VOLUME 6, NO. 3

COMMUNICABLE DISEASES SURVEILLANCE BULLETIN

AUGUST 2008

NICD NHLS

FOREWORD

There has been much excitement following the announcement by the Minister of Health at the 61st World Health Assembly in Geneva, Switzerland that South Africa plans to introduce two new vaccines into the expanded programme on immunisation. These two vaccines, which aim to prevent infections due to *Streptococcus pneumonia* and rotavirus, can be expected to lead to a reduction in mortality in under 5 year olds and thus assist progress towards the millennium development goals. Implementation of new vaccines must always be accompanied by robust surveillance systems and an article in this bulletin presents preliminary results of rotavirus surveillance in the Western Cape. The human papilloma virus (HPV) vaccine is also under discussion for introduction through routine immunisation services. This vaccine is controversial for a number of reasons which are summarised in an article on HPV vaccine prospects for South Africa. Lastly, the article describing the response to an isolated diphtheria case in Cape Town serves as a reminder that we must remain vigilant for the re-emergence of diseases such as diphtheria, which have been reduced to very low levels following the introduction of successful vaccination programmes.

In this bulletin we also launch revisions to the table of numbers of cases of diseases under surveillance at the NICD. The revisions to the tables include:
i) expansion of the disease reported to include additional diseases of public health importance such as anthrax, botulism, plague and novel influenza A virus infections
ii) Reorganising the tables into alphabetical order as well as revisions to formatting for easier reference
iii) The introduction of a second table for reporting laboratory indicators for the NHLS and NICD.

We hope that these revised tables will assist in routinely communicating core epidemiologic data from surveillance and laboratory programmes at the NICD.

Cheryl Cohen, Editor

CONTENTS

HPV VACCINE PROSPECTS FOR SOUTH AFRICA

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Human papillomaviruses (HPVs) are one of the most important causes of sexually transmitted infections in both men and women worldwide because of their association with anogenital cancers[1]. Apart from cervical cancer, HPV is also the most common causative agent of genital warts and other squamous intraepithelial lesions (SIL)[2]. There are more than 100 HPV subtypes including 40 anogenital types based on partially and fully sequenced DNA fragments[3]. At least 16 high-risk (oncogenic) HPV types, such as HPV 16, 18, 31 and 45, are implicated in cervical cancer[4]. Low-risk HPV subtypes, such as HPV types 6 and 11, are responsible for more than 90% of genital warts and 10% of low grade cervical abnormalities[5,6]. Cervical cancer is the most common cancer in women in South Africa (35/100 000 women) and the second most common cancer in women worldwide[7]. There is an estimated global incidence of 470 000 cases of cervical cancer per year with about 233 000 deaths[8]. Developing countries accounted for almost 80% of all cervical cancer cases worldwide in 2002 and 80%-85% of cervical cancer deaths occurred in woman from these regions (Figure 1)[9,10]. Cervical cancer

(Continued on page 2)

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is a leading cause of death among black women in South Africa who are at an increased risk of acquiring cervical cancer compared to white women and are 2.5 times more likely to succumb to the disease[11]. A study conducted by Clifford *et al.* (2005) demonstrated that the HPV prevalence was approximately five times higher in sub-Saharan Africa than in Europe, with an intermediate prevalence in South America and Asia[12].

(Continued on page 3)

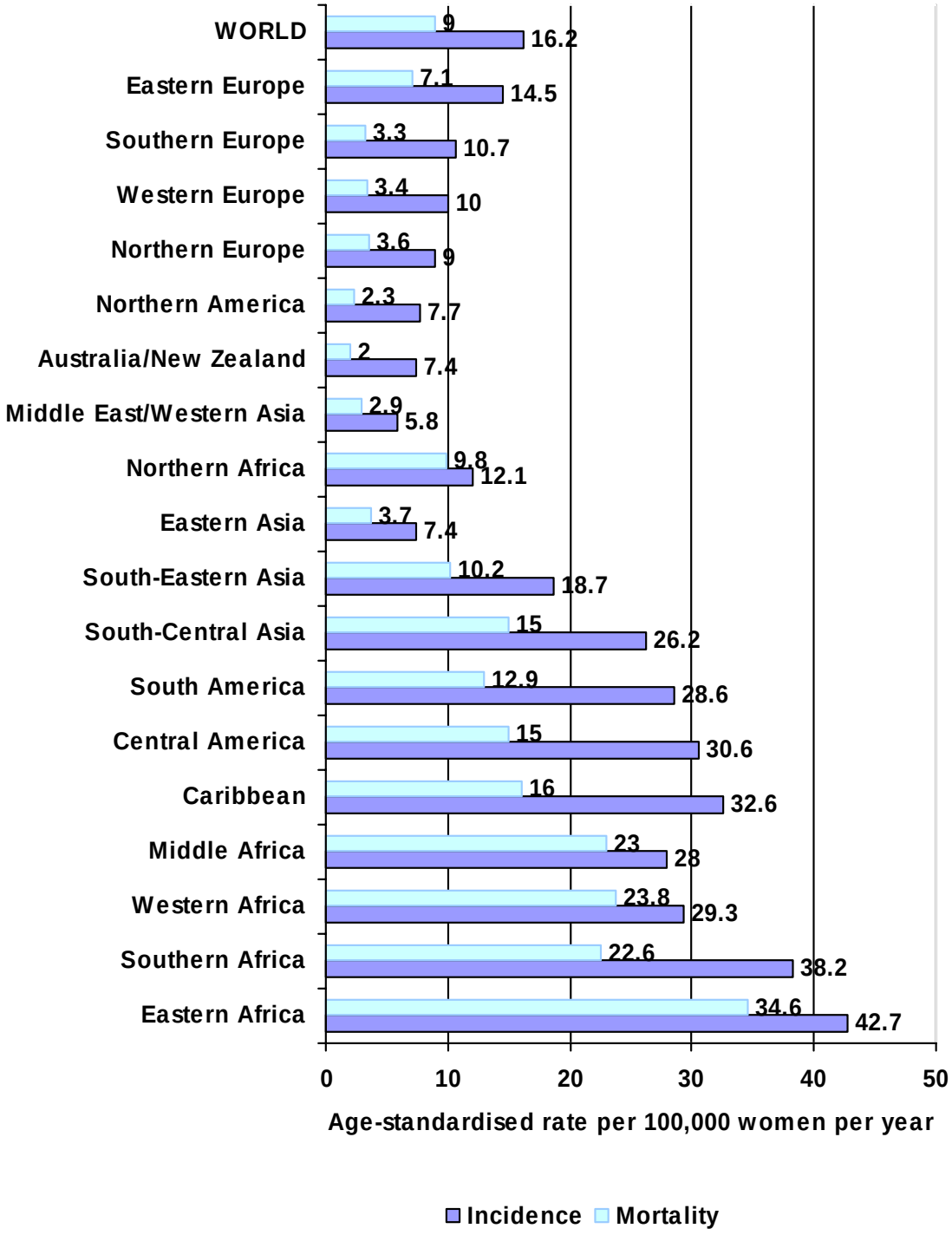

Figure 1: Global cervical cancer cases and deaths according to the International Agency for Research on Cancer (2002)[9]

There are currently two non-infectious recombinant prophylactic HPV vaccine options (Table 1). Both vaccines are prepared from highly purified virus-like particles (VLPs) of the major capsid (L1) protein of the respective HPV types. The first HPV vaccine, called Gardasil (Merck & Co.), is a quadrivalent vaccine which targets HPV types 6, 11, 16 and 18. A second, similar prophylactic HPV vaccine, known as Cervarix (GlaxoSmithKline) was approved and registered with the Medicines Control Council (MCC) early in 2008. This bivalent vaccine was specifically developed by GSK to prevent infection and lesions from HPV types 16 and 18. Both Gardasil and Cervarix protect against the two types responsible for over 70% of cervical cancer cases and approximately 50% of high-grade cervical abnormalities[11]. Gardasil has the additional benefit of providing protection against genital warts, which are very costly to manage due to a high case-load, particularly in countries with a high HIV prevalence, and can significantly reduce the quality of life.

