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Eastern Cape ostriches during an outbreak of avian influenza H5N2 in August 2004.

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EPIDEMIC PRONE DISEASE SURVEILLANCE : JANUARY-AUGUST			CUMULATIVE	ECP	FSP	GAP	KZP	LPP	MPP	NCP	NWP	WCP	RSA
AFP, cases from whom specimens have been received	< = 15 years		2003 2004	23 11	8 6	28 18	29 25	54 51	5 9	3 4	18 17	20 19	188 160
Measles, IgM positive results	All ages		2003 2004	0 0	0 0	7 307	U U	1 2	3 6	1 4	0 0	U 2	13 325
Rubella, IgM positive results from measles IgM negative patients	All ages		2003 2004	23 63	24 2	72 78	U U	27 8	35 56	9 3	36 48	U 8	226 266
CCHF	All ages		2003 2004	0 0	0 1	0 0	0 0	0 0	0 0	0 1	0 2	0 0	0 4
Rabies, human	All ages		2003 2004	0 0	0 0	0 0	5 5	0 0	0 1	0 0	0 0	0 0	5 6
Haemophilus influenzae, invasive	All ages	All serotypes	2003 2004	3 5	10 6	84 88	11 13	0 1	4 3	0 0	3 3	35 30	150 149
	Age < 5 years	Serotype b	2003 2004	0 0	3 2	11 10	0 0	0 0	1 0	0 0	1 0	5 3	21 15
		Non-serotype b	2003 2004	0 0	0 0	9 2	0 1	0 0	0 0	0 0	0 0	2 3	11 6
		Non-typable	2003 2004	1 0	1 2	22 19	4 2	0 0	0 0	0 0	0 0	7 7	35 30
		Unknown serotype	2003 2004	1 3	5 2	2 8	6 4	0 1	1 1	0 0	1 1	9 4	25 24
Meningococcal disease	All ages		2003 2004	5 18	14 15	127 102	6 14	1 9	11 6	4 4	21 13	47 45	236 226
Streptococcus pneumoniae, invasive	All ages		2003 2004	44 97	63 130	1254 1283	119 319	20 47	70 117	9 11	83 73	259 327	1921 2404
	Age < 5 years		2003 2004	20 44	33 42	347 393	46 107	2 13	21 29	2 3	17 20	129 141	617 792
	Penicillin, non-susceptible, all ages		2003 2004	7 20	9 25	246 328	26 75	1 9	10 23	1 0	5 17	61 76	366 573
	Susceptibility unknown, all ages		2003 2004	12 10	1 17	91 143	17 21	3 8	6 16	0 0	28 6	24 39	182 260
Salmonella species - invasive isolates	All ages	All serotypes excl. *S. typhi*	2003 2004	4 2	14 7	183 232	0 22	0 4	4 3	1 0	1 4	31 21	238 295
Salmonella species - enteric isolates	All ages	All serotypes excl. *S typhi*	2003 2004	38 36	11 17	25 93	0 22	0 14	3 2	0 0	1 17	66 58	144 259
Salmonella typhi	All ages		2003 2004	1 5	0 0	6 12	0 5	3 3	0 7	1 0	0 0	0 5	11 37
Shigella species	All ages	All serotypes	2003 2004	24 42	8 17	22 86	0 43	1 13	3 5	0 0	0 5	50 114	108 325
Vibrio cholerae 01	All ages	All serotypes	2003 2004	53 26	0 0	3 3	0 0	0 0	66 217	0 0	1 46	1 0	124 292

U = unavailable, 0 = no isolates received

Note: The above are NICD laboratory data and do not nececessarily reflect a quantitative measure of disease in the country.

AVIAN INFLUENZA IN SOUTH AFRICA

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INTRODUCTION

On the 6th of August, 2004 officials reported an outbreak of highly pathogenic avian influenza (HPAI) A subtype H5N2 in ostriches in the Blue Crane Municipal District of the Eastern Cape. Initial reports reported over 1500 ostrich deaths on 2 farms in Middleton near Somerset East. Subsequently, several additional farms in the area have serological evidence of infection.

