GERMS SOUTH AFRICA

Annual Report 2008

NHLS

NICD

The GERMS-SA Annual Report 2008 was compiled by the National Institute for Communicable Diseases, Johannesburg, South Africa.

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Introduction

The 2008 Annual Report includes a summary of findings from national surveillance including enhanced surveillance sites (ESS), at 25 hospitals in 9 provinces, for the year. A new section highlights the rate of HIV testing amongst patients actively enrolled in the ESS project and the high prevalence of HIV infection amongst cases.

In 2008, routine surveillance audits were conducted for the second year, using the NHLS Corporate Data Warehouse (CDW). A decision was made to collect and process only cryptococcal isolates from case patients diagnosed at enhanced surveillance sites after 1 July 2008. This should not have affected recorded cryptococcal case numbers as the primary source of data for case numbers has been the NHLS CDW in 2007 and 2008. In addition, ongoing submission of case report forms from KwaZulu-Natal and private-sector laboratories, where case data were not captured by NHLS CDW, ensure that these cryptococcal cases were also counted. There were no other major changes to surveillance methodology during 2008.

The surveillance programme is now able to provide several years of data collected systematically in a standardised fashion. This is critical if GERMS-SA is to provide robust data on trends in disease burden over time. GERMS-SA has now entered a stable phase, where data have been translated into information to inform public health policy related to HIV-associated opportunistic infections. This annual report demonstrates this through the provision of core surveillance findings for 2008.

Methods

The methods utilised by the GERMS-SA surveillance programme have been previously described in detail (1).

In brief, approximately 180 South African clinical microbiology laboratories participated in the surveillance programme in 2008. The population under surveillance in 2008 was estimated at 48.3 million. Diagnostic laboratories reported case patients to the NICD using laboratory case report forms, according to standard case definitions. If available, isolates from case patients were submitted on Dorset transport media to the NICD for further phenotypic and genotypic characterisation. From 1 July 2008, surveillance methodology for the cryptococcal project was changed, so that only ESS, NHLS laboratories in KwaZulu-Natal, and laboratories in the private, mining, and military sectors were required to directly report case patients to NICD (Figure 1) . For other cryptococcal case patients, data were obtained directly from the NHLS CDW. Cryptococcal isolates, obtained from case patients at ESS, continued to be characterised by phenotypic and genotypic tests.

At ESS, surveillance officers completed clinical case report forms for patients with 7 laboratory-confirmed diseases (cryptococcosis, *Pneumocystis jirovecii* pneumonia (PCP), invasive salmonellosis, invasive pneumococcal disease, invasive shigellosis, invasive meningococcal disease, and invasive *Haemophilus influenzae* disease), by case patient interview or hospital medical record review, to obtain additional clinical details, including antimicrobial use, vaccination history, HIV infection status, and patient outcome. Case patients were followed up only 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 an Epi Info version 6.04d database (Centers for Disease Control and Prevention (CDC), Atlanta, USA). A surveillance audit was performed for NHLS laboratories in 8 provinces (excluding KwaZulu-Natal) between 1 January and 31 December 2008, using the NHLS CDW. For all diseases under surveillance except cryptococcosis, the audit was designed to detect basic demographic and laboratory data from additional case patients, with laboratory-confirmed disease not already reported to GERMS-SA by participating laboratories. For cryptococcosis, the audit was designed to obtain data, from case patients, which were no longer reported by NHLS laboratories in 8 provinces. In 2008, the audit did not include

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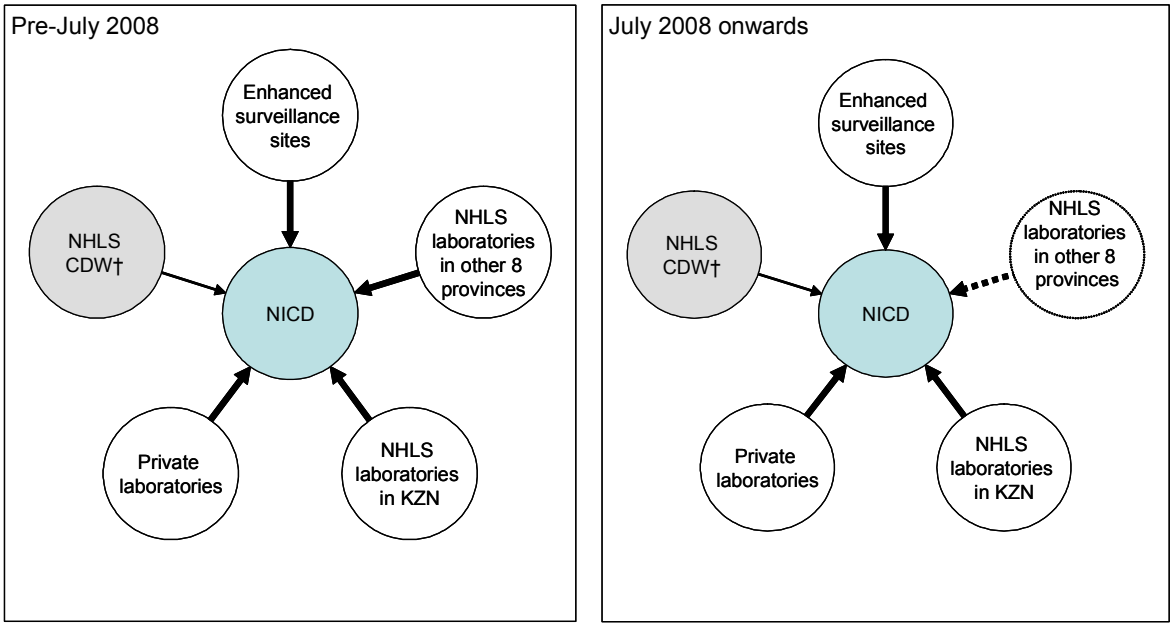

Figure 1: Change in methods for detection of laboratory-confirmed cryptococcal cases by GERMS-SA, pre- and post-July 2008

NICD: National Institute for Communicable Disease; NHLS: National Health Laboratory Services; KZN: KwaZulu-Natal; †NHLS CDW: NHLS Corporate Data Warehouse provided data on laboratory-confirmed cases from all NHLS laboratories (Except KwaZulu-Natal and including enhanced surveillance sites); thick arrows indicate submission of isolates and data, whereas, thin arrows indicate data detection only; dotted lines indicate termination of reporting.

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P. jirovecii and diarrhoeagenic *Escherichia coli*. Data from case patients, detected by audit, were included on the surveillance database, and have been included in this report. Since cryptococcosis is a recurrent disease amongst HIV-infected patients, data from case patients reported in 2008 are compared to similar data reported between 2005 and 2007 to identify patients with "true incident disease" in 2008. However, this de-duplication, data-cleaning process has not yet been completed, so not all case patients with reported, incident cryptococcal disease in 2008 may have truly incident disease. Incidence rates were calculated using mid-year population estimates for 2007 and 2008 from Statistics South Africa (Table 1) (2). Incidence rates in the HIV-infected and AIDS populations were calculated for 2007 and 2008, using estimated population denominators from the Actuarial Society of South Africa (ASSA) 2003 model (Table 1), assuming that HIV/AIDS prevalence amongst cases with known status was similar to those with unknown status (3). All reported incidence rates are expressed as cases per 100,000 population, unless otherwise stated. Reported p-values were calculated using the Mantel-Haenszel chi-squared test and p-values < 0.05 were considered significant.

Ethics approval for the ongoing activities of the surveillance programme was obtained from the Human Research Ethics Committee (Medical), University of Witwatersrand (clearance number M08-11-17). In addition, approval was sought from the Office of the Associate Director for Science, CDC. Surveillance activities were funded by the NICD/ NHLS, and ESS activities continued to be partially funded by a CDC-NICD Cooperative Agreement (U62/CCU022901).

Table 1: Population denominators used to calculate incidence rates, 2007 and 2008.

Province	General population*		HIV-infected population**		AIDS population**	
	2007	2008	2007	2008	2007	2008
Eastern Cape	6,568,754	6,579,245	698,699	728,915	70,031	75,300
Free State	2,865,472	2,877,694	391,527	393,863	48,392	49,656
Gauteng	10,294,862	10,447,246	1,431,389	1,446,094	162,429	165,632
KwaZulu-Natal	10,045,594	10,105,437	1,552,390	1,560,573	200,628	204,976
Limpopo	5,232,681	5,274,836	415,652	433,820	42,559	45,229
Mpumalanga	3,562,197	3,589,909	450,975	455,135	59,017	59,581
Northern Cape	1,123,037	1,125,881	64,610	67,330	6,075	6,787
North West	3,404,643	3,425,153	489,585	496,274	57,718	60,618
Western Cape	5,190,084	5,261,922	283,742	297,669	22,524	25,499
South Africa	**48,287,324**	**48,687,323**	**5,778,569**	**5,879,674**	**669,373**	**693,278**

Data source: *Statistics South Africa; **Actuarial Society of South Africa (ASSA)

Operational Report

Site visits

In 2008, NICD staff members visited 17 surveillance sites in 5 provinces (Table 2). This provided opportunity to engage with the laboratories and hospitals participating in the programme.

Surveillance audit

The surveillance audit detected more than 3,400 additional case patients who had not been reported to the surveillance programme; these included 1,510 patients with cryptococcosis not reported by participating laboratories prior to 1 July 2008, and 127 patients with cryptococcosis not reported by enhanced surveillance sites after this date (Table 3). In addition, after reporting requirements for the cryptococcal surveillance project changed for NHLS laboratories in eight provinces, 2,144 patients from non-enhanced surveillance sites were detected by audit.

Predictors of non-reporting

At the end of 2007, a complete audit of laboratory-confirmed cases reported to GERMS-SA in 2007 was performed using the NHLS CDW. An analytical, cross-sectional study of secondary data obtained from the 2007 audits was conducted, whereby predictors of non-reporting of

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cases were identified by univariate and multivariable logistic regression (Table 4). In 2007, a total of 11,576 patients with laboratory-confirmed invasive disease due to *Salmonella* species*, Shigella* species*, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis* and *Cryptococcus* species were detected from NHLS laboratories by the surveillance programme, 2,890 (25%) of which were not reported to GERMS-SA. Of the 794 cases of *Salmonella* spp. and 56 cases of *Shigella* spp., 168 (21%) and 14 (25%), respectively, were non-reported. A total of 4,017 cases of *S. pneumoniae*, 431 cases of *N. meningitidis*, and 325 cases of *H. influenzae* were detected, of which 804 (20%), 46 (11%), and 85 (26%), respectively, were non-reported. Of the 5,953 cases of *Cryptococcus* spp., 1,773 (30%) were non-reported.

