The Chemoprophylaxis of Meningococcal Disease in the Cape Town City Council Area

An evaluation of programme efficacy

Dissertation

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by

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EXECUTIVE SUMMARY

This dissertation reports the findings of a study which was carried out in the Cape Town City Council area, in order to establish whether the offering of rifampicin to household contacts, of patients with meningococcal disease, resulted in protection of those contacts against developing the disease during a 32 week follow up period. The study took the form of a retrospective follow up of 3 350 household contacts of 412 cases notified over a 4 year period (mid 1988-mid 1992).

It was found that the offering of rifampicin to the household contacts resulted in an odds ratio of not developing meningococcal disease over the 32 week follow up period of 14,17 (SD = 12,34). Although there was a tendency for contacts who were not offered rifampicin to have been younger, and of male gender, when compared to those who were offered prophylaxis, these demographic differences were not statistically significant at the 0,05 level. Furthermore, three out of the four male second cases, all in the younger age group, were in fact offered prophylaxis. It seems desirable that prophylaxis should be given as soon as possible.

It is concluded, therefore, that the offering of rifampicin to household contacts of patients with meningococcal disease, living under the prevailing social circumstances in the Western Cape, has protective benefit for those contacts. It is likely that the chemoprophylaxis programme prevented up to 88 cases of meningococcal disease over the study period of four years, as well as preventing 8 deaths from this disease, in the CCC population.

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The protocol for this study was approved by the ethics committee of the University of Cape Town Medical School.

INTRODUCTION TO THE STUDY

There are two local authorities responsible for the delivery of chemoprophylaxis programmes for the prevention of meningococcal disease (MCD) in the Cape Peninsula. These authorities, the Western Cape Regional Services Council (WCRSC) and the Cape Town City Council (CCC), render their services in two geographically defined separate areas of the peninsula. They also follow different chemoprophylaxis policies, aimed at reducing the risk of disease for household contacts of patients with MCD. These differing policies have differing cost and overtime implications.

Both authorities offer rifampicin chemoprophylaxis to household contacts of notified cases of meningococcal disease. In the CCC area this prophylaxis is offered as soon as practicable following receipt of a notification. This notification may be conveyed by means of a telephone call after hours, or on weekends and public holidays, as well as in writing. Health inspectors are on call to visit the affected homes and weigh the contacts, while doctors are on call to prescribe the rifampicin, in the event of an after hours notification.

During normal working hours, however, nursing staff visit the homes, weigh the contacts, issue the prophylaxis, and record all relevant details in a case book. These records include the names, genders, and ages of all household contacts. Inhabitants of adjacent outbuildings are also offered prophylaxis in many cases, but their details are recorded separately. (See Appendix 1 for CCC protocols).

In the WCRSC, an after hours service is not offered. Nursing staff are responsible for all issuing of prophylaxis, and this is normally done only during working hours. Furthermore, during the first part of this study period, the nursing records were not as complete or as detailed as those kept by the CCC staff. For example, names of contacts were not routinely recorded, so that retrospective follow up of contacts is not possible. (This situation has now changed, and the records are now comparable with those of the CCC).

The WCRSC initiated this study because of concern over the efficacy of their policy, and the CCC supported this study because their staff had asked for a reduction in their after hours responsibilities. Subsequently, the regional infectious diseases committee appealed for information which might help to inform a uniform policy for the peninsula.

The rifampicin chemoprophylaxis programmes for household contacts might be criticised on the grounds that there is inadequate evidence for the effectiveness of the offering of chemoprophylaxis to household contacts. It might be argued that since housing densities in the Western Cape Province are so high, and since there is a frequent change of inhabitants in the houses of the affected community, any advantages of chemoprophylaxis might soon become nullified.

Furthermore, the view might be expressed that many people, offered prophylaxis, do not take the medication they are given. The use of rifampicin monotherapy, in an area with a high incidence of tuberculosis, might result in the selection of rifampicin resistant strains of Mycobacterium tuberculosis.

The purpose of this study was thus to attempt to answer two questions for the health authorities. These questions were:

1. Does the offering of rifampicin chemoprophylaxis to household contacts of patients with MCD reduce the risk to those contacts of becoming diseased?

2. If the answer to question 1 is yes, is it necessary to offer an after hours service?

This study really only attempts to answer the first question, although the second question is also partially addressed. It was decided to scrutinise household contacts in a retrospective study to see whether they became second cases, and whether the tendency to become a second case was associated with not having been offered rifampicin chemoprophylaxis. The study was confined to the CCC area since the CCC records were more complete at the time the study was initiated.

THE STUDY AIM

To estimate the relative risk of secondary attack of meningococcal disease among household contacts not offered rifampicin chemoprophylaxis within 32 weeks of exposure to an index case; based upon data from the Cape Town City Council health area for the period July 1 1988 to June 30 1992.

THE STUDY OBJECTIVES

1. To record the names, ages, genders, and addresses of all household contacts of notified cases of patients with meningococcal disease, resident in the Cape Town City Council area of jurisdiction, during the study period.

2. To separately record the names and addresses of all notified cases of meningococcal disease, resident in the CCC and WCRSC areas during the study period, and for 32 weeks thereafter.

3. For each contact, to record whether or not rifampicin was offered, the number of people living in the same dwelling, and the number of rooms in the dwelling.

4. For each CCC case, to record the number of people living in the same dwelling, and the number of rooms in the dwelling.

5. For each CCC case, to record any fatal outcome.

6. For each CCC case, to record the date of hospital admission, and the date on which prophylaxis was given to the household contacts in those cases where prophylaxis was offered.

DEFINITIONS OF TERMS

1. Cape Town City Council health area

This is defined as the geographical area which includes the areas of jurisdiction of the CCC health department. This study is confined to the CCC area because the pilot study (see Appendix 2) showed that the notifications from the WCRSC, especially those from Tygerberg Hospital, were incomplete, and the hospital computer records were also incomplete. In addition, records of prophylaxis given were too vague in most cases to enable the numbers of contacts offered prophylaxis to be determined, or to be followed up.

2. Meningococcal disease

Since the diagnostic criteria and practices of the different hospitals were not the same (Red Cross Hospital policy was to avoid performance of lumbar punctures, for example, where the clinical picture was convincing, whereas at Tygerberg Hospital these were usually carried out), all cases were accepted as valid where a paediatrician, or paediatrics registrar had made a firm diagnosis, recorded this in the case notes, and notified the case.

3. Second case

This study is only concerned with second household cases. A second case is any case in which the onset of disease was more than 24 hrs, and less than 32 weeks, after the admission of a prior case from the same dwelling.

4. Index case

An index case is defined in relation to a specific second case. It is the last case to have occurred in a dwelling before the onset of symptoms in the related second case.

5. Concurrent cases

Concurrent cases are two or more cases occurring within 24 hours of each other, and in persons normally living in the same dwelling. (This distinction from second cases is made since it is unlikely that the subsequent cases of concurrent cases may be prevented in practice).

6. Household contacts

Household contacts were defined as all the people stated to be normally resident in the same dwelling as a case, and listed as such in the nursing record.

7. Housing density

Housing density is defined as the number of people living in a house divided by the number of rooms in the house. For the purposes of this study "the number of rooms" excludes kitchens and bathrooms.

INCLUSION CRITERIA

All notified cases of meningococcal disease, as defined, were eligible for inclusion, provided that the patient had been resident in the CCC area for at least 36 hours at the time of onset of illness. Only those cases presenting to hospital on or after 1 July 1988 and before 30 June 1992 were included. All household contacts, listed in the records prepared by the nurses during their home visits for these cases, were included as contacts.

Cases notified for the 32 weeks after 30 June 1992 were separately listed, as were all cases from the WCRSC for the same period of 4 years and 32 weeks. (This was to permit adequate follow up of contacts, to establish whether or not they became cases during the 32 week follow up period).

EXCLUSION CRITERIA

Where cultures of blood or CSF provided documented evidence that the patient was suffering from an illness other than meningococcal meningitis, then the case was excluded from the study, as well as from the notification data. In addition, patients with known complement deficiency, splenectomy, or sickle cell anaemia, were excluded, since the epidemiology of the infection in such patients is known to follow a different pattern.

Cases from prisons, school dormitories, hostels and military barracks were also excluded, since these would be difficult to incorporate into the study. Their inclusion would, for example, distort the concept of room density, and may bias the results (large numbers of similar subjects distorting the demographic profiles). Furthermore, the efficacy of rifampicin prophylaxis has already been established for such contacts, and is well documented (in Cartwright et al, 1989), whereas this study was designed to examine the policy of offering chemoprophylaxis to household contacts only.

Where chemoprophylaxis other than rifampicin had been given to household contacts, the case was excluded, since this study was designed to measure the efficacy of chemoprophylaxis with rifampicin, compared to no chemoprophylaxis.

BACKGROUND TO THE PROBLEM

Prior to 1988, in the CCC area, "close contacts" of patients diagnosed with meningococcal disease were offered chemoprophylaxis in the form of oral sulphonamides, to be taken as a single dose as soon as possible after diagnostic suspicion had been established in the index case. This was done in an effort to reduce the risk of subsequent disease among these contacts. In 1988, concern with spreading resistance of the meningococcus organism to sulphonamides led to a change in policy, and rifampicin became the recommended drug for chemoprophylaxis (Dr S Fisher, personal communication; 1989).

Some concern was felt by the Medical Officer of Health for the WCRSC, because the new drug regime had not been evaluated for efficacy, under normal working conditions, for household contacts. Although the published evidence from developed countries was strongly suggestive of the wisdom of offering rifampicin to household contacts (e.g. Cooke et al, 1989; Broome,1986), no follow up study of contacts had ever been published, and, furthermore, conditions of overcrowding prevailing in the Western Cape were quite different from those to be found in developed countries.

Some health authorities were also concerned about the use of rifampicin because of its cost and because of the danger that clinic personnel might abuse the drug, using it more widely to treat other conditions, which might lead to increased drug resistance of the ubiquitous tubercle bacillus.

In addition, studies have suggested that oral rifampicin fails to eradicate the meningococcus from the pharynxes of up to 20% of carriers (Deal and Saunders,1969; Devine et al, 1970; Beam et al,1971). As a result, in 1989 the WCRSC proposed that this study be carried out in their area of

jurisdiction, in order to assess the efficacy of the new drug regime, something which had not been done before, except in the setting of closed communities such as military barracks. Rifampicin had been in use for two years, and it was intended to detect whether there had been any change in the secondary case attack rate. A previous, unpublished, study, carried out by staff of the WCRSC medical staff during the era of sulphonamide usage, had failed to identify any second cases in their area (personal communication, Dr R.Marshall, 1988).