AVIAN INFLUENZA IN OSTRICHES

Avian influenza of low pathogenicity (LPAI) has previously been isolated from ostriches in South Africa. Several subtypes were identified during the 1990's including H7N1 (1991, 1992), H5N9 (1994) and H9N2 (1995). Avian influenza H5N2 occurred in Zimbabwe in 1995 but this subtype had not previously been isolated in South Africa. Generally avian influenza viruses in ostriches are considered to be of low virulence for chickens. The first report of HPAI in ostriches came from Italy during a poultry outbreak in 1999.

INFLUENZA A H5N2 IN THE EASTERN CAPE

In mid-July, farmers on 2 farms in Middleton reported illness and significant deaths in their ostriches which prompted an investigation. The ostriches presented with features of sinusitis, sub-mandibular swelling, green urine and conjunctivitis. The virus was initially isolated at Stellenbosch from tissue taken from an ostrich on the first affected farm. This was confirmed by RT-PCR at Onderstepoort Veterinary Institute as influenza A, ostrich H5N2 subtype. The cleavage site sequence was that of a highly pathogenic virus having multiple basic amino acids at this site. At least 1500 ostriches have died of the disease. Subsequently, at least 3 additional farms have tested positive on serological surveillance.

The Department of Agriculture has responded definitively to the outbreak and has established a quarantine area and extensive serological surveillance.

The quarantine includes an area with a radius of 30 km around the 2 farms where the infection was originally confirmed. In addition, culling of ostriches and poultry in the affected area was performed. Over 13 600 ostriches have been culled thus far in an effort to eliminate the virus and contain its spread. Farmers will be compensated for culled ostriches. Fortunately, there are no commercial poultry farms in the area and testing of backyard poultry has shown no evidence of infection to date. Strict movement restrictions are enforced by road-block cordons and the public is prohibited from removing any poultry (including ostriches, birds, and other fowl) or their products from the area.

The original source of the infection is still unknown. Surveillance of wild fowl in the area has proved negative thus far and epidemiological links are still under investigation. The virus spreads via direct contact with infected birds and indirectly through contaminated environmental sources. Exports of poultry and poultry products from South Africa have been voluntarily suspended.

AVIAN INFLUENZA A AND HUMAN DISEASE

Human disease caused by avian influenza varies in presentation and ranges from conjunctivitis to a flu-like illness, severe pneumonia, adult respiratory distress syndrome and even death. Several subtypes of avian influenza have been associated with clinical disease in humans. A large outbreak of human disease occurred in the Netherlands following influenza A H7N7 in poultry in 2003. Eighty-nine people were infected with one death. More recently, the outbreak of influenza H5N1 in Thailand and Vietnam resulted in at least 34 officially confirmed cases with 23 deaths. Infections in this area are ongoing. Unlike other subtypes of HPAI, influenza A H5N2 has not been shown to cause infection in humans. Previous outbreaks of this subtype in poultry in Italy (1997) and Texas (2004) were not associated with human disease based on serological and clinical surveillance.

An outbreak response team from the NICD has recently visited the affected farms to conduct clinical and serological surveillance for human infection. Serological testing will be performed using a micro-neutralisation assay. Of concern is the extensive exposure of individuals working on the affected farms, initially with little personal protective equipment. Guidelines have also been issued by the NICD regarding the use of personal protective gear in high risk personnel, the detection and management of clinical cases and recommended diagnostic procedures for suspected infection. Human influenza vaccine has been recommended for all exposed personnel to prevent concurrent infection with both human

and avian influenza, which could result in genetic re-assortment and the possible emergence of a human-avian reassortant.

UPDATE ON AVIAN INFLUENZA H5N1 IN SOUTH-EAST ASIA

From January to March 2004, Thailand and Vietnam had reported 34 officially confirmed human H5N1 cases with 23 deaths to the World Health Organisation (WHO). Vietnam announced that it was free of avian influenza in March. However, in June lethal outbreaks among poultry of HPAI H5N1 were again reported to the World Organization for Animal Health by China, Indonesia, Thailand and Vietnam. This was followed by an official report on 12 August by the Vietnamese Ministry of Health of 3 human deaths from confirmed avian influenza H5 infection. These were the first reported human cases of H5 since March. The cases included a woman from Hau Giang and 2 children from Ha Tay in the North of Vietnam. The dead woman was one of 4 people from Hau Giang who died between 29 July and 2 August. None of the others were tested but it is possible that they had also died of avian influenza. More recently, Malaysia reported infection in chickens and China revealed the isolation of influenza A H5N1 in pigs.