Both vaccines are very safe, well-tolerated and effective and have demonstrated efficacy of more than 80% against persistent HPV types 16 and 18 infection after 3 doses of HPV vaccine[13, 14]. Harper *et al*. (2006) reported that antibody levels dropped by about one log between the peak after the third dose and 18 months after vaccination and then leveled off conferring adequate antibody levels for at least 5 years post vaccination[13]. The vaccine efficacy for precancerous lesions caused by HPV types 16 and 18 was 98% for Gardasil and 90% for Cervarix[15, 16]. The Gardasil vaccine also demonstrated 97% efficacy against vulvar and vaginal intraepithelial neoplasias caused by HPV types 16 and 18 and 96% protection against genital warts[17, 18]. No data are available on the cross-protective effect of the Gardasil vaccine although some cross-protection was observed for the Cervarix vaccine [HPV types 45 (60%), 31 (36%) and 52 (32%)][16]. The efficacy and safety of HPV vaccination in immunocompromised individuals and the safety of vaccination in pregnant women are not yet established.

Table 1: Characteristics of the two HPV vaccines

Variable	Gardasil	Cervarix
Manufacturer	Merck & Co.	GlaxoSmithKline Inc.
VLPs of genotypes	6, 11, 16, 18	16, 18
Substrate (antigen expression system)	Yeast	Baculovirus
Adjuvant	Proprietary aluminium hydroxyphosphate sulfate (225µg)	Proprietary aluminium hydroxide (500µg) plus 50 µg 3-deacylated monophosphoryl lipid A
Dose and schedule	0.5 mL intramuscular injection at 0, 2 and 6 months	0.5 mL intramuscular injection at 0, 1 and 6 months
Duration of immune response	96% seropositive to HPV types 6, 11 and 16 at 24 months 68% seropositive to HPV type 18 at 24 months	100% seropositive to HPV types 16 and 18 at 51-53 months
Persistent infection from HPV types 16 and 18[†]	Vaccine efficacy 93.5% (95% CI 83%-98%)[21]	Vaccine efficacy 80.4% (95% CI 70%-87%)[16]
CIN (2 or higher) related to HPV types 16 and 18	Vaccine efficacy 98% (95% CI 93%-100%)[15]	Vaccine efficacy 90.4% (95% CI 53%-99%)[16]
VIN and VaIN (2 or higher) related to HPV types 16 and 18	Vaccine efficacy 97% (95% CI 79%-100%)[17]	No data
Protection against genital warts	Vaccine efficacy 96% (95% CI 86%-99%)[22]	No data

Note: CI = confidence interval; VLPs = virus-like particles; CIN = cervical intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia
[†] = Persistent infection was defined as 4 months in the Gardasil trial and as 6 months in the Cervarix trial

The HPV Advisory Board of South Africa suggested some recommendations for the implementation of HPV vaccines in South Africa (Table 2)[19]. HPV vaccination should be offered to females up to the age of 26 during the vaccine roll-out period on an ad-hoc basis. Current recommendations suggest that vaccination must be determined for each individual population but ideally girls should be routinely vaccinated before the age of sexual debut. The suggested age for HPV vaccination is 11-12 years but this could be as low as 9-10 years at the discretion of the physician. Older women will only benefit from vaccination if they want to prevent new HPV infections. The efficacy of the vaccines in preventing anogenital cancers among men has not yet been established and vaccination in this population is not currently recommended. Vaccinating men could indirectly protect non-immunized women by reducing the transmission of HPV by increased herd immunity. However, at this stage such an intervention will not be a cost-effective option.

(Continued on page 4)

Generally, it takes between 10-20 years from the time a new vaccine is licensed until it is distributed in the public sector in developed countries[20]. Due to the natural history of HPV-induced cervical cancer, it will also take approximately 20 years until a vaccine-induced protective effect is clearly demonstrated. The cost-effectiveness of implementing an HPV vaccination strategy in South Africa will be challenged by the high prices of the vaccines. In South Africa, the vaccine could cost approximately R2 100 for three intramuscular 0.5 mL injections at 0, 2 and 6 months[19]. The estimated costs and benefits from vaccination should be compared to those of other interventions. The magnitude of benefit in South Africa would be great considering the high incidence, mortality and treatment costs of disease caused by HPV 6, 11, 16 and 18. The greatest benefit of HPV vaccination in South Africa would be the potential reduction in cervical cancer deaths. However, a coverage rate of over 70% would be needed to have a significant impact on cervical cancer incidence[19]. It is unclear as to the impact HIV-related immunosuppression will have on protective efficacy of both HPV vaccines in countries with a high HIV prevalence. It is estimated that about 300 000 South Africans should be vaccinated each year, adding up the cost to about R630 million per year. It may be possible to negotiate a realistic vaccine price once HPV vaccination has been adopted by the Government as a national public health policy. Even if a vaccination program was to be implemented the current recommended cytological screening of one smear every 10 years, starting at age 30, should still continue and Government should investigate alternative screening strategies such as HPV DNA testing.

Table 2: HPV vaccination recommendations from the HPV Advisory Board of South Africa[19]

Recommendations for implementation of HPV vaccines in South Africa
• All girls in the population should be immunized at ages 9-12.
• In early years of the programme: “Catch up” vaccination of girls up to 20 or 26 years: after 20 years surveillance is indicated.
• Give 3 doses at months 0, 2 and 6; no boosters offered (no supporting literature to suggest boosters).
• Offer to survivors of rape and sexual violence.
• Continue with cervical screening as per policy.
• Boys are not the target of cervical cancer prevention and should not be vaccinated as a first step.

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ROTAVIRUS SURVEILLANCE IN THE WESTERN CAPE IN 2007

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Diarrhoeal diseases remain a major health burden in many developing countries. Rotaviruses are the foremost etiological agent of gastroenteritis, contributing 20-30% of childhood diarrhoeal episodes and 6% of all deaths among children less than five years old[1,2]. Recent estimates generated by Parashar and colleagues[3] attribute 527 000 deaths in children less than five years of age to rotavirus annually, with 145 000 deaths occurring in sub-Saharan Africa[4]. Improvements in sanitation and the availability of clean water have not decreased the rate of rotavirus diarrhoea in developed countries and the development and implementation of an effective vaccine into the routine Expanded Program on Immunisation schedule is considered the first strategy of prevention[5].

Estimates of mortality associated with rotavirus disease in South Africa calculated in 1996 attributed 6-10 deaths in children below age 5 per day to severe dehydrating rotavirus gastroenteritis[6]. In response to the need to actively address this cause of diarrhoeal disease, the Health Minister, Dr Manto Tshabalala-Msimang, announced at the 61st World Health Assembly, Geneva, Switzerland that South Africa planned the introduction of a rotavirus vaccine into the national EPI program.

While the planned introduction of a rotavirus vaccine into the South African EPI is a triumph, continued surveillance of rotavirus nationally will be required to assess vaccine impact on mortality and hospitalizations due to rotavirus diarrhoea, detection of rotavirus strains that may escape immune responses generated by vaccination and emergence of unusual rotavirus strains in response to vaccine pressure.

