


NIPH
Norwegian Institute of Public Health

Outbreaks

OF FOOD- AND WATERBORNE DISEASES

Guidelines for investigation and response

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OUTBREAKS OF FOOD- AND WATERBORNE DISEASES

Guidelines for investigation and response

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These guidelines contain three template questionnaires, which are available in Word format for editing, translation and adaption to local conditions. The guidelines and the questionnaires can be downloaded from https://www.fhi.no/en/publ/2018/guidelines-for-investigation-of-outbreaks-of-food--and-waterborne-diseases/.

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Preface

Food- and waterborne diseases are a global surge and food safety is a major priority. These diseases tend to occur in widespread outbreaks, and early detection, notification, investigation and control of outbreaks is important to ensure production of safe food and reduce the medical and economic impact of the diseases. With the increasing globalization of the food market and international trade in livestock and animal feed, foodborne outbreaks now often occur over widely dispersed geographical areas.

The outbreak by itself, as well as the control and preventive measures implemented as a result of the investigation, may have considerable medical and socioeconomic consequences, and may confer a high economic burden on food producers and dealers. The outbreak may also influence trade political decisions. For these reasons, the investigation must be conducted in a purposeful and dedicated manner, with optimal use of all available resources across professions and agencies.

Effective routines for detection, notification, investigation and control of outbreaks are required on a local, regional, national and international level. Since foods are increasingly being distributed to many countries, international cooperation is necessary. However, most outbreaks are small and are investigated and managed by local authorities.

These guidelines describe the methods, procedures and responsibilities for investigation and management of outbreaks of diseases in which foods, beverages, drinking water or animals are the source of infection. Outbreak investigation consists of a number of different steps. However, the sequence with which these steps are conducted varies. Several steps are usually carried out at the same time, and not all steps are necessary in every outbreak. Each step is the subject of a separate chapter in these guidelines.

The chapters commence with a table of contents with electronic bookmarks enabling direct access to the sections. A summary of each chapter is provided by a list of highlights.

The appendices include three template questionnaires with user instructions that may be employed for: (1) hypothesis-generating pilot interviews, (2) cohort studies and (3) for systematic collection of information from persons who believe they have become ill from food or water (the primary interview). The questionnaires are available in Word-format to facilitate adaption to the current outbreak and to local conditions and food habits.

These guidelines provide practical tools for all authorities and agencies involved in investigation and management of disease outbreaks in which food, water or animals are the suspected source of infection. Outbreak investigation is a multi-disciplinary and inter-sectorial process. Although the responsibility for investigation and management of outbreaks varies between countries, successful investigation will usually require close cooperation between an agency responsible for the public health sector and the food safety authorities. An important purpose of these guidelines is to emphasize the necessity of this cooperation and describe what it entails in practice.

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1 Introduction

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Highlights

- These guidelines describe the methods, procedures and responsibilities for investigation and control of outbreaks of diseases in which foods, beverages, drinking water or animals are the source of infection.
- Effective routines for detection, notification, investigation and control of such outbreaks are required on a local, regional, national and international level. Since foods are increasingly being distributed on a global market, international cooperation is necessary.
- The most important purposes of the outbreak investigation are to stop the current outbreak and prevent future cases and outbreaks by identifying the source of infection and, subsequently, uncover the ultimate food safety violation or other causative factors that made the outbreak possible, to enable implementation of corrective actions.
- It is not sufficient merely to identify the source of infection (the proximate cause); the investigation must aim at uncovering the reason why the food became contaminated and identifying the initial source of the microbial agent responsible for the outbreak (the ultimate cause).
- Outbreak investigation contributes to general knowledge about occurrence, causes and risk factors for food- and waterborne diseases and zoonoses. Such information is normative for priorities and is crucial for implementation of control and preventive measures by the public health and food safety authorities.
- The investigation may also provide basic information about the disease and the causative agent.

1.1 Food- and waterborne diseases and zoonoses

The present guidelines describe the methods, procedures and responsibilities for investigation and control of outbreaks of diseases in which foods, beverages, drinking water or animals are the most likely source of infection. Such illnesses are designated food- and waterborne diseases and zoonoses, two partly overlapping categories:

Food- and waterborne diseases

In the present guidelines, the term food- and waterborne diseases is used to encompass infections, microbial intoxications, infestations and prion diseases, which may be transmitted to humans from foods, beverages or drinking water:

- *Infections:* Caused by pathogenic microbes (bacteria, viruses, unicellular parasites and fungi)
- *Microbial intoxications:* Caused by pre-formed toxins produced by bacteria, molds or algae
- *Infestations:* Caused by multicellular parasites (i.e. helminths)
- *Prion diseases:* Caused by misfolded proteins responsible for transmissible spongiform encephalopathies in a variety of mammals

The term **agent** is used to cover microbes, parasites, prions and microbial toxins. Chemical intoxications and other diseases caused by chemical contaminants of non-microbial origin are not dealt with here.

Zoonoses

Zoonoses are communicable diseases that may be transmitted from other vertebrates to humans (sometimes from humans to animals as well) under normal conditions:

- directly through contact with animals, their feces, urine or secretions,
- indirectly via vehicles (foods and beverages of animal or vegetable origin, other animal products like wool or hides, water, farm equipment, tools, cutlery and utensils etc.) or
- indirectly via arthropod vectors (insect and ticks).

Many zoonoses are transmitted in several ways: by food consumption, through drinking water, and by contact with animals or persons that harbor and shed the zoonotic microbe. Not all zoonotic agents cause disease in animals. Nevertheless, animals may be healthy carriers capable of conveying the agent to other animals and humans, directly by contact or indirectly through food, water or other inanimate objects.

There are good reasons for considering foodborne and zoonotic diseases together:

- Many communicable diseases in humans are transmitted from animals, directly by contact with the animals or their droppings, or indirectly through food, water or other vehicles.
- Animals are reservoirs for many food- and waterborne agents, and the diseases are consequently classified as zoonoses.
- In developed countries, food and water are among the most frequent sources of infection for a majority of the endemic zoonotic diseases, although other routes of transmission may also be important.

- Outbreak investigation requires close cooperation between the food safety sector and public health authorities (see chapter 2). In many countries, the responsibility of the food safety authorities covers, among other things, all kinds of food of vegetable and animal origin throughout the food chain, including, among other things, livestock, their feed, manure and irrigation water.
- When an outbreak is detected, it is not always clear at the outset whether the causative agent originates from foods, water, animals or other sources. All possibilities must therefore be kept open. In many food- and waterborne outbreaks, animals are the ultimate origin of the causative agent, while food or water is the proximate source of infection.
- The methods, procedures and responsibilities for investigating outbreaks are the same regardless of the source involved.

1.2 An international challenge

Food- and waterborne diseases are a global surge and food safety is a major priority. These diseases tend to occur in widespread outbreaks, and early detection, investigation and control of outbreaks is important to ensure production of safe food and reduce the medical and economic impact of the diseases. With the increasing globalization of the food market and international trade in live animals and animal feed, foodborne outbreaks now often occur over widely dispersed geographical areas.

Effective routines for detection, notification, investigation and control of outbreaks are required on a local, regional, national and international level. Since foods are increasingly being distributed to many countries international cooperation is necessary.

To meet this challenge it is essential to:

- Establish routines for early detection, notification and investigation of outbreaks through elaboration and implementation of contingency plans.
- Specify clearly the responsibilities of, and cooperation between, public health authorities and food safety authorities, as well as other agencies, in investigation and control of outbreaks, if necessary by written agreements and implementation of legislative measures.
- Establish effective procedures for outbreak alert and communication on a local, regional, national and international level.
- Perform surveillance of food- and waterborne diseases, and their causal agents, in the human population.
- Monitor the prevalence of pathogenic agents at all stages in the food chain, including domestic animals.

1.3 Why should outbreaks be investigated?

Investigation of foodborne outbreaks is an important contribution to preventive public health work.

The purposes are:

- Terminate the current outbreak or, at least, reduce its impact by minimizing further spread of the disease.
- Prevent future cases and outbreaks by identifying the food safety violation or other causative factors that made the outbreak possible, so that such failures can be corrected. Even though the outbreak is finished, it is still necessary to initiate an investigation in order to identify the source of infection and, if possible, also the ultimate causal factors. This is a prerequisite for implementation of effective preventive measures.
- It needs to be emphasized that it is not sufficient merely to identify the source of infection (the proximate cause); the investigation must aim at uncovering the reason why the food initially became contaminated and the original source of the microbial agent responsible for the outbreak (the ultimate cause). Unless these factors are revealed, new outbreaks may emerge.
- Outbreak investigation contributes to our knowledge about the occurrence, causes and risk factors for food- and waterborne diseases. Such information is normative for priorities and is crucial for implementation of control and preventive measures by public health and food safety authorities.
- In addition to data obtained by disease surveillance, compilation and analysis of information from outbreaks, makes it is possible to disclose trends and generate reports that may serve as a basis for control and prevention of infectious diseases.
- Obtain experience in outbreak investigation and improve the preparedness for this work.

The investigation may also provide basic information about the disease and the causative agent:

- In outbreaks, symptoms and clinical consequences may be recorded more accurately than in a non-epidemic situation, since it may be possible to identify cases with mild symptoms who otherwise would not have contacted a doctor.
- If the source of infection is identified and is available for sampling, quantification of the causative agent may be achievable, thus providing information on the infective dose, sometimes about survival of the agent as well.
- Outbreaks traced to one single meal (i.e. point-source outbreaks, section 8.3) consumed by a limited group of persons, provide a golden opportunity to determine incubation periods, attack rates and the prevalence of asymptomatic carriers, since it may be possible to contact and interview all persons at risk.

It should be mentioned that the principles and methods described in these guidelines may also be employed in exploration of outbreaks due to other sources of infection than food, water or animals, and in outbreaks caused by chemical contaminants.

2 Responsibility and cooperation

Sections
2.1 Inter-sectorial cooperation is required
2.2 Local and national outbreaks
2.3 Allocation of responsibilities and tasks
- The public health authorities
- The food safety authorities

Highlights

- The agencies and authorities responsible for outbreak investigation and management vary considerably between countries.
- Regardless of which authorities are responsible, successful investigation and control of food- and waterborne disease outbreaks requires close collaboration between the public health and food safety authorities on a local, regional and national level.
- Depending on the characteristics of the outbreak and the suspected sources of infection, cooperation with other authorities, such as veterinary agencies and water works, may also be needed.
- Although the laws and regulations vary, the public health authorities are usually responsible for investigation and control measures within the human population where the outbreak occurs.
- Likewise, the food safety authorities are responsible for investigation and control measures at every stage in the production, processing and distribution chain of all kinds of food (the food chain) as well as for domestic animals.

2.1 Inter-sectorial cooperation is required

The responsibility for investigation and management of outbreaks varies between countries. Regardless of the authorities in charge, successful investigation and control of outbreaks caused by food, beverages, drinking water or contact with animals, requires close inter-sectorial cooperation between the public health sector and food safety authorities. Depending on the characteristics of the outbreak and the suspected sources of infection, cooperation with other agencies may be needed, such as veterinary authorities and agencies responsible for drinking water treatment and supply.

Efficient cooperation depends on prior knowledge about the responsibilities imposed on the different authorities involved. Mutual respect and acceptance of roles should be established before an outbreak occurs. This may preferably be accomplished through joint development of a contingency plan in which allocation of tasks are described in detail. It is crucial to establish clear and compulsory routines ensuring effective notification, information flow, and cooperation.