CONCLUSION

The current outbreak in the Eastern Cape has been devastating for all concerned. It is hoped that the response will be effective in preventing further spread of the infection. Ongoing serological surveillance in the affected area and the rest of the country is essential for containment of the virus. Controlling re-infection will be a challenge as ostriches are raised outdoors and therefore have uncontrolled contact with the environment including wild birds. Although human infection has not been documented, surveillance of exposed personnel will continue and the use of appropriate personal protective equipment must be encouraged. South Africa must continue to be vigilant both for the prevention of further economic losses in the industry and for the global prevention of the emergence of a new human pandemic strain of influenza.

MALARIA IN SOUTH AFRICA

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Malaria is endemic in the low altitude areas (below 1 000 metres above sea level) of the northern and eastern parts of South Africa along the border with Mozambique and Zimbabwe, with transmission mainly in the Limpopo, Mpumalanga and KwaZulu-Natal (KZN) provinces. Occasionally limited focal transmission occurs in the North-West and Northern Cape Provinces along the Molopo and Orange Rivers, respectively. Annual transmission occurs mainly in the rainy summer months, from October to May, peaking from February to April. The population at risk for contracting malaria is approximately 4.3 million. In addition, imported malaria is a significant problem in travellers returning from high malaria transmission areas in African countries, notably Mozambique.

MALARIA CONTROL PROGRAMME (MCP)

The major strategies of the MCP in South Africa are: vector control through Indoor Residual Spraying (IRS); early effective case management; disease surveillance; epidemic preparedness and response; malaria advocacy and information, education and communication. Malaria control policy is formulated at national level, whilst the implementation of policy takes place at provincial, district and local levels. These policies are in keeping with WHO guidelines.

MALARIA TRENDS

Subsequent to robust malaria interventions, notification of malaria cases and deaths declined from 62 200 cases and 480 deaths (case fatality rate 0.8%) in 1999/2000 to 11 025 cases and 75 deaths (case fatality rate 0.7%) in 2002/2003. A change in IRS policy to reintroduce DDT for traditional style dwellings following the identification of *Anopheles funestus* resistant to pyrethroids, and the introduction of artemisinin-based combination therapy contributed significantly to these malaria control successes.

However, malaria cases and deaths reported for the 2003/2004 malaria season have shown an increase of 23% and 50% to 15 544 cases and 150 deaths (case fatality rate 1%) respectively when

compared to the previous season. These increases have largely been attributed to increased rainfall and focal malaria outbreaks in the Limpopo province and parts of KZN. The increase in the number of deaths can be attributed to late presentation of malaria patients and health system failures, especially poor case management.

The Lebombo Spatial Development Initiative (LSDI) malaria project, driven by the Medical Research Council, is showing excellent results with major reductions in malaria cases in South Africa, Mozambique and Swaziland. The spraying operations will extend to further zones in Mozambique and there are plans to introduce combination therapy in Maputo province in the very near future. Inter-country and cross border malaria control initiatives are currently being strengthened with Angola and Zimbabwe.

CASE MANAGEMENT

The goal of the malaria control programme in South Africa is to ensure that malaria cases do not exceed one per thousand in the population at risk and to sustain a case fatality rate of less than 0.5%. Key factors in the successful management of malaria cases are early and accurate diagnosis and urgent treatment using effective drugs. Major challenges are the non specific clinical presentation of malarial disease, the rapid progression of disease in South African patients, all of whom could be considered malaria non-immune, and the development of parasite resistance to anti-malarial drugs. *Plasmodium falciparum* accounts for the majority of infections and all severe disease, although it is likely that there is an underestimate of the number of mixed infections. Non falciparum malaria in South Africa is generally associated with mild illness, and chloroquine is effective for treatment of acute disease. Primaquine is needed to eradicate the latent hepatic stages.

A high index of suspicion is the most important element in the diagnosis of malaria. Any person resident in or returning from a malaria transmission area who presents with fever, and/or headache, rigors or a flu-like illness should be tested for malaria irrespective of the time of the year, or whether the person has taken chemoprophylaxis. The treatment of malaria is based on a definitive diagnosis either by examination of stained peripheral blood smears, or by the use of rapid malaria tests which detect malaria antigen or parasite enzymes.

