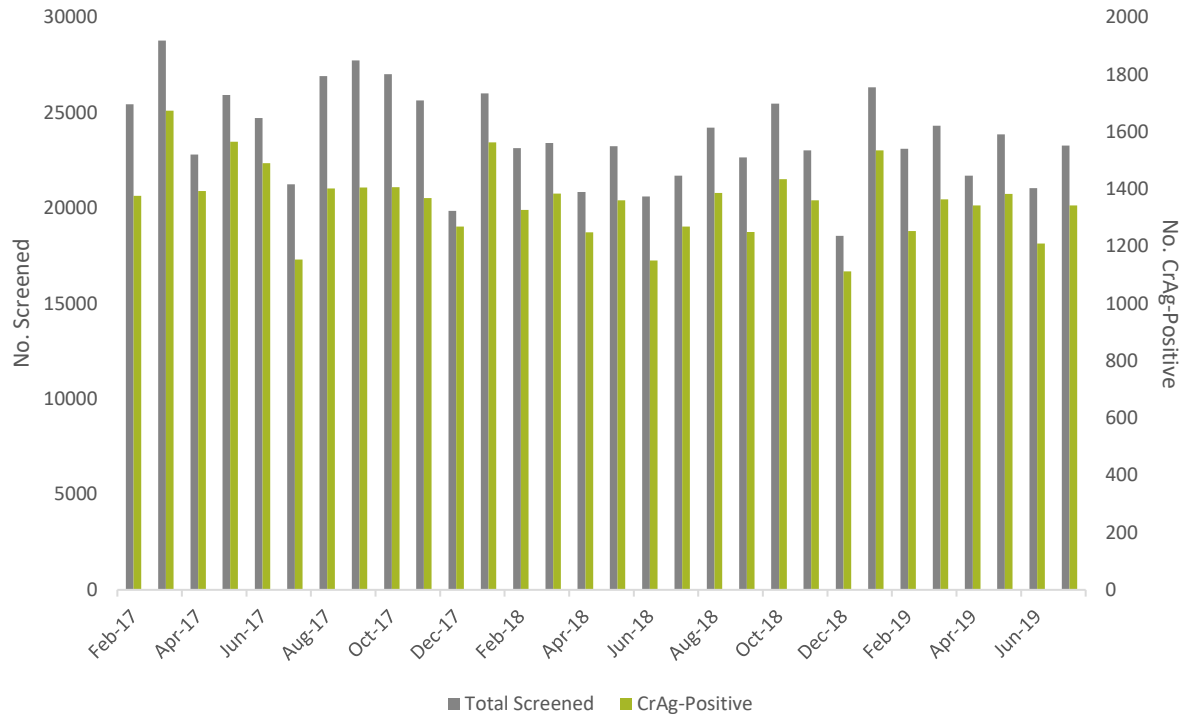

Figure 1. Numbers of patients screened for cryptococcal antigen (CrAg) and total positive by month, February 2017 – July 2019, South Africa.

Geographic distribution

CrAg prevalence and total number of CrAg-positive cases differed vastly by district (Figure 4). The highest prevalence and absolute case load was found in northern and central KwaZulu-Natal Province, while the sparsely-populated Northern Cape Province had the lowest prevalence and case burden. As expected, the metropoles had the largest absolute number of CrAg-positive cases. However, prevalence in Johannesburg, Pretoria, and Cape Town was lower than in Durban, East London and Port Elizabeth where the prevalence was in excess of 7.5%. Although few cases were detected in the northern districts of the Western Cape Province, the proportion of CrAg-positive patients mirrored that of the high-prevalence urban areas.