The CCC was also concerned about the efficacy of their chemoprophylaxis programme, although for different reasons. Whereas the WCRSC policy was to issue chemoprophylaxis to "close contacts" on the first working day after notification of an index case, in the CCC the policy was to issue such prophylaxis without delay. This meant that medical staff were required to be available after hours and over weekends. Some members of the medical staff had questioned whether this was worthwhile.

A study which was carried out in 1989 (Appendix 2) was intended as a pilot study for this present study. It was found that 87% of cases of meningococcal disease from the CCC area could be accounted for in the City Council notification records. Cases were identified from an examination of all public and private sector hospital admission and discharge records in the peninsula, as well as burial and cremation registers, and records of body removal orders. This established the feasibility of conducting a larger study based purely on notification records.

An attack rate of about 1 secondary case per 100 primary cases was found. This rate was similar to reported ratios from Western Europe of about 0,4 and 0.5 second cases per 100 primary cases (Cartwright et al, 1989; Cooke et al, 1989). These studies were carried out over variable periods of

time, generally much shorter than the six month interval allowed in the pilot study. Two out of the 3 second cases identified in the pilot study had not been offered rifampicin prophylaxis. As expected, the number of patients available at that stage was too small to reach any firm conclusions; however, the study did indicate the feasibility of the present study which used data from four years.

The regional infectious diseases committee, a forum for officials from all the different authorities in the region, was subsequently approached to arbitrate by spelling out a uniform policy for the Western Cape. However, this committee has been hampered to some extent by the lack of local epidemiological research, and the inconclusive findings of the pilot study.

This study attempts to help resolve the problem by documenting the efficacy, if any, of the present CCC policy, whereby household contacts of notified cases of meningococcal disease are offered rifampicin chemoprophylaxis as soon as possible after receipt of the notification, in an attempt to reduce the number of second cases arising among these contacts.

A REVIEW OF THE RELEVANT LITERATURE

I: A BRIEF OVERVIEW OF THE CLINICAL PICTURE

Meningococcal disease may have a very variable presentation, ranging from a mild pharyngeal infection, through meningitis, to a fulminant septicaemia with high mortality. In addition to the usual signs and symptoms, which one might expect from the focus taken by the disease (i.e. meningism, high temperature), there are certain findings thought to be pathognomonic, such as a rash which occurs in up to 40% of patients, and which may be petechial or purpuric, limited, or generalised; but scrapings from which are found on light microscopy to contain gram negative diplococci. For a full description of the signs and symptoms see McKendrick, 1977. According to McKendrick there are three clear-cut syndromes encountered:

- meningococcal meningitis, accounting for over 90% of clinical illness;

- acute fulminating septicaemia with a high mortality within hours of onset and;

- chronic meningococcaemia, "a mild low-grade septicaemic illness characterised by fever, rashes, and joint pains".

Diagnosis is by means of examination of skin scrapings by light microscopy, and culture of blood and cerebro-spinal fluid (CSF). However, in endemic areas, the diagnosis may sometimes be made on clinical grounds where skin scrapings are negative and cultures can not be obtained, and may be supported by immunological tests on the CSF for antibodies.

McKendrick has stressed the importance of not delaying treatment, even by half an hour, in order to obtain material for culture, if fulminant disease is suspected. As a result, even when culture material is obtained, the patient may have been pre-treated, and the cultures may then subsequently be found to be sterile. Emphasis must therefore be given to a high level of suspicion, and sound clinical judgement, in the diagnosis of these syndromes, and reliance should not be placed on microbiological evidence alone (Farmer,1993).

Case fatality rates vary, with rates of over 50% for fulminant septicaemia, 10% for meningitis, and very much lower for chronic septicaemia (The Editor, British Medical Journal, 1979; Duerden, 1988; Public Health Laboratory Service [PHLS] Meningococcal Infections Working Party, 1989; World Health Organisation,1989.)

In South Africa, where "meningococcal infections" have been notifiable since 1989 (Minister of National Health and Population development,1989; Minister of National Health,1991), case fatality ratios based on notifications have been under 0,1. (Director General: Department of National Health and Population Development [DNHPD],1991a, and 1992). This compares to ratios of between 0,05 and 0,12 for the 8 years preceding 1979 (Director General:DNHPD, 1980). Prior to 1989 only meningococcal meningitis and

meningococcal septicaemia were notifiable, and it is unclear whether this change in terminology has affected notification practices subsequently (Minister of Health, 1979).

A pilot study for this study, undertaken in the Cape Peninsula region for the year 1988, showed an estimated case fatality rate of 6%, but the rate was as high as 12% at Tygerberg Hospital, and 20% for private patients (see Appendix 2) (These are crude rates, not standardised for age and sex).

II: EPIDEMIOLOGICAL CONSIDERATIONS

Meningococcal disease results from infection with certain strains of the meningococcus, Neisseria meningitidis, in susceptible individuals, and is facilitated by environmental factors. Nasopharyngeal infection with the meningococcus is common, and may be as high as 10–25% of certain age groups of healthy people (Cartwright et al, 1987), usually characterised by a harmless commensal relationship. However, in a small proportion of infected individuals, a fulminating disease may develop, with a high case fatality rate (Peltola, 1993). Carriage rates, without the expression of disease, of up to 80% have been reported from military barracks (Broome, 1986).

An understanding of the factors influencing the expression of disease depends upon understanding the interrelationship between agent, host, and environment. For this reason, the next part of the literature review examines each of these aspects separately and in more detail.

1. The agent

Whether or not disease develops in an infected individual depends on the virulence of the infecting strain, and on host susceptibility factors, not all of which are properly understood.

Environmental factors may play a role, both in the spread of the infecting agent, and in whether or not the virulent organism is able to become invasive, causing disease. These factors will be discussed briefly later.

The meningococcus may be classified into a number of serogroups based on the capsular polysaccharide antigens of the organism, and whereas endemic disease is commonly associated with infections of serogroups B and C, large epidemics, such as occur in the African Sahel, are associated with group A infections (Peltola, 1983). The relative importance of the different groups in a given community, may change with time, however.

In England and Wales, whereas disease was mainly due to infections with group A organisms early on in this century, group A infections are now very uncommon. During the 1970s and 1980s disease was associated with group B infections in over two thirds of cases for which isolates had been typed. More recently there is an increasing percentage of group C isolates reported from those countries (Jones, 1988). Similar patterns have been described from Scotland (Fallon, 1984; 1988), and Australia (Hansman, 1988).

During the last decade, more refined methods of classifying the meningococci have become available, based on clonal typing and a combination of monoclonal antibody typing and subtyping. These methods have made more sophisticated epidemiological study possible, and have also helped to identify strains of particular virulence, explaining in part why not all infected hosts become diseased.

Virulence may therefore be associated with the serogroup, and more specifically, with the type or subtype of the infecting organism. It has also been claimed that sulphonamide resistance is more common in disease producing organisms than in the less virulent isolates (Jones, 1989), although this contention remains unproven and controversial. One study shows that although isolates from diseased adolescents were more likely than not to be sulphonamide resistant, there was no such association for isolates from sick babies (Ward et al, 1987).

In the Western Cape, meningococcal isolates from diseased individuals have predominantly been of the B and C serogroups, and although typing has been carried out on isolates sent to the Netherlands for several years now, epidemiological research has been hampered by the fact that it is not known whether specimens submitted to the South African Institute for Medical Research have been representative of all isolates causing disease in the Peninsula, and many of the isolates have been described as "untypable" (Dr G Coetzee: personal communication).

2. The host

A number of host factors may also play an important role in determining whether or not an infection will result in the development of disease. Splenectomised persons are more susceptible to fulminant disease (Holmes et al, 1981), and in those areas where the sickle cell gene is prevalent the resulting autosplenectomy, which often results by adolescence in persons homozygous for this haemoglobinopathy (Fleming, 1982), may predispose such individuals to meningococcal disease.

The best described predisposing host factor for meningococcal disease is, however, the prior existence of complement deficiencies, especially those lacking the terminal components of the complement cascade. These patients tend to present with recurrent attacks, and to be older than patients with normal complement levels at the time of the first attack (See, for example, Nicholson and Lepow, 1979; Herva, 1983; Zimran et al, 1987; Hummel et al, 1987 and; Cooke, Zafar, and Heaney, 1987; Strate, Olsen and Teisner, 1987).

Potter et al (1990) have described 40 patients with C6 deficiency, 38 of whom were from the Western Cape Province. Twenty two of the 24 probands presented with meningococcal disease. In their publication, these authors show clearly that repeated attacks of MCD may be prevented in these subjects by monthly injections of benzathine penicillin, 2,4 megaunits intramuscularly for adults, and proportionately lower doses, but at the same interval, for children.

The subjects of this report were first described by Orren et al (1987), and it is interesting that 33 came from 10 families, thus illustrating the familial nature of the condition. Potter and coworkers (1993) have subsequently shown that the C6 deficiency is associated with a 12,5-kilobase allele of the MspI restriction fragment length polymorphism of the C6 gene, leading to total C6 deficiency.

Age is another host factor which affects a patient's risk of becoming both infected, and diseased. There appear to be three patterns in this regard:

- in Western Europe, North America, and Australasia, where disease is mainly associated with groups B and C infection, patients tend to be babies and toddlers (de Wals et al, 1981; Broome, 1986; Duerden, 1988; Hansman, 1988; Communicable Diseases Intelligence, 1993, 1994).

- by contrast, in the African Sahel where disease epidemics are mainly due to group A infections (Weekly Epidemiological Record, 1993), patients tend to be older and of school going age (Greenwood and Wali, 1980; Binkin and Band, 1982; Hassan-King, Wall, and Greenwood, 1988).

- the third situation is that which is found in institutions, and the military, where the age profiles reflect the profiles of the members of the affected community.

In the Western Cape, the age profiles are similar to those of Western Europe (Director General: DNHPD, 1993), as are the groups of disease causing isolates (Dr G Coetzee, personal communication).

3. The environment

Environmental factors which have been implicated with an increased risk for Meningococcal disease include household contacts with clinical disease (e.g. Cooke et al, 1989; Stuart et al, 1989). It is perhaps for this reason that overcrowding has often been put forward as an important determinant of the disease attack rate, allthough overcrowding has not been examined as a risk factor for sporadic or primary cases.

The often reported situation whereby outbreaks occur in military barracks and prisons (See Broome, 1986, for example) has also contributed to the belief that crowding of sleeping quarters is a significant environmental factor in the incidence of this disease.

A further environmental factor which has been shown to be important is seasonality. In studies from Western Europe and North America, there is a definite increase in incidence rates during the damp winter months (Broome, 1986; Duerden, 1988).