On univariate analysis, the percentage of cases that were non-reported differed significantly from reported cases by organism, province, specimen type, and ESS. Controlling for potential confounding variables, multivariable analysis showed the following predictors of non-reporting of cases: organism, province, specimen, and non-ESS. As compared to non-reporting of *N. meningitidis*, non-reporting was 2.6 times more likely for *Cryptococcus* spp. and *H. influenzae*, 2.3 times more likely for *Shigella* spp., 1.8 times more likely for *Salmonella* spp., and 1.6 times more likely for *S. pneumoniae*. Compared to non-reporting of cases from Free State Province, non-reporting was 3.5 times more likely from the Eastern Cape, 2.9 times more likely from Mpumalanga, 2.7 times more likely from the Northern Cape, and 2.6 times more likely from Limpopo. Non-reporting of case patients diagnosed from "other" specimen types, including pleural, joint, and unspecified fluid types, was 6.9 times more likely than the non-reporting of both CSF and blood culture specimen types. Finally, as would be expected, cases from non-ESS were 3.3 times more likely to be non-reported than those from ESS, where cases were actively followed up.

In conclusion, predictors of non-reporting of cases of laboratory-confirmed, invasive disease to GERMS-SA included organism type, specimen type, province, and non-enhanced surveillance site. These factors, therefore, need to be targeted in order to improve reporting from participating laboratories in the surveillance network.

Enhanced surveillance site performance indicators

Since 2007, ESS operational reports (ESSOR) have been provided to the site coordinators, laboratory staff members and surveillance officers to enable the ESS team to regularly review site performance, in comparison with set targets. The main objective of these reports was to provide information regarding the overall functioning of the surveillance site, by providing indicators of laboratory participation (submission of isolates), and indicators of surveillance officer performance (completion of clinical case report forms) (Table 5). By reviewing these indicators, problems with data collection were targeted, and recommendations were provided to improve the site performance. In 2008, these reports were provided quarterly.

Coordination meetings

Surveillance Officer meeting, 12-13 March 2008: This meeting, convened at the NICD in Johannesburg, was attended by 19 surveillance officers from 9 provinces. The meeting included two days of training, discussion of ESS performance indicators, and a session on dealing with the terminally-ill patient. The focus of the meeting was on performance.

Principal Investigator (PI) meeting, 5-6 November 2008: Convened at the NICD, this meeting was attended by over 50 local, national and international delegates, including representatives from the Department of Health and CDC. Surveillance and research activities were reviewed, and new NICD projects which could impact on the GERMS-SA network were discussed. The focus of the meeting was on how GERMS-SA should respond to the new vaccines included as part of the South African Expanded Programme on Immunisation (EPI) in 2009.

Surveillance Officer meeting, 13-14 November 2008: This 2-day meeting, convened at the NICD, was attended by 18 surveillance officers from 9 provinces. Data obtained from questions, included on the clinical case report form in 2008, were reviewed, the changes to the clinical case report form for 2009 were reviewed, and feedback from the Principal Investigator's Meeting was provided. The meeting focused on strategies to optimally capture information related to the new vaccines, included as part of the EPI in 2009.

Table 2: GERMS-SA surveillance site visits between 1 January and 31 December, 2008.

Date	Province	Laboratory	Hospital
1 April 2008	Gauteng	NHLS Natalspruit	Natalspruit Hospital
2 July 2008	Gauteng	NHLS Far East Rand	Far East Rand Hospital
31 July 2008	Gauteng	NHLS Helen Joseph	Helen Joseph Hospital
26 August 2008	Gauteng	NHLS Pretoria Academic	Pretoria Academic Hospital
9-10 September	Limpopo	NHLS Mankweng	Mankweng Hospital
2008		NHLS Polokwane	Polokwane Hospital
		NHLS Potgietersrus	Potgietersrus Hospital
		NHLS Jane Furse	Jane Furse Hospital
		NHLS Tzaneen	Tzaneen Hospital
2 July 2008	Mpumalanga	NHLS Ermelo	Ermelo Hospital
14-16 July 2008	Mpumalanga	NHLS Shongwe	Shongwe Hospital
		NHLS Rob Ferreira	Rob Ferreira Hospital
		NHLS Barberton	Barberton Hospital
7 March 2008	North West	NHLS Rustenburg	Rustenburg Provincial Hospital
13-14 May 2008	Western Cape	NHLS Tygerberg	Tygerberg Hospital
		NHLS Greenpoint	-
		NHLS Groote Schuur	Groote Schuur Hospital

Table 3: Cases detected by surveillance audit by province, 2008.

Surveillance case		Percentage of cases detected by audit* n_1/n_2 (%)	Number of cases detected by audit									
			EC	FS	GA	KZ	LP	MP	NC	NW	WC	SA
Invasive	Typhoid**	2/68 (3)	0	0	1	0	0	1	0	0	0	**2**
	Non-typhoidal salmonellosis†	126/934 (13)	47	3	41	0	5	7	2	8	13	**126**
	Shigellosis	12/70 (17)	4	0	7	0	1	0	0	0	0	**12**
	Cryptococcosis†††	1,637/5,362 (31)	439	100	374	0	135	276	12	151	150	**1,637**
	Meningococcal disease	59/456 (13)	4	1	35	0	1	9	0	5	4	**59**
	Haemophilus influenzae disease	112/392 (29)	14	6	45	0	2	9	1	3	32	**112**
	Pneumococcal disease	935/4843 (19)	142	71	411	0	51	115	9	64	72	**935**
Non-invasive	Salmonella Typhi**	0/14 (0)	0	0	0	0	0	0	0	0	0	**0**
	Non-typhoidal salmonellosis†	328/1419 (23)	37	23	129	0	35	35	10	32	27	**328**
	Shigellosis	189/1444 (13)	16	15	70	0	17	22	1	13	35	**189**
	Cholera††	12/197 (6)	0	0	1	0	7	4	0	0	0	**12**
Total		**3,412/15,199 (22)**	**703**	**219**	**1114**	**0**	**254**	**478**	**35**	**276**	**333**	**3,412**

*Percentage of cases detected by audit = number of cases detected on audit (n_1)/total number of cases detected by GERMS-SA (n_2) x 100; **Only *Salmonella enterica* serotype Typhi; †Including *Salmonella enterica* serotype Paratyphi; ††Only *Vibrio cholerae* O1; †††Cryptococcal cases detected by audit = number of cases not reported by all participating NHLS sites prior to 1 July 2008 + cases not reported by enhanced surveillance sites after 1 July 2008; EC: Eastern Cape; FS: Free State; GA: Gauteng; KZ: KwaZulu-Natal; LP: Limpopo; MP: Mpumalanga; NC: Northern Cape; NW: North West; WC: Western Cape; SA: South Africa.

Table 4: Variables associated with non-reporting of *Cryptococcus* species, *Haemophilus influenzae*, *Neisseria meningitidis*, *Salmonella* species, *Shigella* species, and *Streptococcus pneumoniae* in 2007, following multivariable analysis.

Variable	Cases Non-Reported		Univariate Analysis		Multivariable Analysis	
	n/ N	%	OR [95% CI]	p-value	OR [95% CI]	p-value
Organism				<0.001		<0.001
N. meningitidis	46/ 431	10.7	1		1	
Cryptococcus **	1,773/ 5,953	29.8	3.6 [2.6 - 4.8]		2.6 [1.8 - 3.6]	
H. influenzae **	85/ 325	26.2	3.0 [2.0 - 4.4]		2.6 [1.7 - 4.0]	
Salmonella **	168/ 794	21.2	2.2 [1.6 - 3.2]		1.8 [1.2 - 2.7]	
Shigella **	14/ 56	25.0	2.8 [1.4 - 5.5]		2.3 [1.1 - 4.8]	
S. pneumoniae **	804/ 4,017	20.0	2.1 [1.5 - 2.9]		1.6 [1.2 - 2.3]	
Province				<0.001		<0.001
FS	195/ 963	20.3	1		1	
EC **	714/ 1,518	47.0	3.5 [2.9 - 4.2]		3.5 [2.9 - 4.2]	
GA	826/ 5,112	16.2	0.8 [0.6 - 0.9]		1.1 [0.9 - 1.3]	
LP **	257/ 656	39.2	2.5 [2.0 - 3.2]		2.6 [2.1 - 3.3]	
MP **	448/ 1,111	40.3	2.7 [2.2 - 3.2]		2.9 [2.3 - 3.5]	
NC **	40/ 142	28.2	1.5 [1.0 - 2.3]		2.7 [1.7 - 4.1]	
NW	206 /900	22.9	1.2 [0.9 - 1.5]		1.1 [0.9 - 1.4]	
WC	204/ 1,174	17.4	0.8 [0.7 - 1.0]		1.1 [0.9 - 1.4]	
Specimen				<0.001		<0.001
CSF	2084/ 7,713	27.0	1		1	
BC	537/ 3,394	15.8	0.5 [0.5 - 0.6]		1.0 [0.9 - 1.2]	
Other **	269/ 469	57.4	3.6 [3.0 - 4.4]		6.9 [5.5 - 8.8]	
Enhanced Surveillance Site				<0.001		<0.001
Yes	417/ 3,952	10.6	1		1	
No **	2,473/ 7,624	32.4	4.1 [3.6 - 4.6]		3.3 [2.9 - 3.7]	
Age Group				<0.001		<0.001
Adult	2,171/ 8,497	25.6	1		1	
Paediatric (<15y)**	524/ 2,495	21.0	0.8 [0.7 - 0.9]		1.3 [1.1 - 1.5]	
Unknown	195/ 584	33.4	1.5 [1.2 - 1.7]		1.0 [0.9 - 1.3]	
Month				<0.001		<0.001
Jan	278/ 982	28.3	1		1	
Feb	243/ 900	27.0	0.9 [0.8 - 1.1]		1.1 [0.9 - 1.3]	
Mar **	263/ 886	29.7	1.1 [0.9 - 1.3]		1.3 [1.0 - 1.6]	
Apr **	265/ 910	29.1	1.0 [0.9 - 1.3]		1.3 [1.0 - 1.6]	
May	252/ 1,005	25.1	0.8 [0.7 - 1.0]		1.0 [0.8 - 1.2]	
Jun **	160/ 801	20.0	0.6 [0.5 - 0.8]		0.7 [0.6 - 0.9]	
Jul	258/ 1,089	23.7	0.8 [0.6 - 1.0]		0.9 [0.7 - 1.1]	
Aug	257/ 1,144	22.5	0.7 [0.6 - 0.9]		0.9 [0.7 - 1.1]	
Sep	227/ 1,024	22.2	0.7 [0.6 - 0.9]		0.8 [0.7 - 1.1]	
Oct	246/ 1,014	24.3	0.8 [0.7 - 1.0]		0.8 [0.7 - 1.1]	
Nov	228/ 965	23.6	0.8 [0.6 - 0.9]		0.9 [0.8 - 1.2]	
Dec	213/ 856	24.9	0.8 [0.7 - 1.0]		1.0 [0.8 - 1.3]	
Gender				>0.100		
Male	1,304/ 4,052	24.4	1			
Female	1,547/ 4,479	25.7	1.1 [0.9 - 1.2]			

OR, Odds Ratio; CI, Confidence Interval
** Statistically significant at the 5% level.