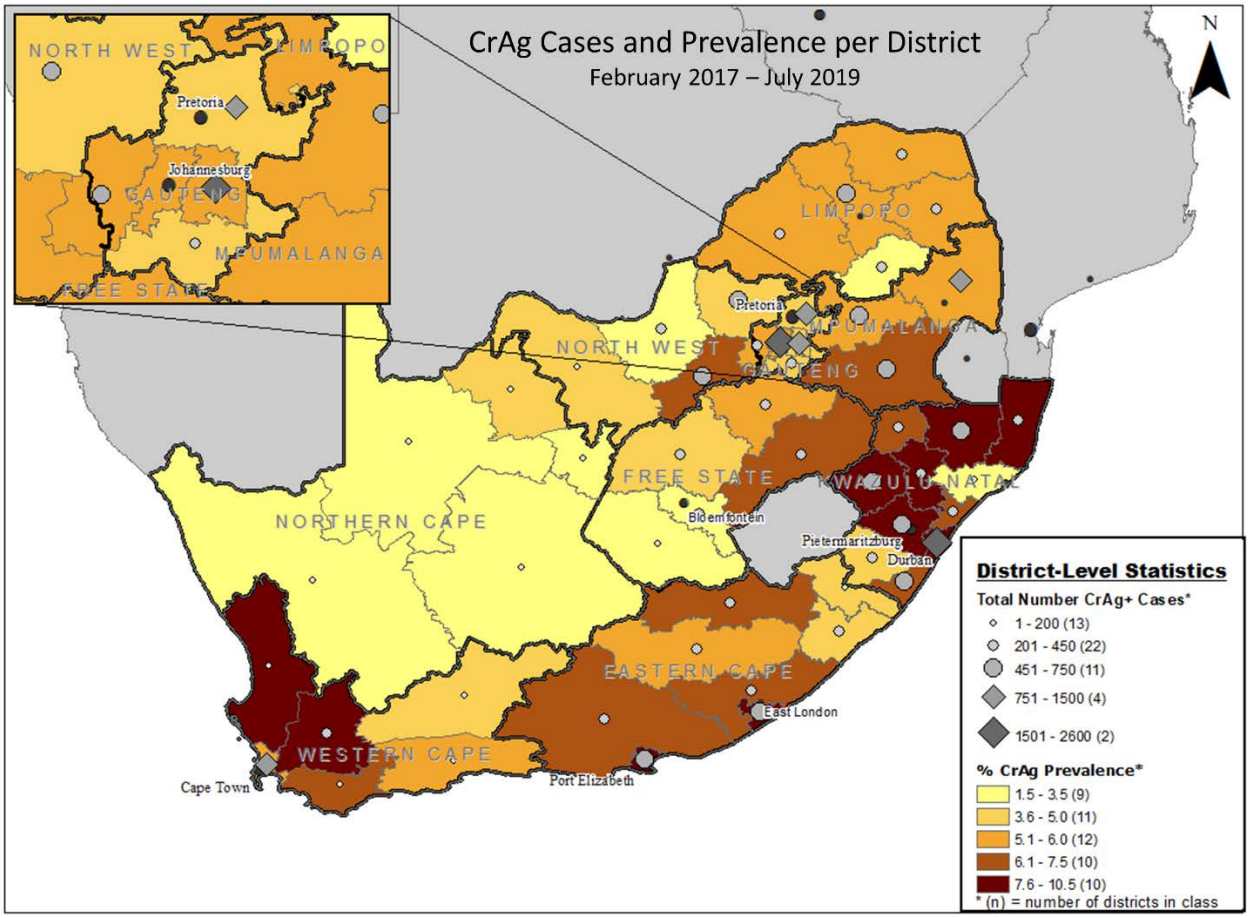

Figure 4. Cryptococcal antigen (CrAg) prevalence and total case counts by district and province, February 2017 - July 2019, South Africa.

Discussion

South Africa's national reflex CrAg screening programme has achieved successes in terms of its laboratory implementation and comprehensive coverage. Within the next year, >1 million patients will have been screened by this programme, making it the largest of its kind in the world. Reflexive screening coupled with functional information systems reveals important information about the epidemiology of cryptococcal disease in South Africa, and highlights the disproportionate disease burden in working age men in specific geographic areas. Such findings can be used to direct resources to key demographics and regions as well as to guide further investigation into the causes behind these trends.

Screening also provides the basis for clinical action to prevent or, at the very least, sooner detect CM in people with advanced HIV disease. Such results give healthcare workers the power to make

informed decisions regarding the management of these patients without the need to order the tests themselves. Test results are currently delivered by NHLS couriers to healthcare facilities and are also available on the NHLS's online TrakCare portal, making the results directly available to clinicians. Additional efforts have been undertaken to promote the receipt of and action on positive CrAg tests, such as the NICD's Results for Action (RFA) email and web portal delivery service for subscribed healthcare providers. Such a test result delivery system is critical to the functioning of South Africa's CrAg screening programme.

