Outbreak investigation and epidemiology - from practice to science -.
Hoebe, C.J.P.A.

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Summary

CHAPTER 1: offers an introduction in the control and epidemiology of outbreaks. Three general topics on outbreaks are discussed. The first part describes the characteristics of outbreaks. The definition of an outbreak, factors needed for an outbreak to start, the mode of transmission and when an outbreak is finished are discussed. The second part is about the present organization of our infrastructure to control outbreaks. It considers the foundation of our defence network or in other words the work of the department of infectious diseases of the Municipal Public Health Services (MHSs). The two mayor Acts for the legal framework are discussed, the Collective Prevention in Public Health Act and the Communicable Disease Act. Moreover, quality standards are mentioned in detail. The third part is about the basics of outbreak investigation and outbreak epidemiology. The process of outbreak management and outbreak investigation is explored in different stages: detection of signals, verification, outbreak management team formation, communication, outbreak analysis and intervention.

CHAPTER 2: evaluates 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 new Dutch Communicable Diseases act. 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.

**CHAPTER 3:** evaluates the confirmation of an outbreak of parvovirus B19 in a primary school using IgM ELISA and PCR on thumb prick blood samples. Although parvovirus infections are usually benign and self-limiting, it is important to confirm the diagnosis in a public health setting, which might involve pregnant women for whom an outbreak could lead to medical consequences. In these situations, microbiological confirmation by thumb prick is a relatively low-invasive method that is simple to carry out.

Because relatively small blood volumes are obtained in thumb prick blood samples, we compared the results of two different techniques during an outbreak of erythema infectiosum: the usual serological detection of IgM antibodies (ELISA) versus PCR-based detection of viral DNA.

In a school-based outbreak, 39 cases (33 schoolchildren, three parents, three pre-schoolers) were registered over a period of 11 weeks. Sera were obtained from 23 of the school cases and two of the three parent cases. Of all thumb prick serum samples, 65% (15/23) tested positive or borderline positive for parvovirus IgM with ELISA, while 70% (16/23) tested positive or borderline positive with PCR. Although the overlap between the two tests was large (11 samples tested positive or borderline positive in both), a substantial number of samples showed contradictory results (9 samples).

The overall picture of 37 clinical cases of erythema infectiosum and two adult cases with arthritis, linked to a primary school, fits in well with positive diagnostic results by either technique for parvovirus B19, convincingly demonstrating an outbreak of fifth disease. The considerable number of discrepancies in sample results demonstrates that maximum sensitivity of parvovirus testing would require both tests to be performed.

**CHAPTER 4:** evaluates a comparison of a cluster analysis of invasive meningococcal disease results by a novel statistical method and field observations. Clusters are recognized when meningococcal cases of the same phenotypic strain (markers: serogroup, serotype and subtype) occur close in place and time. The incidence of such clusters was compared to that expected by chance, using space-time nearest-neighbor analysis of data of 4887 confirmed invasive meningococcal cases identified in the 9-year surveillance period 1993-2001 in the Netherlands. Clustering beyond chance only occurred among the closest (1st-nearest) neighboring cases (comparable to secondary case) and was small (3.1%; 95%CI: 2.1-4.1).

Our findings suggest that apparent clusters are not a valuable entry-point for targeting additional intervention efforts, as these would prevent few further cases. Field clusters are easily misinterpreted as outbreaks, and would require genotyping to rule out misclassification. Our method of nearest-neighbor analysis provides a sensitive novel approach to the epidemiology of meningococcal disease.
CHAPTER 5: describes a study on a gastro-enteritis outbreak among primary school children which was associated with playing in a Norovirus contaminated recreational fountain. A retrospective cohort study was performed to estimate the magnitude of the outbreak and identify its source. An epidemiological investigation included standardised questionnaires about sex, age, school, class, possible risk exposures, and characteristics of the illness. Stool samples and environmental water samples were analysed for the presence of bacteria, viruses and parasites.

Questionnaires were returned for 191 school children (response 83%) with a mean age of 9.2 years, of whom 47% had experienced illness (diarrhoea and/or vomiting). Children were more likely to have been ill if they had played in the recreational fountain (RR 10.4). Norovirus was detected (Birmingham) in 22 (88%) stool specimens from ill children and 6 (38%) specimens of children without symptoms. The water sample derived from the fountain contained a Norovirus strain, which was identical to the Birmingham RNA sequence found in stools.

Not only drinking water, but also recreational water may be the source of gastroenteritis outbreaks. Adequate water treatment such as chlorination can prevent these types of outbreak.