Table 5: Enhanced surveillance site performance indicators.

Enhanced surveillance site*	Case patients, n	Completed case report forms**, n (%)***	Case report forms completed by interview, n (%)†	Completion of select data fields for interviewed patients††, %
Addington/ R K Khan	548	460 (84)	278 (60)	98
Chris Hani Baragwanath	1,388	1,169 (84)	524 (45)	96
Dr George Mukhari	234	197 (84)	104 (53)	97
Edendale/ Greys	239	194 (81)	125 (64)	98
Groote Schuur/ Red Cross/ Victoria	433	408 (94)	162 (40)	100
Charlotte Maxeke Johannesburg Academic	674	656 (97)	439 (67)	100
Karl Bremmer/ Tygerberg	274	196 (72)	59 (30)	95
Kimberley	139	129 (93)	70 (54)	93
King Edward	226	185 (82)	55 (30)	98
Mankweng, Polokwane	120	102 (85)	92 (90)	100
Nelson Mandela Academic/ Mthatha Provincial	193	67 (35)	47 (70)	94
Pelonomi/ Universitas	212	194 (92)	112 (58)	100
Steve Biko Pretoria Academic/ Tshwane District	197	180 (91)	88 (49)	98
Rob Ferreira/ Themba	238	144 (61)	105 (73)	100
Rustenburg	145	98 (68)	40 (41)	87
TOTAL	**5,260**	**4,379 (83)**	**2,300 (53)**	**90**

Note - 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; *There were 5 surveillance officers at Chris Hani Baragwanath and 2 at Charlotte Maxeke Johannesburg Academic in 2008; one surveillance officer was present at all other sites; **Low case report form completion rates at certain sites are due to the turnover of surveillance staff – if other reasons for low completion of case report forms were detected, these were addressed at those sites. ***Target = 90%; †Target = 60%; ††This was calculated by subtracting the number of "unknown" answers from a particular field on the case report form, which could easily have been answered by a patient on interview.

Enhanced Surveillance Site Project

In 2008, of 18,861 surveillance case patients detected by GERMS-SA, 5,260 (28%) were diagnosed at ESS (Table 6). Of case patients with recorded HIV status, 3,058/3,610 (85%) were HIV-infected. The proportion of case patients with confirmed HIV infection varied by disease: unsurprisingly, a very high proportion (>90%) of patients with AIDS-defining infections like cryptococcosis and PCP were HIV-infected, more than three-quarters of patients with invasive pneumococcal disease and non-typhoidal salmonellosis, for which HIV is a known risk factor, were HIV-infected, and interestingly, more than one-third of patients with invasive meningococcal disease were HIV-infected, which is higher than the expected background prevalence of HIV infection in South Africa (4).

Table 6: Number and percentage* of patients, diagnosed with laboratory-confirmed disease at GERMS-SA enhanced surveillance sites, with confirmed HIV infection**, South Africa, 2008, n=5,260.

Pathogen	Case patients, n	Case patients with completed case report forms, n (%)	Case patients with known HIV status, n (%)	Case patients with confirmed HIV infection, n (%)
Cryptococcus species	2,104	1716 (82)	1535 (89)	1516 (99)
Pneumocystis jirovecii	142	119 (84)	115 (97)	106 (92)
Neisseria meningitidis	187	163 (87)	96 (59)	34 (35)
Streptococcus pneumoniae	2067	1745 (84)	1346 (77)	1020 (76)
Haemophilus influenzae	176	136 (77)	100 (74)	57 (57)
Salmonella species	549	474 (86)	399 (84)	314 (79)
Shigella species	35	26 (74)	19 (73)	11 (59)
Total	**5,260**	**4,379 (83)**	**3,610 (82)**	**3,058 (85)**

*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; **HIV infection was confirmed by an age-appropriate, laboratory test and recorded by surveillance officers at enhanced surveillance sites.

Salmonella enterica serotype Typhi

Results

Salmonella Typhi isolation, by month, did not show a marked seasonal pattern, although increased numbers of cases were identified in January 2008, and case numbers increased towards the end of 2008 (Figure 2). *Salmonella* Typhi isolates from both invasive and non-invasive sites are included in these analyses, as both add to burden of infection in South Africa and thus represent a public health risk, although data may not reflect actual burden of disease (Table 7). Two isolates of *Salmonella* Paratyphi A were received from Gauteng; four isolates of *Salmonella* Paratyphi B were received, two from Eastern Cape and one each from Western Cape and KwaZulu-Natal, and one isolate of *Salmonella* Paratyphi C was received from Mpumalanga. The number of isolates within each age group is reflected in Table 8, indicating that most isolates are from children in the 5 – 14 year age group, although infection is seen in both older and younger age groups. No major outbreaks were detected in 2008. Almost all *Salmonella*

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Typhi isolates received in 2008 were susceptible to ciprofloxacin (Table 9), the treatment of choice, and the occurrence of nalidixic acid resistance is cause for concern. The *Salmonella* Paratyphi A isolates were both resistant to nalidixic acid, but susceptible to ampicillin, co-trimoxazole and chloramphenicol. Two of the *Salmonella* Paratyphi B isolates were resistant to ampicillin, one of these was also resistant to chloramphenicol and streptomycin, but the other was susceptible to the remaining antimicrobials tested. The *Salmonella* Paratyphi C was fully susceptible to all antimicrobials tested.

Discussion

Numbers of *Salmonella* Typhi isolates were regarded as a substantial underestimate, and thus incidence rates were not calculated. These results are for culture-confirmed cases, and thus exclude those patients in whom a serological diagnosis was made without culture. Certain antimicrobials were tested for epidemiological purposes only, and should not be used for treatment of typhoid fever. Nalidixic acid resistance may be used as a marker for quinolone resistance; it is indicative of the potential for an organism to develop fluoroquinolone resistance (5). Response to ciprofloxacin may be poor in the presence of nalidixic acid resistance.

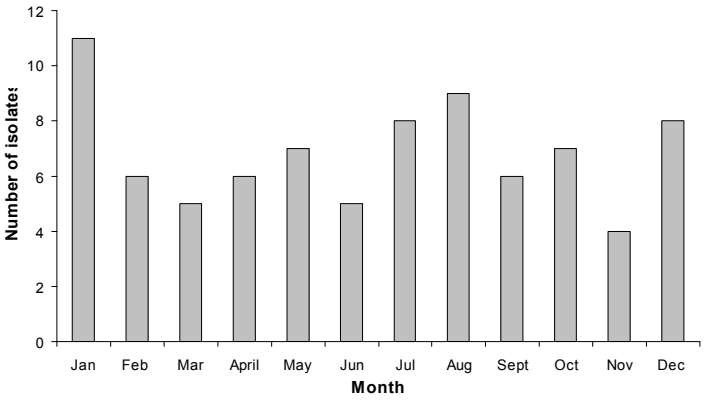

Figure 2: Number of *Salmonella* Typhi isolates, reported to GERMS-SA, by month of specimen collection, South Africa, 2008 n=82 (including audit reports).

Table 7: Number of invasive and non-invasive non-typhoidal *Salmonella* cases reported to GERMS-SA, South Africa, 2008, n=82.

Province	Invasive *Salmonella* Typhi	Non-invasive *Salmonella* Typhi
Eastern Cape	9	1
Free State	1	0
Gauteng	21	1
KwaZulu-Natal	8	3
Limpopo	2	0
Mpumalanga	18	8
Northern Cape	0	0
North West	0	0
Western Cape	9	1
South Africa	**68**	**14**

Table 8: Number of *Salmonella* Typhi isolates reported to GERMS-SA by age category, South Africa, 2008, n=82

Age category (years)	*Salmonella* Typhi isolates
Neonate (<30 days)	0
<1	2
1 - 4	7
5 - 14	35
15 - 24	15
25 - 34	6
35 - 44	7
45 - 54	3
55 - 64	2
≥ 65	2
Unknown	3
Total	**82**

Table 9: Antimicrobial susceptibility test results for all *Salmonella* Typhi isolates received by GERMS-SA, South Africa, 2008, n=80 (excluding audit reports).

Antimicrobial agent	Susceptible (%)	Intermediate (%)	Resistant (%)
Ampicillin	74 (92.5)	0 (0.0)	6 (7.5)
Cotrimoxazole	74 (92.5)	0 (0.0)	6 (7.5)
Chloramphenicol	76 (95.0)	0 (0.0)	4 (5.0)
Nalidixic acid	77 (96.3)	0 (0.0)	3 (3.7)
Ciprofloxacin	80 (100.0)	0 (0.0)	0 (0.0)
Tetracycline	77 (96.3)	0 (0.0)	3 (3.7)
Kanamycin	79 (98.8)	0 (0.0)	1 (1.2)
Streptomycin	75 (93.8)	0 (0.0)	5 (6.2)
Imipenem	80 (100.0)	0 (0.0)	0 (0.0)
Ceftriaxone	80 (100.0)	0 (0.0)	0 (0.0)

Non-typhoidal *Salmonella enterica* (NTS)

Results

Both invasive and non-invasive disease occurred during the warmer months (Figure 3). The number of cases of invasive and non-invasive disease, reported to GERMS-SA, by province, is stated in Table 10. The number of cases of invasive and non-invasive disease, by age group, is shown in Table 11, but incidence rates have only been calculated for invasive NTS, due to differences in stool-taking practices in adult and paediatric medical care. Most invasive isolates were identified from blood cultures, although isolates were frequently identified from blood cultures and another site, including stool, and other normally-sterile sites (Table 12). Multi-drug resistance remains a challenge, including resistance to first-line antimicrobial agents and the quinolones (Table 13). Of those NTS isolates tested, 337 (18.3%) were noted to be resistant to ceftriaxone and to be extended spectrum beta-lactamase (ESBL) producers (Table 13). Multi-drug resistant serotypes included primarily *Salmonella* Typhimurium and *Salmonella* Isangi (Table 14).

Discussion

Non-typhoidal salmonellosis may reflect both a food-borne component of disease, for which data are poorly captured in South Africa, and where the patients normally present with gastro-enteritis, or may be an AIDS-defining illness, in which case the organism frequently becomes invasive. Both invasive and non-invasive disease appear to have a seasonal prevalence in the warmer months. Certain antimicrobial agents were tested for epidemiological reasons only, and should not be used for treatment. Nalidixic acid resistance is a cause for concern, because it is a marker of increasing resistance to the quinolones, and is associated with poor response to fluoroquinolone treatment in clinical cases (5).