The Viral Gastroenteritis Unit (VGU) is a newly established laboratory at the National Institute for Communicable Diseases (NICD/NHLS, South Africa) aimed at providing surveillance of viral diarrhoeal pathogens in South Africa. Limited information is available on the prevalence and diversity of the circulating rotavirus strains in the Western Cape Province and this preliminary report provides a view on the serotypes circulating in the Western Cape region during the 2007 rotavirus season. Diagnostic laboratories (Pathcare Laboratories, 2 Military Hospital, Greenpoint laboratory, Groote Schuur Hospital, Red Cross Children's Hospital and Tygerberg laboratory) in the Western Cape were requested to submit stool specimens to VGU for further analysis. The screening for rotavirus was performed by the individual laboratories prior to submission to VGU, using the Coris Rota-strip (Coris BioConcept, Belgium) according to manufacturer's instructions.

Differences in the outer capsid proteins allow classification according to two antigenic markers i.e. VP4 and VP7. The VP7 and VP4 proteins form the smooth outer capsid (G serotype) and short spike (P genotype), respectively and are the major antigens inducing neutralizing immune responses during rotavirus infections. Although 15 different G serotypes and 28 P genotypes have been detected in humans, serotypes G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] are thought to be an important cause of diarrhoea in infants and young children worldwide[7].

Rotavirus double-stranded RNA was extracted from specimens using the QIAamp viral RNA mini kit (Qiagen, Carlsbad, Ca, USA) according to the manufacturer's instructions. VP7 and VP4 genotyping was performed in a routine multiplex reverse-transcription polymerase chain (RT-PCR) reaction with eight G genotype-specific primers (G1, G2, G3, G4, G8, G9, G10 and G12) and seven P genotype-specific primers (P[4], P[6], P[8], P[9], P[10], P [11] and P[14]) as previously described[8-11].

Between February and December 2007, a total of 765 stool samples were received, representing 56 hospitals and medical institutions in both the private as well as the public sector. The private sector represented 90.1% (n=690) of all specimens submitted. The majority of children affected by rotavirus (93.5%, n=716) were less than 5 years of age and only 49 patients identified in this study were $\geq$5 years old. These results were a reflection of the focus of surveillance rather than an exact picture of what was occurring in the community.

Of the 765 specimens received, 39 (5.1%) were insufficient volume for further analysis. In total, 696/726 (95.9%) stool specimens received could be allocated a genotype, while 30 were negative for rotavirus. Of the 627 specimens received from Pathcare laboratories, 5 were unable to be genotyped (false positives), while 53 (94.6%) referred by NHLS laboratories as negative for rotavirus, were allocated a genotype (false negative).

The distribution of the VP7 and VP4 genotypes is shown in Table 1. Genotype characterization revealed G1 as the common VP7 genotype (74.8%) with G1P[8] being the most predominant strain (63.6%), followed by G2P[4] (18.2%). Novel strains, G12P[6] and G12P[8], were detected towards the end (September) of the 2007 rotavirus season (Figure 1) and were identified in 15 children <2 years of age. It was interesting to note that G1P[8], predominant at the beginning of the season (February till May), was gradually replaced by the G2P[4] with the emergence of G12P[6] and G1P[6] strains. This emergence coincided with the second seasonal peak seen in October (Figure 2). Mixed infections comprised 6.3% of the specimens received and could be detected throughout the year.

(Continued on page 6)

Table 1: Distribution of VP7 and VP4 genotypes [*number* (%)] circulating in the Western Cape during 2007 (most prevalent genotypes are highlighted in bold red)

	P[4]	P[6]	P[8]	Mixed infection	*Total G-type*
G1	**31(4.5%)**	**28(4%)**	**443(63.6%)**	19(2.7%)	521
G2	**127(18.2%)**	2(0.3%)	3(0.4%)	0	132
G3	1(0.1%)	0	2(0.3%)	0	3
G12	0	18(2.6%)	1(0.1%)	0	19
Mixed infection	10(1.4%)	5(0.7%)	2(0.3%)	4(0.6%)	21
Total P-type	169	53	451	23	696

Rotavirus infection is a seasonal occurrence, usually with peaks in the colder winter months. The data from this study showed that the rotavirus season started a month earlier (March) in the Western Cape than what was seen in the Ga-Rankuwa area (April) during the same time period. The rotavirus season might even have started earlier as the low number of specimens received in February is likely a reflection of the collection of specimens rather than the seasonality (Figure 2).

Although the majority of specimens represented the private sector (Pathcare laboratories), only 5 false positives were detected, while 94.6% of specimens referred by the NHLS laboratories as negative for rotavirus were found to be positive by PCR. The discrepancy of the results generated by the private versus the public laboratories is not seen as a reflection of the ability of the public laboratory staff but rather a difference in the collection policies in the different settings. In private health care settings, stools are probably taken soon after admission and rotavirus is easily detected during the acute phase of infection. However, in public health care settings very few stools are taken for testing due to the costs involved and those specimens that are taken are probably taken from severely ill children or children who fail to respond to treatment i.e. late in the infection. In these cases, the rotavirus antigen is probably below the detection limit of an ELISA-based assay and can only be detected by PCR-based methods.

The molecular epidemiology of the rotavirus strains detected in the Western Cape indicates that the rotavirus vaccines currently available on the South African market should provide adequate protection against rotavirus

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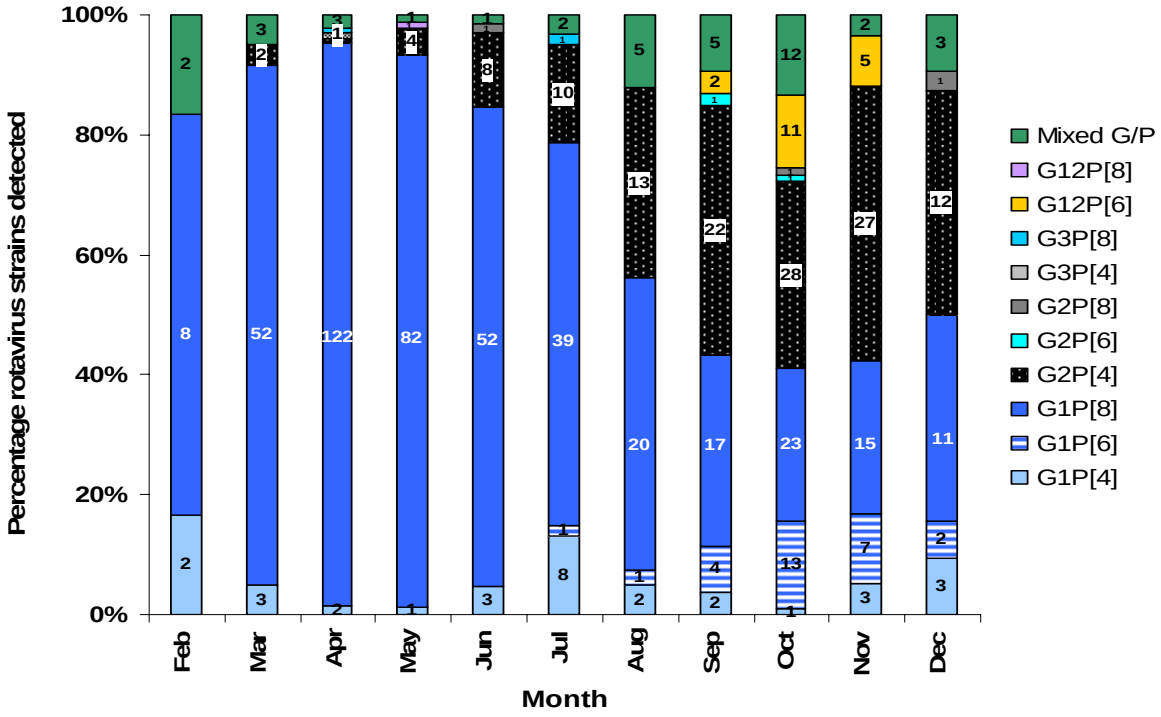

Figure 1: Distribution of rotavirus genotypes in the Western Cape, South Africa, February 2007 – December 2007.