CHAPTER 6: discusses the technical, microbiological and epidemiological investigation following two cases of fatal Legionella pneumonia. Faced with two nosocomial cases in a rehabilitation centre in the South of Limburg, the Netherlands, the water supply was investigated. Water temperatures from different taps were measured. Legionella cultures were made from respiratory patients' specimens, water samples and smears from all mixing taps (used in showers), samples from hot and cold water taps from the infected ward and from the five other wards. The strains were typed by serotyping and polymerase chain reaction. The circulating cold water sometimes warmed up to 40°C (within the Legionella growth range). From the sputum of the two male patients with rheumatoid arthritis who died of Legionella pneumonia the same Legionella pneumophila (serotype 1) was cultured as from the water supply. Of the showers on the contaminated ward 19% (12/63) were positive for Legionella as were 59% (35/59) of the cold water taps. Cultures from the hot water supply were negative just like control cultures from five other wards and swabs from showerheads and hoses. The cold-water tubes ran next to the hot water tubes and the central heating system in the same shaft. On the infected ward patients were absent during the weekends. As one of the subsequent measures, the cold water pipes were relocated to another shaft.

The combination of an elevated cold water temperature caused by heating along a distance by nearby hot water and heating piping and the regular stasis of water during the weekends when the ward was closed, most probably stimulated the multiplication of Legionella in the water supply. In order to minimize contamination of cold water, its temperature must be below 20°C. Surveillance of intramural water systems is necessary to prevent nosocomial infections.
CHAPTER 7: evaluates the controlling of an alleged outbreak of meticillin-resistant Staphylococcus aureus (MRSA) in a Dutch nursing home. Following the identification of an index patient with MRSA in a Dutch nursing home with 175 residents, microbiological diagnosis having been obtained from a foreign laboratory, a survey was carried out to trace contacts by means of the ‘ring principle’ of outbreak management. Whenever positive cultures were found in the first ring of residents, the contact and source tracing procedure was extended. In accordance with the Dutch guidelines for MRSA in nursing homes, a range of preventive measures was taken regarding colonised residents and employees and the cleaning of rooms. Ten days after the occurrence of the index case, 29 persons, 9 employees and 20 residents, were found to be colonised with MRSA. Because of this extraordinary count compared with earlier Dutch findings (only 0.16% of inhabitants colonised) there were doubts about the laboratory results. A counter-expertise from the PHL and the RIVM showed no MRSA, but meticillin-sensitive S. aureus.

This alleged outbreak had very serious consequences for residents and employees and major financial consequences for the nursing home. There was a very adequate response to the crisis by a multidisciplinary team including external specialists. Incorrect identification of MRSA is not restricted to this incident, as proficiency-testing programmes have shown that MRSA has not always been reported accurately. The IGZ emphasised the importance of standardised quality and interpretation of laboratory results by microbiological experts. This should be kept in mind when contracting foreign laboratories, particularly because the Dutch policy is to avoid MRSA in intramural settings. The verification of the diagnosis once again proved to be an essential step in outbreak management.

CHAPTER 8: offers a general discussion on the lessons learned from outbreak investigation and the bottlenecks that are revealed and suggestions for improvement are presented.

Recently, infectious diseases and outbreaks of infectious diseases are back on the top of the priority lists of politicians as an emerging threat for the stability of our society. Outbreaks due to natural causes on one hand and the threat of bioterroristic outbreaks on the other hand have accelerated this incline in attention. In this scope of (re)emerging threats with possible aggravating consequences for individuals, the community and possibly even humankind, we need a robust communicable disease control system in a clear public health infrastructure. An effective communicable disease control system is essential to protect the health status of our society. Before we know if we are prepared for the worst scenario, we have to learn from the control and epidemiology of less serious outbreaks. I raise three mayor concerns that should be improved: the detection of outbreak signals, the place of diagnostic assays and a microbiological laboratory in communicable disease control and performance of outbreak investigations.

The MHS has to make every effort to create awareness among potential notifiers of their essential role in the communicable disease control infrastructure. The better the
relationships between the MHS and physicians, microbiological laboratories and institutions are, the quicker and the more often signals reach the MHS. When the MHS is able to create a general awareness among the public that they can always give notice in case of infectious disease questions and observations, many signals can be received from them too.

A relationship of close cooperation with a PHL and a proper arrangement to finance diagnostic assays is an essential precondition for outbreak investigation. In daily practice, there are difficulties with timely access to laboratory testing and laboratory results. Furthermore, low invasive diagnostic public health assays (e.g. with saliva) and specific molecular typing methods to verify epidemiological assumptions are not always available for outbreak investigations by the MHS.

Infection dynamics change constantly over time and precisely with outbreaks, they can show us new sources, new routes of transmission and new patterns of disease. Thorough outbreak investigations can thus prevent illness in direct related persons but also indirect by a decline in the incidence of disease through adjusted infection control policies.