Although this programme's reflex approach maximises coverage and reduces the turnaround time of CrAg test results, it does not guarantee action on the part of healthcare providers. Clinical information and data related to patient outcomes is not routinely captured in laboratory-based surveillance and is not freely available for integration into such systems, making it difficult to ascertain the clinical successes or gaps of the screening programme on the ground. The CAST-NET study, a 5-year National Institutes of Health (NIH)-funded programme evaluation, seeks to fill this knowledge gap through collection of data from medical records and clinical outcomes of CrAg-positive patients in 27 sampled sub-districts covering all of South Africa's provinces. In this retrospective evaluation, the CAST-NET study seeks to collect data on over 5000 CrAg-positive patients at over 400 health facilities to determine whether clinical action was taken on CrAg test results and to assess the benefit realised by CrAg screening. Programmatic findings are expected in mid- to late-2020 and will provide insight into the functioning of this CrAg screening programme in the various contexts of South Africa's complex health system.

Conclusions

South Africa is the first country to fully implement a routine CrAg screening programme through its extensive CD4 laboratory network. Hundreds of thousands of patients were screened in two-and-a-half years, and tens of thousands identified with cryptococcal antigenaemia. CrAg prevalence varied by age, sex, CD4 count and geographic region, highlighting key groups and areas for future focus. More work needs to be done to assess and improve clinical action following receipt of positive CrAg results.

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INSECTICIDE RESISTANCE IN THE MAJOR ARBOVIRUS VECTOR *AEDES AEGYPTI* FROM JOHANNESBURG, SOUTH AFRICA, 2016

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Executive summary

Aedes aegypti is a major vector of dengue, chikungunya, Zika and yellow fever viruses. Currently, none of these viruses are in circulation in South Africa. Nevertheless, human-biting *Ae. aegypti* populations are abundant in KwaZulu-Natal, Eastern Cape and Gauteng provinces. Control of this species generally involves the use of insecticides. The aim of this project was therefore to assess the insecticide susceptibility status of two *Ae. aegypti* populations sampled in Johannesburg, Gauteng Province, as part of a broader assessment of the risk of future arbovirus circulation within South Africa in 2016. Using *Aedes* discriminating dosages of insecticide for the CDC bottle bioassay method, the peri-urban Muldersdrift population was fully susceptible to deltamethrin and tentatively resistant to bendiocarb, DDT and pirimiphos-methyl. The urban Linden population showed resistance to DDT and pirimiphos methyl, possible resistance to deltamethrin and full susceptibility to bendiocarb. Molecular sequence analysis showed no evidence of any knock-down resistance mutations within the voltage-gated sodium ion channel. It is concluded that insecticide susceptibility in *Ae. aegypti* in Johannesburg is variable and localised. Should control of this species become necessary in Johannesburg in the future, these data can be used to inform the choices of insecticide to be used.

Introduction

Aedes aegypti is a major vector of arboviruses including dengue (DENV), chikungunya (CHIKV), Zika (ZIKV) and yellow fever.[1] Transmission of these viruses is primarily of concern in tropical and sub-tropical regions.[2,3]

Human-biting *Ae. aegypti* occur sporadically in urban environments throughout much of South Africa and are most abundant along the east coast, particularly KwaZulu-Natal and Eastern Cape provinces, as well as in the high altitude Gauteng Province.[4] There are no recent reports of locally acquired cases of dengue, chikungunya, Zika or yellow fever in South Africa although it has been experimentally shown that local *Ae. aegypti* populations can potentially support dengue and yellow fever transmission.[5,6] All recent dengue cases recorded in South Africa were imported from other regions, especially southeast Asia, and central and West Africa.[7] Historically, local dengue cases occurred during an outbreak in Durban in 1926/27.[8] However, the occurrence of dengue in northern Mozambique[9] and along the east coast of Africa suggests that an outbreak could occur in South Africa, particularly where there are sizeable and competent *Ae. aegypti* populations that could set up a secondary transmission cycle.

Control of *Ae. aegypti* generally involves the use of insecticides for larval control and/or space-spraying against adult mosquitoes. In addition, management and removal of known and potential breeding sites, small water containers in particular, is advocated through a multi-sectoral approach. However, burgeoning resistance to insecticides in *Ae. aegypti* populations in the Americas, Africa and Asia pose a significant threat to the efficacy of this approach.[10]

Given the occurrence of dengue in Mozambique and the recent global outbreaks of Zika virus, it is necessary to assess the risk of such arbovirus circulation occurring in South Africa (last reviewed by Jupp & Kemp in 1996[4]). This includes surveillance for significant *Ae. aegypti* populations followed by assessments of their competence as vectors and their susceptibility to insecticides, should control of this species become necessary in the future. The aim of this project was therefore to assess the insecticide susceptibility status of two *Ae. aegypti* populations sampled in Johannesburg, Gauteng Province, South Africa.