In contrast, in the African Sahel, the incidence is greatest during the dry, dusty hot weather (Lapeyssonie, 1963), so that the significance of the seasonality is unclear. In keeping with the apparent association between type B or C infection, younger age profile, and winter and spring incidence, the Western Cape has persistently shown a predominance of cases, with higher incidence rates, during the winter and spring months of the year (Director General, DNHPD, 1991b,; 1992,; 1993).

Passive smoking and recent upper respiratory infections have both been suggested as being associated with increased risk of developing meningococcal disease (Haneberg et al, 1983), although the study by Cooke et al (1989) failed to support this, and these theories remain unproven (Broome, 1986).

The term environment, strictly speaking, refers to the human interaction with the non-human surroundings, while ecology is used to describe the interaction between those non-human elements. From this perspective the ecology of the human naso-pharyngeal tract has also been found to play a significant role in the environmental disposition towards becoming diseased from meningococcal infection. Jones (1994) has suggested that infection with the influenza virus may in some way promote the development of meningococcal disease in subjects infected with the meningococcus.

A series of studies of meningococcal infection (Filice et al, 1984; Counts et al 1984;) has focused on inhabitants of "skid row" in the United States of America, since the incidence of disease is higher in this marginalised community than among their fellow citizens.

Filice and co-workers, in a second published report (1985) found that, in those skid row inhabitants who did not become ill in a prospective study, there was a high prevalence of antibodies to other organisms present (Bacillus pumilis and Streptococcus faecalis). These antibodies cross reacted with the group A meningococcal lipo-polysaccharide antigenic sites.

This finding has been interpreted as suggesting that prior infection with certain other organisms may result in acquisition of immunity against meningococci, by a mechanism of cross-reactivity. Additional support for this theory has come from studies which have demonstrated such cross-reactivity with various micro-organisms, including Escherichia coli (Guirguis et al, 1985; van Alpen, Arends, and Hopman, 1988; Kabat et al, 1988; Raff et al, 1988) and Neisseria lactamica (Kim, Mandrell, and Griffiss, 1989).

4. Incidence rates

A report from the World Health Organisation gives the annual incidence rate of MCD in France at 3-4 cases per 100 000 (WHO,1979), although an editorial in the Lancet (1978) states that incidence is around 1 per 100 000 per year in most countries, and as high as 1 per 1 000 in parts of West Africa. The Communicable Diseases Intelligence from Australia (1994) gives the current incidence rates for New Zealand and Australia as 4,6 and 1,73 cases per 100 000 per year respectively.

In South Africa, the total number of cases reported to the Director general: NHPD each year varies between 800 and 1 000, and depending on the denominator, this might represent incidence rates of between 2 and 4 per 100 000 per annum (Director General, DNHPD; 1980, 1993). Up to half of these cases are reported from the Western Cape, so that the incidence in this region may be as high as 20 or more per 100 000 per year during years of high incidence.

There is considerable variation in the total number of cases reported from the Western Cape, varying between 300 and 500 per year, and although some have claimed that patterns and cycles are discernible, such patterns have failed to hold up over time, so that the annual variation is currently unpredictable.

A British report (PHLS Meningococcal Infections Working Party, 1989) cites figures from Belgium to suggest that the subsequent incidence rate of meningococcal disease is up to 1 200 times higher in household contacts of those who have been diagnosed as suffering from a meningococcal illness, 76 for day care nursery contacts, and 23 for nursery school contacts. These studies were conducted before the introduction of chemoprophylaxis programmes.

III: THE CONCEPT OF A SECONDARY OR SECOND CASE

It has been customary to refer to subsequent cases occurring in close contacts as "secondary" cases in the medical literature. Although it might be argued that all cases are in fact secondary cases, Broome (1986) points out that most patients with menigococcal disease have no known contact with ill people. The causative organism has no known reservoir outside man, and is in fact ubiquitous among healthy people, especially during epidemics.

Nevertheless, the organism must have been acquired from some other human being, whether healthy or not, in all patients with meningococcal disease. For this reason the PHLS Meningococcal Infections Working Party prefer to refer to subsequent cases developing in close contacts as "second" cases (1989). The term has not been widely adopted in the literature, and in fact the two terms may be used interchangeably.

IV: STRATEGIES FOR PREVENTION

1. Vaccination

Polysaccharide vaccines have been developed against meningococci of the groups A, and C, as well as some other pathogenic strains which occur less commonly (Galazka,1982). Unfortunately there is only limited success with eradication of the carrier state (Hassan-King, Wall and Greenwood,1988), the vaccine may only protect against disease for up to 5 years, and the vaccines are poorly immunogenic in the under 2 year olds who have the highest mortality from disease (PHLS Meningococcal Infections Working Party, 1989).

An additional problem is an unusually high incidence of neurological side effects occurring in children receiving the existing vaccines (Hood and Edwards, 1988). Nevertheless, these vaccines have proved very helpful in the African Sahel where school-going children are the main disease victims, and group A and C epidemics are the norm (Mohammed and Zaruba,1981; Greenwood and Wali,1980; Binkin and Band, 1982; Masterton et al, 1988).

In the Western Cape, however, as in Europe and North America, the under 5 year olds are the main victims and group B is the main strain encountered in epidemics, so that existing vaccines have little to offer. They might be used on older household contacts where the infecting strain is shown to be of either group A or C, and may be useful in splenectomised or immunocompromised individuals.

There has been some progress with the development of a vaccine against group B virulent strains, with significant elevation of bactericidal antibodies in the blood of adult volunteers following immunisation (Frasch et al, 1988). However, the same results have not been reported in children as yet, and the protective efficacy in the younger age groups has yet to be demonstrated.

2. Chemoprophylaxis

The increased risk of illness among close household contacts following meningococcal disease (Meningococcal Disease Surveillance Group, 1976; de Wals et al, 1981), in one of the members of the household, has led to efforts to eliminate the organism from healthy contacts through the use of oral and parenteral antibiotics. This is especially important where group B organisms are responsible for epidemics of the disease, since no effective vaccine against this strain exists. It may also be important where disease has been caused by type A or B organisms, however, since immunisation may not result in protection for 5 days or more (Pasteur Merieux, undated).

Studies have shown a higher than usual pharyngeal carrier state for meningococcus among close household contacts, although carriage rates in the general public do not appear to be related to the incidence of disease (Broome,1986). Antibiotics which have been shown to reduce the pharyngeal carriage rates by varying amounts include rifampicin (Deal and Saunders,1969; Nicolle et al, 1982), sulphonamides and minocycline (Nicolle et al, 1982), and erythromycin (Wall and Gruneberg, 1982).

Recently, ciprofloxacin and parenteral ceftriaxone (which is safe in pregnancy) have also been found to be effective, with almost 100% clearance of the carrier state (Schwartz et al, 1988). Unfortunately, there is now widespread resistance of organisms to sulphonamides, and trials of most of the antibiotics mentioned above, as well as both oral and parenteral penicillin, have shown that reductions in carriage rates are not always very good (Broome,1986).

The assumption underlying the issue of chemoprophylaxis to close contacts is that reduction of the carrier state in close contacts will result in a lower secondary attack rate.

Although this has been shown in closed communities such as military barracks, and three studies suggest that it may be true for household contacts (Meningococcal Disease Surveillance Group, 1976; Cooke et al,1989; Stuart et al,1989), it still remains to be shown whether rifampicin chemoprophylaxis is effective in the prevention of secondary cases among

household contacts. Various studies have demonstrated that rifampicin clears meningococci from infected pharynges by between 70% (Deal and Saunders, 1969) and 96% (Stuart et al, 1989). Clearance, in closed communities, may persist for at least 5 months (MacIntyre et al, 1993).

A worrying aspect is that there are emerging reports of meningococci which are resistant to rifampicin, especially in military establishments where it has been used as a single agent for prophylaxis (Broome, 1986). Resistance has also been implicated in the failure of rifampicin chemoprophylaxis (Berkey et al, 1988).

Abramson and Spika (1985) have shown that Neisseria meningitidis often persists in the upper respiratory tract, after intravenous therapy for disease, suggesting that pre-discharge treatment with oral rifampicin or parenteral ceftriaxone should be considered as an important part of any prophylaxis programme (Schwartz et al,1988). Otherwise the discharged patient may simply re-infect household contacts following their chemoprophylactic therapy.

The PHLS Meningococcal Infections Working Party has recommended that a two day course of rifampicin be offered to persons "sharing living accommodation" with the case, as well as to "mouth kissing contacts of the case within the 10 days preceding admission" (1989). They recommend a dose of 600mg 12 hrly for 2 days in adults (10mk/Kg per dose in children aged over 1 year, and 5mg/Kg in infants).

Schwartz et al (1988) have shown that a single intramuscular dose of ceftriaxone (250mg for adults, 125mg in children) is very effective at eliminating the carrier state; on this basis it has been advocated as a means of chemoprophylaxis among contacts, especially pregnant women, or in cases where compliance with oral therapy may be difficult to ensure.

It should be pointed out, however, that ceftriaxone has not been evaluated in terms of its ability to reduce the secondary attack rate, the drug is expensive, and it needs to be given by injection. it is also unclear as to why ceftriaxone should be especially indicated for use in pregnant women. Rifampicin is not contraindicated for longer term use in pregnant women with tuberculosis, so presumably it is also safe for use, over 2 days, as a prophylactic agent.

In South Africa, the Department of National Health and Population Development has recommended that chemoprophylaxis be offered to household contacts, daycare centre contacts, and close contacts in military barracks, prisons, and overcrowded hostels. In addition, hospital contacts should be offered prophylaxis if intensive and intimate exposure (mouth to mouth resuscitation) has occurred (Director General:NHPD, 1991b). They recommend rifampicin be given in doses which are the same as those suggested by the PHLS Meningococcal Infections Working Party.

The Cape Town City Council also recommends that rifampicin be taken by household contacts, but uses a more detailed dosing schedule in which the dose is adjusted according to weight (see Appendix 1). Where rifampicin cannot be taken due to allergy, they recommend doxycycline for non-pregnant contacts.

V EVALUATION OF CHEMOPROPHYLAXIS PROGRAMMES

Most programmes directed to the household contacts of patients with meningococcal disease, where they are in existence, are fairly similar in approach. The basic principles have been well described by Cartwright et al (1989), and do not differ materially from those followed by CCC since 1988. The principles have been developed on the basis of the ability of a drug to clear the meningococcus from infected pharynges. However, no published studies have been found in which the efficacy of rifampicin, given to household contacts, has been evaluated in practice.

The two studies which come closest to doing so were both published in the British Medical Journal in 1989. In the first, Cooke et al determined the incidence of secondary meningococcal infection in household contacts. They found that the ratio of second cases to index cases was 0,5%, and that only 1 out of 7 second cases had taken the rifampicin prophylaxis. This ratio, of 0,5%, is considerably lower than the more than 1000 fold attack rate documented in the era before chemoprophylaxis was widely offered to household contacts. However, these authors did not attempt to identify the contacts (about 3 per patient) and follow them up, or to calculate an odds ratio.