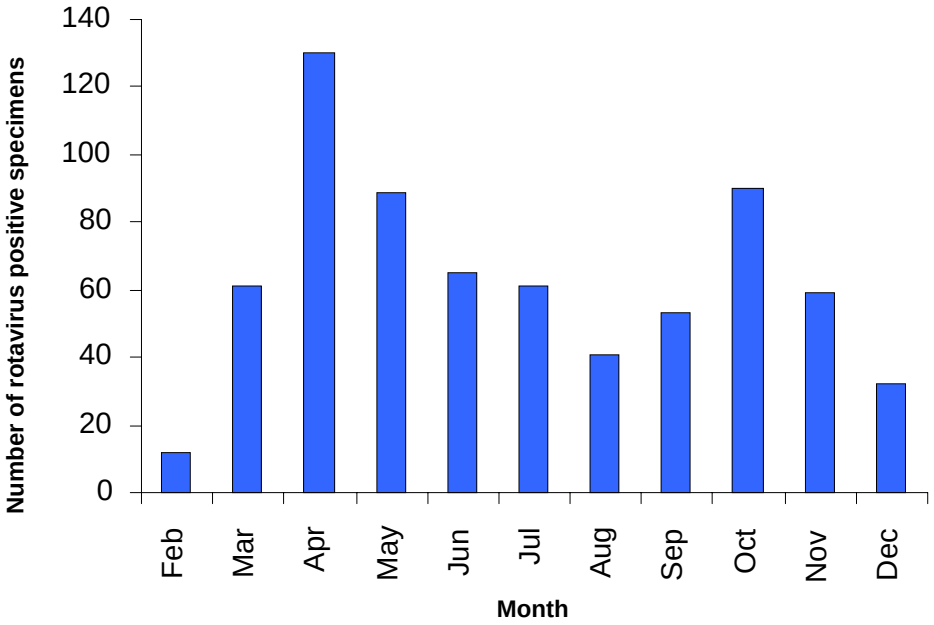

Figure 2: Number of laboratory-confirmed rotavirus cases by month in the Western Cape, South Africa, February 2007 – December 2007.

disease. The study also highlighted the continued spread of serotype G12P[6] strains into naïve populations and is consistent with recent reports of the increasing epidemiologic importance of these strains globally. The ability of the current vaccine formulation to protect against novel strains cannot be predicted and therefore, continued monitoring of rotavirus strains circulating within communities before and after the widespread introduction of rotavirus vaccines will be required.

Acknowledgements

We would like to thank all clinical as well as laboratory staff from the following institutions who contribute to the continued surveillance at VGU: Pathcare Pathology laboratories (Drs Dietrich, Voigt and Mia & Partners), 2 Military Hospital and NHLS laboratories (Greenpoint laboratory, Tygerberg Hospital, Groote Schuur Hospital, Red Cross War Memorial Children's Hospital).

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IT STARTED WITH A SORE THROAT…….. RESPONSE TO AN ISOLATED DIPHTHERIA DEATH IN CAPE TOWN, SOUTH AFRICA, 2008

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Abstract

The incidence of clinical diphtheria has been significantly reduced worldwide and in South Africa due to increasing immunization levels. This article reviews the clinical presentation of an isolated laboratory-confirmed diphtheria case and critically evaluates the public health response to this case. The patient was admitted to Red Cross War Memorial Children's Hospital on the 12th of March with a sore throat, fever and swelling of the submandibular region and died on the 15th of March. The health department was notified of the case on the 26th of March 2008. Laboratory confirmation was obtained by culture of a throat swab and toxigenicity testing. The public health response included contact tracing and administration of immunization where indicated in the community and hospital. Review of the public health response identified a delay in case-notification possibly due to failure to consider the diagnosis or to inform the laboratory that diphtheria was part of the differential diagnosis. It was also identified that there are no national guidelines for diphtheria case management and that there are no stocks of diphtheria antitoxin available in South Africa. Clinicians and other health care workers must be made aware of the possibility of a clinical diagnosis of diphtheria and the importance of notifying suspected cases as well as good communication with the laboratory. High routine childhood immunization against diphtheria must be ensured.

Introduction

Diphtheria is a contagious, airborne, toxin producing infection by *Corynebacterium diphtheriae* spread by coughing or sneezing or through contact with skin infections.[1] Classical respiratory diphtheria is characterized by the insidious onset of membranous pharyngitis with fever, enlarged anterior cervical lymph nodes, and oedema of the surrounding soft tissue, which gives rise to a "bull neck" appearance.[2] Diphtheria should be considered in the differential diagnosis of bacterial (especially streptococcal) and viral pharyngitis, Vincent's angina, infectious mononucleosis, oral syphilis, candidiasis, a chronic unilateral rhinitis or impetigo.[4] The incubation period of diphtheria is 2 to 5 days (range 1 – 10 days). Human carriers are the reservoir for *C. diphtheriae* and inapparent infections outnumber clinical cases. Both toxigenic and non-toxigenic strains of *C. diphtheriae* may be harbored in the nasopharynx, skin, and other sites of asymptomatic carriers.[7] Severe complications of diphtheria may be due to laryngeal disease (respiratory obstruction) or the effects of diphtheria toxin on systemic organs. This may involve the heart (myocarditis, heart block and heart failure) and central nervous system (neuritis and paralysis). The overall case-fatality rate for diphtheria is 5 -10% with higher death rates (up to 20%) among persons younger than 5 and older than 40 years of age.[5]

Diphtheria is still common in many parts of the world, including the Caribbean and Latin America. With increasing levels of immunization there has been a corresponding drop in the number of diphtheria organisms in circulation, and less opportunity for boosting immunity through natural exposure. Over time, even with consistent high levels of immunization coverage in children under one year of age – vaccine induced immunity wanes and groups of non-immune individuals build up, creating the ideal conditions to seed an epidemic.[1] The collapse of the Soviet Union resulted in a breakdown of the health care system and was followed by more than 150,000 cases of diphtheria and 5,000 deaths from 1990 to 1997.[5] Outbreaks have also been documented in Algeria, China and Ecuador.[3] More recently in the United Kingdom, on the 8th of May 2008, an unvaccinated child died in London due to diphtheria.[9] There had only been 3 deaths due to diphtheria in the United Kingdom since 1994. In 2000, 30 000 cases and 3 000 deaths due to diphtheria were reported worldwide. The global figures from the World Health Organization (WHO) indicates 3 978 reported cases in 2006.[10]

Two key groups of people are particularly vulnerable to disease – adults who have lost their immunity due to waning immunity and children who have not been immunized against diphtheria.[1]