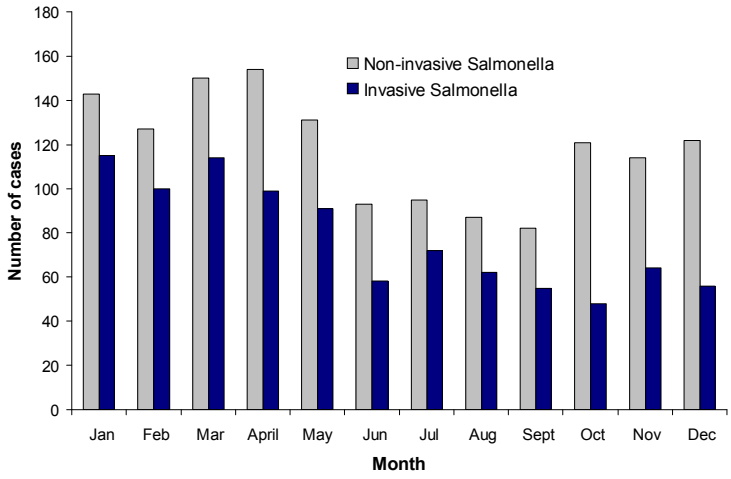

Figure 3: Number of non-invasive and invasive, non-typhoidal *Salmonella* cases, reported to GERMS-SA, by month of specimen collection, South Africa, 2008, n=2353 (including audit reports).

Table 10: Number* of invasive and non-invasive non-typhoidal *Salmonella* cases reported to GERMS-SA, by province, South Africa, 2008, n=2353 (including audit reports).

Province	Non-invasive, non-typhoidal *Salmonella* isolates	Invasive, non-typhoidal *Salmonella* isolates
Eastern Cape	229	105
Free State	61	30
Gauteng	505	491
KwaZulu-Natal	192	112
Limpopo	59	14
Mpumalanga	121	46
Northern Cape	22	20
North West	53	28
Western Cape	177	88
South Africa	**1,419**	**934**

*Incidence rates were not calculated as there may have been regional differences in specimen collection practices

Table 11: Number of cases and incidence rates for invasive* non-typhoidal *Salmonella* reported to GERMS-SA by age category, South Africa, 2008, n=2353 (including audit reports).

	Cases		
Age Category (years)	**Non-invasive**	**Invasive**	**Incidence rate for invasive disease****
< 1	332	185	18.20†
1 - 4	185	102	2.47
5 - 14	137	50	0.47
15 - 24	112	49	0.49
25 - 34	152	203	2.45
35 - 44	170	167	3.61
45 - 54	105	80	1.91
55 - 64	90	32	1.14
≥ 65	49	30	1.33
Unknown	88	35	-
Total	**1,420**	**933**	**1.92**

*Incidence rates for non-invasive non-typhoidal *Salmonella* were not calculated because specimens may not have been submitted for culture from all patients, with gastroenteritis due to non-typhoidal *Salmonella,* in clinical practice; **Incidence rates are expressed as cases per 100, 000 population; †Combined incidence rates are calculated for neonates and children under one year of age. One mixed *Salmonella* infection was identified on blood culture.

Table 12: Number of non-typhoidal *Salmonella* cases reported to GERMS-SA by anatomical site of isolation*, South Africa, 2008, n=2353 (including audit reports).

Specimen	n	%
CSF	34	1.4
Blood culture	804	34.2
Stool	1099	46.7
Other	416	17.7
Total	**2,353**	**100**

*Many cases had multiple isolates of the same serotype, including those with isolates from an invasive site and a second isolate from stool.

Table 13: Antimicrobial susceptibility test results for all non-typhoidal *Salmonella* isolates received by GERMS-SA, South Africa, 2008, n=1845 (excluding audit reports).

Antimicrobial agent	Susceptible (%)	Intermediate (%)	Resistant (%)
Ampicillin	1226 (66.5)	2 (0.1)	617 (33.4)
Cotrimoxazole	1220 (66.1)	0 (0.0)	625 (33.9)
Chloramphenicol	1281 (69.4)	35 (1.9)	529 (28.7)
Nalidixic acid	1382 (74.9)	0 (0.0)	463 (25.1)
Ciprofloxacin	1838 (99.6)	3 (0.2)	4 (0.2)
Tetracycline	847 (45.9)	342 (18.5)	656 (35.6)
Kanamycin	1686 (91.4)	72 (3.9)	87 (4.7)
Streptomycin	1246 (67.5)	0 (0.0)	599 (32.5)
Imipenem	1845 (100.0)	0 (0.0)	0 (0.0)
Ceftriaxone	1508 (81.7)	0 (0.0)	337 (18.3)

Table 14: Commonest invasive and non-invasive non-typhoidal *Salmonella* serotypes reported to GERMS-SA by province, South Africa, 2008, n=1520 (excluding audit reports).

	Serotype				
Province	Dublin	Enteritidis	Isangi	Typhimurium	Virchow
Eastern Cape	12	16	101	86	0
Free State	1	20	1	34	0
Gauteng	17	151	71	443	5
KwaZulu-Natal	8	35	67	103	5
Limpopo	0	5	7	8	1
Mpumalanga	7	17	0	70	4
Northern Cape	0	8	0	17	0
North West	0	5	4	12	14
Western Cape	6	62	13	83	1
South Africa	**51**	**319**	**264**	**856**	**30**

Shigella species

Results

Higher isolation rates in January to March and increasing numbers from October to December in 2008 suggest seasonality (Figure 4). Although the primary burden of disease due to *Shigella* is non-invasive dysentery or diarrhoea, invasive disease remains an important cause of morbidity in South Africa (Table 15). The predominant burden of disease is in the under-five-year age group (Table 16). Fluoroquinolone resistance remains low (Table 17). Eight of 1304 (0.6%) isolates tested were ESBL-producers. Predominant serotypes confirm that *S. flexneri* 2a remains the commonest cause of shigellosis in South Africa and *S. dysenteriae* type 1 is still rarely isolated (Table 18).

(Continued on page 16)

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Discussion

Shigella infection is largely due to water-borne outbreaks in South Africa. Although water-borne outbreaks did occur in 2008, the impact on burden of disease due to *Shigella* appeared less than in 2007. Certain antimicrobials were tested for surveillance purposes only, and should not be used for treatment.

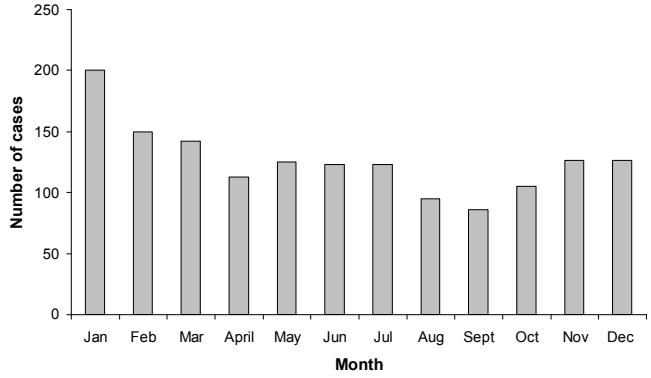

Figure 4: Number of non-invasive and invasive *Shigella* isolates, reported to GERMS-SA, by month of specimen collection, South Africa, 2008, n=1514 (including audit reports).

Table 15: Number of invasive and non-invasive *Shigella* isolates reported to GERMS-SA by province, South Africa, 2008, n=1514 (including audit reports).

Province	Invasive *Shigella*	Non-invasive *Shigella*
Eastern Cape	7	180
Free State	1	84
Gauteng	30	480
KwaZulu-Natal	13	129
Limpopo	1	32
Mpumalanga	3	93
Northern Cape	0	28
North West	1	22
Western Cape	14	396
South Africa	**70**	**1,444**

Table 16: Number of cases* and incidence rates for *Shigella* (invasive and non-invasive)** reported to GERMS-SA by age category, South Africa, 2008, n=1514.

Age category (years)	Cases*	Incidence rates**
Neonate (<30 days)	11	14.56†
< 1	126	
1 - 4	509	12.34
5 - 14	269	2.55
15 - 24	79	0.80
25 - 34	178	2.15
35 - 44	111	2.40
45 - 54	79	1.89
55 - 64	38	1.35
≥ 65	48	2.12
Unknown	66	-
Total	**1,514**	**3.11**

*Cases may be under-reported due to local clinical practices: no mixed infections were identified. **Incidence rates are expressed as cases per 100, 000 population; †Combined incidence rates were calculated for neonates and children less than one year of age.

Table 17: Antimicrobial susceptibility test results for *Shigella* isolates received by GERMS-SA, South Africa, 2008, n=1304.

Antimicrobial agent	Susceptible (%)	Intermediate (%)	Resistant (%)
Ampicillin	683 (52.3)	2 (0.2)	619 (47.5)
Cotrimoxazole	222 (17.0)	1 (0.1)	1081 (82.9)
Chloramphenicol	875 (67.1)	2 (0.2)	427 (32.7)
Nalidixic acid	1286 (98.6)	0 (0.0)	18 (1.4)
Ciprofloxacin	1303 (99.9)	0 (0.0)	1 (0.1)
Tetracycline	585 (44.9)	24 (1.8)	695 (53.3)
Kanamycin	1296 (99.4)	1 (0.1)	7 (0.5)
Streptomycin	560 (42.9)	0 (0.0)	744 (57.1)
Imipenem	1304 (100)	0 (0.0)	0 (0.0)
Ceftriaxone	1298 (99.5)	0 (0.0)	6 (0.5)

Table 18: Commonest* invasive and non-invasive *Shigella* serotypes reported to GERMS-SA by province, South Africa, 2008, n=949 (excluding audit reports).

Province	*S. dysenteriae* type 1	*S. flexneri* type 1b	*S. flexneri* type 2a	*S. flexneri* type 6	*S. sonnei* phase I/II
Eastern Cape	0	17	57	19	25
Free State	0	7	26	9	10
Gauteng	0	48	113	37	121
KwaZulu-Natal	0	22	41	10	26
Limpopo	0	2	5	1	1
Mpumalanga	0	7	22	12	12
Northern Cape	0	3	9	7	3
North West	0	1	6	0	1
Western Cape	1	58	127	32	51
South Africa	**1**	**165**	**406**	**127**	**250**

*Including *Shigella dysenteriae* type 1: Although these isolates are currently rare in South Africa, the potential for future epidemics remains while these strains are in circulation.

Diarrhoeagenic *Escherichia coli* (DEC)

Results

Enteropathogenic *E. coli* (EPEC) remains the commonest cause of diarrhoea, due to this pathogen, identified in South Africa (Table 19). The predominance of cases in younger children under five years of age may reflect, in part, specimen-taking practices, as well as the burden of diarrhoeal disease in this age group (Table 20). Incidence rates were not calculated as numbers were not viewed as being fully representative. A range of serotypes were associated with STEC/EHEC, including O26 and O111. Serotypes associated with EPEC included O55, O111, O119, O127 and O142. Diverse serotypes were also noted for other enterovirulent *E. coli* isolates. Identification of both EHEC and STEC was incidental (6).

Discussion

Actual burden of disease due to diarrhoeagenic *E. coli* is probably greatly underestimated in South Africa, as management is primarily syndromic and centres on rehydration. As a result, clinicians are unlikely to prioritise stool-taking in uncomplicated cases of diarrhoea. Disease in the past appears to have been primarily associated with water-borne outbreaks, due to high level of faecal contamination in water sources, and this

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trend appears to be continuing. The predominance of isolates received in children under the age of one year may reflect culturing practices; infants are more likely to have stools taken for culture due to the devastating effects of diarrhoea in children of this age. Seasonality is not reflected as it is believed that the current specimen-taking and laboratory-diagnostic practices may not be optimal to accurately reflect burden of illness in South Africa of disease due to diarrhoeagenic *E. coli*.