In the second paper, Stuart et al assessed effectiveness in terms of the number of second cases occurring, and investigated the possible reasons for failure of the programme in these cases. They do not appear to have questioned the wisdom of the chemoprophylaxis programme, however, and

concentrated their attention, rather, on describing the persistence of the carrier state in some contacts post-prophylaxis. No attempt was made to calculate an odds ratio.

STATEMENT OF THE PROBLEM AND HYPOTHESIS

This study attempts to provide an answer to the question of whether or not the offering of rifampicin to household contacts of patients, notified as having meningococcal disease, will prevent the development of disease in some of these contacts, over a 32 week period. Although this is widely believed to be so, such a programme has never been critically evaluated for efficacy to date, other than in a military setting. The following hypothesis is the subject of this study:

Chemoprophylaxis, with rifampicin, given to household contacts of patients with meningococcal disease, prevents second cases of meningococcal disease in those contacts during the 32 weeks subsequent to the onset of illness in the patient.

A second problem, that of how soon this prophylactic measure should be carried out if it is to be effective, is only a problem if the first hypothesis, as stated above, is accepted. This problem, therefore, was not the focus of this study, although some insight has been offered by the comparison of intervals between sickening of index and second cases, and intervals between date of admission of index cases, and date of offering prophylaxis to contacts.

RESEARCH METHODOLOGY

This was a comparitive retrospective study (Fleiss, 1973; page 56) of the results of a natural experiment. A pilot study had already established its feasibility.

1. THE STUDY POPULATION:

The pilot study was carried out just prior to an anticipated epidemic, based on historical trends. 147 cases were notified during the pilot study period, and so it was anticipated that a four year study would yield about 500 cases from the CCC area. Since 3 second cases were identified during the pilot study, it was expected that these 500 cases would yield at least 10 second cases; probably more, since the full study would involve a more rigorous search for cases. The similarity of the findings in the pilot study to those reported from Britain (Cooke et al, 1989) lent confidence to these expectations.

Furthermore, in the pilot study, it was found that 2 out of the three second cases had not been offered rifampicin. (The British study reported 6 out of 7 second cases had not received rifampicin). Hence it was expected that about 10 second cases would be identified, and that of these, 6 would have been offered rifampicin. The pilot study also showed that rifampicin was not offered to about 10% of contacts. Based on these findings, and on the assumption that there would be about 6 household contacts per case, a 4 year study was planned, since this would be expected to yield an odds ratio of about 6, with SD of 3,9.

2. THE IDENTIFICATION OF CASES:

Cases were identified from the CCC notification records. These records included cases which were not notified but which were subsequently discovered by CCC health inspectors on routine perusal of burial and cremation records. Details required for fulfilling the various objectives were obtained from patient hospital case notes and from the CCC nursing records. WCRSC cases were also listed, in order to identify cases among contacts who might have moved to the WCRSC area between the time of sickening of their index cases, and falling ill themselves. These case details were provided by the WCRSC staff, in the form of a computer print out.

3. THE IDENTIFICATION OF HOUSEHOLD CONTACTS:

Household contacts were identified from the CCC nursing records. The nursing staff opened a booklet for every new case brought to their attention, and in this booklet they listed all household contacts by name, giving the age and gender for each case, and whether or not prophylaxis was issued. Where prophylaxis was not issued, reasons were given. Other contacts, such as people living in an outbuilding, or close contacts living elsewhere, were separately detailed.

These records were completed even for those cases where a decision had been taken not to offer rifampicin to the contacts (for example, in the case of a late notification).

4. THE IDENTIFICATION OF SECOND CASES:

Particulars, including names and addresses, were written onto a separate card for each case. The names of household contacts were written on the backs of these cards, along with details of sex, age, and whether or not the contact was offered rifampicin.

This information was encoded (for example, case = 1; contact = 2) and entered into Lotus 1-2-3 spreadsheets. The entries were then sorted, first by surname, and then by street address, and the resulting lists were checked to see whether someone encoded as a contact (i.e. code 2) subsequently became a case (i.e. code 1). If the interval between two such occurrences was less than 224 days (32 weeks) then the case was included as a second case.

5. THE CALCULATION OF HOUSING DENSITIES:

The number of household inhabitants used was the number of contacts plus the case, at the time of the nursing home visit, as recorded in the nursing record.

The number of rooms was recorded by the nurse during this visit for the first three years of the study. During the last year of the study, CCC policy changed and the nurses were no longer required to record the number of rooms in the house. For these cases, a randomly selected list of 30 houses was drawn up and the CCC nursing staff kindly visited the dwellings and recorded the number of rooms retrospectively.

In addition, a randomly selected list of 20 houses was drawn up from the first three years of the study for repeat visits, in order to record the number of rooms for a second time. This data was used to assess the repeatability of the records of numbers of rooms.

6. STATISTICAL ANALYSIS:

Statistical analysis was carried out manually. Significance of association was estimated by calculating the value of Chi square, and 95% confidence intervals for the odds ratio was calculated using the method described by Fleiss (1973; pages 57-58). Demographic profiles were compared by means of the Chi square test.

Confidence intervals were not calculated for those rates and proportions which were based on whole population data, rather than on a sample taken from the population.

The definitions used for the odds ratio, relative risk, risk difference, and attributable fraction, were those given by Mausner and Kramer (1985) and Beaglehole et al (1993).

Repeatability scores (Kappa), and their standard errors, were calculated according to the method described by Fleiss (1973).

For the purposes of this report the term "standard deviation" (SD) has been used for population parameters, while the term "standard error" (SE) has been used for sample parameters.

RESULTS

The study included the contacts of all notified cases admitted between midnight of June 30 1988 and midnight of the 30 June 1992. Notification records were scrutinised for patients who became ill between midnight of 1 July 1988 and midnight of 9 February 1993, to see whether these contacts became notified cases. Only contacts of patients notified as having sickened in the Cape Town City Council reporting area were included in the study.

In order to determine whether any of these contacts subsequently became cases, their names were checked against the names of notified cases from both the Cape Town City Council area and the Western Cape Regional Services Council area, in case some contacts had sickened after moving between the two areas.

1. THE NUMBER OF CASES STUDIED

There were 425 cases recorded for the period. An additional 54 cases occurred between the 1 July 1992 and the 9 February 1993. The contacts of 421 of the initial 425 cases were eligible for enrolment for scrutiny to determine whether they subsequently became cases. Thus, four cases were discarded. The reasons are as follows;

2 cases-	the contacts were issued tetracyclines
1 case-	the patient lived in dormitory accommodation
1 case-	the patient sickened in the Transkei

No immunocompromised patients were identified.

Three concurrent cases and 6 second cases were recorded. No relapses were noted until 1993, and two linked cases were not counted as second cases due to excessive time lapses (8 months and 18 months respectively). Table I gives the age and sex distributions of the cases included in the study.

TABLE I: THE AGE AND SEX DISTRIBUTION OF CASES FOLLOWED UP

AGE (YEARS);	<1	1	2	3	4	5-9	10-14	15+
MALES:								
INDEX CASES	66	42	32	23	13	31	11	17
2nd CASES					1	2	1	
FEMALES:								
INDEX CASES	44	29	20	18	10	36	5	18
2nd CASES							1	1

There is a tendency for male cases to be younger, overall, than female cases; however this difference was not statistically significant ($X^2 = 12,04$; $p = 0,1$).

2. INCIDENCE RATES

The population of the City of Cape Town is estimated at 1,16 million, for the mid point of the study period (Medical Officer of Health, Cape Town City Council, 1994).

Using this figure, the incidence of Meningococcal disease is calculated as 9,07 cases per 100 000 population per year.

The incidence among persons living in affected households is 44,78 cases per 100 000 inhabitants per year (0,04478%).

The incidence of second cases among the contacts is 291,8 second cases per 100 000 contact years.

The ratio of second cases to index cases is 6:421 or 1,425%.

3. THE CASE FATALITY RATE

Thirty seven of the 421 cases followed up proved to be fatal, a crude case fatality rate of 1 death per 11,38 cases (8,79%). The crude case fatality rate for males was 17/239 (7,11%) and that for females was 19/182 (10,44%). Table II shows the age and sex specific case fatality rates.

TABLE II AGE AND SEX SPECIFIC CASE FATALITY RATES

AGE (YEARS)	<1	1	2	3	4	5-9	10-14	15+
MALES:								
CASES	66	42	32	23	14	33	12	17
DEATHS	6	4	3	1	0	1	0	2
RATE	0,090	0,095	0,093	0,043	0	0,030	0	0,118
FEMALES:								
CASES	44	29	20	18	10	36	6	19
DEATHS	5	2	1	2	0	1	2	7
RATES	0,114	0,069	0,05	0,111	0	0,028	0,333	0,368

If the age specific death rates are compared between the two sexes it appears that there is a consistently higher death rate among female patients for almost all age groups. However, the differences are only statistically significant for cases aged 15 years and over ($0,001 < p < 0,01$).

4. THE CONTACTS FOLLOWED UP RETROSPECTIVELY

There were three concurrent cases, and their contacts were not included, since this would have resulted in a double counting. There

were six second cases, and their contacts were counted again, since they were twice placed at risk. In six cases the contacts were not recorded, so these could not be included in the study. In two of these cases the contacts were noted to have been given prophylaxis at the admitting hospital, but details were not available. In three cases the families could not be traced, and in one the family refused to deal with the investigating nurse. Thus the contacts were recorded for 412 cases; the total number of contacts was 3350, or 8,13 contacts per case. Table III shows their demographic characteristics.

TABLE III: THE AGE AND SEX DISTRIBUTION OF CONTACTS

AGE (YEARS):	<1	1	2	3	4	5-9	10-14	15+
MALES:								
1st CONTACTS	44	46	48	49	38	159	186	920
2nd CONTACTS*	2		1		12	33	6	14
FEMALES;								
1st CONTACTS	53	33	44	43	58	222	132	1164
2nd CONTACTS*						6	12	25

*Refers to the contacts of index cases connected to secondary cases

Of the 3350 contacts, 3234 were offered (and accepted) rifampicin chemoprophylaxis, and 116 were either not offered any prophylaxis (109) or refused to accept it (7). No contacts were offered ceftriaxone, and the contacts of the two patients offered tetracycline were excluded from the study. The reasons recorded for not issuing prophylaxis were as follows:

Late notification of index case	70 contacts
Unknown/unclear	16 contacts
Contact was pregnant	13 contacts
Contact refused medication	7 contacts
Contact away	6 contacts
Contact on oral contraceptives	4 contacts

Table IV illustrates the age and sex specific attack rates for second cases of meningococcal disease per 100 inhabitants. Although the attack rates are higher for males in all age categories, there was no difference between the two sexes with respect to the age specific attack rates when submitted to statistical testing ($X^2 = 6,31$; $p = 0,5$). (NOTE: These are not population based incidences, merely the attack rates in the affected households, calculated to see whether there is any difference within these households which might be caused by differences in gender composition of the inhabitants.)

