Outbreak investigation and epidemiology - from practice to science - .
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CHAPTER 2

A primary school classroom outbreak of scarlet fever, impetigo and pharyngitis caused by the same Streptococcus pyogenes M4T4-type

2.1 ABSTRACT

This chapter discusses a primary school classroom outbreak of scarlet fever, impetigo and pharyngitis. Following the reporting of an unusual number of scarlet fever cases within the same primary school, the epidemiological and clinical features of the outbreak were investigated. Questionnaire information about the cases was collected by telephone from parents and general practitioners. Throat samples were taken, before and after treatment, and culturing and specific typing of streptococci was performed to determine the level and mode of transmission.

Within a period of one month, 21 schoolchildren in a class of 29 pupils, with a mean age of 5 years, presented with symptoms caused by streptococcal infection (attack rate 72%). Eight developed scarlet fever, five suffered from impetigo and eight children had pharyngitis. A further six children, outside the class, had complaints of scarlet fever, impetigo or pharyngitis. Throat cultures were taken from 90% (26/29) of the schoolchildren. Twelve positive cultures of the same strain of beta-haemolytic group A streptococcus, T4M4 exotoxin C gene positive, were found. The advice given was to treat all positive children with azithromycin for three days to prevent complications and further spreading of the disease. After two weeks only one child, who had not taken the antibiotics, still had a positive throat culture. No further cases or complications were reported.

The pattern of the outbreak was typical of person-to-person transmission. This was confirmed by typing of the isolates. The results of this study demonstrate the importance of mandatory notification of infectious clusters by institutions such as schools, as introduced in the Dutch Communicable Diseases act of 1999. Notification gives the MHSs the opportunity to analyse the source and transmission dynamics, as well as to prevent disease and complications. Specific microbiological typing of the bacteria proved very useful as an instrument to verify epidemiological assumptions.
2.2 INTRODUCTION

At the end of December 1999, a primary school reported several cases of scarlet fever. The Communicable Diseases act of 1999 in the Netherlands has introduced mandatory notification for institutes where vulnerable groups of people, such as children, attend or reside, when unusual numbers of persons become ill through suspected infection. Scarlet fever is caused by Lancefield group A beta-haemolytic streptococci (Streptococcus pyogenes). This chapter describes the outbreak, which was mapped out to obtain a better understanding of the source, transmission, possible measures to be taken and evaluation of these interventions.

Background information on scarlet fever

Approximately 5% and sometimes up to 20% of apparently healthy children aged between 3 and 15 years are asymptomatic carriers of group A streptococci. Carriage rates in other age groups are considerably lower. Asymptomatic carriers seem to experience fewer complications and are much less likely to transmit the organism to others than persons with a symptomatic infection. Scarlet fever is a streptococcal infection often resulting in pharyngitis, fever and a characteristic erythema, with "sandpaper" texture of the skin, "strawberry tongue" and marked circumoral pallor of the face (the so-called "anaesthetic face mask"). Some toxicogenic strains of streptococci produce either exotoxin A or C, responsible for the fever and the scarlatinal rash. The incidence of scarlet fever has dropped over recent years, for reasons that remain unclear, because there are enough strains of streptococci circulating in the population that are capable of producing pyrogenic exotoxins. Although group A streptococcal pharyngitis can be found in all age groups, it is one of the most common bacterial infections of childhood, the age group in which 20-40% of all cases of pharyngitis are observed. Streptococcal infection is rare in children below 3 years of age, in whom the disease manifests itself as a mild clinical syndrome with low-grade fever, malaise and lymphadenopathy. The disease is ordinarily spread by direct person-to-person contact via respiratory droplets, although indirect transmission through contaminated materials or objects such as toys may play a limited role in contagion. The usual incubation period of streptococcal pharyngitis is 1-4 days. Apart from a sore throat, fever and malaise are common in children, while abdominal pain and vomiting are occasional complaints. In the absence of complications, the disease is self-limiting, and fever abates within 3-5 days. Although antibiotics barely shorten this period, eradication of the bacteria from the throat prevents complications such as peritonsillar abscess, meningitis, endocarditis, glomerulonephritis and streptococcal pneumonia. The drug of choice in the treatment of streptococcal infection is penicillin, continued for 10 days.