Table 19: Number of diarrhoeagenic *Escherichia coli* isolates reported to GERMS-SA by province, South Africa, 2008, n=377*.

Province	DAEC	EAggEC	STEC/ EHEC	EIEC	EPEC	ETEC
Eastern Cape	5	17	2	1	45	13
Free State	1	2	7	1	3	0
Gauteng	13	15	0	3	110	3
Kwazulu-Natal	1	0	0	0	1	0
Limpopo	0	2	0	0	6	0
Mpumalanga	42	30	0	7	17	15
Northern Cape	0	2	0	0	1	1
North West	1	0	0	1	2	0
Western Cape	2	1	1	0	2	1
South Africa	**65**	**69**	**10**	**13**	**187**	**33**

*Representing 362 infectious episodes, including those patients who had more than one pathotype;
DAEC: diffusely-adherent *E. coli*; EAggEC: enteroaggregative *E. coli*; STEC/EHEC: Shiga-toxigenic *E. coli* or enterohaemorrhagic *E. coli*; EIEC: enteroinvasive *E. coli*; EPEC: enteropathogenic *E. coli*; ETEC: enterotoxigenic *E. coli.*

Table 20: Number of diarrhoeagenic *E. coli* isolates reported to GERMS-SA by age category, South Africa, 2008, n=377.

Age category (years)	DAEC	EAggEC	EHEC/ STEC	EIEC	EPEC	ETEC
Neonate (<30 days)	4	6	1	0	14	4
< 1	12	27	5	1	79	5
1 - 4	17	10	2	2	70	12
5 - 14	4	3	0	2	1	1
15 - 24	6	1	0	1	5	1
25 - 34	9	7	0	3	3	3
35 - 44	6	5	0	1	2	2
45 - 54	0	2	1	1	4	0
55 - 64	3	2	0	0	2	2
≥ 65	0	1	0	1	1	0
Unknown	4	5	1	1	6	3
Total	**65**	**69**	**10**	**13**	**187**	**33**

Results

Figure 5 shows the temporal clustering of the cholera outbreaks in South Africa in 2008.

The number of laboratory-confirmed cases reported to EDRU in 2008 by province is shown in Table 21. This does not reflect the actual number of cases that have been identified clinically. All age ranges were affected (Table 22). Multidrug resistance is increasingly common and was noted with each outbreak, although resistance profiles differed (data not shown), including resistance to the quinolones (Table 23). In 2008, a number of cases were known to be imported, including one in January, from Mozambique, and numerous cases in November, from Zimbabwe. A cluster of two cases in April in Gauteng and in May to July in Mpumalanga could not be linked to known contact with cholera patients from outside South African borders. The case distribution highlights the two major outbreaks in the Barberton district in the middle months of the year, that was contained, and the epidemic that started in November 2008, following an epidemic in Zimbabwe, and which is currently ongoing.

Discussion

Imported cases of cholera add to burden of infection in South Africa, and thus represent a public health risk. The organism in all outbreaks has been multi-drug resistant, but as these resistant patterns have not been consistent between outbreaks, cumulative (for the year) resistance patterns cannot be used to guide patient management in severely-dehydrated patients. These patterns are cumulative and cannot be used to predict treatment for current or future outbreaks. Antimicrobial treatment should be reserved for cases of severe dehydration amongst hospitalised patients, as resistance is rapidly emerging to antimicrobials in this organism. Certain antimicrobials were tested for epidemiological purposes only and are not suitable for treatment.

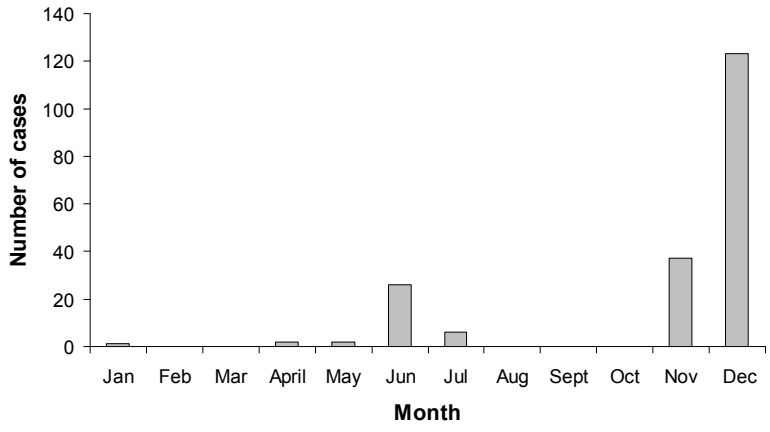

Figure 5: Number of laboratory-confirmed cholera cases, reported to GERMS-SA, by month of specimen collection, South Africa, 2008, n=197 (including imported cases and audit reports).

Table 21: Number of *Vibrio cholerae* O1 isolates reported to GERMS-SA by province, South Africa, 2008, n=185 (excluding audit reports*).

Province	*Vibrio cholerae* O1 El Tor Inaba	*Vibrio cholerae* O1 El Tor Ogawa
Eastern Cape	0	1
Free State	0	1
Gauteng	3	24
KwaZulu-Natal	0	0
Limpopo	0	114
Mpumalanga	1	34
Northern Cape	0	1
North West	1	1
Western Cape	0	4
South Africa	**5**	**180**

*12 audit reports

Table 22: Number of *V. cholerae* O1 cases, reported to GERMS-SA, by age category, South Africa, 2008, n=197 (including audit reports).

Age category (years)	*V. cholerae* O1 cases
Neonate (<30 days)	1
< 1	3
1 - 4	12
5 - 14	16
15 - 24	55
25 - 34	40
35 - 44	19
45 - 54	12
55 - 64	15
≥ 65	10
Unknown	14
Total	**197**

Table 23: Antimicrobial susceptibility test results for four outbreak clusters of *V. cholerae* O1 reported to GERMS-SA, South Africa, 2008, n=185.

Antimicrobial agent	Susceptible (%)	Intermediate (%)	Resistant (%)
Ampicillin	151 (83)	0 (0.0)	31 (17)
Cotrimoxazole	0 (0.0)	0 (0.0)	182 (100.0)
Chloramphenicol	89 (48.9)	88 (48.4)	5 (2.7)
Nalidixic acid	0 (0.0)	0 (0.0)	182 (100.0)
Ciprofloxacin	182 (100.0)	0 (0.0)	0 (0)
Tetracycline	158 (86.8)	18 (9.9)	6 (3.3)
Kanamycin	151 (83.0)	13 (7.1)	18 (9.9)
Streptomycin	2 (1.1)	0 (0.0)	180 (98.9)
Imipenem	182 (100)	0 (0.0)	0 (0.0)
Ceftriaxone	150 (82.4)	0 (0.0)	31 (17.6)
Erythromycin*	164 (92.1)	0 (0.0)	14 (7.9)

*Where standard CLSI breakpoints do not exist, susceptibility categories were determined according to the methods of Ng *et al*. (7)

Cryptococcus species

Results

During 2008, 8,240 case patients, with laboratory-confirmed, incident cryptococcal episodes, were reported. The overall incidence rate for the general South African population increased from 15/100,000 in 2007 to 17/100,000 in 2008 (Table 24). The incidence amongst HIV-infected individuals increased from 133/100,000 in 2007 to 146/100,000 in 2008, and amongst people sick with AIDS remained stable at 12/1000 for both years (8). Incidence rates increased in 5 provinces from 2007 to 2008, but remained fairly stable in the remaining four provinces (Free State, Gauteng, Limpopo and Northern Cape) (Table 24). The peak incidence of cryptococcosis was recorded amongst patients aged 30-34 years (Figure 6). Two hundred and twenty five children, younger than 15 years, had laboratory-confirmed cryptococcosis, detected by the surveillance programme. Where gender was known (8,137/8,240, 99%), 53% patients were female. Most patients (7,730/8240; 94%) were diagnosed with meningitis (laboratory tests on cerebrospinal fluid positive for *Cryptococcus* species), and 475/8,240 (5.7%) were diagnosed with fungaemia (Table 25). The remainder of case patients (n=32) were diagnosed by culture of urine, sputum, pleural fluid and other specimen types. At ESS, 2,102 patients were diagnosed with cryptococcosis, with viable isolates received from 1,585/2,102 (75%) patients. Of 1,582 isolates which were typed, 1,542 (97%) were identified as *Cryptococcus neoformans*; the remaining 40 were identified as *Crypto-*

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coccus gattii. Outcome at the end of the hospital admission was known for 1,677/2,104 (80%) patients at ESS; 523/1,677 (31%) of these patients died.

Discussion

Overall, the number of patients with incident, laboratory-confirmed cryptococcosis increased by >1000 in 2008, compared with 2007. The increased case numbers are unlikely to only reflect improved detection of case patients by the surveillance programme in 2008 compared with 2007, because active case-finding methods did not change substantially. However, this data set is preliminary and data-cleaning is required to remove cases that were incident in previous surveillance years. The reported increase may also represent a complex interplay of factors, including an increased pool of patients at risk for cryptococcosis (with "maturation" of the South African AIDS epidemic), and late access to highly active antiretroviral treatment (HAART), or may be explained by increased specimen submission to laboratories for diagnosis of cryptococcosis, either due to increased clinician awareness of the disease or changed clinical practices with better access to life-saving HAART. Fairly-stable incidence rates in four provinces (Free State, Gauteng, Limpopo and North West) may indicate that the National HIV/AIDS Comprehensive Care, Management and Treatment (CCMT) Programme has made an impact, although this will only be confirmed with ongoing surveillance data. Most patients continued to be diagnosed with meningitis, which reflects clinician specimen-taking practices. The demographic profile of patients with cryptococcosis continued to mirror the profile of HIV-infected patients in South Africa. Very few children were diagnosed with cryptococcosis, and a constantly low proportion of all patients were infected with *C. gattii*. The in-hospital mortality of patients with cryptococcosis remained unchanged, and unacceptably high, and may be due to patients entering the health care system with advanced cryptococcal disease.

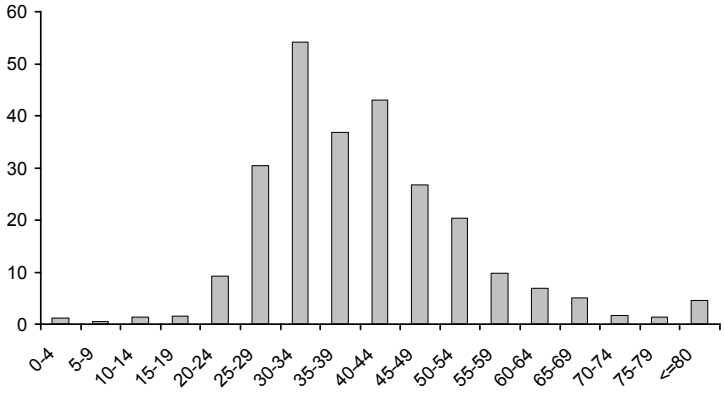

Figure 6: Age-specific incidence rates for laboratory-confirmed, cryptococcal cases, reported to GERMS-SA, South Africa, 2008, n=8,240 (age unknown for n=548).