The outbreak by itself, as well as the control and preventive measures implemented as a result of the investigation process, may have considerable socioeconomic consequences (e.g. in terms of days of illness, deaths, sequelae, sickness leaves, treatment and hospitalization), and may confer a high economic burden on food producers and dealers. The outbreak may also influence trade political decisions.

For these reasons, the investigation must be conducted in a purposeful and dedicated manner, with optimal use of all available resources across professions and agencies.

2.2 Local and national outbreaks

In many countries, the responsibility for outbreak investigation rests with local authorities if the outbreak occurs in one single municipality, whereas national or regional authorities are responsible if several municipalities or counties are involved.

In these guidelines, the following definitions are employed:

Local outbreak

An outbreak is defined as local if the source of infection is confined to one municipality, even though the patients may be residents of several municipalities. Such outbreaks should be investigated in collaboration between local public health and food safety authorities. For example, if an outbreak is confined to the guests in one hotel, it is obvious that the source of infection is to be found somewhere within the hotel, and the outbreak will consequently be investigated by local authorities, regardless of whether the patients come from various municipalities.

National authorities may provide information, advice, supervision and assistance in local outbreaks if the local resources and experiences are limited, including deployment of a national outbreak investigation team.

National outbreak

An outbreak is defined as national if the source of infection is active in several municipalities. In such outbreaks national leadership and coordination is necessary, and the responsibility for investigation and control resides in the national food safety and public health authorities. Local authorities may be imposed to provide information and assistance in the investigation.

If a regional level is inserted, the above definitions and responsibilities must be adjusted accordingly.

2.3 Allocation of responsibilities and tasks

Regardless of whether the outbreak is defined as local or national and irrespective of the particular authorities involved the following allocation of responsibility and tasks may be recommended, albeit depending on the legislation that applies (Figure 2.1):

The public health authorities

Although the laws and regulations vary, the public health authorities are usually responsible for investigation and control measures within the human population where the outbreak occurs. In a local outbreak: the local public health office or public health physician. In a national outbreak: usually the national public health institute or a similar agency. Their responsibilities entail the following tasks:

- Characterize the outbreak (who, where, when and what) and follow its progression (chapter 8)
- Ensure a tentative and etiological diagnosis is established (chapter 6)
- Make a case-definition (chapter 7)
- Contribute to identification of the source of infection by epidemiological and microbiological investigations within the population where the outbreak occurs (the population at risk)(chapters 9 and 10)
- Implement control and preventive measures within the outbreak population (e.g. vaccination, passive immunization, excluding patients and carriers from situations where they can transmit the disease, provide information and advice to the population about how they can avoid becoming infected) (chapter 12).

Medical decisions regarding individual patients (e.g. treatment, sick leave prescription etc.) are made by the patients' health care providers.

It needs to be emphasized that this responsibility does not require that they perform the tasks themselves. For instance, it may be an advantage to let the food safety authority conduct hypothesis-generating pilot interviews with case-patients on behalf of the health service, even though this kind of work belongs to the responsibility of the public health sector (see section 9.3).

The food safety authorities

In many countries, the food safety authorities are responsible for control, inspection, legislation, regulations and guidelines for all stages of production, processing, distribution and sale throughout the food chain for all foodstuff of animal as well as vegetable origin, and sometimes also for drinking water. This responsibility encompasses not only the food itself but also all its ingredients and raw materials, and may include food producing animals and their feed, manure, irrigation water, and any other factor "from farm to fork". During outbreak investigation, their responsibilities entail the following tasks:

- Perform site inspections of incriminated businesses and premises where foods are produced, processed, prepared, sold or served (section 9.2), in order to identify any food safety violations or other adverse conditions that may explain why the outbreak occurred
- Conduct interviews with food handlers and staff members in food businesses
- Ensure samples are collected and analyzed from all relevant stages in the food chain (chapter 9 and 10)

- Perform traceback and trace-forward investigations in the food chain in cooperation with the food businesses (chapters 10 and 11)
- Uncover the reason why the food became contaminated and the ultimate source of the microbial agent responsible for the outbreak
- Ensure effective control and preventive measures are being implemented in the food chain (chapter 12)

FIGURE 2.1 The responsibility of public health and food safety authorities in outbreak investigation

3 Steps in the outbreak investigation

Highlights

- An outbreak investigation consists of a number of different steps. The sequence with which these steps are conducted varies, and several steps are usually carried out simultaneously. Not every step is required in each outbreak.
- The investigation is a dynamic process: Hypotheses about the cause of the outbreak are continuously being formulated, tested, revised and discarded during the course of the investigation as additional information is becoming available.
- Using the precautionary principle, control and preventive measures may be implemented at an early stage in the investigation based on preliminary results, in order to stop the outbreak or prevent further spread of the disease. Measures that are more specific are put into action when the source of infection has conclusively been identified (chapter 12).

The investigation process

Outbreak investigation is a multi-disciplinary and inter-sectorial process which employs microbiological, epidemiological and clinical methods in concert with site inspections, interviews and tracing in the food chain, with the aim of formulating hypotheses about the source of infection (chapter 9) and test these hypotheses (chapter 10). In addition, implementation of control and preventive measures will require skills in risk management and risk communication.

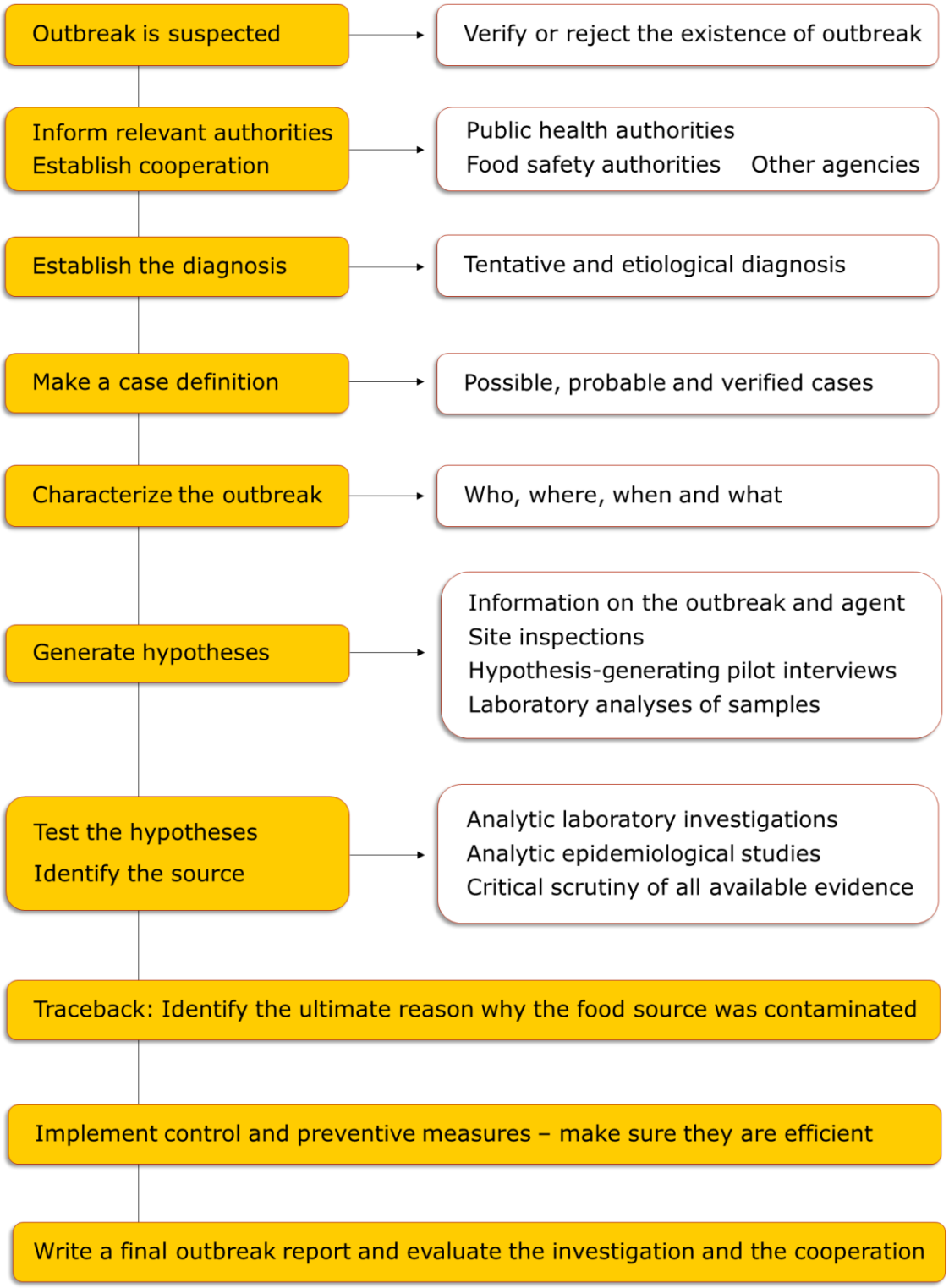
The investigation process is dynamic: Hypotheses about the cause of the outbreak are continuously being formulated, tested, revised and discarded during the course of the investigation as additional information is becoming available.

It may be necessary immediately to implement control and preventive measures at an early stage of the investigation based on preliminary results, using the precautionary principle, in order to stop the outbreak or limit further spread of the disease. Measures that are more specific are set in train when the source of infection has conclusively been identified (chapter 12).

Outbreak investigation consists of a number of different steps (Figure 3.1). However, the investigation does not follow a gradual step-by-step approach. The sequence with which the steps are conducted varies, and several of them are usually carried out at the same time. Furthermore, not every step is required in all outbreaks. Each step is the subject of a separate chapter in these guidelines:

Steps in the outbreak investigation	Chapter
Deciding whether an outbreak is ongoing	4
Alerting responsible authorities and establishing cooperation	5
Making a tentative and final (etiological) diagnosis	6
Establishing a case definition	7
Characterizing the outbreak (who, where, when and what)	8
Formulating hypotheses about the source of infection	9
Testing the hypotheses and identifying the source	10
Traceback: Identifying the ultimate cause of the outbreak	11
Implementing control and preventive measures	12
Writing a final outbreak report and evaluating the investigation	13

FIGURE 3.1 Flow chart for investigation of outbreaks of food- and waterborne diseases



4 Outbreak detection

Deciding whether an outbreak is in progress

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4.1 Definition of an outbreak
4.2 The suspicion that an outbreak is in progress
- Local level
- Regional level
- National level
4.3 Outbreak or pseudo-outbreak?
- Other reasons for increased number of cases
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4.5 Investigation of single (sporadic) cases
4.6 Is the outbreak caused by food, water or contact with animals?
4.7 The primary interview – the first contact with an informant
- Information collection form - questionnaire
- Implementation of measures to prevent that an outbreak will arise

Highlights

- The suspicion that an outbreak is in progress arises if there is an unusual increase in the number of cases of a disease, within a specific area and period of time.
- The suspicion may arise on a local, regional or national level. Most outbreaks are small and are initially detected locally.
- To confirm or disprove the suspicion, the observed increase is compared with the expected number of cases (the endemic level, the normal background incidence of the disease).
- Other possible explanations of the increase should be excluded (pseudo-outbreaks).
- The decision to initiate an outbreak investigation must take into account the available resources, priorities, and the severity and consequences of the outbreak.
- General practitioners, the public health service and the food safety authorities are occasionally contacted by persons who believe they have become ill from foods or water. The information provided by such informants may be sufficient to evoke the presumption that an outbreak is in progress. These guidelines contain an information collection form, which may be used on such occasions.
- Moreover, information obtained from one single person may prompt immediate implementation of precautionary and pro-active measures in order to prevent an outbreak will occur.