Impetigo or pyoderma is a primary superficial pustular infection of the skin, caused by group A streptococci. This skin disease is predominantly found in young children during the warm summer months, and often affects the circumoral area of the face.
2.3 OUTBREAK

Patients

Following the reporting of an unusual number of scarlet fever cases in one class of a primary school, an investigation was started into the prevalence of scarlet fever, pharyngitis and impetigo, and the presence of streptococci. On December 23rd 1999, two days after the notification and almost one month after the first case of scarlet fever had been diagnosed in one of the pupils an outbreak investigation was started. Throat swabs for culturing were taken from all children, after informed consent of the parents had been obtained, in order to gain a better understanding of the transmission of the bacteria in the class. During the Christmas holidays, the parents were interviewed over the telephone using semi-structured questionnaires, to collect information on the household situation, possible symptoms in the children, and – if applicable – the first day of illness, visits to the general practitioner (GP) and the use of antibiotics. If the general practitioner had seen a child, the diagnosis was verified with the patient’s GP. Nine GPs were found to be involved in the management of the outbreak. They were informed about the outbreak, asked to report new cases and requested to take a throat swab for culturing, preferably, before any therapy was started. Children with a positive culture for streptococci were treated by the GP in accordance with the recommendations of the MHS. After the antibiogram had become available, it was recommended to prescribe azithromycin 200 mg suspension for three days to prevent complications and to interrupt transmission. This choice was motivated by the ability of azithromycin suspension to be effective within three days, while penicillin has to be prescribed for ten days to achieve eradication of the streptococci. The short course is likely to improve the patient’s compliance. In addition, azithromycin causes fewer allergic reactions. After the Christmas holidays, on January 13th (approximately two weeks after the treatment), the throat culture was repeated in order to evaluate the effectiveness of the therapy.

Bacteriology

The streptococci were cultured on blood agar plates and drug susceptibility was tested with the disk diffusion method. Further determination of the group of streptococci was done with the help of Streptex (Murex Biotech; Dartford, United Kingdom). Group A streptococci can be differentiated into various T and M types, based on differences in the amino acids of two outer membrane proteins. Thirty types of T protein have been identified using specific antisera (T-serotyping). More than 100 varieties of the M protein have been identified, not only by means of specific antisera (M-serotyping) but also with a genetic method (M-genotyping). In M-genotyping the gene coding for the M protein is amplified by means of the polymerase chain reaction (PCR). Part of the amplified product consists of the nucleotide sequence of the M-gene that codes for the variable part of the M protein. Each variety (M-genotype) of the amplified M-gene of a group A streptococcus can be detected...
and characterised by nucleic acid hybridisation with different M-type-specific DNA probes. In order to determine whether the streptococci isolated in the outbreak described here belonged to the same M-genotype and T-serotype, M-genotyping was performed ('reversed-line blot' method), while T-serotyping was done with monospecific antisera. In addition, a toxin-gene test was carried out using an exotoxin-A-and-C-gene PCR.

Clinical symptoms and positive cultures

The class consisted of 14 girls and 15 boys, with an average age of 5 years. Table 2.1 shows that of these 29 pupils, eight developed scarlet fever (28%), with three of them suffering from pharyngitis as well. Five children had impetigo (17%) and one experienced pharyngitis at the same time. Eight children only complained of pharyngitis (28%). This amounts to an attack rate of 72% (21/29) within one month. Other symptoms mentioned were lymphadenopathy, fever, diarrhoea, vomiting and ear infection. A throat culture could be performed for 26 of the 29 pupils; the parents of three children (two of whom suffered from pharyngitis) refused permission. Of the 26 throat cultures obtained, 46% (12/26) proved to be positive for group A beta-haemolytic streptococci. As illustrated in table 2.1, two of the cultures taken from the eight patients with scarlet fever revealed streptococci. Four patients had already received an effective antibiotic treatment from their GP (penicillin in three cases and erythromycin in one) before the throat swab was taken, which could explain the negative culture results. The cultures for the remaining two children may have been false negative, or the streptococcus may have disappeared from their throats as a result of the long interval between the onset of illness and the culture.

In the group of five impetigo patients, four cultures proved to be positive, while the result of the last culture may have been false negative. Although the GP had prescribed fusidic acid ointment for two patients, streptococci were nevertheless detected in the throat. Streptococci were also found in four of the six patients who complained of pharyngitis and in whom a throat culture had been performed. In the other two children, the culture result may have been false negative, or perhaps a streptococcus did not cause their pharyngitis. One of the patients with a positive culture had been prescribed an unspecified antibiotic by the GP, which had apparently not been effective.