Table 24: Number of cases and incidence rates of cryptococcal disease reported to GERMS-SA by province, South Africa, 2007 and 2008, n=15,459.

	2007*		2008*	
Province	**n**	**Incidence rate****	**n**	**Incidence rate****
Eastern Cape	1,023	16	1,359	21
Free State	528	18	542	19
Gauteng	2,076	20	2,158	21
KwaZulu-Natal	1,286	13	1,442	14
Limpopo	471	9	455	9
Mpumalanga	743	21	809	23
Northern Cape	61	5	62	6
North West	590	17	787	23
Western Cape	441	8	626	12
South Africa	**7,219**	**15**	**8,240**	**17**

*A similar surveillance audit was performed for NHLS laboratories in 8 provinces (excluding KwaZulu-Natal) in 2007 and 2008, detecting additional microscopy (India ink) and culture-confirmed cases. In 2008, patients diagnosed with the cryptococcal antigen test alone were also detected by audit; **Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100,000 population.

Table 25: Number and percentage of cases of cryptococcal disease reported to GERMS-SA by specimen type, South Africa, 2008, n=8,240.

Site of specimen	n	%
CSF	7,730	94.0
Blood	475	5.7
Other	32	0.3
Unknown	3	<0.1
Total	**8,240**	

Pneumocystis jirovecii

Results

In 2008, 407 cases of *P. jirovecii* pneumonia (PCP) were reported (Table 26). Numbers of *P. jirovecii*-positive specimens peaked in children less than one year of age and in the 21 to 50 year age group (Figure 7). Of cases with known gender, 67% (221/332) were female. Of all reported case patients, 144 (35%) were diagnosed at enhanced surveillance sites and clinical data were available. During admission, 102/144 (71%) of cases tested positive for HIV. Thirty-nine of these patients (38%) were on antiretroviral treatment during their hospitalisation. Where outcome was known, in-hospital mortality rate was 30% (78/111). Of patients who recovered, 98% (109/111) were discharged with a lower respiratory tract infection as a final diagnosis. Many of the case patients had concurrent infections, of which clinically-diagnosed candidiasis was the most common (Figure 8).

Discussion

The number of cases reported for 2008 has increased by almost a third compared to the previous years. This might be attributable to increased awareness and testing for the disease by clinicians. Despite this increase in numbers, PCP still remains severely under-reported, the main reasons being that there are only 8 NHLS laboratories testing for PCP, and specialised equipment and trained personnel are required to obtain adequate samples, e.g. induced sputum, for testing (9).

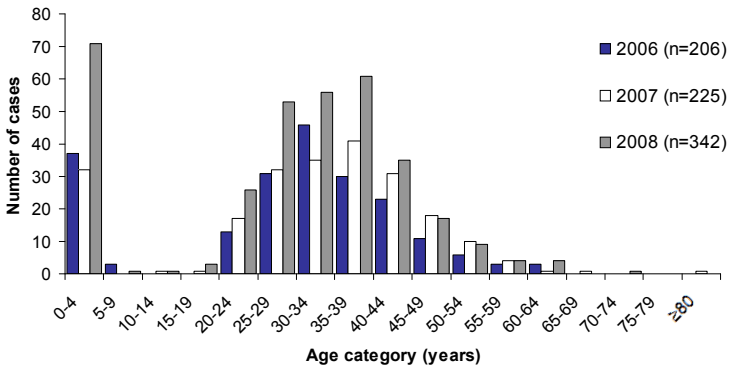

Figure 7: Number of laboratory-confirmed, *Pneumocytis jirovecii* pneumonia (PCP) cases reported to GERMS-SA, by age category, South Africa, 2006-2008, n=773.

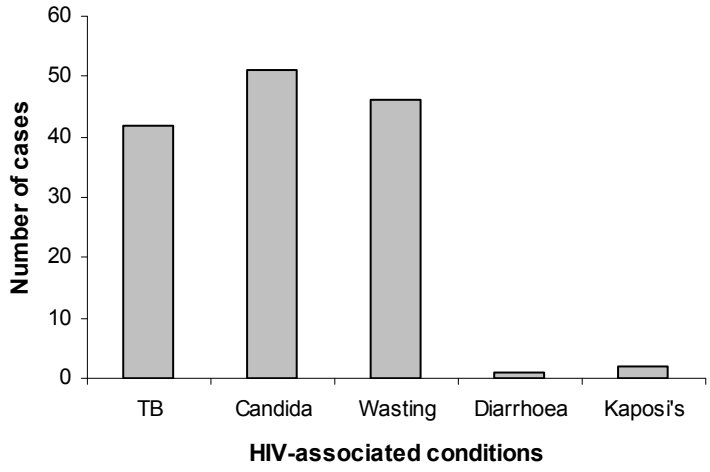

Figure 8: Number of laboratory-confirmed, *Pneumocystis jirovecii* pneumonia (PCP) cases with reported, HIV-associated conditions, South Africa, 2008, n=142.

Table 26: Number of *Pneumocystis jirovecii* pneumonia (PCP) cases reported to GERMS-SA by province, South Africa, 2006-2008, n=997.

Province	2006	2007	2008
Eastern Cape	25	30	30
Free State	6	16	19
Gauteng	177	144	221
KwaZulu Natal	7	20	29
Limpopo	0	0	1
Mpumalanga	17	12	14
Northern Cape	0	0	3
North West	0	13	25
Western Cape	72	51	65
South Africa	**304**	**286**	**407**

Neisseria meningitidis

Results

In 2008, 397 cases of meningococcal disease were reported, and an additional 59 cases were identified on audit: a total of 456 cases of laboratory-confirmed meningococcal disease were identified by the surveillance system during the year (Table 27). The number of cases reported increased during the winter and spring months (Figure 9). Of all cases reported, cerebrospinal fluid (CSF) was the most common specimen yielding meningococci (Table 28). However, the number of cases diagnosed on blood culture increased in 2008 compared to 2007 (p=0.02). Cases of W135 disease were reported from all provinces. In Gauteng Province, the incidence of meningococcal disease was estimated at 2/100,000 population, and most of that disease was due to serogroup W135 (103/162, 64%) (Table 29). The preponderance of serogroup B disease in Western Cape Province was still noted: 31/78 (40%) of all cases serogrouped.

Disease confirmed to be caused by serogroup C increased in Gauteng Province, from four cases in 2007 to 21 cases in 2008. Burden of overall disease was greatest in children less than five years of age. Age and serogroup-specific incidence rates show that infants were at greatest risk of disease for all serogroups (Figure 10).

Preliminary analysis of case-fatality rates, as calculated in enhanced surveillance sites, where in-hospital outcome is specifically looked for, was 42/162 (26%), and has increased during the last three years (30/224, 13% in 2006, 40/200, 20% for 2007; p=0.002 for chi-squared test for trend comparing all three years). Only 3/287 (1%) isolates had penicillin minimum inhibitory concentrations (MICs) > 0.06µg/ml (10), and would be considered intermediately resistant.

Discussion

Overall incidence of disease did not change substantially from 2007. Serogroup W135 disease remained stable compared to 2007 (11), (12). The increase in serogroup C in Gauteng Province highlights the importance of surveillance to monitor meningococcal strain fluctuations. Case-fatality rates have increased over the last three years, and may be related to an increase in proportion of cases presenting with meningococcaemia, as well as other pathogen and/or host factors (13), (14). Reviewing several years, intermediate penicillin resistance was detected among all meningococcal serogroups in South Africa and there was no observed increase in prevalence over the study period (14). The prevalence of intermediate resistance remained low in 2008. The clinical relevance of increasing MICs is unclear, and penicillin is, at present, still being recommended as the drug of choice for therapy for confirmed meningococcal disease.

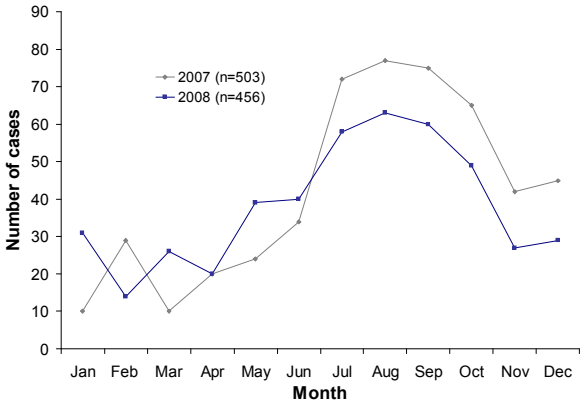

Figure 9: Number of laboratory-confirmed, invasive, meningococcal cases, reported to GERMS-SA, by month and year, South Africa, 2007-2008, n=959.

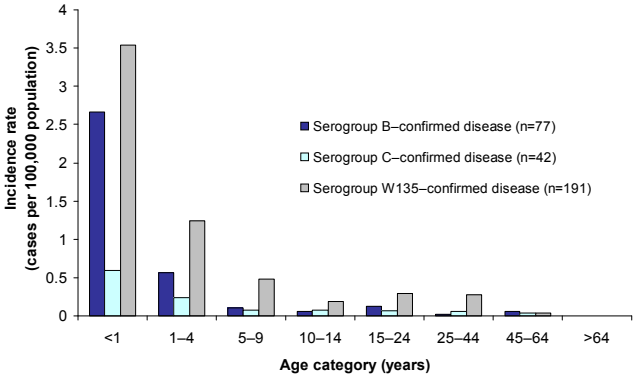

Figure 10: Age-specific incidence rates for laboratory-confirmed, invasive, meningococcal cases, by serogroup, South Africa, 2008, n=456

Table 27: Number of cases and incidence rates of meningococcal disease reported to GERMS-SA by province, South Africa, 2007 and 2008, n=959.

Province	2007		2008	
	n	Incidence rate*	n	Incidence rate*
Eastern Cape	18	0.27	28	0.43
Free State	39	1.36	21	0.73
Gauteng	260	2.53	224	2.14
KwaZulu-Natal	33	0.33	34	0.34
Limpopo	9	0.17	5	0.09
Mpumalanga	25	0.70	35	0.97
Northern Cape	9	0.80	8	0.71
North West	33	0.97	14	0.41
Western Cape	77	1.48	87	1.65
South Africa	**503**	**1.04**	**456**	**0.94**

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

Table 28: Number and percentage of cases of meningococcal disease reported to GERMS-SA by specimen type, South Africa, 2007 and 2008, n=959.