4.1 Definition of an outbreak

In these guidelines, an outbreak is defined as:

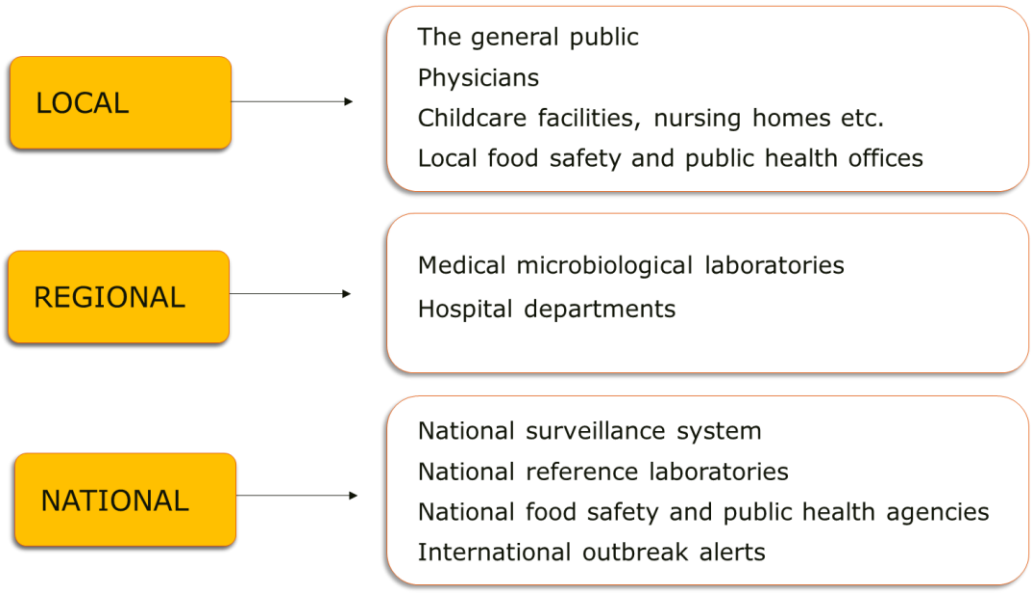
- Two or more cases of the same disease for whom a common source of infection is suspected, or
- A number of cases clearly exceeding the expected incidence (the endemic level, the normal background incidence of the disease) in a specific area and period of time.

4.2 The suspicion that an outbreak is in progress

Apparently sporadic cases of disease may represent an unrecognized outbreak in which several persons are involved (section 4.7). By comparing information from individual patients, it may be possible to discover common characteristics indicating that an outbreak is ongoing. Such common features may be simultaneous occurrence in time or place, common exposure, similar symptoms, or isolation of the same microbial pathogen.

Outbreaks may be detected at a local, regional or national level (Figure 4.1):

FIGURE 4.1 The suspicion that an outbreak is in progress may arise at a local, regional or national level



Local level

Most outbreaks are small and are initially detected at the local level:

- The suspicion that an outbreak is occurring may arise among the general public, for instance when several persons became ill after a party, a restaurant visit etc. where they consumed the same foods.
- In the primary health service after being consulted within a short period by several patients with the same symptoms or the same anamnesis or food history.
- At municipal institutions as childcare facilities, nursing homes, care facilities for the elderly etc.
- By municipal public health officers when notified by doctors, other healthcare professionals, the local food safety authority, or residents in the municipality.
- By local surveillance activities including monitoring of sickness absence.
- Through local newspapers or other mass media, social media or web-based discussion groups.
- At restaurants or other food businesses after receiving customer complaints.
- At the local food safety office when contacted by one or more consumers, doctors or public health officers, restaurants, hotels, food producers, travel agencies etc. (A standardized form for collection of such information is described in section 4.7).

Regional level

Some outbreaks, in which several municipalities are involved, are not detected at a local level because the number of cases in each municipality is too low to evoke local attention. Other outbreaks are not detected locally even though the number of cases should have made it possible. Such outbreaks may, nevertheless, be discovered at the regional level:

- At regional medical microbiological laboratories after receiving an increased number of samples or following detection of a specific microbial agent in an unusually high proportion of the samples. Regional laboratories receive human clinical samples from several municipalities and may therefore be the first place where an outbreak is suspected.
- At hospital departments after admission of patients with foodborne or zoonotic diseases.
- By regional surveillance activities.

National level

Many outbreaks are initially discovered at the national level:

- By a national surveillance system, which monitors continuously the incidence of communicable diseases, by means of notifications from doctors and medical laboratories.
- At reference laboratories in medical microbiology where human clinical isolates of microbial pathogens are being verified and characterized in detail using epidemiological marker analyses, such as serotyping and DNA-profiling (section 10.1). Reference laboratories may detect an

outbreak when discovering an unusual cluster of a particular microbial species, subtype or variant, even though the total number of generic isolates is unchanged.

- At the national public health agency or food safety authority based on notifications from regional or local offices.
- Through alerts and enquiries from other countries or international authorities.

The cases identified by surveillance systems or reference laboratories represent just the tip of the iceberg since many cases are undiagnosed and there may be considerable under-reporting of diagnosed cases. Moreover, the time lag between disease onset and notification of laboratory-confirmed cases is substantial. Consequently, surveillance and reference laboratories are not very effective systems for early detection of outbreaks, and it is likely that small outbreaks may be overlooked at this stage.

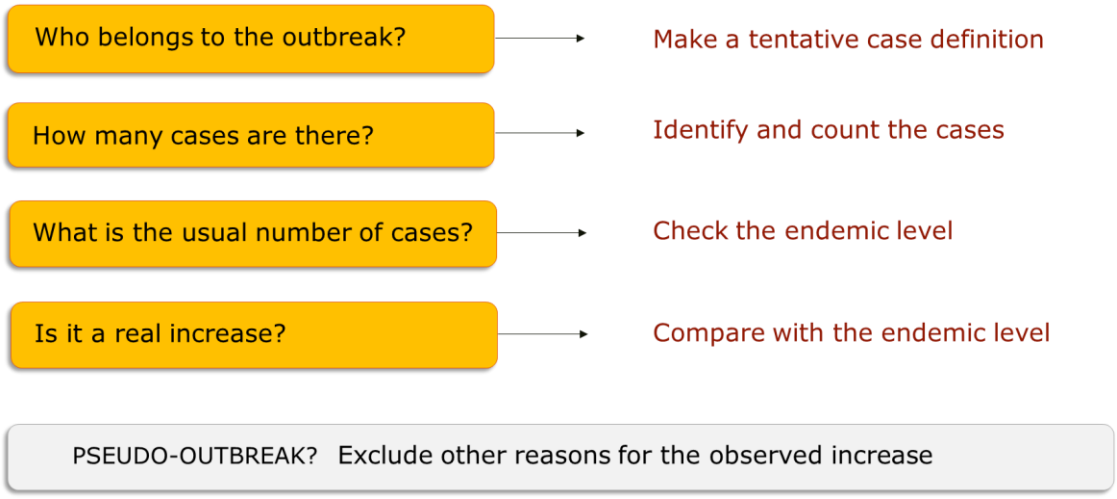
4.3 Outbreak or pseudo-outbreak?

Once an outbreak is suspected, the next step is to ascertain whether the increased number of cases observed clearly exceeds the expected level (i.e. the endemic level, the normal background incidence of the disease) and to determine whether an outbreak does indeed occur. To this avail, the following steps can be outlined (Figure 4.2):

- Make a tentative case definition (chapter 7).
- Identify and count the patients who meet that case definition, if necessary through active case-finding efforts (section 8.5).
- Compare the observed number of cases with the expected number using information from public health authorities about the usual incidence of the disease in the particular population and period concerned.
- If the number of observed cases clearly exceeds what would be expected, the next step is to exclude other reasons for the increase (pseudo-outbreak).

In many cases, however, it is obvious that an outbreak is in progress and there is no need for a formal procedure as that outlined above.

FIGURE 4.2 Steps in the procedure to determine whether an outbreak occurs



Other reasons for increased number of cases

- **The patients have different diagnoses:** Although the symptoms are similar, the etiological diagnoses are different. Hence, there is no real increase.
- **Different variants of the same pathogenic agent:** The microbial isolates recovered from the patients exhibit clearly different phenotypic or genotypic properties, for instance different serotypes of *Salmonella* or distinct DNA-profiles. If so, it is unlikely that there is an outbreak with a common source and, in many cases, the outbreak suspicion can be rejected – unless the same variability is found in the suspected source of infection (see section 10.1).
- **The population has increased:** The number of cases has increased because the population in which the suspected outbreak occurs has increased significantly, for example at a ski resort during the winter vacation, or during a festival of sport event.
- **Seasonal variation:** The observed increase represents a seasonal variation that occurs every year.
- **Random variation:** The increase may be explained by random variations in the incidence. Information on seasonal and random variations may be obtained from surveillance systems.
- **Increased awareness:** Patients seek medical attention more frequently than previously, and the doctors are more inclined to take samples, for example because foodborne diseases have attracted increased publicity in the media.
- **More sensitive laboratory method:** The diagnostic laboratory has implemented a more sensitive analytic method leading to detection of more positive samples.
- **Laboratory error**: The increase is caused by a laboratory error resulting in contamination of initially negative samples with a pathogenic microbe or with DNA from such a microbe.

- **New notification criteria:** The surveillance system has introduced new criteria for notification, which leads to an increased number of recorded cases.
- **Research project:** The increased number of cases detected is due to an ongoing research project that employs more sensitive analytic methods or entails collection of more samples than usual.

Other reasons for increased number of cases:

- The patients have different diagnoses – there is no real increase
- The patients harbor different variants of the same agent
- The population has increased significantly
- Seasonal variation
- Random variation
- Increased awareness among the public or doctors
- More sensitive laboratory analysis has been introduced
- Laboratory error
- New notification criteria have been implemented
- Research project

Example

During a large outbreak of waterborne giardiasis in Bergen, Norway, the local medical laboratory observed a marked increase of campylobacteriosis in the municipality. However, the suspicion that an outbreak of that disease was simultaneously taking place could be disproved after closer inspection:

- Pilot interviews of selected patients did not disclose any common exposures that could explain the increase.
- Isolates of *Campylobacter* obtained from the patients showed a variety of distinctly different DNA-profiles, indicating that the patients did not share a common source of infection (section 10.1).
- It turned out that the number of fecal samples submitted to the laboratory had increased substantially, probably due to greater awareness of diarrheal diseases in general because of the ongoing giardiasis outbreak. Since all samples were examined for bacterial pathogens as well as for parasites, it was concluded that the *Campylobacter* increase was most likely a sampling artifact.

4.4 Should an outbreak investigation be initiated?

When other reasons for the increased number of cases have been excluded (section 4.3) and it has been confirmed that an outbreak is ongoing, the next step is to decide whether an outbreak investigation should be initiated.

Ideally, all outbreaks should be investigated. However, since the resources are limited it is necessary to give priority to some outbreaks. The greatest attention should be directed towards outbreaks that represent a considerable public health threat, and outbreaks in which a significant health threat may arise, unless the outbreak is halted and preventive measures implemented.

Outbreaks that require priority:

- Outbreaks of serious life-threatening diseases (for example botulism, typhoid fever or hemolytic uremic syndrome)
- Outbreaks of severe diseases or diseases with a high propensity to spread
- Outbreaks affecting institutions where the disease may have serious consequences (e.g. childcare facilities, hospitals, nursing homes etc.)
- Outbreaks in which a large number of persons is affected or is at risk of becoming affected
- Outbreaks in which the suspected source of infection is a commercial food product consumed by many people
- Outbreaks associated with a food business or an outlet where food is prepared and served to many persons.