Of the throat cultures of the seven asymptomatic pupils, two revealed streptococci. The parents of one of these two apparently healthy children recalled complaints of 'diarrhoea'. The strains of streptococci found were sensitive to penicillin and erythromycin.

Contacts

The symptomatic pupils had a total of 15 brothers and sisters aged below 10 years. On further inquiry, two children from this group were diagnosed with impetigo (in one case together with pharyngitis) and one child was found to have pharyngitis. This translates into an attack rate of 20% (3/15). In addition, a friend of one of the sick children reportedly
suffered from impetigo and pharyngitis. These four children also had an average age of 5 years. During the Christmas holidays, the MHS was notified about two children from another classroom of the primary school, who also showed signs of streptococcal infection. These were two 9-year-old girls with symptoms that had started just before the Christmas holidays; one girl developed scarlet fever, the other impetigo. Both children were treated by their GP, who had been informed by the MHS.

**Table 2.1: Summary of streptococcal infections by clinical picture and identification by culture.**

<table>
<thead>
<tr>
<th>Children</th>
<th>Syndrome</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected classroom (age 6-8 years):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 children;</td>
<td>8 scarlet fever (28%)</td>
<td>2 positive</td>
</tr>
<tr>
<td></td>
<td>of which 3 with pharyngitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 impetigo (17%);</td>
<td>4 positive</td>
</tr>
<tr>
<td></td>
<td>of which 1 with pharyngitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 pharyngitis (28%)</td>
<td>4 positive;</td>
</tr>
<tr>
<td></td>
<td>8 not ill (28%)</td>
<td>2 culture refusals</td>
</tr>
<tr>
<td>Brothers and sisters in different school (&lt;10 years):</td>
<td>2 impetigo (13%)</td>
<td>2 positive</td>
</tr>
<tr>
<td>15 children</td>
<td>of which 1 with pharyngitis</td>
<td>1 culture refusal</td>
</tr>
<tr>
<td></td>
<td>1 pharyngitis (7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 not ill (80%)</td>
<td></td>
</tr>
<tr>
<td>Classes 5 and 6:</td>
<td>1 impetigo</td>
<td>-</td>
</tr>
<tr>
<td>2 children</td>
<td>1 scarlet fever</td>
<td>-</td>
</tr>
<tr>
<td>Girlfriend of a patient</td>
<td>1 impetigo with pharyngitis</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 2.1. Epidemic histogram of the outbreak: number of cases (●). The figure shows the 27 patients by day of onset of symptoms in intervals of 2 days. Each patient is shown only once: when scarlet fever was diagnosed, comorbid pharyngitis was not mentioned. The first few cases were an incubation period (1-4 days) apart. After that, most cases were seen in two waves round 7 to 9 December and 15 to 17 December. The weekends of 11 and 12 December and 18 and 19 December probably restricted the transmission temporarily.

Epidemic histogram

The epidemic histogram (figure 2.1) shows all 27 symptomatic children (21 from the same primary school class and six contacts) with their first day of illness. The outbreak started with some individual patients being reported, with an interval corresponding to one incubation period, after which the majority of the cases can be seen in two peaks: one between 7 and 9 December and a second around 15 to 17 December. The weekends of 11-12 December and 18-19 December have probably temporarily interrupted the transmission. The epidemic histogram illustrates that the bacteria were most probably introduced into the school class by a patient with scarlet fever; the index case of the outbreak seems to have been a 4-year-old girl. However, her two sisters remained without any complaints and since an asymptomatic carrier state is common, no precise conclusions can be drawn regarding the actual source.

Follow-up investigations

Repeated throat cultures taken from the 12 initially positive children showed that 11 of them were no longer carrying the streptococci. The only child with a second positive culture had not received antibiotics. After completion of the treatment and the follow-up cultures, no new cases of streptococcal infection were notified.