DRUG POLICY FOR TREATMENT

The ongoing development of parasite drug resistance necessitates frequent updating of treatment and chemoprophylaxis policies. In South Africa chloroquine resistance in KZN and later in Mpumalanga and Limpopo provinces necessitated a change to sulfadoxine-pyrimethamine (SP) in 1988, 1997 and 1999 respectively. The development of significant SP resistance in KZN resulted in a further policy change to artemether-lumefantrine (Coartem®) in 2001 as first line treatment for uncomplicated *Plasmodium falciparum* infections.

In order to halt the pattern of continued parasite resistance to sequential single drug therapy, combination chemotherapy, including an artemisinin derivative is recommended. Additional benefits include an improved therapeutic response, a decrease in malaria transmission and thereby greater cost effectiveness. The potential to delay anti-malarial resistance is a further motivation for the widespread implementation of artemisinin-based combination therapies. Mpumalanga introduced a combination of SP plus artesunate (Arsudar) in 2003 and artemether-lumefantrine will be introduced in Limpopo during the 2004/2005 malaria season as first line treatment for uncomplicated malaria. The artemisinin group of drugs are rapidly acting, highly effective and well tolerated. Resistance to date has not been demonstrated. These drugs should always be used in combination with a second effective drug to prevent recrudescence and development of resistance. Sentinel sites to monitor drug efficacy and in-vivo resistance have been established in all three malaria transmission provinces. Relatively higher costs of these artemisinin drugs are a major obstacle to their introduction into resource poor, high transmission countries, but public- private partnerships are being forged to address this issue.

Quinine remains highly effective for the treatment of both uncomplicated and severe malaria, and the addition of doxycycline or clindamycin is recommended to ensure cure. Parenteral artemisinins, although highly affective for severe malaria, are not currently available in South Africa. The administration of artemisinins as artesunate suppositories has been shown to be highly effective in the treatment of patients with moderately severe malaria.

CHEMOPROPHYLAXIS

The major focus of prevention of malaria is on the use of personal protective measures to prevent mosquito bites. These measures include the application of DEET containing repellents to exposed skin, insecticide impregnated bednets, mats impregnated with insecticide, the wearing

of long trousers and socks, and the use of screened windows and doors.

Chemoprophylaxis should be considered if visiting malaria transmission areas where the risk of acquiring malaria outweighs any potential serious adverse drug reaction. The choice of chemo prophylactic drug should be individualised and is dependent on patient factors such as age, co-morbidity, allergy, medication, pregnancy, previous experience with the drug, duration of the visit and drug resistance at the destination. Weekly mefloquine or daily doxycycline are considered highly effective but a number of contra indications exist for their use. The efficacy of weekly chloroquine and daily proguanil has decreased due to widespread chloroquine resistance and this regimen is no longer recommended first line. Atovaquone-proguanil (Malanil®) has been recently registered as a chemo prophylactic in South Africa. It is highly effective, relatively well-tolerated and is as an alternative option to mefloquine or doxycycline. As atovaquone-proguanil is considered to be a causal prophylactic, the drug needs to be taken only for the duration of the malaria exposure and for 7 days thereafter.

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TYPHOID FEVER

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Typhoid fever is a systemic bacterial disease, characterised by an insidious onset of fever, malaise, relative bradycardia, splenomegaly and a non-productive cough. Constipation is commoner than diarrhoea and a mild rash (rose spots) may be noted on the trunk. The disease is caused by *Salmonella typhi*, less frequently by *S. paratyphi* A, B, or C, and has significant epidemic and hence public health potential. For this reason, it has been a notifiable disease since 1919. Paratyphoid fever tends to be a less severe disease, with a lower case fatality rate.

S. typhi is acquired via the faecal–oral route, most frequently through contaminated water or foods. The incubation period is between 1 and 3 weeks, depending on the infective dose. Patients remain infective as long as they actively excrete the bacillus in their stool. In endemic areas attack rates decline with advancing age due to the acquisition of immunity. In these areas, the peak incidence is between the ages of 5 and 15 years. In areas of poor water supply, incidence rates may be 5 times higher than those of the rest of the country and in past years high endemicity was noted in Limpopo, Mpumalanga, Eastern Cape and Kwa-Zulu-Natal. The last major epidemic in South Africa was noted in 1994 in Delmas, Mpumalanga. It is note-worthy that as delivery of treated water improves in an area, the incidence of typhoid fever decreases. The incidence of the disease and death rate over the last few years, according to clinical notifications received by the Department of Health in Pretoria, is reflected in figures 1a and b.