4.5 Investigation of single (sporadic) cases

A sporadic case is a patient with no known association with any recognized outbreak. Sometimes, assessment of such cases may enable prevention of future outbreaks. For instance, if closer investigations reveal food safety violations or other hygienic errors, an outbreak may arise unless such errors are promptly being corrected. Moreover, it may be necessary to exclude the patients from situations where they can transmit the disease and thus preventing the emergence of an outbreak (section 4.7).

Even a single case of disease may deserve investigation if:

- The disease is not endemic (for instance a case of domestically acquired cholera in Norway)
- The endemic level is very low (for example botulism)
- The disease is serious and life-threatening, and it is crucial to find the source of infection in order to prevent further people becoming ill (for instance botulism)
- It is suspected that the patient represents a hitherto undetected outbreak, which may have serious consequences, or
- There are other public health, administrative, legislative, legal, economical or principal reasons.

4.6 Is the outbreak caused by food, water or contact with animals?

The presumption that an outbreak is caused by food, water or contact with animals, and not another sources of infection, is based on clinical and anamnestic information, and laboratory results:

Clinical information

- Acute gastroenteritis in patients without any other known diseases (allergy, intolerance, chronic gastrointestinal conditions etc.) or exposures (e.g. medication, alcohol, stress) that may explain their gastroenteritis.
- Specific symptoms characteristic for certain foodborne or zoonotic disease (for instance botulism and hepatitis A). An overview of symptoms for selected diseases is presented in Appendix 1:
    - Food- and waterborne diseases

Anamnestic information

Information that all, or a majority, of the patients in the outbreak:

- have consumed the same food, beverage or meal, or have drunk water from the same source,
- have visited the same farm, have been in contact with the same animal herd, or have been exposed to the same species of wild animals,
- have eaten high-risk products such as mushrooms, mussels, shellfish, raw, rare or undercooked meat, unpasteurized milk or products thereof, or have drunk water with insufficient hygienic quality,
- have eaten foods with unpleasant taste, smell or color,
- have been in contact with diseased animals, or animals that have died due to illness, including cadavers, or
- have eaten food prepared or served in an establishment where the food safety standard is known to be suboptimal (for instance a certain restaurant).

Laboratory results

- Isolation from patients' samples of a pathogenic microbe that usually is transmitted through food, water or animals.
- Detection of the causative pathogen, microbial toxins, or indicator bacteria (i.e. bacteria indicating poor hygienic quality) in food or water consumed by the patients, or in ingredients or raw materials the finished product contains.
- Isolation of the causative pathogen or indicator bacteria from the environment in which the suspected food has been produced, processed, prepared or served, or from a food-handler.
- Isolation of the causative pathogen from wild or domestic animals or farm environment, with which the patients have been in contact.

4.7 The primary interview – the first contact with an informant

Occasionally, persons who suppose they have become ill from something they have eaten or drunk, contact their general practitioner, the public health service or the food safety authorities. In such cases, it may be convenient to have at hand an information registration form or questionnaire to fill out while talking to the informant, in order to record systematically the details entrusted. The data so collected may be sufficient to raise the suspicion that an outbreak is in progress.

Persons who contact their health care provider, the public health service or food safety authority, are not always aware they are involved in an outbreak. Although they know about other people with similar symptoms, they do not necessarily mention this spontaneously.

To disclose whether an outbreak is ongoing, it is therefore important to ask the informant if others have recently been ill with a similar disease.

Information collection form

These guidelines contain a template information registration form, which may be edited and adapted to local conditions. User instructions for conducting the interview are also provided:

- The primary interview – template questionnaire (Appendix 4)
- The primary interview – user instructions (Appendix 3)

Below is an overview of the kind of questions included in the information registration form:

- Whom am I talking to?
- When did you become ill?
- What kind of symptoms did you have?
- Did you go to a doctor? Was a sample collected?
- Do you know about other persons who were ill with similar symptoms?
- What did you eat and drink prior to the onset of your illness?
- Did you visit a restaurant or did you eat food from another catering establishment?
- Were you in contact with wild or domestic animals or birds?
- Did you drink untreated water?
- What do you believe is the reason for your illness?
- Do you work with production, processing, preparation or serving of food?

- Do you work in a hospital, childcare facility, nursing home or care facility for the elderly? (or in another institution where infections may have serious consequences)
- Did you travel abroad?
- Do you have food allergy, intolerance or chronic gastrointestinal problems? (to exclude other conditions that might explain the patient's symptoms)
- How can I get in touch with you later? (e.g. phone, e-mail)
- Thank you for calling me!

The interviewer should refer to the patient's health care provider for collection of clinical samples, medication, and other medical issues.

All information about individuals, healthy or sick, is strictly confidential and is subject to moral and statutory secrecy. Information enabling identification of persons must always be treated in accordance with the current laws and regulations.

It should be emphasized that the form is intended to serve mainly as a reminder that makes it easier to remember all information it is important to obtain. The informant should be allowed to speak freely without unnecessary interruption. This, however, does not preclude that the interviewer should try to steer the conversation to ensure all relevant data are being collected.

The primary interview does not replace the comprehensive hypothesis-generating pilot interview which is an in-depth interview aiming at identification of common exposure among patients involved in an outbreak that has already been recognized (section 9.3). The primary interview, on the other hand, is intended for collection of information from people who initially cannot be linked to any known outbreak.

Implementation of measures to prevent that an outbreak will arise

Information obtained from one single person may trigger immediate implementation of precautionary and pro-active measures in order to prevent eruption of an outbreak. This is particularly important if the informant have an occupation that entails increased risk of transmitting infections:

- Persons who handle foodstuff, including production, processing, preparation and serving of food (for instance in a restaurant kitchen).
- Employees in hospitals, nursing homes and long-term care facilities for the elderly, as well as children and staff in kindergartens and daycares, where the clients are more susceptible to infection and for whom an infectious disease may have more serious consequences than for others.

Such persons should be excluded from their work until they no longer shed the pathogen (see details in section 12.1). Informants, who present with gastrointestinal symptoms and belong to one of the high-risk groups above, should be encouraged to seek medical attention in order to ascertain whether they are shedding a pathogenic microbe.

5 Outbreak alerts

Alerting responsible authorities and establishing cooperation

Sections
Highlights
5.1 Outbreak alerts
- Statutory alerts to the authorities responsible for investigation
- Notification to other agencies
5.2 Why is it important to submit alerts?
- The purpose of alerting local authorities
- The purpose of alerting national authorities
- The purpose of alerting international authorities
5.3 The outbreak investigation team
5.4 Information to the public through mass media

Highlights

- Once an outbreak has been recognized or suspected, it is important to issue an alert to all authorities responsible for the investigation, as soon as possible, so cooperation can be established to ensure rapid implementation of effective and coordinated action.
- An outbreak alert is a notification, which is submitted immediately in such a manner that the sender can be sure the message has been received.
- Alerts should be forwarded as soon as an outbreak is suspected, to prevent valuable time from being lost.
- If the outbreak is serious, or if immediate contact is required, the alert should be communicated on telephone.
- It is of particular importance to establish routines for rapid exchange of alerts between the public health services and the food safety authorities.
- Information to the general public through mass media must be coordinated to avoid different authorities presenting divergent messages.

5.1 Outbreak alerts

An outbreak alert is a notification that is submitted immediately in such a manner that the sender can be sure the message has been received. Alerts may be communicated by telephone (preferentially via an emergency line operated on 24 h basis), e-mail or a web-based reporting system.

Once an outbreak is recognized or suspected, it is important to alert all authorities responsible for the investigation, as soon as possible, so cooperation can be established to ensure rapid

implementation of effective and coordinated action. In addition, it may be necessary to inform other agencies, even though they are not directly responsible for the investigation.

Alerts should be submitted as soon as an outbreak is suspected, to prevent valuable time from being lost.

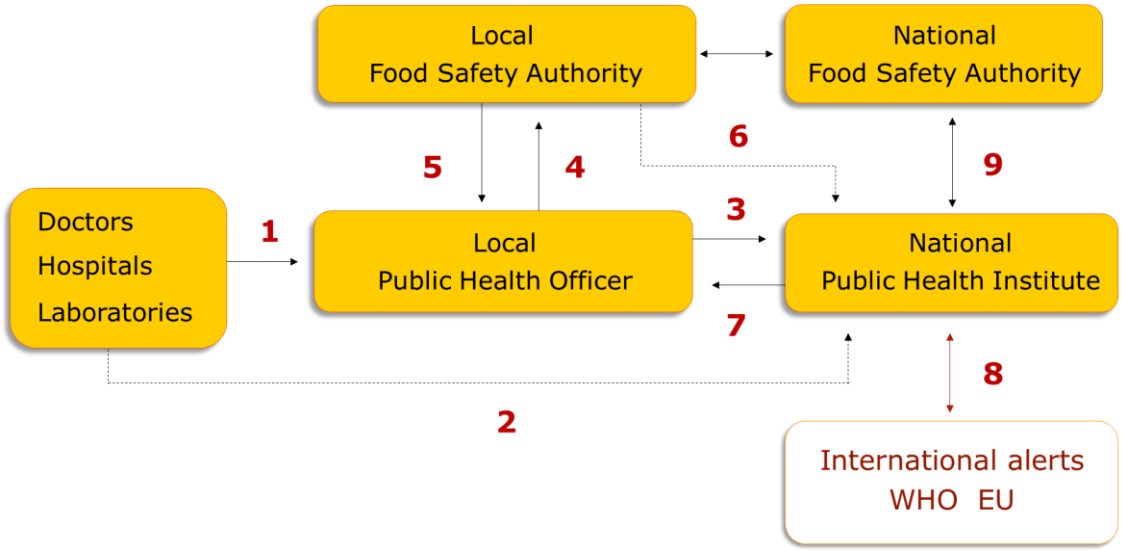
Statutory alerts to the authorities responsible for investigation

The regulatory provisions on statutory outbreak alerts or notifications differ considerably between countries. Regardless of the legislation that applies, it is particularly important to establish compulsory routines for rapid exchange of alerts between the public health services and the food safety authorities, as well as from doctors, hospitals and medical laboratories to the public health authorities.

The following outbreak alert flow (see Figure 5.1) is meant as a suggestion, taking into account that the organization of public health and food safety sectors, and their respective responsibilities, may vary widely between countries. If a regional level is inserted the routines and the corresponding regulations should be adjusted accordingly:

1. General practitioners, hospital departments and medical laboratories should be imposed to notify promptly to the local public health officer in the municipality where the patients live, if they suspect or recognize an outbreak.
2. If the public health officer is not available, and the outbreak requires immediate attention, the national public health authority should be contacted directly.
3. The local public officer alerts the national public health institute or a similar agency.
4. If the outbreak may be caused by foods, drinking water or contact with animals, the public health officer alerts the local food safety authority.
5. Likewise, when the local food safety authority suspects or recognizes an outbreak (e.g. after having been contacted by consumers), the municipal public health officer is alerted.
6. If the public health officer is not available, and the outbreak requires immediate attention, the national public health authority should be contacted directly.
7. In case the outbreak is detected at the national level, the national public health institute alerts the local public health officer, who notifies the local food safety authority as above.
8. The national public health institute exchange information with international agencies to ascertain whether other countries are affected by the outbreak.
9. At the national level, it is important to implement routines for mutual exchange of information between the national public health institute and the national food safety authority.