The only effective control is active immunization with diphtheria toxoid. The WHO recommends that all countries should give priority to ensure that at least 90% of children under one year of age are immunized with three doses of Diphtheria Tetanus Pertussis (DTP) vaccine.[1] The 2006 global estimated 3 dose DTP vaccine coverage was 79%, and 26% of countries reached ≥80% of coverage with 3 DTP doses in all districts in 2006.[10] The recommended schedule for vaccination against diphtheria varies considerably between countries.[13] According to the WHO/ EPI schedule, the primary series should be administered in 3 doses, where resources permit - additional booster doses can be given after the completion of the primary series. Timing of doses and the number of booster doses is based on epidemiological surveillance, immunological and programmatic considerations.[13] In South Africa, the DPT-Hib (Diphtheria, Pertussis, Tetanus – *Haemophilus influenzae* type B) vaccine is administered at 6, 10, 14 weeks. It is followed by the DPT (Diphtheria, Pertussis, Tetanus) vaccine at 18 months. Since February 2008, the Expanded Programme on Immunisation has introduced the

(Continued on page 9)

Td (Tetanus and reduced diphtheria) vaccine, known as Diftavax, into the routine immunization schedule. It is administered to children aged 6 and 12 years of age as booster doses.[6] DT vaccine is no longer given at 5 years of age. Td contains reduced amounts of diphtheria toxin and is registered for use at 6 years of age and older to reinforce active immunity.

Control measures for suspected diphtheria cases include:

- Isolation and treatment of the index case
- Tracing and managing close contacts (all household members and other persons with a history of habitual, close contact with the patient, as well as directly exposed to oral secretions of the patient) to prevent secondary transmission of C*. diphtheriae*

The management of contacts should include:

- taking nose and throat swabs for diphtheria diagnosis
- provision of prophylactic antibiotics – benzathine penicillin G or a 7 to 10 day course of oral erythromycin
- booster vaccination appropriate for age
- observation for symptoms and signs of diphtheria with administration of antitoxin at the first sign of illness

Diagnostic tests used to confirm infection include isolation of *C. diphtheriae* on culture and toxigenicity testing.[3] All suspected cases and their close contacts should have specimens taken from the nose and throat (i.e. both a nasopharyngeal and a pharyngeal swab) for culture. The laboratory should be alerted to the suspicion of diphtheria because isolation requires special culture media (containing tellurite). Toxigenicity testing using the Elek test should be performed to determine if the *C. diphtheriae* isolate produces toxin.

Various challenges are identified with the control and eradication of diphtheria namely:[8]

- Continued diphtheria circulation in some settings, even in populations with >80% childhood immunization coverage.
- The existence of an asymptomatic carrier state even among immune individuals.
- Waning immunity over time, and booster doses are required to maintain protective antibody levels.
- Large populations of adults are susceptible to diphtheria in developed and increasingly in developing countries due to waning immunity.

Diphtheria is a notifiable medical condition in South Africa. The incidence of diphtheria in South Africa has been low, with only 18 reported cases from 1997 to 2007. Nationally, no cases were reported in 2004 and 2 cases were reported in 2005 (National Department of Health, Epidemiology Unit, Notifiable Medical Conditions System). In the City of Cape Town since 2000, only one other case was notified in September 2006 from Red Cross Hospital through the notifiable medical disease system. The electronic hospital information system reflects the same case, with the inpatient diagnosis for diphtheria, ICD10 code of A36 (Data from Provincial Health Information). The case turned out to be positive for *Streptococcus* spp. and ironically this 8-year- old child was from the same area as the case/death described in this report. Similarly the report of a laboratory confirmed fatal case from Red Cross Hospital in March 2008, led to renewed awareness of diphtheria.

Methodology

The clinical records of an isolated laboratory-confirmed diphtheria case were reviewed. The public health response to this case was critically evaluated.

Laboratory Methods and Diagnosis

All specimens were processed at the National Health Laboratory Service (NHLS) laboratory at Groote Schuur Hospital. Laboratory confirmation for the index case was obtained by culture of a throat swab and toxigenicity testing through the Elek test. The swab was initially inoculated onto blood agar only, as diphtheria had not been indicated on the specimen request form. The laboratory was later contacted, the swab retrieved and inoculated onto tellurite agar and incubated in 5% CO_2 for 48 hours. Black pigmented organisms were identified by Gram stain in the first instance, and Gram-positive bacilli were biochemically identified using the BBL Crystal identification kit. Isolates biochemically identified as *C. diphtheriae* were referred to the NHLS laboratory at Greenpoint for an ELEK test to determine whether the strains were toxigenic. Throat swabs from contacts were inoculated onto tellurite agar only, incubated and followed up as described above.

Results

Case Report

On the 26th of March 2008, the provincial health department was alerted to the death of a laboratory-confirmed case of diphtheria (Figure 1). The patient, an 11-year-old boy from Samora Machel, Mitchell's Plain, Cape Town, had been referred from a local clinic on the 12th of March to Red Cross War Memorial Children's Hospital for admission. A General Practitioner had been consulted a week prior to admission and had prescribed antibiotics.

On admission the patient gave a one-week history of a sore throat, fever, vomiting, coughing and nose bleeds. On examination necrotizing pharyngitis was noted with swelling of the submandibular region and evidence of upper airway obstruction. The child was lethargic and shocked. Laboratory testing confirmed evidence of acute renal failure with hyperkalaemia. Investigations included cultures from throat and blood, serology for infectious mononucleosis as well as a screen for collagen vascular disease in view of renal failure. A necrotic soft palate with a pseudomembrane was noted. The patient was treated with intravenous penicillin (600000IU), cefotaxime (2.4g) and metronidazole (240mg) and intravenous fluid resuscitation.

(Continued on page 10)

The patient was previously well, had no other major illnesses, and according to his mother, was on schedule with his immunizations. Immunization status however could not be verified with the Road-to-Health Chart. There was no history of any recent travel, the patient had always lived in Cape Town, nor was there any history of traditional medicines.

The patient was admitted to the Intensive Care Unit (ICU) on the 13th of March with increasing respiratory distress due to upper airway obstruction, signs of pneumonia and rising creatinine levels. On arrival in ICU, a bronchoscopy and laryngoscopy under general anesthetic were performed, which illustrated necrotizing pharyngitis with no involvement below the cords. The trachea was intubated with size 5.5 cuffed endotracheal tube (ETT), and ventilation commenced. Lasix and aminophylline infusions were started in an attempt to improve urine output. ECG demonstrated a rate of approximately 100/minute with nodal rhythm and broad complexes with poor R-wave progression and deep ST depression. Echocardiography demonstrated an anatomically normal heart with apparently normal function. Blood pressure stabilized after the addition of a dopamine infusion and fluid administration. Chest X-ray now showed increasing bilateral infiltrates. A renal biopsy was performed on 14th of March which was unfortunately complicated by bleeding for which resuscitation was required. The following day the patient died in ICU following an episode of profound bradycardia and hypotension. The patient did not respond to attempts at resuscitation. On post-mortem examination extensive ulceration and acute fibrinosupparative pseudo-membranous inflammation was present in histological examination of the epiglottis, vocal cords and trachea. The Gram stain highlighted numerous clusters of Gram-positive cocci as well as Gram-positive bacilli within the exudates.

Public Health Response (since 26 March 2008)

The public health response to this case commenced from the 27th of March 2008 by the Mitchell's Plain sub-district public health officials and Red Cross Hospital staff. Provisional guidelines on the diagnosis and management of diphtheria from the National Institute for Communicable Diseases were made available to all role-players, in the absence of official national diphtheria guidelines.