THE ORGANISM

Salmonella typhi is a gram-negative bacillus. The nomenclature is confusing, as it is a serotype within *S. enterica* subspecies *enterica* (serotype Typhi), but because it only infects humans and is of major clinical and public health significance compared with other salmonella serotypes, common practice is to give it species status. It has the ability to become encapsulated (Vi antigen) and blood culture isolates may be agglutinated with anti-Vi antisera.

DIAGNOSIS

Diagnosis primarily depends on the recovery of the organism from blood or bone marrow, or through serological diagnosis; specifically the Widal test is still widely used. The Widal may be negative in up to 30% of cases. For clinicians to rely on a diagnosis using the Widal test, they must be familiar with the local population antibody titres to the O (somatic) and H (flagellar) antigens of *S. typhi* as well as local resistance patterns of the organism. Other disadvantages of the Widal are that two specimens are necessary to see a change in antibody titre; seroconversion only occurs after one to two weeks after the onset of disease (table 1) and antibiotic resistance patterns would not be recognised. For these reasons, the Widal has no definitive role in the diagnosis of typhoid fever in South Africa today.

Newer serological tests are currently under evaluation. Some of these are specific for IgM, and appear more specific even than culture.

However, even in these instances repeat specimens may be necessary and antimicrobial resistance patterns would not be elucidated.

Blood culture remains the optimal method for identification of typhoid fever. More than 80% of patients will have the organism in their blood and the optimum time for recovery of the organism is after 7 to 10 days of fever. Bone marrow culture is the gold standard, but is more invasive, and should be conserved for those patients who have been previously treated or where the blood culture was negative, with a long history of illness. Laboratory diagnosis using blood cultures usually confirms the result within 48 hours, with antibiotic susceptibilities taking a further 24 hours. Syndromic treatment should be started as soon as the blood culture is taken, depending on local resistance patterns. Optimal times of diagnoses depending on the clinical stage of disease are indicated in table 1.

ANTIBIOTIC MANAGEMENT

Antimicrobial resistance in *S. typhi* has been described in South Africa, but is found in the minority of strains. Most of these isolates are from northern KwaZulu-Natal. Until recently, the isolates received by the EDRU from other provinces, have been fully susceptible to all antimicrobials tested, including ampicillin, chloramphenicol and co-trimoxazole. In 2004, the numbers of resistant isolates appear to be increasing. A worrying feature is that resistance has been observed in Eastern Cape, where the practice of using the Widal test for the diagnosis of typhoid fever is still common.

Recent studies have shown that the fluoroquinolones are highly effective in the treatment of typhoid fever, given as short course therapy, as is ceftriaxone. Both of these antibiotics have also shown better GIT clearance of the organism and patients treated with these are less likely to become long-term carriers. A second advantage is these antibiotics decrease in-hospital time of the patient. Oral fluoroquinolones are the treatment of choice in patients if there are no contra-indications to this class of antibiotics. It is important to note that fluoro-quinolone resistance in *S. typhi* has been documented on the Indian subcontinent and there have been anecdotal reports of extended-spectrum beta-lactamase production from this area. Should multi-drug resistance continue to emerge, it has been postulated that combination therapy with a fluoroquinolone and extended spectrum cephalosporins may become necessary. Appropriate current treatment regimens for South

Table 1 : Yield of cultures and Widal test during the course of untreated typhoid fever.