Site of specimen	2007		2008	
	n	%	n	%
CSF	385	77%	316	69%
Blood	116	23%	133	29%
Other	2	0.4%	7	1.5%
	503		**456**	

Table 29: Number of cases of invasive meningococcal disease reported to GERMS-SA by serogroup and province, South Africa, 2008, n=456*.

Province	Serogroup						
	Serogroup not available	A	B	C	W135	Y	Total
Eastern Cape	6		9	4	6	3	28
Free State	6		5	2	6	2	21
Gauteng	62	3	28	21	103	7	224
KwaZulu-Natal	8		3	2	20	1	34
Limpopo	2				3		5
Mpumalanga	12		1	4	18		35
Northern Cape	3		1		2	2	8
North West	6		3		4	1	14
Western Cape	9		31	11	35	1	87
South Africa	**114**	**3**	**81**	**44**	**197**	**17**	**456**

*342 (75%) with specimens or viable isolates available for serogrouping.

Haemophilus influenzae

Results

The number of cases of *Haemophilus influenzae* invasive disease reported in 2008 was 280, while an additional 112 cases were identified during the national audit (total number of cases available for analysis was 392). Of these, 207 (53%) had isolates or specimens available for serotyping, and 90/207 (43%) were confirmed as serotype b (Table 30). Serotype b isolates were more likely to be isolated from CSF than non-typeable *H. influenzae* (47/90, 52% vs. 7/74, 9%, p<0.001) (Table 31). In 2008, a total of 62 cases of *H. influenzae* serotype b (Hib) were reported in children <5 years (Figure 11); four cases were identified on polymerase chain reaction (PCR) testing of transport specimens. Serotype b is the more common *H. influenzae* causing disease in infants (Figure 12). Since 2002, rates of Hib disease as recorded by our surveillance network in infants <1 year of age have increased, and there seems to be a continued increase in 2008 (p=0.002, chi-squared test for trend, 2002 to 2008) (Figure 13). Thirteen percent of serotype b strains were resistant to ampicillin (MIC>1mg/L (9) (all producing beta lactamase), 11 of 82 isolates tested, while 14% (10/71) of non-typeable strains were resistant.

Discussion

Since the introduction of the Hib conjugate vaccine into the Expanded Programme on Immunisation (EPI) for South Africa in 1999, there has been a reduction in cases reported due to this serotype (15). The recent increase in reported cases of Hib disease in children <1 year needs to be monitored carefully, and further analysis of these cases will follow.

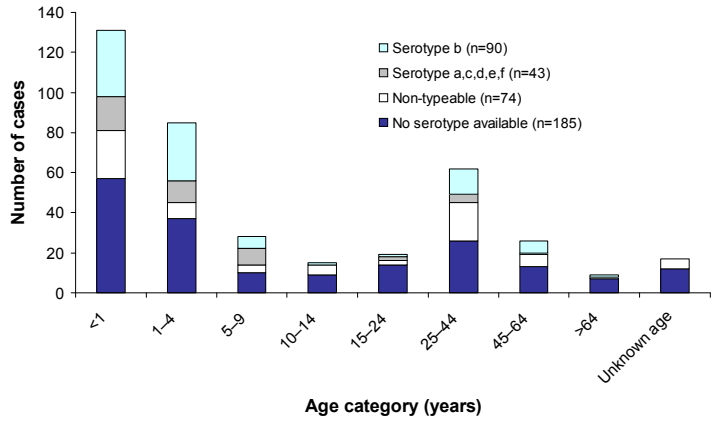

Figure 11: Number of laboratory-confirmed, invasive, *Haemophilus influenzae* cases, reported to GERMS-SA, by serotype and age group, South Africa, 2008, n=392 (age unknown for n=17; specimens or viable isolates unavailable for serotyping for n=185).

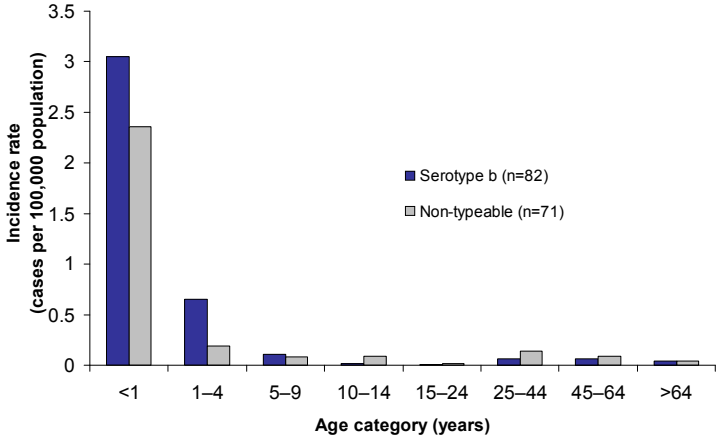

Figure 12: Age-specific incidence rates for laboratory-confirmed, invasive *Haemophilus influenzae* disease, reported to GERMS-SA, by serotype, South Africa, 2008, n=392 (age unknown for n=17; viable isolates unavailable for serotyping for n=185).

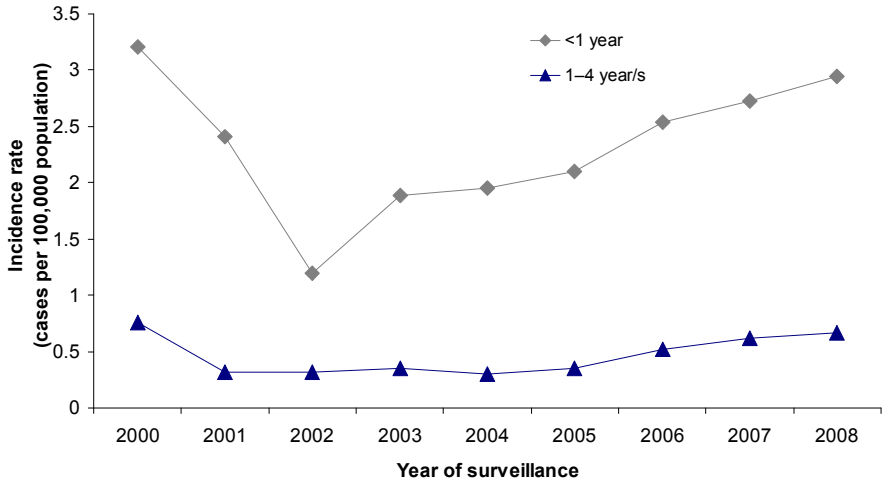

Figure 13: Incidence rates of laboratory-confirmed, *Haemophilus influenzae* serotype b disease, reported to GERMS-SA, in children <5 years old, South Africa, 2000-2008, n=386 (excluding cases identified using polymerase chain reaction (PCR) on specimens which was only done in 2007 and 2008).

Table 30: Number of cases of invasive *Haemophilus influenzae* disease reported to GERMS-SA by serotype and province, South Africa, 2008, n=392.

Province	Serotype								
	Serotype not available	a	b	c	d	e	f	Non-typeable	Total
Eastern Cape	20	0	6	1	0	1	1	3	32
Free State	7	0	9	0	0	0	3	5	24
Gauteng	74	6	35	3	4	1	12	35	170
KwaZulu-Natal	19	0	14	0	0	0	1	8	42
Limpopo	2	0	2	0	0	0	0	0	4
Mpumalanga	11	1	6	0	0	0	1	2	21
Northern Cape	2	0	2	0	0	0	0	0	4
North West	3	0	3	0	0	0	0	0	6
Western Cape	47	2	13	1	1	3	1	21	89
South Africa	**185**	**9**	**90**	**5**	**5**	**5**	**19**	**74**	**392**

*207 (53%) with specimens or viable isolates available for serotyping.

Table 31: Number and percentage of cases of invasive *Haemophilus influenzae* disease reported to GERMS-SA by specimen type, South Africa, 2008, n=392.

Site of specimen	No serotype available		Serotype b		Serotypes a, c, d, e, f		Non-typeable	
	n	%	n	%	n	%	n	%
CSF	41	22	47	52	16	37	7	9
Blood	91	49	39	43	25	58	56	76
Other	53	29	4	4	2	5	11	15
Total	**185**		**90**		**43**		**74**	

Streptococcus pneumoniae

Results

Incidence of reported invasive pneumococcal disease varied widely by province (Table 32). The age group at highest risk of disease in South Africa was infants <1 year of age (Figure 14). The majority of episodes reported to RMPRU were diagnosed from positive blood culture specimens (Table 33). Penicillin non-susceptible isolates (2008 CLSI breakpoints for penicillin [oral penicillin V], MIC>0.06mg/L) (16), have decreased slightly from 2007 (1430/3330, 43% in 2007 compared to 1246/3288, 38% in 2008, p<0.0001), and this ranged from 33% to 47% in different provinces (Table 34). Non-susceptible isolates were common in children less than 5 years of age (Figure 15). A non-meningitis-causing pneumococcus with an MIC of ≤2mg/L, according to updated CLSI guidelines (penicillin parenteral non-meningitis), can be considered susceptible (16). Using these breakpoints, all isolates not cultured from CSF were susceptible to penicillin. The percentage of disease in 2008 in children <5 years due to the seven serotypes in the vaccine (4, 6B, 9V, 14, 18C, 19F and 23F), and serotype 6A (ongoing evidence for cross-protection within this serogroup (17)), in South Africa ranges from 65% to 79% by province according to our data (Table 35). Newer-valency vaccines will be licensed in the near future, and these show additional coverage for serotypes causing disease in our children (Table 35, Figure 16).

Discussion

Our data for 2008 show no further increases in penicillin resistance. As has been documented for many years now, most isolates are intermediately resistant to penicillin, and if these pneumococci are isolated from patients with pneumonia, the new 2008 CLSI breakpoints will classify them as susceptible (10). We will continue to use the penicillin [oral penicillin V] MICs as a more sensitive method to monitor trends over time. PREVENAR® (7-valent conjugate pneumococcal vaccine, PCV7) was launched in South Africa in the private sector in 2005 by Wyeth South Africa (Pty) Ltd, and is at present the only vaccine for the prevention of pneumococcal disease in children <2 years. This vaccine will be introduced into the EPI in South Africa from 1 April 2009. New vaccine formulations containing 10 (PCV10) or 13 serotypes (PCV13) will be available in 2009 and 2010. These vaccines have the potential to markedly reduce the burden of invasive pneumococcal disease in future. Ongoing surveillance is essential to document this reduction and monitor ongoing patterns of serotype distribution.