A. Notification of the case and notification of all stakeholders

The GW17/5 notification form was completed on the 26th of March by Red Cross Hospital and sent to the local authorities. The National Department of Health (Communicable Diseases) and the NICD were informed on the 26th of March. There was a delay in notifying the case to the health authorities, as 14 days elapsed between the admission of the child at Red Cross Hospital and the notification of the case to the health authorities. The case was finally notified based on the post-mortem report and laboratory confirmation of the case as diphtheria.

B. Management of contacts

Prevention measures were initiated through the tracing of close contacts, provision of chemoprophylaxis and booster diphtheria doses, and surveillance of contacts for signs of diphtheria. Facilities and clinicians in the area of the case were alerted to have a high index of suspicion.

i) Community Contacts:

The case was an only child residing with the mother only. Two additional adult and 5 paediatric contacts (aged 1, 4, 5, 9 and 10 years) were identified who were visited regularly by the child. Throat swabs for culture were taken from these contacts on the 27th of March 2008. Chemoprophylaxis (Benzathine Penicillin) was given to all contacts. In addition Td vaccination was given to all contacts over the age of 6 years and the 1-year-old child received DTP vaccination (was behind schedule with immunization). As the 4- and 5-year-old children were in the age group when Td or DPT can not be given, Infanrix Hexa (combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B, Poliovirus and *Haemophilus influenzae* type b vaccine) injections were given to the 4- and 5-year-old on the 31st of March 2008.

ii) School Contacts:

As it was school holidays (20 March to 14 April 2008), a decision was taken to administer the Td vaccine to the close school contacts when the school re-opened. A total of 40 children and 1 school teacher at the school which the case attends had throat swabs taken on the 15th of April and all 41 received Td booster immunization on the 18th of April.

iii) Red Cross War Memorial Children's Hospital

A total of 22 staff members (health care workers) received a Td booster dose, 20 had throat swabs taken, and no prophylaxis was given as more than 10 days had elapsed since admission of the patient. These interventions were done from the 28th of March to 14th of April, due to the fact that staff worked shifts. The decision to give booster Td vaccination was based on the fact that immunity from childhood immunization wanes and no staff member had documented booster diphtheria immunization.

The throat swab taken from the child at presentation on 12 March cultured *C. diphtheriae* (result available 24 March 2008), which was shown to be a toxigenic strain by the ELEK test (result available 2 April 2008). All throat swabs from contacts were negative for *C. diphtheriae*.

Discussion

The occurrence of this isolated diphtheria case (and unfortunate death of a child) leaves us with many unanswered questions e.g. our preparedness to detect and manage isolated cases or importations or potential outbreaks, whether the diphtheria organism is circulating in the Western Cape and whether there are gaps in the immunization coverage of diphtheria toxoid. According to the routine District Health Information System (DHIS), the childhood DPT3 coverage in the Western Cape was 97,7%

(Continued on page 11)

and 105.6% in 2005/06 and 2006/07 (financial year) respectively (Provincial Health Information). However, a large scale 30x7 cluster household immunization survey conducted in the Western Cape Province in 2005 revealed that immunization coverage is 76.8% for vaccines due by 9 months and 53.2% for vaccines due by 18 months, which is not as high as it should be to reasonably prevent outbreaks of vaccine preventable diseases.[11] Therefore, there exists a possibility of an isolated case or outbreak due to diphtheria importation into the Western Cape.

A. Evaluation and discussion of the response

i) Clinical diagnosis and management of case

The case presented with various signs and symptoms, indicative of a suspected diphtheria case however the diagnosis of diphtheria was not made. Reasons for missed or delayed diagnosis include limited epidemiological, clinical and laboratory expertise on diphtheria as most clinicians and laboratorians have never encountered a case because it is so rare.[8,2] In the context of low diphtheria incidence, clinicians considered that the diagnosis of infectious mononucleosis was more likely than diphtheria. Ongoing reminders are needed to encourage prompt diagnosis and treatment of diphtheria cases and preventative treatment of close contacts. The mainstay of therapy is administration of diphtheria antitoxin and antibiotics; this should be given when diphtheria is suspected, without waiting for laboratory confirmation. Erythromycin or penicillin is recommended to be administered for a 14-day treatment course. The disease is usually not contagious after 48 hours after antibiotics are instituted. Antitoxin is said to neutralize circulating (unbound) toxin and would prevent progression of the disease. It is unclear whether administering diphtheria antitoxin would have affected the clinical course of the case as the disease progressed rapidly. There is no supply of antitoxin in South Africa.

ii) Late notification of the case to the local authorities

The delay in case notification could have been due to failure to consider the diagnosis of diphtheria while awaiting the confirmatory laboratory results All suspected cases of any of the notifiable medical conditions (including diphtheria, with or without laboratory confirmation) must be notified on the official form (GW17/5), so that a public health response can be elicited. Health care workers are legally obliged to notify any of the listed notifiable medical conditions.

iii) Laboratory procedures, confirmation and notification

The laboratory plays a pivotal role in confirming the diagnosis of diphtheria. Clinicians had requested a throat culture but did not indicate that diphtheria was suspected as they were not aware that routine cultures would not detect diphtheria. Consequently results were only obtained well after the patient had died.

iv) National guidelines and antitoxin availability

At the time of the report no official national diphtheria guidelines were available. This case should be seen as an alert to the department to put national guidelines in place outlining the immediate actions that should be instituted once a suspected case is identified. Challenges were experienced with the availability and procurement of antitoxins with previous suspected cases at Red Cross Hospital (personal communication, Prof Andrew Argent). The diphtheria antitoxin is no longer registered in South Africa, and is only available from the Instituto Butantan, Brazil. Challenges in terms of procurement, price, shelf life, and stocking of essential stocks of antitoxin (that are readily and 24-hour available) are all issues that need to be addressed.

It is evident from the case report and the evaluation of the response to this isolated case that the major challenge is to establish a system that ensures the early detection of cases, with appropriate treatment and minimized risk of spread.

B. Specific Recommendations:

Figure 2 gives an illustration of the recommendations that could inform a health system that would be able to detect and respond effectively to suspected diphtheria cases in the context of low incidence in the province and country.

Conclusion

This case report once again highlights the importance of high immunization coverage in our communities against diphtheria and the other vaccine-preventable diseases. The possibility of instituting booster Td immunization to health care workers at high risk of patient exposure in health facilities (like Red Cross War Memorial Children's Hospital) should be investigated and considered. In the context of low diphtheria incidence and reasonable immunization coverage, the challenge now is to ensure that clinicians and other health care workers are made aware of the possibility of a clinical diagnosis of diphtheria. Clinicians and nurses should consider the diagnosis of respiratory diphtheria in patients with membranous pharyngitis; they should be trained in the recognition of suspected cases; and the notification and reporting of such cases to the specific health authorities irrespective of laboratory confirmation. Official guidelines and the availability of antitoxin in the country should be addressed to deal with any potential diphtheria cases. Research into the knowledge of health care workers in the recognition, management, notification and report of suspected cases is essential.

Acknowledgements

We hereby wish to acknowledge Red Cross War Memorial Children's Hospital and staff for access to clinical records, public health officials (Provincial, Cape Town district, Mitchell's Plain sub-district), NHLS staff (University of Cape Town), and staff of the Epidemiology Unit at the NICD for their guidance, support and advice. Special thank you to the clinicians who managed the case, Prof Anthony Westwood, Ms Charmaine Rinquist and Ms Ludick from Red Cross Hospital, Ms Fawzia Desai from the Provincial Office and Ms Nomsa Nqana, Ms Lebo, Ms Fredericks (Mitchell's Plain sub-district, Weltevreden Clinic, School Health Services).