Materials and Methods

Mosquito collections

During the months of January to March, 2016, samples of *Ae. aegypti* females were collected indoors and outdoors using hand aspirators at two localities in the greater Johannesburg area. Muldersdrift (25.9903S; 27.9E) is a peri-urban area approximately 25km north of Linden (26.1342S; 28.0023E), an urban suburb of Johannesburg. The Muldersdrift property sizes average around 9 hectares (21 acres) and are used for small-scale agricultural purposes with mostly open grassland environments. The Linden properties are no bigger than half an acre and the suburb is well covered with many large trees creating an urban forest. The collected mosquitoes were transported to the Botha De Meillon insectary of the National Institute for Communicable Diseases (NICD) where they were induced to lay eggs. Their progeny were used to establish locality-specific laboratory colonies.

Insecticide susceptibility bioassays

Once the colonies were established through four generations, samples of 2-5 day old females were drawn from each for insecticide susceptibility assessments. These were conducted using the standard Centres for Disease Control & Prevention (CDC) bottle bioassays for assessing insecticide susceptibility in *Aedes* mosquitoes.[11] Glass bottles of 250 ml volume were treated with discriminating concentrations of insecticides according to standard specifications and using insecticides and solvents supplied by the CDC. Table 1 gives the insecticides used, their discriminating concentrations and exposure times. Note that these discriminating concentrations are designed to distinguish between insecticide susceptible and resistant mosquitoes based on a response-to-exposure endpoint assay.[11] For each assay, 20 – 25 mosquitoes per bottle were exposed to insecticides for fixed periods of time (Table 1) following which they were transferred to holding cups for a 24-hour recovery period during which survivors were given access to cotton wool pads soaked in a 10% sucrose solution. Exposures to each insecticide were replicated four times and controls included concurrent exposures to bottles treated with solvent (acetone) only. Knock-down in each bottle was recorded immediately after each exposure and final mortalities were recorded 24 h post exposure.

Table 1. Insecticides (by class), concentrations per bottle and exposure times used to assess the susceptibilities of two populations of *Aedes aegypti*.[11]

Insecticide (class)	Concentration (ug active ingredient per 250 ml bottle)	Exposure time (mins)
Bendiocarb (carbamate)	12.5	30
DDT (organochlorine)	75	30
Deltamethrin (pyrethroid)	10	45
Pirimiphos-methyl (organophosphate)	20	30

Molecular assessment of knock-down resistance mutations

Sequence analyses of the voltage-gated sodium channel (*VGSC*) gene were conducted using 2 DDT susceptible and 5 DDT resistant *Ae. aegypti* from the Linden laboratory colony. DNA was extracted from each sample using prepGEM® DNA Extraction Kits (ZyGEM™). PCR was performed on the samples using different primers sets to amplify the regions corresponding to knock-down resistance (*kdr*) type mutations in the *VGSC* gene (Table 2). Primer3 software was used for the design of the primer sets 1 - 3. The PCR cycling conditions were: initial denaturation at 94°C for 3 min, followed by 35 cycles of 94°C for 30 sec, 52.6°C for 30 sec for primer sets 1 and 4 or 57°C for 30 sec for primer sets 2 and 3, 72°C for 1 min and a final elongation step at 72°C for 7 min.

Table 2. Sets of primers used to amplify regions corresponding to knock-down resistance (*kdr*) mutations in the voltage-gated sodium channel (VGSC) gene (AAEL006019, VectorBase) of *Aedes aegypti* from Linden, Johannesburg.

Primer set		Primer sequence	Possible *kdr* mutation in region of amplification
1	Forward	TTCATCTAACGCAACCCACA	G923V
	Reverse	GCTTCCATTCGAAATGCTGT	
2	Forward	AATCTCGTATAAAATACTGAACAAACG	L982W; S989P; I1011M/V; V1016I/G
	Reverse	TGAGATGATTGTGCTGCTCAC	
3	Forward	TACGTCCTCGATCCTTCCAG	T1520I; F1534C
	Reverse	GCAAACTGCGTTCTTAACGAT	
4	Forward	GTCAAGGGTGCCAAAGGT (Li et al., 2015)	D1763Y
	Reverse	TTCCGAGCGAAGAAGTCC (Li et al., 2015)	

PCR products were purified and sequenced via Macrogen. The electropherogram of the sequences were manually analysed using BioEdit version 7.2.5.[12] Subsequently, the nucleotide sequences were aligned with the *VGSC* gene (AAEL006019, VectorBase: https://www.vectorbase.org/) using either MUSCLE multiple sequence alignment (https://www.ebi.ac.uk/Tools/msa/muscle/) or EMBOSS Needle Pairwise sequence alignment (https://www.ebi.ac.uk/Tools/psa/emboss_needle/nucleotide.html).