TABLE IV AGE AND SEX SPECIFIC ATTACK RATES

AGE (YEARS):	<1	1	2	3	4	5-9	10-14	15+
MALES:								
INHABITANTS*	112	88	81	72	63	223	203	951
CASES	66	42	33	23	14	33	12	17
RATE	53,57	47,73	40,74	31,94	22,22	14,80	5,91	1,79
FEMALES:								
INHABITANTS*	97	62	66	61	68	264	149	1207
CASES	44	29	20	18	10	36	6	19
RATE	45,36	46,77	33,33	29,51	14,71	13,64	4,03	1,57

*These numbers reflect the index cases plus their contacts

5. DETAILS OF THE SECOND CASES IDENTIFIED

Six second cases were identified. Of this number, the contacts of four were offered rifampicin, and two were not, according to the records available. Ages and genders of these patients were as follows:

Rifampicin offered:	3 males (aged 4,5,6)	1 female (aged 11)
No rifampicin offered:	1 male (aged 13)	1 female (aged 18)

Nursing records specifically indicate that prophylaxis had not only been issued, but, according to the mothers, it had been taken, for two of the second cases (the 6 year old male and the 11 year old female) to whom rifampicin had been offered.

In the second cases who were not offered prophylaxis, the male patient became ill after an interval of three days from the date of onset of illness of his index case, while the rifampicin was only subsequently offered to the household (four days after the index case sickened). The 18 year old female patient was absent from her home on the day prophylaxis was issued.

6. BEING OFFERED RIFAMPICIN AND REMAINING DISEASE FREE

Table V is a table illustrating the association between being offered rifampicin, and remaining disease free during the specified follow up period. The 3350 contacts have been sorted into those who were offered rifampicin, and those who were not; they have then been further categorised depending on whether or not they developed meningococcal disease on follow up.

The "contact years" referred to in the table are based on the fact that contacts were followed up for 224 days; illness occurring after this interval was not regarded as "second" disease.

TABLE V FOLLOW UP DISEASE STATUS VS PROPHYLAXIS CATEGORY

	WELL	ILL	TOTAL	CONTACT YEARS
RIFAMPICIN	3230(a)	4(b)	3234	1984,70(x)
NO RIF	114(c)	2(d)	116	71,19(y)
TOTAL	3344	6	3350	2055,89

$X^2 = 8,34$; $(0,001 < p < 0,01)$

ODDS RATIO (OR) = 14,17 (SD = 12,34); RELATIVE RISK (RR) = 13,94

{where OR = ad/bc; and RR = [d/(c+d)]/[b/(a+b)]}

These numbers represent the relative increase in risk of falling ill if not offered rifampicin. OR is an approximation of RR, used in cases where precise incidences cannot be calculated, and justified where these incidences are very low.

RISK DIFFERENCE (RD) = 2607,84

(2ND CASES/100 000 CONTACT YEARS)

(Or: 21,84 second cases prevented per year of the study)

{where RD = [(d/y)-(b/x)] X 100 000; and the equivalent number of cases/**year of study**= [(RD/100 000) X (a+b+c+d)/4}

The risk difference estimates the numbers of cases prevented by the issuing of rifampicin to household contacts.

ATTRIBUTABLE FRACTION (AF) = 0,93

{where AF = [RD/100 000]/[(RD/100 000) + (b/x)]}

This represents the fraction of second disease among household contacts prevented by offering them rifampicin.

7. POSSIBLE CONFOUNDING FACTORS

The association, odds ratio, relative risk, risk difference, and attributable fraction, calculated from the data displayed in Table V, are based on crude data. Standardisation for age and sex distribution, and for differing housing densities, has not been possible, since the number of second cases discovered is too low for this to be done. In order to assess the validity of the findings a number of comparisons needs to be made.

7.1 Age and sex distributions of the index and second cases have been displayed in Table I, and the age and sex distribution of the contacts has been presented in Table III. From Table III it can be shown that households in which second cases occurred, when compared to those in which the contacts all remained well, there are certain demographic differences:

TABLE VI DEMOGRAPHICS IN WELL VS ILL HOUSEHOLDS

	WELL HOUSEHOLDS	ILL HOUSEHOLDS
MALES(%):	46,53	61,26
UNDER 10(%):	28,30	48,65

Both these differences are statistically significant, $p < 0,01$.

7.2 Different housing densities may explain why some contacts became cases and others did not, independent of the offering of prophylaxis. Housing densities were calculated by dividing the number of inhabitants by the number of rooms in the dwelling, excluding the kitchen and bathrooms(s). Twenty households were visited again by the nursing staff, up to five years later, and assessed for the number of "rooms" present, in order to validate the accuracy or repeatability of the initial estimate taken from nursing records.

It was found that the mean housing density of those contacts who were offered rifampicin was 3,05 persons per room, while that for contacts not given rifampicin was lower at 2,55 per room. Table VII shows the results of the repeat recording of the numbers of rooms in the houses on a random subsample of 20 dwellings.

TABLE VII REPEATABILITY OF ROOM NUMBERS

		NUMBER OF ROOMS NOTED ON 1ST VISIT				
		1	2	3	4	
	1	3				
SECOND	2		2			
VISIT	3		2	9		
	4			1	3	
TOTAL						20

Kappa = 0,7701; SE = 0,135; $p < 0,0001$

In addition, it was found that, in a number of instances, the nursing staff had visited a household twice for various reasons, and independently recorded the number of inhabitants. This occurred 14 times, and represents a convenience sample which may not be assumed to be random. Nevertheless, the information collected provides an opportunity to validate the findings in those 14 homes.

Six of the fourteen homes were those in which secondary cases had occurred, 3 were homes of concurrent cases, 2 were homes of relapsed cases outside of the study period, and 3 had independent sources (i.e. hospital records and visiting records) of information available. The calculated repeatability score was Kappa = 0,6763. If this was by chance a representative sample, then the standard error would be 0,0914 and $p < 0,0001$.

Of the fourteen cases with repeat visits,the numbers of inhabitants had changed in four. One dwelling had reduced from 10 inhabitants to 9; one had increased from 8 to 9; one from 14 to 15; and one had increased from 7 to 13.

7.3 It has already been shown that there are demographic differences between households in which second cases occurred, and those which remained well. It needs to be established whether there were differences between the

inhabitants who were offered rifampicin and those not offered prophylaxis, since such a difference may also be a confounder of the results and invalidate any conclusions.

A comparison has thus been made between the demographic characteristics of contacts who were, and those who were not, offered prophylaxis. The findings are presented in table VIII.

TABLE VIII: DEMOGRAPHIC PROFILES OF INHABITANTS BY PROPHYLACTIC STATUS

AGE (YEARS)	<1	1	2	3	4	5-9	10-14	15+
RIFAMPICIN OFFERED:								
MALES	46	44	47	48	49	185	183	899
FEMALES	51	33	43	43	56	227	139	1141
TOTALS	97	77	90	91	105	412	322	2040
NO RIFAMPICIN OFFERED:								
MALES	0	2	2	1	1	7	9	35
FEMALES	2	0	1	0	2	1	5	48
TOTALS	2	2	3	1	3	8	14	83

Comparison of the overall age distributions (rifampicin vs no rifampicin): $X^2 = 7,1$ $(0,3 < p < 0,5)$.

With regard to overall gender differences, 3,66% of male contacts were not offered rifampicin while 3,29% of females were not offered rifampicin. This difference was not statistically significant (z = 0,672).

When the contacts are divided into three groups, namely those under 10 years old, those aged 10 to 14, and those aged 15 and over, then the proportions of male and female contacts offered prophylaxis in each of the three groups may be compared, and these figures are shown in table IX.

TABLE IX PROPORTIONS OF CONTACTS NOT OFFERED CHEMOPROPHYLAXIS (AS PERCENTAGES)

AGE (YEARS)	<10	10-14	15+
MALES (%)	3,1	4,9	3,9
FEMALES (%)	1,3	3,6	4,2

The contents of Table X have been generated from Table VIII. Expected numbers have been calculated by applying the male proportions not receiving prophylaxis to the female totals in each age group.

TABLE X **ACTUAL VS EXPECTED NUMBERS OF FEMALES BY AGE GROUP (EXPECTED BASED ON MALE PERCENTAGES)**

AGE (YEARS)	<10	10-14	15+
ACTUAL	6	5	48
EXPECTED	14,05	6,84	44,42

$X^2 = 5,39;\ 0,10 > p > 0,05$

7. THE DELAY TO PROPHYLAXIS

A sub study concerned the timing of the offering of rifampicin, relative to the date of admission of the cases. These findings are of interest, since, if there is a delay between the date of sickening of the cases, and the offering of prophylaxis to household contacts, which exceeds the interval between the onset of illness of the cases, and onset of illness in any second cases, then this study will fail to show the benefits of chemoprophylaxis for household contacts. In addition, the staff of the City Council Health department requested that this sub study be carried out.

Unfortunately, this study was not designed to test any hypotheses concerning the necessary timing interval. Such a study would require a much larger group of contacts in order to ensure large enough groups of contacts offered prophylaxis after different delays for comparison of outcomes. However, it is of interest to note the time delays recorded for delay to prophylaxis in these study subjects, relative to the occurrences of known

second cases, and towards this end the following diagrammatic representation of the delays, relative to the delays to onset of second ccases, is presented. Date of admission of index cases has been used, as it is a documented date, and also since little can be done regarding the issuing of prophylaxis until the index case has been recognised.