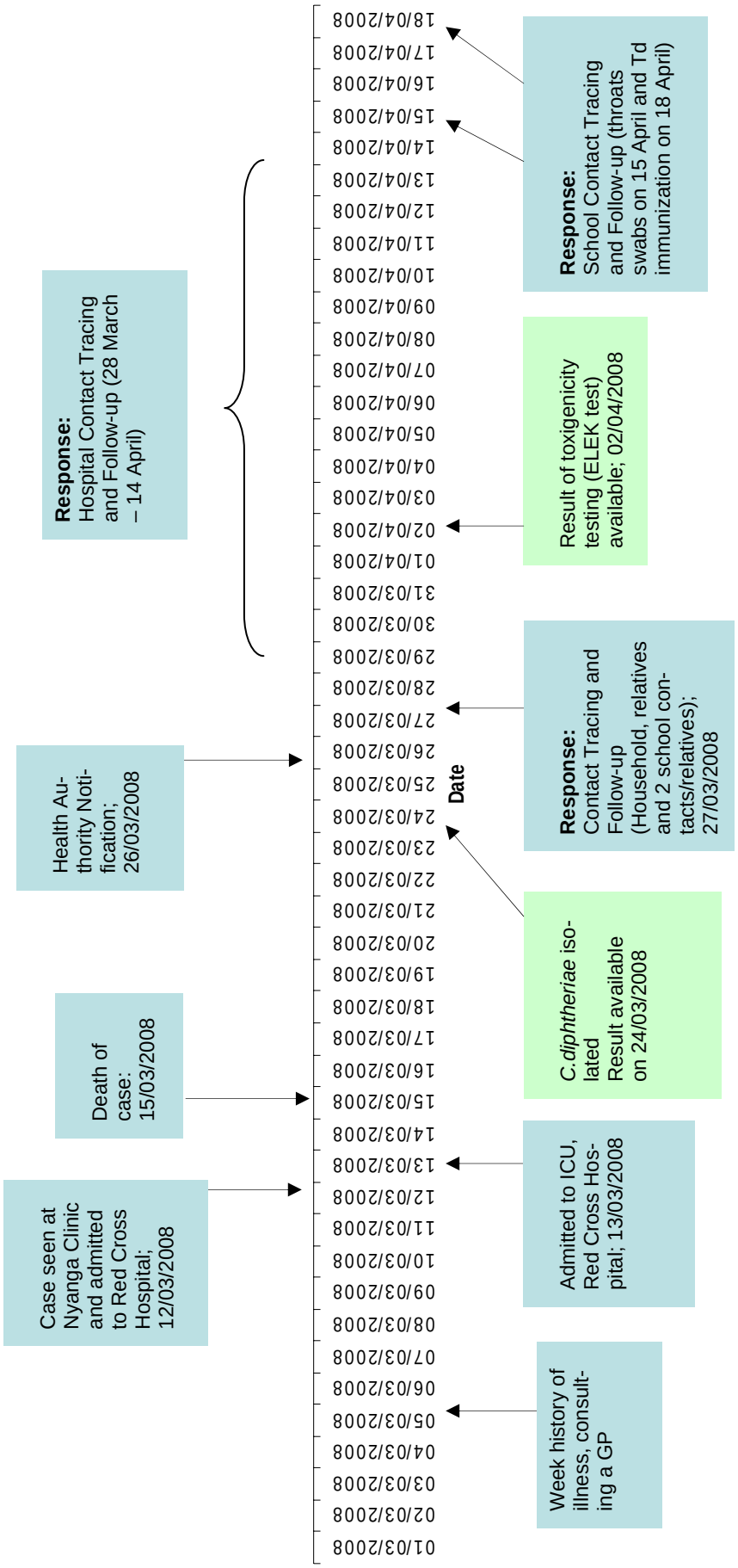

Figure 1: Public health response to an isolated diphtheria death, March 2008, Cape Town, South Africa: Time-line of events

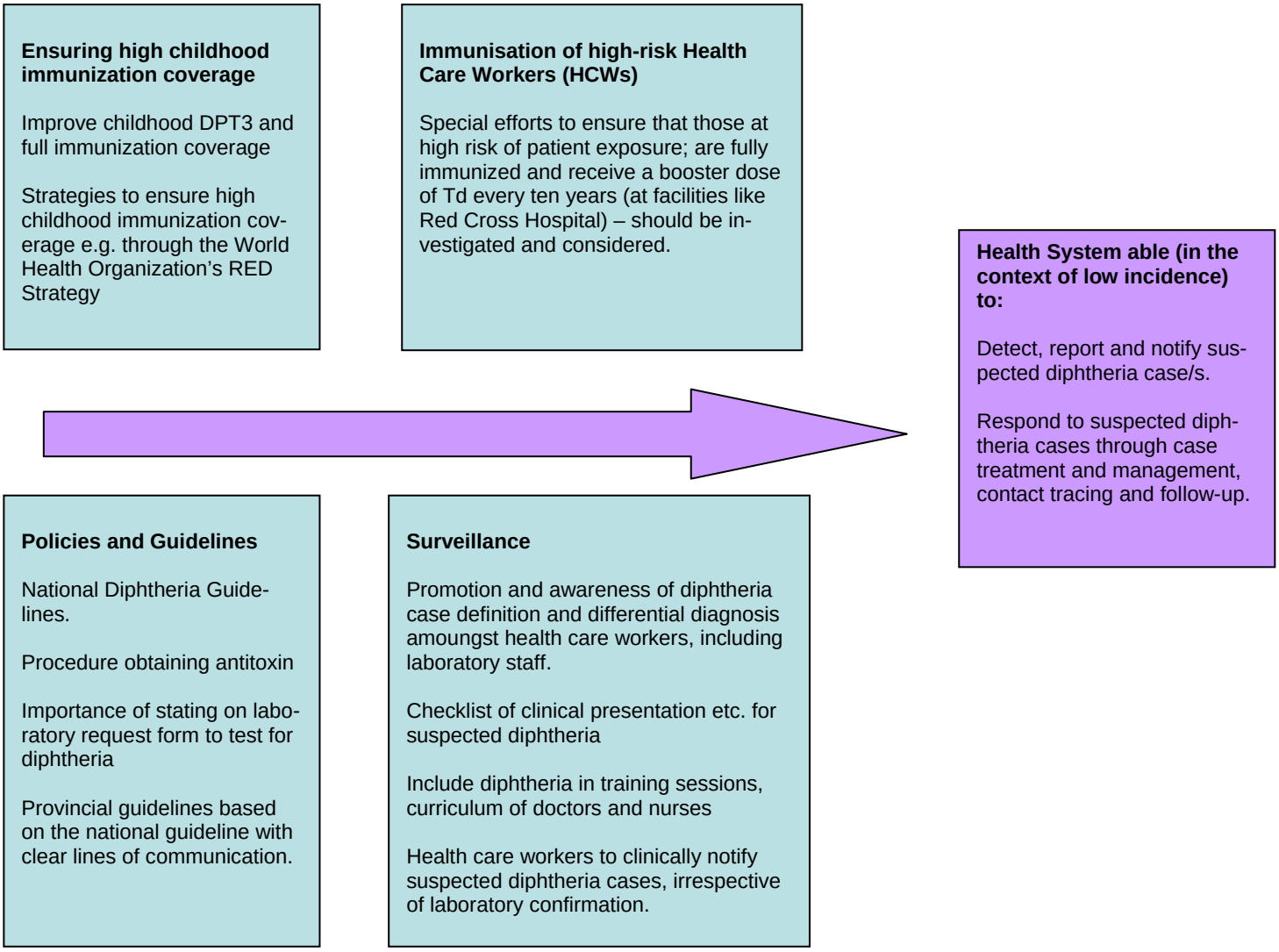

Figure 2: Diagram of recommendations to ensure that the health system is able to respond to suspected diphtheria cases.