FIGURE 5.1 Suggested outbreak alert flow



Notification to other agencies

The regulatory provisions on compulsory alerts do not preclude exchange of information with other agencies not responsible for outbreak investigation. Which authorities or agencies that should be informed, in addition to those responsible for outbreak investigation and management, depend on the extent and severity of the outbreak, the kind of disease, and the suspected source of infection. All those who need to know should be included.

The health care service may be encouraged to pay increased attention during an outbreak in order to identify case-patients, if necessary through modification of their diagnostic routines. This may include changes in or reinforcement of laboratory procedures. The main purpose is to assess the extent of the outbreak, monitor its progress, and recruit cases to the investigation (e.g. to pilot interviews or epidemiological studies). However, for some diseases it may also be important to identify patients who need treatment, or who should be excluded from situations where they can spread the disease. Among the agencies that may be approached to help identify case-patients, are:

- General practitioners and emergency centers in the municipalities where the outbreak occurs
- Local public health officers in neighbor municipalities
- Medical microbiological laboratories, including reference laboratories
- Hospital departments

The following agencies may be able to provide additional insight and information facilitating identification of the cause of the outbreak and implementation of control measures:

- The water work and other technical agencies in the municipality concerned
- Veterinary authorities
- National Reference Laboratories for Food and Feed (NRL)

5.2 Why is it important to submit alerts?

The purpose of alerting local authorities

- Not infrequently, it turns out that an outbreak has a greater extent than you first got the impression. When local public health and food safety authorities receive an alert, they are given the opportunity to consider the outbreak in context with other information and incidents in the municipality, so the actual size of the outbreak can be assessed and hypotheses about the cause can be formed.

  Moreover, alerts submitted to the local level may:

- Provide local public health and food safety authorities with an opportunity to:
  - determine whether the occurrence of an outbreak can be confirmed (section 4.3),
  - decide whether an outbreak investigation should be initiated (section 4.4), and
  - coordinate the investigation, provide resources, allocate tasks and establish procedures for reporting progress and results, and if necessary appoint an outbreak investigation team (section 5.3)
- Supply the information local authorities need for their notification to national authorities (section 5.1).

The purpose of alerting national authorities

- In an early phase of an outbreak, it is important that national authorities is provided an opportunity to consider the outbreak in national and international perspective, in order to evaluate whether other municipalities or counties are affected, or are at risk of becoming affected. National authorities can also ascertain whether the outbreak has international extensions by alerting international systems for outbreak notification. Conversely, they may have received information from other countries about contaminated foods that may be relevant to the present outbreak investigation (see also section 8.2).
- National authorities may offer information, advice, guidance and information that are valuable in local investigations, including deployment of a national outbreak investigation team, and give advice on how to communicate information to the public and manage media enquiries (section 5.4).
- Alerts submitted from the local level to national authorities may:
  - contribute to national surveillance of outbreaks and their causes, allowing national authorities to compile information from all outbreaks reported and, based on such data, determine priorities and take decisions on implementation of preventive measures
  - supply information required for alerts to international agencies and other countries, and for mandatory periodic reporting (see below)
  - make it possible to uncover bioterrorism

The purpose of alerting international authorities

As part of the international cooperation, every country has a statutory obligation to submit alerts to international agencies and other countries about outbreaks in which other countries may be affected, or are at risk of becoming affected. National authorities are also imposed to warn of contaminated foods that may have international distribution. Conversely, notifications received from abroad about outbreaks or contaminated foods enable national authorities to assess whether there are cases or outbreaks in their own country, and to implement preventive measures accordingly (e.g. withdraw foods from the market).

5.3 The outbreak investigation team

In many outbreaks, it may be appropriate to appoint an outbreak investigation team in which all responsible authorities are represented, in order to ensure effective and coordinated investigation of the outbreak. Once the team has been established, the team members should be informed about the legal responsibilities imposed on the different authorities (outlined in chapter 2). (This should be settled in advance, before an outbreak occurs, to prevent important time being wasted on discussions.) It is of critical importance that the team takes due account of this, as well as the internal line management in each organization, and allocates tasks and coordinates the investigation accordingly.

The tasks of the outbreak investigation team may include:

- Establish procedures for reporting progress and results, through meetings, by telephone, e-mail etc.
- Discuss implementation of relevant control and preventive measures (chapter 12).
- Decide on collection of clinical and environmental samples and requisition of analyses (sections 6.2, 9.1 and 10.1).
- Take decisions to perform site inspections of food businesses and premises under suspicion (section 9.2).
- Conduct hypothesis-generating pilot interviews and decide who will perform the interviews (section 9.3)
- Design and conduct analytic epidemiological investigations (section 10.2).
- Plan and publish information to the public through the mass media, and ensure that the information provided is coordinated, timely and accurate. Decide what the information should contain, how it should be designed, and who should respond to enquiries from the media and the public (section 5.4). The operative investigators should be shielded from being distracted from their important work by time-consuming media enquiries.
- In local outbreaks, submit an outbreak alert to national authorities and, if needed, request external advice, assistance, guidance and information, including deployment of a national outbreak investigation team (section 5.1 and chapter 2).

- Inform other relevant agencies which need to know and which can provide additional insight or assistance (e.g. the primary health care service, laboratories, hospitals, veterinary authorities, water works and other technical agencies) (section 5.1).
- Write a final outbreak report (chapter 13).

5.4 Information to the public through mass media

Depending on the laws and regulations that apply, both the public health service and the food safety authority may be entitled to, and sometimes obliged to, inform the public about foodborne outbreaks and food-associated health threats. When an outbreak occurs, the authorities must attempt to agree on how the information should be communicated and what messages should be conveyed, to avoid disclosure of divergent information. Routines for coordinated external communication should, preferentially, be delineated and implemented *before* an outbreak erupts, for instance by legal measures or by means of a signed agreement specifying the routines and procedures to be followed.

The contents of the information

Information to the public may contain one or more of the following components (Figure 5.2):

- Information about the outbreak, its progression and how the situation evolves, without unnecessary drama. If the source of infection is unknown, this should be stated.
- Information on what is being done to identify the cause, what is planned, what measures are implemented, and which authorities are responsible for different parts of the investigation. It is important to convey information that something is being done to bring the situation under control.
- One should promote understanding that the investigation may take time, and that many outbreak are never solved. The public should also be informed that preliminary identification of presumed sources of infection, incriminated early in the investigation, might be subject to reassessment as the work advances.
- Information about the disease that caused the outbreak, including symptoms, duration, severity and possible sequelae. Medical terminology, jargon and abbreviations should be avoided.
- Advices to the public on precaution they can take to prevent becoming infected (e.g. boil the water or refrain from consumption of certain foods). It may be helpful to add photos of the incriminated products.
- Information explaining what people can do if they become sick and how they should behave to prevent transmitting the infection to other persons.
- Information on how the public and journalists can obtain answers to questions. (The investigators should be shielded from enquiries).
- Encourage those who have become ill to take contact with the authorities (e.g. for sampling, treatment or interview) (section 8.5).

- Explanation of why previous information and advices have to be changed in the light of recent evidence.
- General information on foodborne diseases or zoonoses and how such infections can be prevented.
- Updated information on the situation, and a final report summarizing data about the outbreak and the investigation, with due credit to everyone who has contributed (chapter 13).

The information should be concise and focused

It is not recommended to include all the above information in one single announcement. The information should be as brief and concise as possible, with focus on the main message. Decide what the purpose is: Giving advice on how people can prevent becoming infected? Recruiting interviewees? Reassuring the public that something is being done?

The information should be coordinated and identical

It is important that all information about the outbreak and the disease is coordinated and identical, to prevent different authorities presenting divergent messages. Messages on websites should include links to other authorities' sites. It is desirable that both the public health and food safety authorities and other partners involved, signing press releases, other information and the final report.

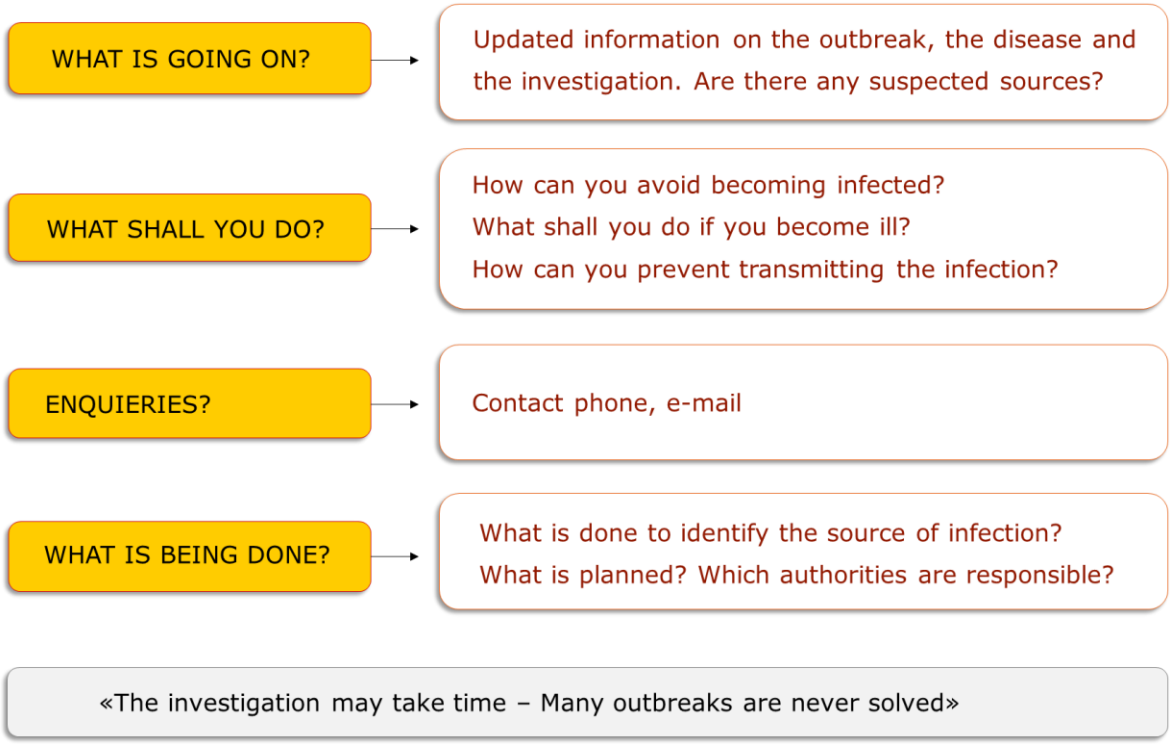
The information should not contain sensitive facts

The information should not enable identification of individuals. Confidential information about operating conditions or production routines in food businesses must not be revealed.

The information may promote health education

Disease outbreaks often obtain considerable publicity, thus providing an excellent opportunity to promote impactful health education. It is likely that the public is susceptible to such information when an outbreak occurs. The messages being conveyed need not only be directed at the specific outbreak, but should, if possible, also aim to prevent disease in the future, through information on general food safety principles pertaining to preparation and storage of foods, and how people can prevent transmission of foodborne diseases.