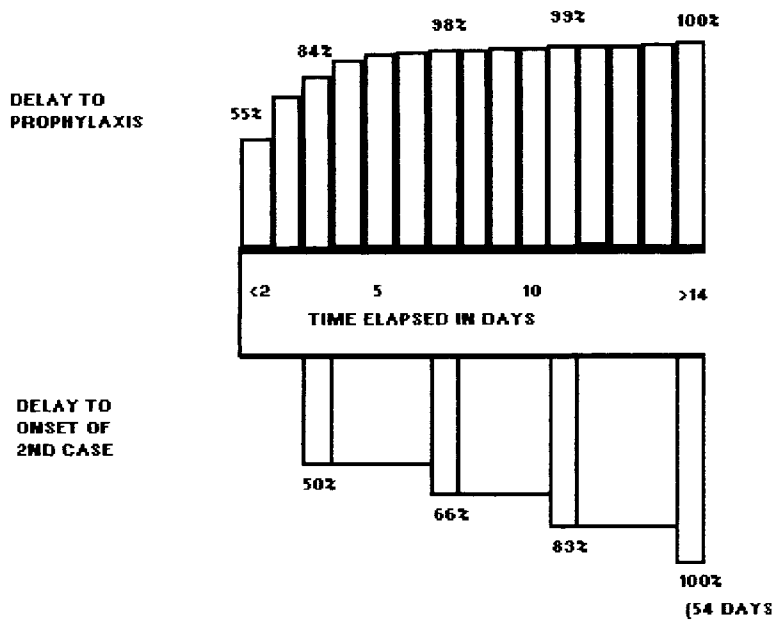

FIGURE 1: GRAPHIC DEPICTION OF THE DELAYS TO OFFERING OF PROPHYLAXIS COMPARED TO ELAPSED INTERVAL BETWEEN DATE OF ADMISSION OF INDEX CASES AND KNOWN SECOND CASES (CUMULATIVE FREQUENCIES)

DISCUSSION

THE IMPORTANCE OF THE PROBLEM UNDER INVESTIGATION

Meningococcal disease is a condition which is particularly prevalent in the Western Cape Province, with an incidence, based on notifications, of approximately 9 cases per 100 000 population per year. This compares to the quoted incidence rates of less than 1 in developed countries, and 15 or more during epidemics in endemic countries in West Africa. In this study, the disease carries a mortality of about 10%, similar to findings reported from the United Kingdom. In addition, survivors may experience neurological sequelae.

Studies conducted in Europe, during the pre-antibiotic era, have shown that the household contacts of cases of meningococcal disease may have an increased risk of developing disease, in excess of 1000 times greater than that in the general population. In the post antibiotic era, with the introduction of chemoprophylaxis for household contacts, a study from Manchester (Cooke et al, 1989) has shown that the ratio of second to index cases was 1:200. The comparable rate from the present study is higher, at 2,9:200; perhaps partly due to the higher number of household contacts (8 vs 3).

The problem of meningococcal disease is thus an important problem in the Western Cape Province. Furthermore, contacts of MCD patients are at considerable risk of becoming diseased, and so it is important to identify interventions which might reduce the risk, at least in the short term, in this targeted group.

Rifampicin chemoprophylaxis, offered to close household contacts as soon as possible after the sickening of the index case, is the accepted intervention practised in most developed countries, as well as in the area where this study was conducted. The practice has, however, never been properly evaluated in these countries, and there has been some criticism that this intervention may not be effective under the conditions prevailing in countries such as South Africa.

It might be argued, for example, that since numerous studies have indicated the carriage of pathogenic strains, in otherwise healthy individuals in the community, clearance of the organism from the upper airways of household contacts might be superseded by reintroduction of the organism to the household. This tendency might be particularly likely in a community where there is serious over-crowding of accommodation, and a frequent change of address; with new, untreated, inhabitants moving into the household at a higher rate than is experienced in, say, Western Europe. Housing densities in this study indicated between 2,5 and 3 inhabitants per room.

PREVENTION STRATEGIES

A number of possible strategies, aimed at the reduction of second cases among household contacts, have been described. These include vaccination, as well as chemoprophylaxis. It is clear, from the review of the literature, that vaccination is only of proven benefit where the disease causing organisms are not of the type B strain, a situation which is not applicable in the Western Cape at present.

Furthermore, vaccination may only result in immunity after 5 to 6 days, by which time half the second cases might have already occurred, so that chemoprophylaxis is still required as an adjunct. It seems that vaccination, even in communities where type B organisms are not responsible for epidemics, is mainly useful as a tool for aborting epidemics, and not as a measure, in isolation, for the protection of household contacts. It is reasonable, therefore, for the Local Health Authorities to be placing their emphasis on a strategy of chemoprophylaxis in the Cape Town City area.

CHOICE OF DRUG

From the literature, it appears that there are 4 currently recognised drug options for chemoprophylaxis. The question arises whether the use of rifampicin is an appropriate choice in the Western Cape. Each of these is considered in turn:

1. Sulpha drugs have the advantage that they are very cheap. However, they are also associated with unacceptable side effects, and may be unsuitable for pregnant women at certain stages of gestation. Furthermore, there is widespread resistance to these drugs among meningococci. They are, therefore, no longer recommended.

2. Minocycline has been used quite extensively for chemoprophylaxis. It is relatively inexpensive, but is contraindicated in children under the age of 12, and in pregnant women. Care needs to be taken when this drug is given to women on oral contraceptives. Although effective, it has, therefore, only limited usefulness.

3. Rifampicin is now the most widely used drug for chemoprophylaxis. It is more expensive than the two previously mentioned, but the cost is still relatively low at under R2, on average, per contact. An advantage is that it colours the urine orange, so that patient adherence may be checked on second day follow up. The drug is suitable for use in children and in pregnant women. Although some studies have indicated that rifampicin may clear the nasopharynges of meningococci in only 70% of cases, the study by Stuart et al (1989) has indicated an efficacy of 96%. One problem is that women on oral contraceptives are at increased risk of falling pregnant if they take rifampicin concurrently. This problem can be overcome if supplementary methods are used during the cycle following its use. A further potential problem is that four doses are required, and this may result in poor compliance.

The problem of promoting resistance to rifampicin among tubercle bacilli, if the bacilli are exposed to rifampicin monotherapy, has been raised in some quarters as an objection to the use of rifampicin for meningococcal prophylaxis. The fact that tuberculosis is epidemic in the Western cape has lent substance to these fears.

However, the tubercle bacillus is relatively slow growing, and needs to be exposed in large numbers for a period of time if it is to become resistant to the drug, and it is unlikely that the use of rifampicin for two days, in people who usually do not have active disease, will result in resistance emerging. This is borne out by the fact that over the period during which rifampicin has been used for prophylaxis in the Western Cape, the resistance to rifampicin has declined (Dr K Weyer, personal communication).

4. Ceftriaxone has been shown to clear almost 100% of upper airways of meningococci after a single dose. It is safe for use in pregnant women. However, there are two major disadvantages. The drug is very much more expensive, and it needs to be given by injection. For practical purposes, therefore it will be suitable for use only under special circumstances. Although ciprofloxacin has been shown to be very effective, and might be considered for use in the future,it is currently too expensive in South Africa for consideration as an agent for use in large numbers of contacts.

From the foregoing discussion it appears that the use of rifampicin, as the agent for the chemoprophylaxis of meningococcal disease among household contacts, by the City Council Health Department, is the most affordable and practical choice.

AGENT, HOST, AND ENVIRONMENT

None of the cases in this study were noted to be immunocompromised. This is surprising, since, in the pilot study, two such patients were identified (one from the City Council area). In addition, the gene for sickle cell anaemia is prevalent, albeit at a low rate, in this community.

The occurrence of cross immunity, acquired after exposure to other organisms, may partially explain why meningococcal disease is so much more common in some communities than others, although the relevance of this argument for the high incidence in the Western Cape Province is unknown. Social circumstances are at least as poor in other parts of South Africa, where the incidence of the disease is much lower.

Overcrowding has long been regarded as an important environmental factor associated with the occurrence of meningococcal disease. However, this association does not hold in isolation in South Africa, where the disease is less common, for example, in other urbanised and peri-urban areas with similar problems of overcrowding. It is possible that overcrowding plus poor ventilation might explain these differences in part.

In the Western Cape high density housing areas there is a summer problem with wind and dust, and a winter problem with rain and cold. These factors might encourage people to keep their homes closed up for a major part of the year. If this is so, then electrification and dust control measures may be important in helping to bring the epidemic under control.

THE NUMBER OF CASES STUDIED

There has been a gradual decline in incidence of meningococcal notifications since the pilot study was carried out. This may be due to a decline in notification practices, but is more likely to reflect actual trends, since the time interval is only four years. Nevertheless, this resulted in fewer cases (and hence fewer second cases) than expected.

A notable factor is that, during the time of the pilot study, numerous private practitioners were still using sulpha drugs for prophylaxis. No case of this happening was found during this study, and it is possible

that the pilot study influenced this change of practice, since the practitioners concerned were all individually contacted in the course of that study. This evidence of a possible effect of being involved in a study makes it more likely that the recent decrease in notifications reflects an actual decrease in disease, since the pilot study might have influenced awareness in the area.

It would appear that the second cases observed tend to be more likely to be male, and that these male cases tend to be younger than their female counterparts. This is difficult to explain, since there were no differences between the age distributions of male and female contacts. Neither were males more common, in general, among the contacts. However, the age specific attack rates among inhabitants were consistently higher for males in each age category, and were also higher for the younger age categories.

Thus the noted difference may simply reflect a greater vulnerability to disease among young males. This is supported by the different demographic profiles of the cases studied. Once again, there was a tendency for there to be more, younger, males, among the cases. Although these trends are striking, it should be remembered that none was statistically significant at the 0,05 level.

CASE FATALITY RATES

The case fatality rates are higher than those experienced during the pilot study. In general, notifications of deceased patients are less

complete than are notifications for survivors. Thus one might expect death rates based on notification data to be underestimates. However, in the Cape Town City Council area, City Health Department staff regularly peruse burial and cremation records, body removal orders, and mortuary records, specifically to circumvent this problem.

Since it is likely that some survivors will not be notified, it is probable that these disease specific mortality rates are overestimates in this area. Nevertheless, the mortality rate compares to rates quoted in the literature for developed countries, so it probably indicates a relative completeness of notifications for this disease, confirming the findings of the pilot study.

Of interest, is that the age specific case fatality rates were so much higher in the older age group, especially among women aged 15 and over. Meningococcal disease is less common in this age group, and so these higher rates may reflect a delay in diagnosis (lower index of suspicion). Alternatively, they may indicate that there was some unknown factor which affected the level of immuno-susceptibility in these patients, since the disease does not ordinarily affect these, older, people.

THE HOUSEHOLD CONTACTS

There were 8,13 household contacts, on average, per notified case. This is higher than the 3 contacts per case in the Birmingham study reported by Cooke et al (1989). The ratio of these two values is 3,01. This

difference may well explain the approximately 2,7 fold higher number of second cases per index case experienced in Cape Town. The fact that the risk of a contact becoming a second case is similar in the two countries under very different housing density conditions, lends support to the earlier stated opinion that housing densities alone cannot adequately explain differences in attack rate.

THE SECOND CASES

Fewer second cases were discovered than anticipated. This must be partly due to the lower incidence of disease encountered, but may also be due to the fact that 96,5% of the contacts received prophylaxis, an increase since the pilot study.