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Table 1: Provisional number of laboratory confirmed cases of diseases under surveillance reported to the NICD - South Africa, corresponding periods 1 January - 30 June 2007/2008*

Disease/Organism	Cumulative to 30 June, year	EC	FS	GA	KZ	LP	MP	NC	NW	WC	South Africa
Anthrax	2007	0	0	0	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0	0	0	0
Botulism	2007	0	0	0	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0	0	0	0
Cryptococcus spp.	2007	528	283	991	612	208	363	36	292	215	3528
	2008	711	306	1125	755	232	457	29	457	322	4394
Haemophilus influenzae, invasive disease, all serotypes	2007	18	14	91	26	3	10	0	2	33	197
	2008	14	14	83	19	2	11	4	2	36	185
Haemophilus influenzae, invasive disease, < 5 years											
Serotype b	2007	1	1	13	8	0	2	0	1	10	36
	2008	3	4	13	3	0	2	2	1	7	35
Serotypes a,c,d,f	2007	1	1	6	2	0	0	0	0	3	13
	2008	1	1	8	0	0	1	0	0	3	14
Non-typeable (unencapsulated)	2007	0	1	19	4	0	0	0	0	1	25
	2008	1	2	9	1	0	1	0	0	5	19
No isolate available for serotyping	2007	10	4	18	4	2	4	0	0	10	52
	2008	6	1	24	5	1	5	0	1	11	54
Measles	2007	2	0	4	0	0	3	0	1	1	11
	2008	1	0	4	2	0	1	1	3	2	14
Neisseria meningitidis, invasive disease	2007	5	12	52	10	1	5	2	10	30	127
	2008	10	7	92	7	0	16	4	5	27	168
Novel Influenza A virus infections	2007	0	0	0	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0	0	0	0
Plague	2007	0	0	0	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0	0	0	0
Rabies	2007	3	0	0	3	1	0	0	0	0	7
	2008	5	0	0	5	3	0	0	0	0	13
**Rubella	2007	60	4	22	37	24	10	9	16	32	214
	2008	68	3	39	57	29	18	0	18	13	245
Salmonella spp. (not typhi), invasive disease	2007	20	25	187	42	8	8	2	13	36	341
	2008	27	21	272	50	4	24	10	10	42	460
Salmonella spp. (not typhi), isolate from non-sterile site	2007	78	15	135	65	20	61	7	10	42	433
	2008	115	17	215	84	9	56	7	9	77	589
Salmonella typhi	2007	6	0	9	5	1	5	0	2	5	33
	2008	3	1	13	4	2	10	0	0	5	38
Shigella dysenteriae 1	2007	0	1	0	0	0	0	0	0	0	1
	2008	0	0	0	0	0	0	0	0	0	0
Shigella spp. (Non Sd1)	2007	55	38	180	62	9	26	23	6	141	540
	2008	79	32	279	64	7	32	11	5	220	729
Streptococcus pneumoniae, invasive disease, all ages	2007	149	145	998	200	54	123	25	105	274	2073
	2008	134	129	925	228	38	111	37	74	259	1935
Streptococcus pneumoniae, invasive disease, < 5 years	2007	54	46	300	86	19	37	6	24	107	679
	2008	36	54	287	86	11	40	13	14	91	632
Vibrio cholerae O1	2007	0	0	0	0	0	0	0	0	0	0
	2008	0	0	2	0	0	26	0	0	0	28
Viral Haemorrhagic Fever (VHF)											
Crimean Congo Haemorrhagic Fever (CCHF)	2007	0	0	0	0	0	0	0	0	0	0
	2008	0	2	0	0	0	0	2	0	0	4
Other VHF (not CCHF)***	2007	0	0	0	0	0	0	0	0	0	0
	2008	0	0	4	0	10	4	0	0	0	18

Footnotes

*Numbers are for cases of all ages unless otherwise specified. Data presented are provisional cases reported to date and are updated from figures reported in previous bulletins.

**Rubella cases are diagnosed from specimens submitted for suspected measles cases

***For 2008 all cases are Rift Valley Fever

Provinces of South Africa: EC – Eastern Cape, FS – Free State, GA – Gauteng, KZ – KwaZulu-Natal, LP – Limpopo, MP – Mpumalanga, NC – Northern Cape, NW – North West, WC – Western Cape

U = unavailable, 0 = no cases reported

Table 2: Provisional laboratory indicators for NHLS and NICD, South Africa, corresponding periods 1 January - 30 June 2007/2008*

Programme and Indicator	Cumulative to 30 June, year	EC	FS	GA	KZ	LP	MP	NC	NW	WC	South Africa
Acute Flaccid Paralysis Surveillance											
Cases < 15 years of age from whom specimens received	2007	22	14	36	30	16	14	6	13	14	165
	2008	30	12	35	18	23	14	2	5	15	154
Laboratory Programme for the Comprehensive Care, Treatment and Management Programme for HIV and AIDS											
CD4 count tests											
Total CD4 count tests submitted	2007	106407	39863	190319	215289	51907	59807	18684	70267	69284	821827
	2008	139450	58360	256669	428242	89520	84356	22344	93033	88845	1260819
Tests with CD4 count < 200/µl	2007	39664	15786	73526	73130	23262	21757	5312	24973	16816	294226
	2008	54381	19692	97986	109058	31946	30863	6683	30676	25383	406668
Viral load tests											
Total viral load tests submitted	2007	40824	14507	74736	81759	17670	17408	6357	26186	21590	301037
	2008	58743	25197	114935	131295	38303	29001	9038	37560	29064	473136
Tests with undetectable viral load	2007	16038	7249	40049	44565	8115	8486	3023	14359	17130	159014
	2008	28053	14543	67855	73546	21871	15817	4761	23210	23283	272939
Diagnostic HIV-1 PCR tests											
Total diagnostic HIV-1 PCR tests submitted	2007	7734	2029	18353	18225	3219	3262	1365	4845	6681	65713
	2008	11755	4914	26499	26933	7458	4394	1527	6706	8699	98885
Diagnostic HIV-1 PCR tests positive for HIV	2007	1568	614	3622	3996	829	877	244	1149	761	13660
	2008	1523	917	4060	4977	1367	922	224	1250	877	16117

Footnotes

*Numbers are for all ages unless otherwise specified. Data presented are provisional numbers reported to date and are updated from figures reported in previous bulletins.

Provinces of South Africa: EC – Eastern Cape, FS – Free State, GA – Gauteng, KZ – KwaZulu-Natal, LP – Limpopo, MP – Mpumalanga, NC – Northern Cape, NW – North West, WC – Western Cape

The Communicable Diseases Surveillance Bulletin is published by the National Institute for Communicable Diseases (NICD) of the National Health Laboratory Services (NHLS), Private Bag X4, Sandringham, 2131, Johannesburg, South Africa.

Suggested citation: [Authors' names or National Institute for Communicable Diseases (if no author)]. [Article title]. Communicable Diseases Surveillance Bulletin 2008; 6 (3): [page numbers]. Available from http://www.nicd.ac.za/pubs/survbull/2008/CommDisBullAug08.pdf