FIGURE 5.2 Information to the public through mass media



6 The diagnosis

Establishing a tentative and etiological diagnosis

Sections
Highlights
6.1 The etiological diagnosis
- The etiology provides information about the incubation period
- The etiology provides information about possible sources of infection
- Microbial isolates from patients and suspected sources of infection can be compared
- The etiology enables formulation of a specific case definition
- The etiological diagnosis may guide the implementation of specific control measures
6.2 Collection of samples from selected patients
- The sample
- Laboratories
- Analysis of samples
6.3 Tentative diagnosis
- Bacterial intoxications
- Localized enteric infections
- Systemic infections
- Special intoxications

Highlights

- The etiological diagnosis specifies which pathogen caused the disease. The etiological diagnosis is not always required for treatment of the patients, but in foodborne outbreaks the diagnosis provides an important piece of evidence that may essential in the investigation.
- The etiology provides information about the incubation period for the outbreak disease, thus enabling delineation of an approximate number of days, weeks or hours prior to illness onset, within which the infection most likely took place. Hence, the subsequent investigation can focus on exposures that occurred within exactly that period.
- Knowledge of the etiology contributes to generation of hypotheses about the source of infection and the underlying causal factors, since most etiological agents are associated with specific sources, reservoirs, and food handling errors.
- Such knowledge may also guide the implementation of specific control measures appropriate for the agent involved.
- Microbial pathogens isolated from the patients may be compared with any isolates obtained from putative sources of infection, in order to support, substantiate or refute a causal connection.
- To establish the diagnosis it is necessary to take samples of patients who are representative of the outbreak.

- Pending establishment of the etiological diagnosis, a preliminary diagnosis should be formulated using available clinical information.

6.1 The etiological diagnosis

For a majority of foodborne infection, establishment of the etiological diagnosis requires detection of a causative pathogen or specific antibodies in samples from patients. The clinical manifestations of the diseases are rarely so distinct that the diagnosis can be determined based on symptoms alone.

The etiological diagnosis is not always required for treatment of the patients, but in foodborne outbreaks the diagnosis provides an important piece of evidence that may be essential for the investigation:

- **The etiology provides information about the incubation period for the disease**:

  Information about the incubation period for the outbreak disease makes it possible to delineate an approximate number of days, weeks or hours prior to illness onset, within which the infection most likely occurred (see Appendix 1, Food- and waterborne diseases). Hence, the subsequent investigation can focus on the exposures, which took place within exactly that period. However, for almost all localized enteric infections caused by bacteria or viruses, the incubation periods are overlapping. Nevertheless, certain foodborne infections may have prolonged incubation (e.g. hepatitis A, typhoid fever and listeriosis), and foodborne microbial intoxications are characterized by their short incubation periods.

- **The etiology provides information about possible sources of infection:**

  Most foodborne pathogens are associated with specific sources of infections, risk factors, reservoirs, and food safety breaches. Knowledge of the etiology may therefore help generating hypotheses about the most likely sources of infection as well as the food handling errors involved.

  An overview of reservoirs, sources of infection and risk factors for selected agents is presented in Appendix 2:

  - Reservoirs and risk factor

- **Microbial isolates from patients and suspected sources of infection can be compared:**

  For many foodborne diseases, establishment of the etiological diagnosis requires isolation of the causative pathogen from patients involved in the outbreak. Hence, the microbial isolates so obtained may be compared with any pathogens of the same kind that are found in suspected food sources. Such comparison entails description of phenotypic and/or genotypic properties of the microbes (i.e. epidemiological marker analyses). In this manner, a causal relationship between the disease and exposure to the suspected source, may be supported, substantiated or refuted (details about epidemiological markers are presented in section 10.1).

- **The etiology enables formulation of a specific case definition:**

  Using an etiological (laboratory-based) case definition, the investigation can be focused on exactly those patients involved in the outbreak; information provided by these patients is the key to identify the cause. The probability of including illegal cases can be minimized by excluding patients who do not meet the specific case-definition; information from such persons would be misleading (chapter 7).

  In an outbreak population where the endemic background level of the gastrointestinal infections is considerable, it may be necessary to include only laboratory-confirmed cases in the investigation, to avoid inclusion of cases with an irrelevant etiological diagnosis. The case definition may be narrowed further by specifying the DNA profile or other characteristics that facilitate distinction between the outbreak strain and endemic strains of the microbe (see the detailed discussion in chapter 7).

- **The etiological diagnosis may guide the implementation of specific control measures:**

  Pathogenic microbes vary considerably in their ability to survive and grow in foods, water, production premises, and in the kitchen environment. Moreover, their potential for survival and multiplication at different storage and preparation conditions, as well as their susceptibility to disinfectants and growth inhibitory additives (including starter cultures) differ substantially. Therefore, the kind of measures implemented to prevent further spread of infection, depends on which microbe is involved. The procedures for exclusion of persons from work, childcare facilities, nursing homes or other situations where they can transmit the infection, also varies with the pathogen (chapter 12).

6.2 Collection of samples from selected patients

The clinical manifestations of foodborne and zoonotic diseases are rarely so specific that the diagnosis can be determined solely on this basis, although the nature, sequence and duration of the symptoms may make it possible to form hypothesis about the etiology. In order to establish the etiological diagnosis, it is necessary to collect samples from selected patients who are representative of the outbreak regarding disease onset, clinical manifestations and demographic parameters.

The sample

The kind of sample material required depends on which agent is suspected. For the vast majority of food- and waterborne diseases examination of stool specimens is required. Blood culture samples are relevant if the infection is systemic. Blood samples are also required when botulism is suspected, or for detection of antibodies against certain pathogens (e.g. hepatitis A virus, *Toxoplasma*).

Laboratories

Analysis of human clinical samples is performed at the local or regional medical microbiological laboratory. The laboratory may provide information and advice regarding the kind of sample material needed, and how the sample should be collected, stored and submitted, including the appropriate transport medium.

Analysis of samples

The number and type of agents examined varies between countries and between individual laboratories within a country. In some laboratories, stool samples from diarrheic patients are routinely analyzed for a series of enteric pathogens (e.g. *Salmonella*, *Campylobacter*, *Shigella*, *Yersinia* and *Vibrio*). Other agents, like *E. coli*, viruses and parasites, are not being analyzed unless requested in the requisition following the sample to the laboratory. Detection of such agents may require specialized and technically complicated methods not available at the local laboratory, and it may be necessary to submit the sample to a reference laboratory that is proficient in the analyses concerned, including DNA-based methods. Moreover, samples to be tested for viruses or parasites will require other transport media and conditions than those intended for analyses of bacteria.

In foodborne outbreaks caused by microbial intoxications, detection of the microbes or their toxins in stool samples is not an easy matter; the findings may be difficult to interpret and, hence, the results may be inconclusive. Therefore, cultivation of stool samples for the recovery of spore-forming bacteria (*Bacillus cereus* and *Clostridium perfringens*) or *Staphylococcus aureus* is only exceptionally attempted. Rather, the diagnosis can be assumed by detection of the bacteria, their spores or toxins in foods the patients have consumed. If such a diagnosis is suspected, it may nevertheless be appropriate to take samples from the patients to exclude other etiological agents.

6.3 Tentative diagnosis

Laboratory analyses of clinical samples may take several days. Verification of the diagnosis and detailed characterization of the microbial isolates at a reference laboratory may require additional time. Pending establishment of the etiological diagnosis, a preliminary diagnosis should be formulated using clinical information to prevent the outbreak investigation from being delayed.

An overview of symptoms, infective dose, duration and incubation period for selected foodborne and zoonotic diseases is presented in Appendix 1:

- Food- and waterborne diseases

Such a tentative diagnosis may be supported by anamnestic information, for instance consumption of a particular type of food, the use of a special cooking method, or contact with an animal species, known to be associated with the agent concerned. Reservoirs, risk factors and sources of infection for selected agents are described in Appendix 2:

- Reservoirs and risk factor

At this stage, one can at best distinguish between the following disease groups (group numbers in parentheses refer to the overview of Food- and waterborne diseases in Appendix 1):

- **Bacterial intoxications** (Group 1)

  Diseases with a short incubation period (≤ 8 hours) and short duration (2 days or less). Typically characterized by vomiting as the initially dominating symptom, rarely with fever. Since the incubation period is short, all patients in a point-source outbreak (section 8.3) will usually become ill within few hours. Such an illness onset pattern is, therefore, indicative of this kind of disease.

Agents: *Staphylococcus aureus*, *Bacillus cereus* (the emetic type). Botulism differs from other intoxications by its characteristic neurological manifestations and longer incubation period (≥ 12 hours).

- **Localized enteric infections** (Groups 2-4)

  Diseases with moderate or long incubation (several days) and quite long duration (1-2 weeks). Usually characterized by diarrhea as the prominent symptom, frequently with fever.

  Examples of agents: *Salmonella*, *Campylobacter* and *Yersinia enterocolitica*. Infections due to *Bacillus cereus* (the diarrheic type) and *Clostridium perfringens* are characterized by shorter durations (≤ 48 hours, exceptionally longer) and shorter incubation (6-24 hours) than the other infections. (The two last-mentioned agents produce enterotoxins during multiplication in the intestinal lumen, without colonizing the epithelium).

  Viral gastroenteritis: Norovirus is the viral agent most frequently transmitted through foods and water. The incubation period is usually 6-48 hours and the duration of the disease range from 24 to 72 hours. In addition to diarrhea, vomiting is often present, particularly among children. The virus is readily transmitted to other persons, so secondary cases are common.

- **Systemic infections** (Group 5)

  Severe diseases usually characterized by significantly impaired general condition, cerebral impact and high fever.

  Agents: *Salmonella* Typhi, *Salmonella* Paratyphi and *Listeria monocytogenes*. Hepatitis A differs by its hepatological manifestations (icterus).

- **Special intoxications** (Group 8)

  The suspicion arises if the patients report the consumption of high-risk foods like mushrooms, shellfish or scombroid fishes (mackerel, tuna etc., which may cause histamine intoxication).

The above attempt to place foodborne diseases in distinct categories is no easy task: Note that classical bacterial intoxications and infections caused by norovirus, *Clostridium perfringens*, and the diarrheic variants of *Bacillus cereus*, may have overlapping incubation periods and disease durations.

7 Making a case definition

Sections
Highlights
7.1 The case definition has two components
7.2 What is the purpose of the case definition?
7.3 Temporary case definitions
7.4 The case definition is of significant importance for the investigation

Highlights

- The case definition is used to determine which patients belong to the outbreak, thus enabling the investigations to be focused on exactly those persons involved in the outbreak.
- The case definition has two components: Clinical and diagnostic criteria, and limitation with respect to the variables of time, place and person.
- At an early stage of the investigation, it may be necessary to use a temporary case definition, based on possible or probable cases, pending identification of more verified cases.
- The case definition selected is of significant importance for the investigation of an outbreak.

7.1 The case definition has two components

- **Clinical and diagnostic criteria:**

  Has the diagnosis been established? Which infectious agent caused the disease? Are there any characteristics that distinguish this agent from endemic strains, such as a special DNA-profile or serotype? The procedure for making a diagnosis is described in chapter 6.

  The case definition is, however, not the same as the diagnosis (Figure 7.1), but also includes a number of limitations:

- **Limitations with respect to the variables of time, place and person:**

  Time - when did the patients become ill? Place – where does the outbreak occur (e.g. geographic area)? Person – who is affected (e.g. the general population or a particular sub-population, for instance attendees or participants at a meeting, party, or guest at a restaurant etc.)?

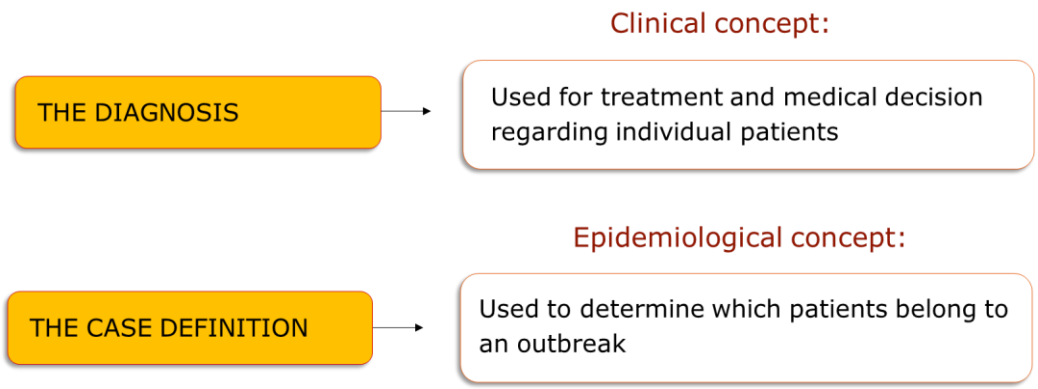
  Characterization of the outbreak by time, place and person is described in chapter 8.