Bacterial typing

All isolates of streptococci were identified as T type 4 and M type 4 (T4M4) and exclusively contained exotoxin C, a typical scarlet fever toxin.
2.4 DISCUSSION

The pattern of the epidemic histogram corresponds very well with serial person-to-person transmission. Apart from some early cases, with an interval exactly matching one incubation period, the majority of the sick children presented in two peaks: one between 7 and 9 December and a second around 15 to 17 December. The weekends of 11-12 December and 18-19 December have probably temporarily interrupted transmission. The consistent finding of 12 identical T4M4 exotoxin-C-gene-positive strains of beta-haemolytic streptococci seems to confirm the impression that the infection was spread by direct person-to-person contact. Serotyping and genotyping proved to be very useful as epidemiological instruments to verify the unique clone of streptococci.

A great diversity of T/M type streptococci is found in the Dutch population, and more than 50 different strains have been identified. The T4M4 type responsible for the outbreak described here covers less than 5% of all streptococcal isolates examined in the Netherlands by the National Institute of Public Health and the Environment (RIVM). In a Dutch study, Zwart et al. found T4M4 type group A streptococci in 6% of all culture-positive patients with an exudative pharyngitis, against 11% among healthy asymptomatic controls with a positive culture for group A streptococci. The numerous streptococcal T/M types found in the Dutch population, together with the small proportion of the T4M4 type identified in various groups of patients and controls, justifies the conclusion that the detection of identical strains of streptococci in all culture-positive patients in the outbreak described above proves person-to-person transmission.

The clinical picture in the reported outbreak, with scarlet fever and impetigo combined in one outbreak, is unusual. Streptococci responsible for impetigo generally belong to a different M type than those causing pharyngitis and scarlet fever. A correlation between scarlet fever and serotype T4 was detected in previous outbreaks of scarlet fever in Japan. In the United Kingdom streptococci were isolated from 25 of 105 patients with symptoms of scarlet fever, and the M type 4 was found to be most prevalent. This 1983 British survey estimated the annual incidence of scarlet fever at 0.3 per 1,000. Morbidity studies in GP practices in the Netherlands from 1991 reported the same incidence for the general population. In the 0-4 age group, scarlet fever had an incidence of 7.6 per 1,000 children per year. Among 5-15 year-olds, this incidence was 4.0 per 1,000. This same study found an annual incidence of impetigo of 29.6 per 1,000 in the 0-4 age group, against 14.8 per 1,000 among children between the ages of 5 and 15 years.

Although upsurges of streptococci causing scarlet fever probably occur fairly often, they are frequently not reported or investigated. In 1994 and 1995, an increase in the incidence of scarlet fever was seen in Amsterdam, The Hague and Zeist. The cases of scarlet fever in Amsterdam were observed over a period and appeared to be scattered over many parts of the city. A total of 15 isolates were examined, in which nine different T/M...
types were identified, though the T4M4 type was not represented (Dr P. Peerbooms, MHS Amsterdam, personal communication, 2000). In The Hague, four isolates were examined and three different T/M types were detected; T4M4 was not among these either. In all eight cases in Zeist, type T12 was involved but the M type varied (Dr B.M. de Jongh, Lorentz Hospital, Department of Medical Microbiology, personal communication, 2000). From this perspective, the outbreak described here and the high attack rate are extraordinary.

The results of the present study underline the importance of mandatory notification of infectious clusters by institutions such as schools, as introduced in the Dutch Communicable Diseases act. Following the notification of the outbreak described, an investigation was set up, the dimension of the outbreak was evaluated and interventions were implemented to control further spread of the infection and to prevent potential illness and complications. Specific microbiological typing of the bacteria proved very useful as an instrument to verify epidemiological assumptions.

2.5 REFERENCES


Schoolepidemie door parvovirus


**Vijfde ziekte heerst in Limburg**

De Limburgse GGD's hebben dit voorjaar veel telefoontjes over de kinderziekte vijfde omvangen van kinderziekte en basisscholen. Infecties met parvovirus mogen in Nederland een abortus zijn van 4 jaar, naast de 2e seizoenspiek in het jaar. Dit jaar is meer ziekte heerst in Limburg, op de voorgrond met de kenmerkende rode appelwangen, terwijl deze ziekte verder is geïntegreerd voor volwassenen vaak acute gewrichtsklachten veroorzaakt. Hoeveel de meeste infecties met parvovirus relatief mild zijn, zijn infecties bij volwassenen, zwangerschappen en bij specifieke risicogroepen van belang in verband met hun ernstigere beloop.

**Onrust door vijfde ziekte**