Results

Complete survival of all control samples in the exposure bioassays indicated that no mortality test data needed to be adjusted. According to WHO criteria[11], an overall mortality of >98% indicates susceptibility to the test insecticide, 90-98% mortality indicates a possibility of resistance development that should be explored further and <90% indicates established resistance, assuming an adequate sample size and number of replicates. Using these criteria, the Muldersdrift population was fully susceptible to the pyrethroid deltamethrin and gave indications of possible resistance to bendiocarb, DDT and pirimiphos-methyl (Table 3, Figure 1). The Linden population showed

resistance to DDT and pirimiphos-methyl, possible resistance to deltamethrin and full susceptibility to bendiocarb (Table 4, Figure 1).

Table 3. Overall and mean percentage mortalities 24 h post exposure of *Aedes aegypti* samples originating from Muldersdrift to listed insecticides. Standard deviations (SD) are given in parentheses. Insecticide susceptibility status is given as R=resistant, PR=potentially resistant, S=susceptible, based on standard WHO criteria.[11]

Insecticide	# Alive	# Dead	Overall % mortality	Mean % mortality (SD)	Susceptibility status
Bendiocarb	4	89	95.7	96 (8)	PR
DDT	6	96	94.1	94.5 (4.66)	PR
Deltamethrin	2	108	98.2	98 (4)	S
Pirimiphos-methyl	3	89	96.7	97.15 (3.57)	PR
Controls	83	0	0	0	-

Table 4. Overall and mean percentage mortalities 24 h post exposure of *Aedes aegypti* samples originating from Linden to listed insecticides. Standard deviations (SD) are given in parentheses. Insecticide susceptibility status is given as R=resistant, PR=potentially resistant, S=susceptible, based on standard WHO criteria.[19]

Insecticide	# Alive	# Dead	Overall % mortality	Mean % mortality (SD)	Susceptibility status
Bendiocarb	2	112	98.24	98.2 (3.55)	S
DDT	32	78	70.9	71.33 (8.86)	R
Deltamethrin	4	102	96.2	96 (8)	PR
Pirimiphos-methyl	22	79	78.2	77.6 (6.34)	R
Controls	99	0	0	0	-