Examples of case definitions

- Guests who attended the wedding dinner for Jenny and John on 15 May 2017, and who became ill with diarrhea during the week following the party.

- Inhabitants in Belgium having bacteriologically verified *Salmonella* Typhimurium infection, who became ill during August through October 2013, and where analysis of DNA from the bacterial isolates showed a specified profile.

FIGURE 7.1 The case definition is not the same as the diagnosis



7.2 What is the purpose of the case definition?

- The case definition makes it possible to focus the investigation on exactly those patients involved in the outbreak. Information provided by these patients is the key to identify the cause.
- Patients not belonging to the outbreak can be excluded. Information from such patients would be irrelevant and misleading.
- The size and geographic distribution of the outbreak can be determined, and its progression can be monitored.
- The population where the outbreak occurs (the outbreak population – the population at risk) may be delimited (section 8.2). It is within that population the cause must be sought, and it is there control measure should be implemented.

7.3 Temporary case definitions

At an early stage of the investigation, it may be necessary to use a temporary case definition, pending the identification of more verified cases, to prevent the investigation from being delayed. Such a temporary case definition is based on possible or probable cases. The aim is to include as many case-patients as possible before they forget important details and valuable information is lost. Later, when a sufficient number of verified cases have been identified, the investigation can be restricted to incorporate such patients only.

Example

On 15 May 2014, an outbreak of acute diarrheal illness, apparently limited to residents of one particular municipality, was detected. At this initial stage, only a few laboratory-confirmed cases had been identified, all of which were caused by *Salmonella* Typhimurium with an uncommon DNA-profile. Many of the ill persons had not visited a doctor, and the doctors had rarely taken samples for bacteriological examination.

- **Possible cases:**

  A possible case was defined as a person in the outbreak population (i.e. residents in the municipality) who developed diarrhea, lasting at least two days, during the outbreak period (a specified number of weeks before and after May 15). This case definition is highly sensitive but not very specific; it includes almost all cases of *Salmonella* Typhimurium infection, but also a number of patients with other etiological diagnoses who do not belonging to the outbreak (false positives).

- **Probable cases:**

  A probable case was defined as a person in the outbreak population who were diagnosed with laboratory-confirmed *Salmonella* Typhimurium infection during the specified outbreak period. This case definition is more specific than above, but there are still a few false positives consisting of any endemic cases not belonging to the outbreak. However, such a definition is not particularly sensitive since a considerable number of patients with *S.* Typhimurium infection have not been diagnosed.

- **Verified cases:**

  A verified case was defined as a person in the outbreak population from whom *S.* Typhimurium with the unusual DNA profile was isolated. This is a highly specific case definition. There are no false positives except from any endemic cases caused by bacteria with the same DNA profile as the outbreak strain. As above, such a definition is not particularly sensitive since a number of patients with *S.* Typhimurium infection have not been diagnosed.

In a population where the endemic background level of *S.* Typhimurium infection is considerable, it is necessary to narrow the case definition by specifying the DNA profile or other characteristics that distinguish the outbreak strain from endemic strains of the bacterium, as was done for the verified cases above. The purpose is to exclude patients not belonging to the outbreak from whom information will be misleading.

Even in a population where the endemic level is low, further characterization of the outbreak strain is required to allow comparison with similar isolates received from patients in other municipalities or from abroad. In this way, it can be ascertained whether the outbreak has a wider occurrence than you first got the impression. Most importantly, the causative agent may be compared with any microbes recovered from suspected foods, animals, water or the environment, and thereby contribute to identification of the source of infection (section 10.1).

7.4 The case definition is of significant importance for the investigation

In many outbreaks, the investigation entails extensive pilot interviews of the case-patients to uncover common exposures and thus formulate hypotheses about the source of infection (section 9.2). Subsequently, the hypotheses may be tested by analytic epidemiological investigations, which require interviews with case-patients and control persons from the outbreak population (section 10.2). The case definition employed is therefore of essential importance for the validity of the results, both from pilot interviews and epidemiological studies.

If only verified cases are included, the validity of the investigation will be optimal. However, since this approach allows enrollment of quite few patients, the statistical power of the analyses may be insufficient to identify significant associations between the illness and exposure to potential sources of infection.

On the other hand, if possible or probable cases are included in the case definition, the validity will be reduced, but since many patients are enrolled, the statistical power is increased. It is important to realize, however, that possible and probable cases may encompass patients who do not belong to the outbreak. Information from such patients is irrelevant and misleading, with the possible consequence that the true source of infection is overlooked or, at worst, a wrong source is identified.

Nevertheless, at an early stage in the investigation, it is sometimes justified to depart from the optimal requirements, since the number of verified cases is limited; it is important to conduct interviews as soon as possible before the patients forget important details. Later, when a sufficient number of verified cases have been identified, the analysis of the dataset may be repeated including the confirmed cases, only.

Bottom line in epidemiology: Validity is more important than statistical power.

8 Characterizing the outbreak

Who, what, where and when?

Sections
Highlights
8.1 Who, what, where and when
- Line listing – registration of patients in a database
- Calculation of incidence rates
8.2 Identify the outbreak population – the population at risk
- The outbreak may be greater than your first impression
- It is important to submit an alert to determine the size of the outbreak
8.3 The epidemic curve
- Patients with atypical illness onset
8.4 Delineate the time of infection – in point-source outbreaks
- The diagnosis is known
- The diagnosis has not been established
8.5 Active case finding
- The diagnosed cases are just the tip of the iceberg
- The purpose of active case finding
- Methods for active case finding
8.6 Secondary cases
- Exclusion of secondary cases

Highlights

- An essential and continuous task during the investigation of an outbreak is to describe what has happened so far, when the outbreak began, how many have become ill, how the outbreak evolves, where it occurs, and who are affected (i.e. descriptive epidemiology). All other steps in the investigation depend on the results of this description.
- At an early stage, it is critical to identify the population where the outbreak occurs (the outbreak population – the population at risk): It is within that population the cause must be sought, and it is there control measures should be implemented.
- The outbreak is characterized by combining the epidemiological standard parameters of time, place and person, including the patients' illness onset, their number, age, gender, geographic distribution, occupation and other demographic parameters.
- The distribution of the patients on a timescale and the progression of the outbreak may be visualized by a histogram, the epidemic curve.
- The information provided by characterization of the outbreak may contribute to formulation of hypotheses about the source of infection.

- During the investigation, it may be necessary to make efforts to identify patients who have not yet been detected (active case finding).
- All information about persons, whether they are ill or healthy, is strictly confidential and subject to statutory and ethical secrecy.

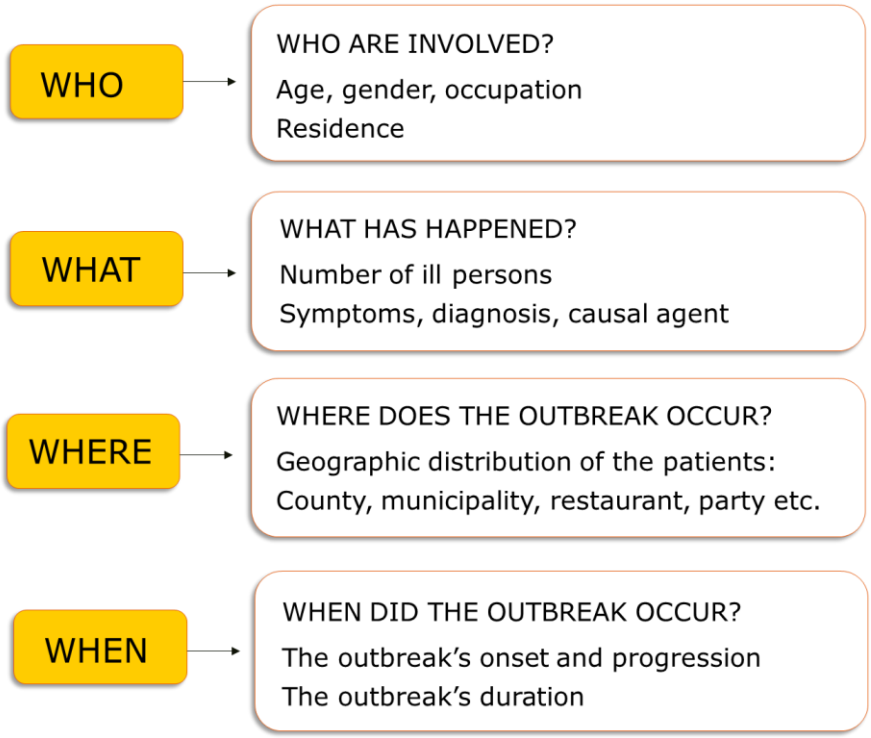
8.1 Who, what, where and when

An essential and continuous task during the investigation of an outbreak is to describe what has happened so far, when the outbreak began, how many have become ill, how the outbreak evolves, where it occurs, and who are affected (i.e. descriptive epidemiology) (Figure 8.1). All other steps in the investigation depend on the results of this description. Before the outbreak characterization can begin, it is a prerequisite that the occurrence of an outbreak has been confirmed (chapter 4), and a case definition has been established, describing which patients belong to the outbreak (chapter 7).

The outbreak is characterized by combining the epidemiological standard parameters of time, place and person, including the patients' illness onset, their number, age, gender, geographical distribution and occupation. The purposes are:

- Delineate the population where the outbreak occurs (i.e. the outbreak population, section 8.2)
- Identify the persons who are at risk of becoming infected
- Monitor the size of the outbreak, the geographical distribution of the patients, and the outbreak's progression
- Contribute to further elaboration or revision of the case definition (chapter 7)
- Formulate hypotheses about the source of infection based on the information achieved through the outbreak characterization

FIGURE 8.1 Characterization of the outbreak: Who, what, where and when



Line listing – registration of patients in a database

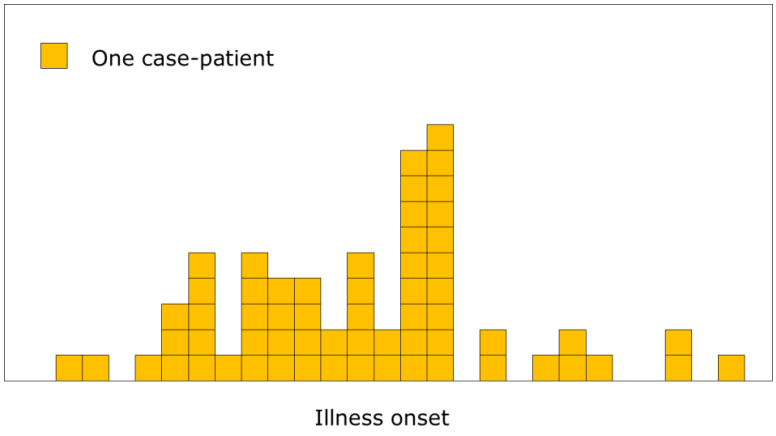
To facilitate formulation of hypotheses about the cause of the outbreak, the patients should successively be recorded in a database or a table where each row contains information about one single patient, in the order the patients are being identified. The columns contain personal and demographic data, symptoms and diagnosis, as well as information about exposures and presumed sources of infection (if applicable). This is called a line listing.