	Incubation ↓	**Active invasion**	**Established disease**	**Convalescence**	**Late complications**
Time course	Ingestion / Wk 1 / Wk 2		Wk 3	Wk 4 / Wk 5	Indefinite
Blood cultures	Negative	← 80-90% →		Negative unless continued disease or relapse	
Stool cultures	Transiently positive	Negative	← 80% positive →	← 50% → positive	Decreasing incidence of positive cultures with time : 20% at 2 mo 3% at 1 yr
Urine cultures	Negative	Negative	← 25% positive →	← 10% → positive	Decreasing incidence of positive cultures
Bone marrow	Negative	Negative	← 80-90% positive →	Decreasing incidence of positive cultures	
Widal test	Negative	← 20% → positive	← 50% → positive	← 80% positive →	

Table 2 : Treatment of uncomplicated typhoid fever

Susceptibility	Optimal Therapy	Alternative effective drugs
Fully sensitive	- Fluoroquinolone - Third generation cephalosporin	- Chloramphenicol - Ampicillin - Trimethoprim-Sulphamethoxazole
Multidrug resistance	- Fluoroquinolone - Third generation cephalosporin	- Azithromycin

Africa are listed in table 2. Drug dosages should be tailored according to the age and weight of the patient.

TYPHOID VACCINES

Currently there are three vaccines available for use in the prevention of typhoid fever. The old whole cell killed vaccine was highly effective, but due to the severity of side effects, compliance was poor. Subsequently two new vaccines, one based on the Vi antigen and the second a live attenuated bacterial enteric vaccine, have been developed.

The Vi polysaccharide vaccine is given as a single subcutaneous or intramuscular dose. Protection begins seven days after vaccination. The vaccine is approved for persons over 2 years of age and protection lasts for at least 3 years.

The live oral Ty21A vaccine is available as an enteric-coated tablet and requires three doses two days apart on an empty stomach. It elicits protection 10 to 14 days after the last tablet is taken. It may be associated with nausea and can be taken by adults and children after the age of 5 years. Travellers should be revaccinated annually. Herd immunity has been demonstrated, but it is theoretically contra-indicated in immune suppressed individuals. The vaccine may be inactivated by concomitant use of antibiotics, and although theoretically there is no interference by antimalarials, it is recommended that a three-day interval be maintained between completion of vaccination and malaria prophylaxis.

Newer vaccines under development include Vi-conjugate candidates, which can be used in children under the age of two years, as well as newer live attenuated *S. typhi* candidates, based on the deletion of virulence genes.

Current WHO recommendations for typhoid vaccination are targeted at travellers to areas that are highly endemic for typhoid fever, inhabitants of refugee camps, microbiologists, sewage workers and school children in areas where disease control is a priority.

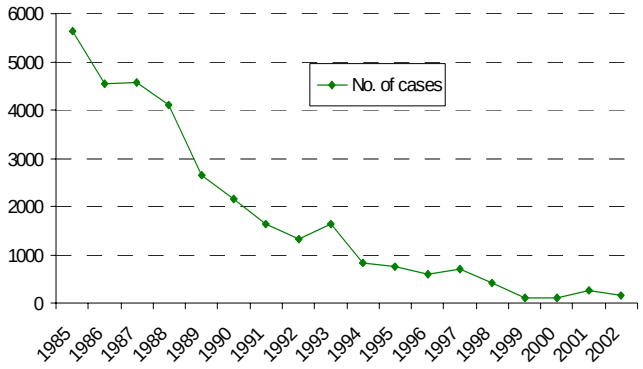

Figure 1a. Reported typhoid cases, Department of Health, South Africa, 1985-2002 (Source: *Epidemiological Comments*, Department of Health, South Africa)

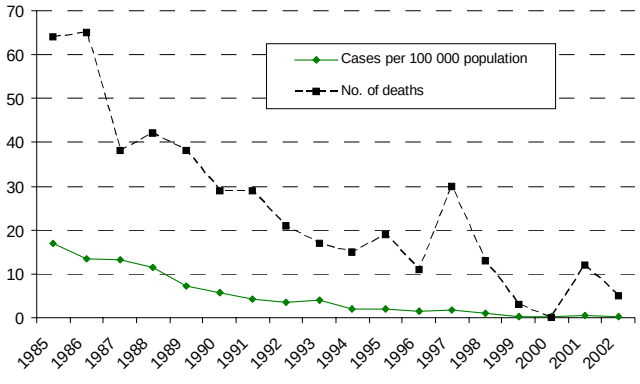

Figure 1b. Reported typhoid case incidence and total number of deaths, Department of Health, South Africa, 1985-2002 (Source: *Epidemiological Comments*, Department of Health, South Africa and derived from Statistics SA).

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