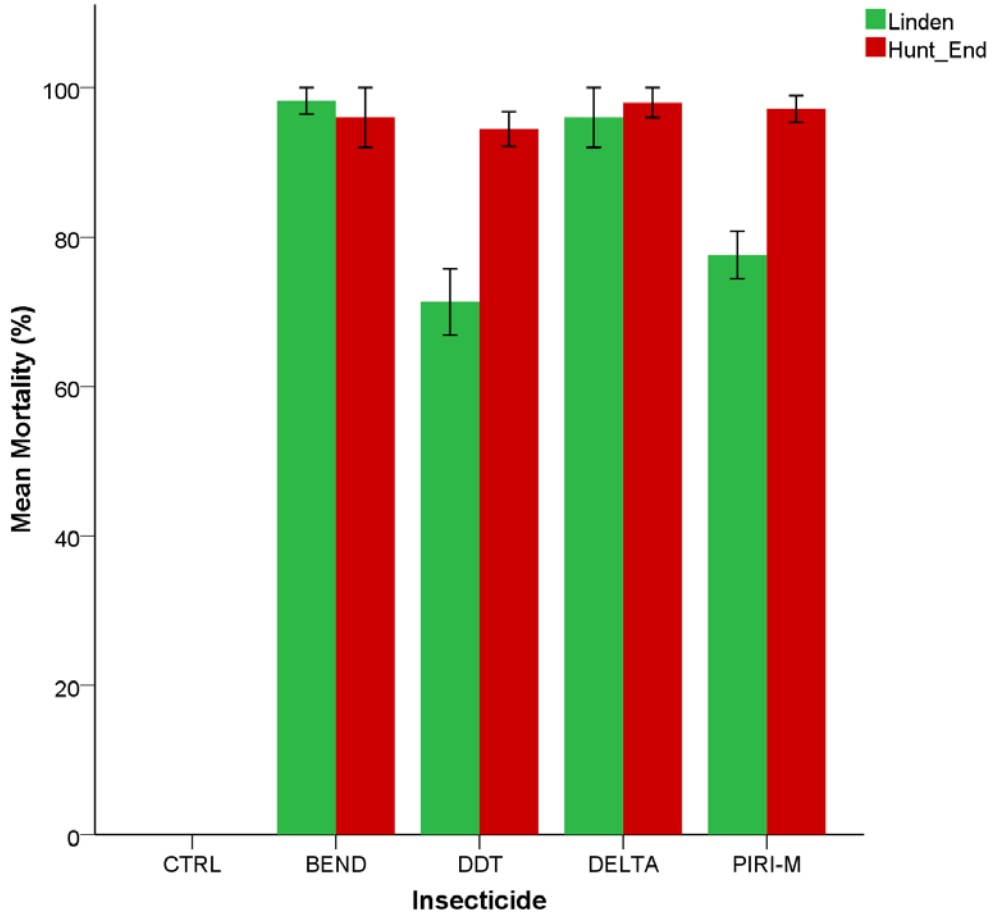

Figure 1. Mean percentage mortalities 24 h post exposure of *Aedes aegypti* samples originating from Muldersdrift (Hunt-End) and Linden to listed insecticides. CTRL=controls; BEND=bendiocarb; DDT= diethyl-dichloro-trichloroethane; DELTA=deltamethrin; PIRI-M=pirimiphos-methyl.

Molecular sequence analysis using DDT/pyrethroid phenotypically characterised samples showed no evidence of any knock-down resistance mutations in positions G923, L982, S989, I1011, V1016, T1520, F1534 and D1763 of the voltage gated sodium ion channel.

Discussion & conclusion

Aedes aegypti adults tend not to disperse far from where they acquire their blood meals, especially when there are sufficient oviposition sites available. There is therefore likely to be little, if any, gene flow between the Muldersdrift and Linden populations which are approximately 25 km apart, except for the fact that they could be inadvertently dispersed between these sites by ground transportation. Nevertheless, the variation in the insecticide susceptibilities between these populations suggests that there is very limited gene flow between them.

Linden is a suburb of Johannesburg which is typically urban and in which land use is primarily residential interspersed with commercial retail clusters. The clear resistances to DDT and pirimiphos-methyl in this *Ae. aegypti* population are somewhat surprising because neither of these insecticides are used in commercially available pesticide products (such as domestic aerosols), with the possible exception of organophosphates in garden pest sprays, and there are no specific public health interventions in this suburb that incorporate their use. These resistance phenotypes may therefore be by-products of general adaptation to a wide range of toxicants that leach into urban environments, including mosquito breeding sites. For example, a link between resistance to DDT and heavy metal pollutants in the malaria vector *Anopheles arabiensis* has been described.[13]

The Muldersdrift *Ae. aegypti* colony showed only possible resistances to bendiocarb, DDT and pirimiphos-methyl, suggesting that commercial insecticide use and environmental pollution are much less and not imposing intense adaptive selection on this population. This may not be surprising considering that this area is devoted mostly to equine associated activities and small-scale cattle farming. Agricultural farming is restricted to vegetable production in tunnels or grass cultivation for animal feed. Nevertheless, the small number of exposure survivors to these insecticides raises the likelihood that genetic resistance is developing in this population, albeit at low frequency.

There is little information on the current status of insecticide susceptibility in African populations of *Ae. aegypti* with data limited to localised surveys in the west and central African regions. From the global data that are available, it is interesting to note that resistance to the organochlorines (including DDT) is consistently high in *Ae. aegypti*, congruent with the results from the Linden population, whereas resistance to other insecticide classes are more variable and localised. Mechanistically, knock-down resistance (*kdr*) mutations conferring pyrethroid and DDT resistance

are especially common in *Ae. aegypti*. Moyes et al.[10] describe 10 mutations at 8 codon positions in domains II – IV of the voltage gated sodium channel, comprising 15 haplotypes. It is therefore surprising that no *kdr*-type mutations were detected in either population sampled here, suggesting that the DDT and pyrethroid (tentative) resistances are metabolically mediated.

It is concluded that insecticide susceptibility in *Ae. aegypti* in Johannesburg is variable and localised with clear evidence of resistant phenotypes in the Linden population. Should a vertically managed insecticide-based control programme aimed at this species become necessary in Johannesburg in the future, these data can be used to inform the choices of insecticide to be used amongst other interventions, such as breeding site clearance.

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