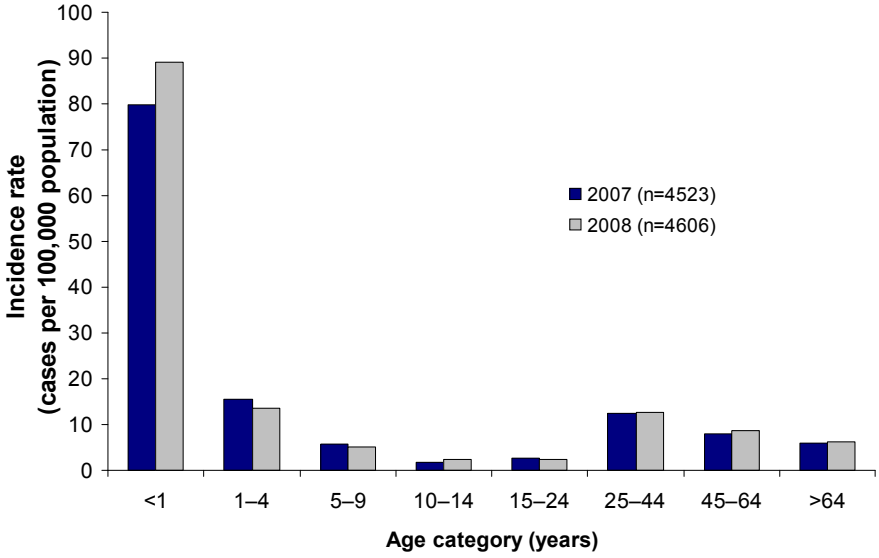

Figure 14: Age-specific incidence rates for laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, South Africa, 2007 and 2008 (2007: n=4732; age unknown for n=209; 2008: n=4843; age unknown for n=237).

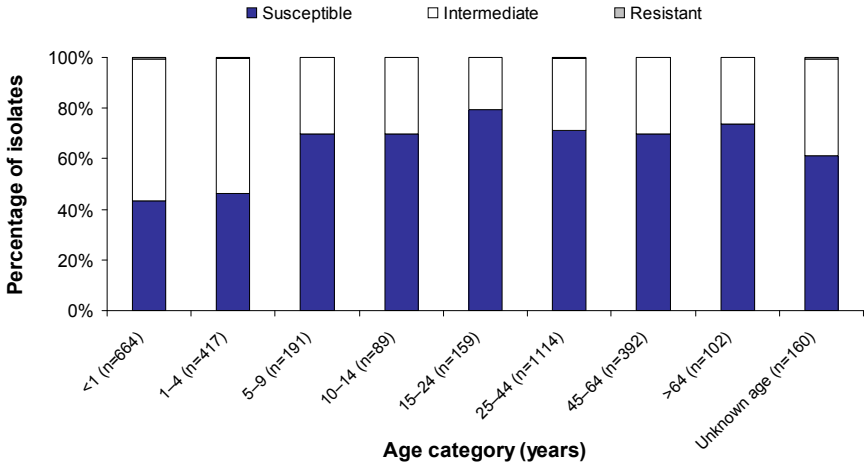

Figure 15: Number of laboratory-confirmed, invasive pneumococcal disease cases, reported to GERMS-SA, by age group and penicillin susceptibility, South Africa, 2008, n=4843 (n=3288 with viable isolates).

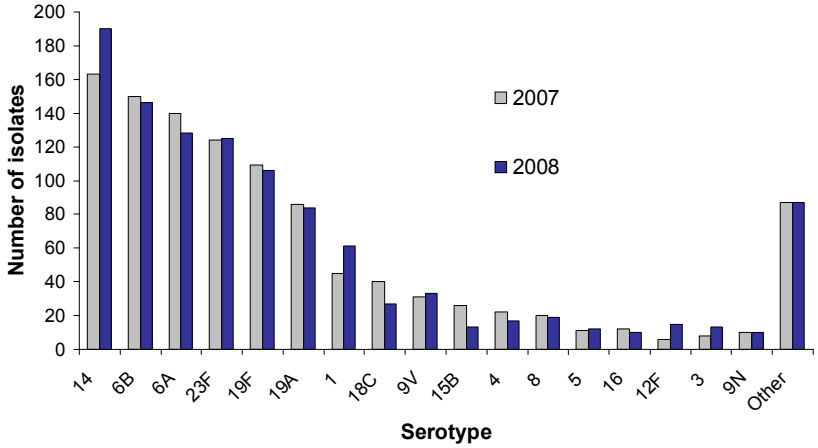

Figure 16: Pneumoccocal serotypes, in descending order, causing laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, in children <5 years, South Africa, 2007-2008 (2007: n=1471, n=1090 with viable isolates, 2008: n=1464; n=1096 with viable isolates).

Table 32: Number of cases and incidence rates of invasive pneumococcal disease reported to GERMS-SA by province, South Africa, 2007 and 2008, n=9575.

Province	2007		2008	
	n	Incidence rate*	n	Incidence rate*
Eastern Cape	354	5.39	359	5.46
Free State	316	11.03	319	11.09
Gauteng	2,272	22.07	2,357	22.56
KwaZulu-Natal	538	5.36	573	5.67
Limpopo	146	2.79	113	2.14
Mpumalanga	282	7.92	258	7.19
Northern Cape	56	4.99	85	7.55
North West	201	5.90	192	5.61
Western Cape	567	10.92	587	11.16
South Africa	**4,732**	**9.80**	**4,843**	**9.95**

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

Table 33: Number and percentage of cases of invasive pneumococcal disease reported to GERMS-SA by specimen type, South Africa, 2007 and 2008, n=9575.

Site of specimen	2007		2008	
	n	%	n	%
CSF	1,725	36%	1,752	36%
Blood	2,586	55%	2,650	55%
Other	421	9%	441	9%
	4,732		**4,843**	

Table 34: Number and percentage of penicillin non-susceptible isolates from invasive pneumococcal disease cases reported to GERMS-SA by province, South Africa, 2008, n=4843.

Province	Isolate not available	Susceptible*		Intermediate*		Resistant*	
	n	n	%	n	%	n	%
Eastern Cape	169	116	61	74	39		0.0
Free State	94	136	60	89	40		0.0
Gauteng	789	1,012	65	552	35	4	0.3
KwaZulu-Natal	94	252	53	226	47	1	0.2
Limpopo	66	28	60	19	40		0.0
Mpumalanga	131	75	59	51	40	1	0.8
Northern Cape	13	48	67	24	33		0.0
North West	95	64	66	33	34		0.0
Western Cape	104	311	64	168	35	4	0.8
South Africa	**1,555**	**2,042**	**62**	**1,236**	**38**	**10**	**0.3**

*2008 CLSI breakpoints for penicillin (oral penicillin V) were used.

Table 35: 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, 2008, n=1096.

Province	Total isolates available for serotyping	7-valent serotypes (including 6A)*		10-valent serotypes*		13-valent serotypes*	
		n	%	n	%	n	%
Eastern Cape	56	39	70	41	73	48	86
Free State	71	52	73	58	82	63	89
Gauteng	511	330	65	387	76	430	84
KwaZulu-Natal	176	135	77	141	80	157	89
Limpopo	7	5	71	6	86	6	86
Mpumalanga	43	33	77	33	77	38	88
Northern Cape	28	19	68	20	71	22	79
North West	19	15	79	16	84	16	84
Western Cape	185	144	78	145	78	164	89
South Africa	**1,096**	**772**	**70**	**847**	**77**	**944**	**86**

*7-valent serotypes: 4, 6B (6A), 9V, 14, 18C, 19F, 23F ; 10-valent serotypes: 4, 6B (6A), 9V, 14, 18C, 19F, 23F, 1, 5, 7F ; 13-valent serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 19A, 3, 6A.

Discussion

Almost 19,000 case patients were detected through the GERMS-SA surveillance programme in 2008. It is likely that the vast majority of these patients, meeting GERMS-SA case definitions, were HIV-infected, as suggested by data from 25 ESS hospitals. This reflects the focus of the surveillance programme on HIV-associated opportunistic infections, as well as the high, background prevalence of HIV infection amongst patients who seek hospital care in South Africa, and who are ultimately diagnosed with disease due to the pathogens under surveillance.

Ongoing surveillance for cryptococcal infection has demonstrated that despite the increasing access to HAART, numbers of cryptococcal cases continue to increase. This provides a call-to-action that more needs to be done to address issues of uptake of HIV-testing, and access to care, and addresses a key strategic programme objective, i.e. the provision of information regarding trends in the burden of HIV-associated opportunistic infections in South Africa, which, in turn, provides an indirect measure of the impact of the HIV epidemic and the public health interventions undertaken to mitigate this impact.

Another surveillance objective of this laboratory-based, surveillance programme was to provide information on antimicrobial resistance and molecular epidemiology of isolates identified. During the cholera outbreaks in 2008, the GERMS-SA programme was able to document the antimicrobial resistance profile of bacterial isolates responsible for the outbreak. In addition, molecular epidemiologic data were used to assist in identifying the possible source of outbreak strains.

The 7-valent, pneumococcal, conjugate vaccine will be introduced into the EPI in April 2009. The GERMS-SA programme was able to provide key, strategic information on the proportion of invasive pneumococcal disease, potentially preventable through vaccination. These data have contributed to the implementation of a key intervention to reduce deaths due to this common opportunistic infection. The existence of robust baseline data will allow GERMS-SA to document the expected reduction in disease following programme implementation. These data will not only be of use to local policy makers, but will also inform decision makers in other African countries with a high prevalence of HIV-infection.

Publications

Publications in peer-reviewed journals

1. du Plessis M, von Gottberg A, Cohen C, de Gouveia L, Klugman KP. *Neisseria meningitidis* intermediately resistant to penicillin and causing invasive disease in South Africa in 2001 to 2005. *J Clin Microbiol* 2008;46:3208-14.

2. du Plessis M, von Gottberg A, Madhi SA, Hattingh O, de Gouveia L, Klugman KP. Serotype 6C is associated with penicillin-susceptible meningeal infections in human immunodeficiency virus (HIV)-infected adults among invasive pneumococcal isolates previously identified as serotype 6A in South Africa. *Int J Antimicrob Agents* 2008;32S:S66-S70.

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5. von Gottberg A, du Plessis M, Cohen C, Prentice E, Schrag S, de Gouveia L, Coulson G, de Jong G, Klugman K. Emergence of endemic serogroup W135 meningococcal disease associated with a high mortality rate in South Africa. *Clin Infect Dis* 2008;46:377-86.

6. von Gottberg A, Klugman KP, Cohen C, Wolter N, de Gouveia L, du Plessis M, Mpembe R, Quan V, Whitelaw A, Hoffmann R, Govender N, Meiring S, Smith AM, Schrag S. Emergence of levofloxacin-non-susceptible *Streptococcus pneumoniae* and treatment for multidrug-resistant tuberculosis in children in South Africa: a cohort observational surveillance study. *Lancet* 2008;371:1108-13.

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Publications in non-peer-reviewed journals

1. Predictors of non-reporting to a national, laboratory-based surveillance programme. Communicable Diseases Surveillance Bulletin November 2008; 6(4) 2-4. Available from: http://www.nicd.ac.za/pubs/survbull/2008/CommDisBullNov08_Vol0604.pdf

2. GERMS-SA Surveillance Report, South Africa, 2007. Communicable Diseases Surveillance Bulletin March 2008; 4 (2):5-8. Available from:http://www.nicd.ac.za/pubs/survbull/2008/CommDisBullMarch08_Vol0601.pdf

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