Four of the six second cases were males, and three of these were under 10 years old; whereas both female patients were over 10 years old. There is also a strong suggestion that the index cases were also more likely to be young males in spite of the fact that the inhabitants of the affected homes were equally likely to be of either gender.

Three of the four male patients had been offered rifampicin prior to their becoming ill, and it was documented that the medication had actually been taken in one case, 5 days prior to becoming ill. This observation is of relevance later when the demographic characteristics of those offered and those not offered prophylaxis are discussed.

THE ODDS RATIO FOR REMAINING WELL

The odds ratio and relative risk are high, at 14,17 and 13,94 respectively. However, the standard deviation of the odds ratio is also high (12,34). The reasons for this are, that fewer second cases were discovered than expected, and the proportion of second cases who were offered prophylaxis was 0,66 (expected:0,33). The risk difference is equivalent to about 22 cases a year prevented by the City Council prophylaxis programme. If the case fatality rate among these cases had been 10% then about 2 deaths were averted each year.

It is of note that this odds ratio has been calculated for remaining well, having been **offered** rifampicin. No assumption is made as to whether or not the rifampicin was actually taken. It is possible that the drugs prescribed were not always taken, and in this case the ratio might be an overestimate of the advantage from actually taking the medication, unless, of course, the degree of non-compliance is the same among those who became second cases, and those who did not.

If the actual taking of rifampicin offers protection against becoming a second case, then this last possibility becomes unlikely, and the calculated odds ratio must, then, be considered as an overestimate of the advantage of the prophylaxis programme. The implication is that the estimate of 22 cases and 2 deaths averted per year is probably an overestimate.

As pointed out, at the top of page 58, the risks of a household contact falling ill are similar in the Western Cape, and in Britain, populations for which a 4 fold difference in general incidence rates is reported. This

observation holds for these two populations, which pursue similar prophylaxis policies. If it were also true during the pre-prophylaxis era, then this would imply that the ratio, between the risks of falling ill, for household contacts and the general public, is a function of the general incidence rate, so that the ratio of 1 200 reported by de Wals (1981), from Belgium, before prophylaxis became routine in that country, implies a household incidence of about 3 000 cases per year per 100 000 contacts, if no prophylactic measures are taken.

Applying this ratio to the Western Cape population, one would thus expect about (3350/100 000) X (1/4) X (3 000) second cases to occur each year in the absence of a prophylaxis programme, or about 25 cases. In fact, 1,5 cases, on average, were observed per year, suggesting that 23,5 cases were prevented. This compares well with the figure of 21,84 cases prevented per year, calculated from the estimated risk difference (Table V), and lends credibility to the findings of this study.

DEMOGRAPHICS OF HOUSEHOLDS OF SECOND CASES

Households in which second cases occurred tended to contain younger inhabitants, who were more likely to be male. It has already been shown that such demographics favour higher attack rates for meningococcal disease. This is a potential confounding factor, if in fact there was any tendency for such households to be less likely to be offered prophylaxis.

The contents of Table X suggest that, in fact, persons who were not offered prophylaxis were more likely to be males under 10, and females

aged 15 and over. The latter observation is explained by the higher number of females who were specifically denied prophylaxis on account of being pregnant, or because they were taking oral contraceptives. However, it is argued that this did not act as a confounding factor, since all 3 under 10 year old male second cases had, in fact, been offered rifampicin.

HOUSING DENSITIES

Housing density is one factor which has been widely accepted as a possible association with susceptibility to disease. If, for some reason, persons living in more severely overcrowded housing are less likely to be offered prophylaxis, then this may be a confounding factor in this study. For example, overcrowding may be more severe in poorer areas, and staff may be reluctant to visit such areas during times of unrest, or over weekends.

It was important, therefore, to compare housing densities of persons who were, and those who were not, offered rifampicin. In fact, it was found that households of persons who were offered rifampicin had higher housing densities (3,05 persons per room) than those who were not (2,55).

It is unlikely, therefore, that housing density was a confounding factor in this study, except that the differences may have resulted in an underestimate of the odds ratio, in favour of the offering of prophylaxis. Nevertheless, as has already been discussed, it is possible that housing density on its own is not as important a factor in the aetiology of meningococcal disease as is commonly thought.

The method used in this study, of calculating the housing densities, was rather robust and led to good repeatability. However, more refined methods are commonly used, such as weighting the inhabitants for age, and counting only those rooms which are stated to be used for sleeping purposes. In practice, in a 3 roomed house with 9 inhabitants (8 contacts plus the index case) it is likely that all three rooms are used.

PRE-DISCHARGE PROPHYLAXIS

It is advocated that patients with meningococcal disease should be given pre-discharge rifampicin or ceftriaxone. The reason for this is that the parenteral treatment with penicillin, which they usually receive in hospital, is poorly effective in clearing the naso-pharyngeal mucosa of pathogenic organisms. If patients are not given pre-discharge prophylaxis, the danger is that their household contacts may rapidly become recolonised, on the patient's return home, thereby nullifying the household chemoprophylaxis programme.

During the time of this study newly diagnosed patients with meningococcal disease tended to be transferred early on, from the hospital of initial admission, to the City Hospital for further care. At the City Hospital, pre-discharge prophylaxis was routine. However, at the Red Cross Hospital, to which most of the patients initially reported, only about 30% of patients were treated in this way, since not all paediatricians believed that it was important.

It was also shown in the pilot study that Red Cross Hospital staff tended to notify cases less often, relying on the staff at the City Hospital to do so. It is possible that seriously ill patients, who would be treated entirely at the Red Cross Hospital, would thus be less likely to be notified , and would be less likely to have been given pre-discharge prophylaxis. Household prophylaxis, in the case of non-notified cases, would be less comprehensive, since no home visit would be involved. This scenario might result in a tendency for the linkage of a higher incidence of second cases with a "no prophylaxis" status. If the failure to issue pre-discharge prophylaxis is important in the prevention of second cases, then this might be a confounding factor in this study.

Unfortunately, this possible confounding factor has not been ruled out in this study, and this is an important limitation. However, it is unlikely that the effect of not giving pre-discharge prophylaxis, involving, as it does, only one member of the household, would be as significant a factor in the aetiology of second cases as the issuing of prophylaxis to all the other household members.

THE DELAY TO PROPHYLAXIS

This study was not designed to address the importance of timing of chemoprophylaxis. However, reference to Figure 1 shows that if prophylaxis is to be given at least 24 hrs before the onset of disease, if it is to be effective in aborting the disease, then 50% of the second cases could only be aborted if rifampicin had been offered within 3 days. In fact, only 75% of the prophylaxis issued had been issued by this time. Furthermore, second cases continued to occur up to 54 days after the

admission of the relevant index case, so that although early intervention is important, this does not imply that if an early opportunity has been missed, then there is no point in giving prophylaxis to the household contacts later on. (The study reported by Cooke et al, 1989, which made use of sub-typing, indicated that in fact, second cases will continue to be seen up to a year later, but that there is little advantage to be gained after 32 weeks, or 224 days).

CONCLUSIONS

1. Rifampicin is a good choice of drug for any chemoprophylaxis programme aimed at preventing second cases of meningococcal disease among household contacts. It may be given to pregnant women, and may also be given to women using oral contraceptives, provided they are also counselled to use other, additional, methods during their subsequent cycle.

2. The routine offering of rifampicin to household contacts of patients with meningococcal disease results in considerable protection against second cases of disease among these contacts, with an odds ratio of 14,17 (SD = 12,34). This is in spite of the particular social conditions prevailing in the CCC area.

3. Rifampicin should be given to household contacts as soon as possible after suspicion of meningococcal disease in the index patient. Furthermore, delays in notification should not preclude the giving of prophylaxis to these contacts.

RECOMMENDATIONS FOR THE CAPE TOWN CITY COUNCIL

1. Continue with the policy of

   - encouraging telephonic notification on suspicion of meningococcal disease
   - offering rifampicin to household contacts of patients suspected of having meningococcal disease
   - offering prophylaxis as soon as possible, including an after-hours, weekend, and public holiday, service

2. However, consideration should be given to the following modifications of existing policy

   - rifampicin should be offered to pregnant women
   - rifampicin may be offered to women on the oral contraceptive pill, along with further advice about additional methods (barriers, spermicides, abstinence) to be taken during the subsequent cycle
   - consider giving prophylaxis to household contacts when there have been delays of 2 months and even up to 224 days
   - nurses should be trained to issue rifampicin to household contacts, since this may lead to a reduction of any delays

3. Further studies are indicated

   - knowledge, attitude, and perception studies of clinicians as a prelude to improving early notification of Meningococcal disease
   - the importance of pre-discharge prophylaxis

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APPENDIX 1

THE CAPE TOWN CITY COUNCIL PROPHYLAXIS PROTOCOL

CITY OF CAPE TOWN : HEALTH DEPARTMENT

MENINGOCOCCAL MENINGITIS (CSF) PROPHYLAXIS PROCEDURE
USING RIFADIN (RIFAMPICIN) 150MG CAPSULES AND RIFADIN SYRUP 100MG PER 5ML

Prior to administering prophylaxis the following facts must be DISCREETLY ascertained.

1. Is the contact pregnant or on oral contraceptives?
   If pregnant - no prophylaxis to be given but contact carefully observed.

   If on oral contraceptives - prophylaxis can be given but advise contact to take precautions for 9 days from the time Rifadin commenced and explain the reasons why.

2. If allergic to Rifampicin and not pregnant - Tetracycline can be given e.g. Doxycycline 100mgs twice a day for 3 days. (6 doses)

3. If there is or has been disorder of the liver - no prophylaxis but observe contact carefully.

DOSAGE FOR INFANTS UNDER ONE MONTH OF AGE (SYRUP 100MGS PER 5ML)

Calculation is made according to body weight and recommended dosage is 5mgs Rifampicin per kg body weight 12 hourly (i.e. morning and evening) for 4 doses (i.e. 2 days).

WEIGHT KG	RIFAMPICIN MG		SYRUP ML		TOTAL DOSAGE (4 DOSES) MG		ML
2	10	=	0.5	12 hourly	40	=	2
3	15	=	0.75	"	60	=	3
4	20	=	1	"	80	=	4
5	25	=	1.25	"	100	=	5

DOSAGE FOR INFANTS AGED ONE MONTH AND CHILDREN UNDER THE AGE OF 5 YEARS (SYRUP 100MG PER 5ML)

Calculation is 10mgs Rifampicin per kg by weight 12 hourly (i.e. morning and evening) for 4 doses (i.e. 2 days).

WEIGHT KG	RIFAMPICIN MG		SYRUP ML		TOTAL DOSAGE (4 DOSES) MG		ML
3	30	=	1.5	12 hourly	120	=	6
4	40	=	2	"	160	=	8
5	50	=	2.5	"	200	=	10
6	60	=	3	"	240	=	12
7	70	=	3.5	"	280	=	14
8	80	=	4	"	320	=	16
9	90	=	4.5	"	360	=	18
10	100	=	5	"	400	=	20
11	110	=	5.5	"	440	=	22
12	120	=	6	"	480	=	24
13	130	=	6.5	"	520	=	26
14	140	=	7	"	560	=	28
15	150	=	7.5	"	600	=	30
16	160	=	8	"	640	=	32
17	170	=	8.5	"	680	=	34
18	180	=	9	"	720	=	36
19	190	=	9.5	"	760	=	38
20	200	=	10	"	800	=	40
21	210	=	10.5	"	840	=	42

CHILDREN AGED 5 TO 14 YEARS (CAPSULES 150MGS)

WEIGHT KG	CAPSULES MORNING		CAPSULES EVENING		TOTAL DOSAGE (4 DOSES) MG		CAPSULES
15	1	+	1		600	=	4
22.5	2	+	1		900	=	6
30	2	+	2	For 2 days	1200	=	8
37.5	3	+	2	(4 doses)	1500	=	10
45	3	+	3		1800	=	12

ADULTS (15 YEARS OR OLDER) (CAPSULES 150MGS)

WEIGHT KG	CAPSULES MORNING		CAPSULES EVENING		TOTAL DOSAGE (4 DOSES) MG		CAPSULES
LESS THAN 60 KG	3	+	3	For 2 days	1800	=	12
MORE THAN 60 KG	4	+	4	(4 doses)	2400	=	16

Signed

City of Cape Town
CITY HEALTH DEPARTMENT
CIVIC CENTRE, 12 HERTZOG BOULEVARD
P O BOX 2815, CAPE TOWN, 8000

Stad Kaapstad
STADSGESONDHEIDSDEPARTEMENT
BURGERSENTRUM, HERTZOG-BOULEVARD 12
POSBUS 2815, KAAPSTAD, 8000

ENQUIRIES: Deputy Medical Officer of Health
210-2250/2700
After Hours: 210-2311: Ask for
Deputy Medical Officer of Health

ADVICE TO CONTACTS OF A PATIENT SUFFERING FROM MENINGOCOCCAL DISEASE (CEREBRO-SPINAL FEVER, CSF, MENINGOCOCCAEMIA)

The diseases associated with meningococcal infection are usually very acute in onset and frequently present with a severe headache, stiffness of the neck, nausea, vomiting, fever and/or a rash.

Any such symptoms within a week since last exposure to risk should be reported to your usual medical attendant at once together with this letter. In addition the health inspector or nurse who has visited you should be informed of any such symptoms. This disease is very dangerous if not treated but with prompt treatment the recovery rate is very good indeed.

In order to rid the household of the bacteria which could be present there you have been provided with supplies of antibiotics to be taken as prescribed. Please advise the nurse or health inspector supplying the antibiotics if you are pregnant, taking oral contraceptives, also if you have had a liver disorder or suffer from any type of allergy. Please co-operate in taking these tablets/syrup/capsules as directed by ensuring that a record is kept of the fact that all contacts in the house have taken all the necessary doses.

Should you feel any ill-effects from the antibiotics you should also inform this Department or your usual medical attendant at once. Rifampicin often causes urine, saliva, faeces, sweat, tears and other body secretions to become reddish in colour - this is nothing to be alarmed about.

If in any doubt as to what to do please telephone one of the above numbers should you be unable to obtain further advice from the staff who originally contacted you.

Signed

for MEDICAL OFFICER OF HEALTH

Handed to : _____

Date : _____

By : _____

(For Afrikaans version see overleaf)

Address Correspondence to: THE MEDICAL OFFICER OF HEALTH — Vear aan: Korrespondensie met: DIE MEDIESE GESONDHEIDSBEAMPTE

APPENDIX 2

REPORT ON THE PILOT STUDY

A COPY OF THE ORIGINAL REPORT

AN ESTIMATE OF THE MINIMUM SECONDARY ATTACK RATE FOR MENINGOCOCCAL INFECTION IN THE CAPE TOWN CITY COUNCIL AREA DURING 1988, AND AN INVESTIGATION INTO SOME OF THE POSSIBLE ASSOCIATED FACTORS

All infections with Neisseria Meningitidis have been acquired somewhere, and so it is necessary to define what is implied by a secondary case.

For the concept of secondary attack to have meaning in practice, it will be limited to cases occurring amongst the population targetted for prophylaxis treatment under existing Cape Town City Council policy.

During 1988 Community Health Sisters, or, as was usually the case, Health Inspectors, visited the homes of all notified cases. The quality of information, and the scope and detail of that information was quite outstanding in every case.

A survey of telephonic notifications, written notifications, Health Inspectors reports, hospital admission and discharge registers, computer data, case notes, and registers of deaths, burial orders, and cremation orders, was carried out for the year 1988.

The findings are summarised in the following tables.

TABLE 1 - NOTIFICATION BY PRIMARY SOURCE

* PRIMARY SOURCE (I.E. WHERE DIAGNOSIS WAS FIRST APPARENT)	TOTAL NUMBER OF CASES DISCOVERED	NOTIFICATIONS FROM PRIMARY SOURCE. TELE-PHONIC	WRITTEN	ALL MEANS	NOTIFICATIONS FROM OTHER SOURCES TELE-PHONIC	WRITTEN	ALL MEANS	NEVER NOTI-FIED
RED CROSS HOSPITAL	108	38	37	51 (47,2%)	52	0	52 (48,1%)	17 (15,7%)
ALL OTHER PUBLIC HOSPITALS	29	19	20	27 (93 %)	3	0	3 (10,3%)	1 (3,5%)
ALL PRIVATE HOSPITALS	10	7	2	7 (70%)	2	0	2 (20%)	1 (10%)

Overall notification by all means is 128/147 $\simeq$ 87,1%

* There were no notifications from Tygerberg Hospital, and no cases were discovered at Tygerberg following a computer search.

TABLE II - MORTALITY RATES

	RED CROSS HOSPITAL	ALL OTHER PUBLIC HOSPITALS	ALL PRIVATE HOSPITALS
Number of Patients	108	29	10
Number of deaths	6	2	2
% Patients who died	5,5%	5,9%	20%

TABLE III: RATE OF PROPHYLAXIS AND ORIGINS OF PROPHYLAXIS

PRIMARY SOURCE	PROPHYLAXIS GIVEN FIRST BY	NOTIFIED CASES	NON-NOTIFIED CASES	TOTALS	% OF KNOWN CASES IN WHICH PROPHYLAXIS WAS DISTRIBUTED
RED CROSS HOSPITAL	a. CCC	29	0	29	92,6% - 99,1%
	b. 1° Source	61	10	71	
	c. Not known	0	7	7	
	d. Nil	1	0	1	
ALL OTHER PUBLIC HOSPITALS	a. CCC	14	0	14	82,8% - 86,2%
	b. 1° Source	10	0	10	
	c. Not known	0	1	1	
	d. Nil	4	0	4	
ALL PRIVATE HOSPITALS	a. CCC	4	0	4	70% - 100%
	b. 1° Source	3	0	3	
	c. Not known	0	3	3	
	d. Nil	0	0	0	

Overall rate of prophylaxis is 131/147 - 142/147 i.e. 89,1% - 96,6%

Possible secondary cases using the restricted definition discussed in the introduction.

1. A patient with proven C_6 deficiency. He and his contacts were given Rifampicin prophylaxis by C C C and long acting (Depot) Penicillin for the patient from Groote Schuur Hospital. He had a second attack four months later.

2. Two children attending the same crêche went down with meningitis ten weeks apart. Although prophylaxis was given out at the crêche, for some reason the second child did not receive any. It is possible he was absent on the days of the community visit.

This gives a possible secondary attack rate of 1,36%.

Confirmation or exclusion of these two cases depends on the results of subtyping, which is not yet available; under the criteria in pre-subtyping days, they would qualify as secondary cases and the expected secondary attack rate in Western Countries would be of the order 0,3% to 0,6% according to published data.

DISCUSSION

The validity of this estimate for secondary attack rate depends on validity of both numerator and denominator.

An estimate of the validity of the denominator is given by the mortality. A mortality of 5% is accepted in Western countries as well as in South Africa according to published data.

The mortality rate experienced in 1988 is somewhat higher. This may imply that unnotified cases have not been discovered by the methods used, and would suggest that the denominator should be higher than 147; this would reduce the secondary attack rate estimate.

On the other hand the Cape Peninsula area is in the upswing phase of a twelve yearly peak in meningococcal infections. Previous experience has shown these upswings to be accompanied by an increase in Type C Neisseria Meningitidis infections and South African epidemiological data shows Type C infections to be associated with a higher mortality.

The numerator should be treated with caution until results of sub-typing are available. However, the actual number of cases is low (2) and if this were to only fall by one, there would be a 50% decrease in the estimate of secondary attack rate; it would be unwise, therefore, to conclude anything from this estimate, even if these cases are confirmed.

In conclusion, the secondary attack rate is within reasonable expectations and has not been shown to be significantly different from estimates in developed Western Countries.

Whether / -

Whether this is due to the issuing of Rifampicin to contacts remains to be seen; the data for the entire peninsula area over the years 1988 and 1989 should provide a sufficiently large number of secondary cases, to make statistical analysis of the importance of Rifampicin in preventing secondary cases, feasible. The results of this study will not be available until the end of 1991.

With regard to the issue of timing of notifications and prophylaxis issue, the following comments are offered:

i. The occurrence of secondary cases up to a year after the primary case is now very well documented in the literature, and comments such as "late notification - no prophylaxis issued" are no longer reasonable in the light of this new knowledge.

ii. A significant number of notifications are being left to officials at City Hospital with resulting delay of several days.

iii. Legal opinion (Professor Smith, UCT) is that the responsibility for notification rests with the **doctor** who first makes the diagnosis. New legislation requires **telephonic** notification on **suspicion**. These facts of life should be conveyed to doctors, particularly at Red Cross Hospital.

iv. In view of the fact that such a high proportion of cases, for one reason or another, are at present being notified after several days have elapsed, no attempt has been made to analyse these delays; the number of cases which are not notified at all is a further problem. However, as a generalisation, the cases notified to City Council have invariably been followed up with **immediate** effect once the notification (telephonic or otherwise) is first received.

B V GIRDLER-BROWN
REGISTRAR,
DEPARTMENT OF COMMUNITY HEALTH
UNIVERSITY OF CAPE TOWN

cc: Dr M Popkiss, MOH, City of Cape Town
Professor J Klopper, Dept of Community Health, UCT