The database should contain all criteria that determine the case definition, to enable differentiation between possible, probable or verified cases, including whether the diagnosis is laboratory-confirmed (section 7.3). It may be convenient to create a separate column that specifies the category to which each patient belongs. Thus, the database can quickly be updated as soon as a possible or probably case has been verified.

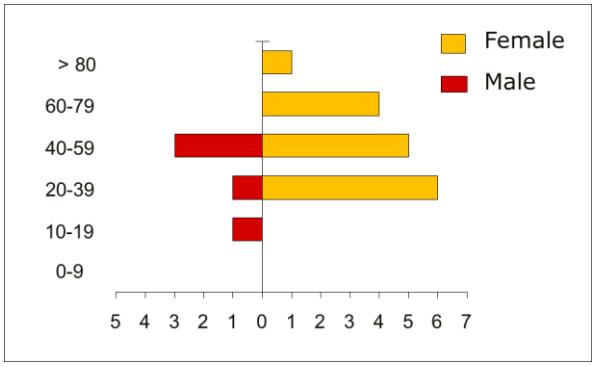
Such a database provides an easily accessible overview of the outbreak and its progression. It may be used to compile the data consecutively in the form of tables, diagrams or maps (Figure 8.2). The purpose is to disclose any features that are common to the patients, and assess whether there is an accumulation of patients in certain age groups, gender, occupations, other demographic categories, geographic areas or time periods. The distribution of the patients on a timescale, and the outbreak's progression, can be visualized by an epidemic curve as outlined in section 8.3. Geographical distribution may be displayed by plotting patients on a map.

FIGURE 8.2 Characterization of outbreaks by the variables of time, place and person

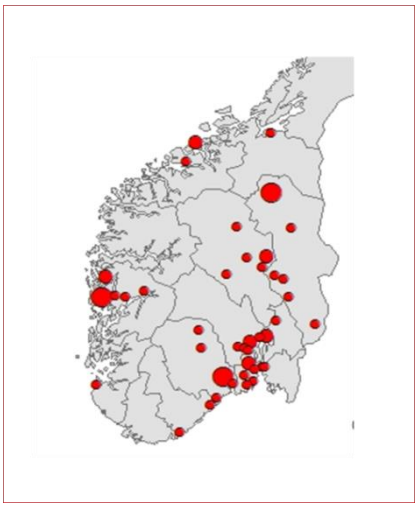
TIME: The epidemic curve



PERSON: Age and gender distribution



PLACE: Geographical distribution



Calculation of incidence rates

To compare the occurrence of disease within different sub-populations or areas, it may be necessary to calculate incidence rates. Not infrequently, an apparent accumulation of patients within a particular area, age group or gender is being detected. This, however, may be due to the fact there are actually more people in that group or area than elsewhere. Hence, direct comparison of crude numbers, instead of rates, is sometimes misleading.

8.2 Identify the outbreak population

The outbreak population – the population at risk

The outbreak population is the group of people within which the outbreak occurs, and to which the case-patients belong.

The outbreak population consists not only of the patients affected but also of all other persons in the same population who are at risk of becoming exposed to the source of infection, or already may have been exposed (the population at risk).

Description of the outbreak population is one of the components included in the case definition, in addition to clinical and diagnostic criteria (chapter 7).

It is important to identify the outbreak population at an early stage in the investigation, for the following reasons:

- *It is within this population the cause of the outbreak must be sought.* What is special for this group? Have they eaten or done something that distinguishes them from other people who do not belong to this population? For example, do they receive drinking water from the same supply or have they attended the same party?
- *It is within this population control measures should be implemented* to stop the outbreak or prevent further spread of the disease, and to protect vulnerable risk groups. For instance, this population may be advised to boil the water or to avoid certain foodstuffs under suspicion.
- *It is from this population interviewees, both case-patients and control persons, must be recruited* for participation in analytic epidemiological investigations (section 10.2).

The outbreak may be greater than your first impression

An apparent accumulation of patients with diarrheal disease among the guests at a particular restaurant may later turn out to be a part of a larger outbreak in which the whole municipality, several counties or even other countries are affected. It is therefore important to ascertain whether there are patients who meet the case definition in the surrounding populations. Local or national

public health authorities may provide such information based on data from private practitioners, hospitals, sick leave statistics, surveillance systems and medical microbiological reference laboratories. An active case-finding procedure may also be undertaken (section 8.5).

It is important to submit an alert to determine the size of the outbreak

In an early phase of an outbreak, it is important to submit an alert to national authorities, thus enabling assessment of the outbreak in national and international perspective. National authorities can scrutinize their records to decide whether other municipalities are affected or are at risk of becoming affected, and they can ascertain whether the outbreak has international extensions (chapter 5). The food safety authorities may have received notifications about contaminated foods, which can be relevant for the ongoing outbreak investigation.

8.3 The epidemic curve

The distribution of the patients on a timescale, and the progression of the outbreak, may be visualized by an epidemic curve. The epidemic curve is a histogram in which each case-patient is placed on a timescale (the X-axis) by means of the time or date when their illness started.

The units on the axis depend on the incubation period of the disease and the duration of the outbreak, and are chosen to give the best presentation of the outbreak and its progression. For food- and waterborne infections, days or weeks are usually employed as the unit, whereas microbial intoxications are best illustrated when hours are indicated on the axis. As a rule of thumb, it is often appropriate to use 1/3 – 1/4 of the incubation period.

In order to illustrate the endemic background level of the disease, the X-axis may be extended to include periods before and after the outbreak.

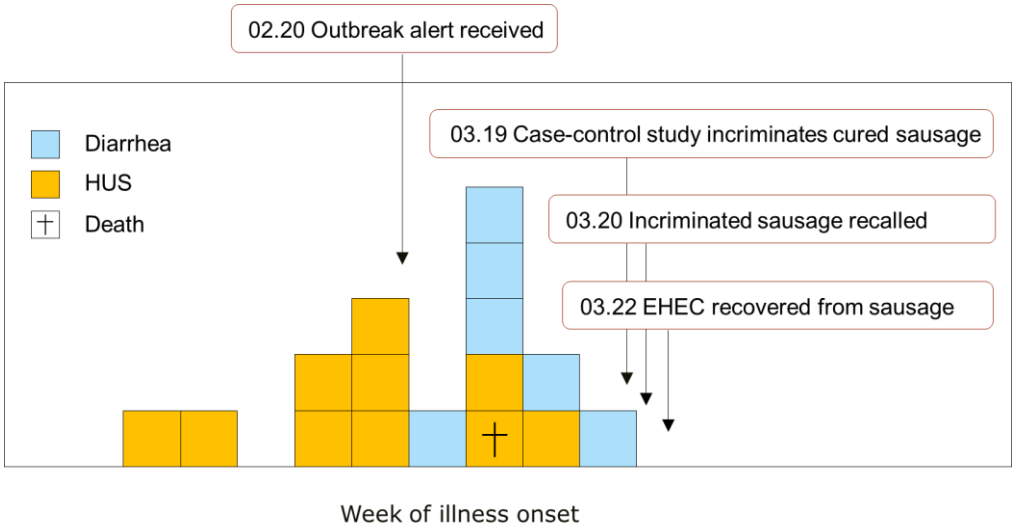
Results obtained during the investigation, any measures implemented, and other important events may be indicated on the X-axis; for instance, the dates when suspected foods were served at a restaurant, the period when foods were on sale, or the date products were recalled from the market (Figure 8.3). This makes it easier to get an overview, formulate hypotheses about the cause, and evaluate the impact of control measures.

The epidemic curve makes it possible to:

- Determine the onset, progression and duration of the outbreak
- Visualize the extent and impact of the outbreak
- Evaluate the effect of control measures
- Decide when the outbreak is finished
- Delineate the time interval when infection most likely was transmitted (section 8.4)
- Formulate hypotheses about the source of infection and the causative pathogen

FIGURE 8.3 Epidemic curve from an outbreak of EHEC infection

(Adapted from Schimmer et al. BMC Infect Dis 2008; 8: 41).



The shape of the epidemic curve may indicate whether the outbreak is caused by a point source, continuous source or intermittent source (Figure 8.4):

- *Point source:*

  In a point-source outbreak, the source of infection is available for consumption in only a limited time interval, for instance during one single meal or when a food product is sold and consumed in a short period. Hence, new case-patients will appear within a few days after the infection took place (in infectious diseases) or a few hours (in bacterial intoxications).

- *Continuous source:*

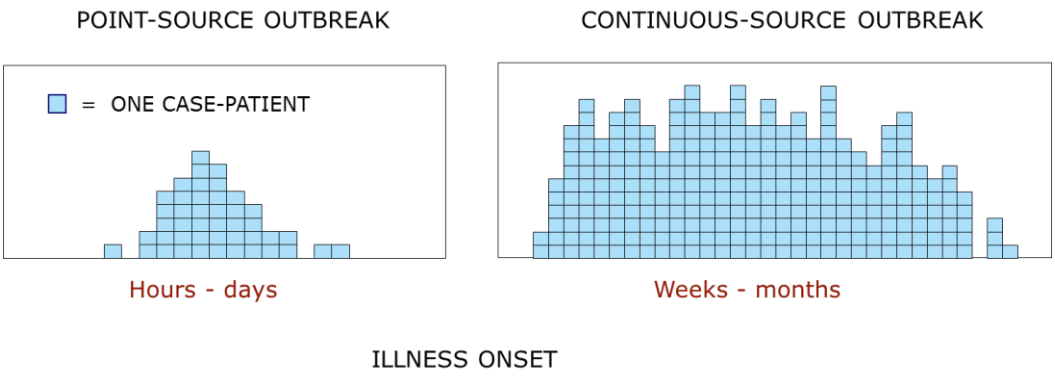
  In a continuous-source outbreak, the source of infection is available for a prolonged period, for instance when a contaminated food is sold and consumed over days or weeks. In such outbreaks, new case-patients are being identified in several days, weeks or even months, until the source is eliminated or the chain of infection has been broken.

- *Intermittent source:*

  In intermittent-source outbreaks, the source of infection is not accessible continuously but at separate periods or points in time. In such outbreaks, the epidemic curve will exhibit two or more peaks corresponding to the periods when the source was available for consumption. This may occur if a contaminated food product is sold or served intermittently.

The presence of secondary cases may obscure the interpretation of the epidemic curve, because such cases may appear after the suspected source of infection has been eliminated, thus giving the false impression that a wrong source has been identified (section 8.6).

FIGURE 8.4 Schematic epidemic curves showing point-source and continuous-source outbreaks



Patients with atypical illness onset

Occasionally, some case-patients report an illness onset that is considerably earlier or later than the other cases. The epidemic curve is particularly useful for detection of such cases. There are several possible explanation for an aberrant illness onset:

- The patients concerned have been exposed earlier or later than the other cases. Such patients may provide valuable clues for the investigation (section 9.2).
- Their incubation period have been unusually short or long.
- They did not remember when they became ill and reported a wrong illness onset date.
- The data have been recorded incorrectly.
- The patients represent the endemic background level of the disease and do not belong to the outbreak.
- The patients are not eligible cases. They have a different disease with similar symptoms.
- In case of late illness onset: They may be secondary cases who have acquired their infection from other patients, without having been exposed to the causal source (section 8.6).

8.4 Delineate the time of infection – in point-source outbreaks

In point-source outbreaks (section 8.3), the epidemic curve can be used to delineate the time interval within which the infection most likely took place. The procedure varies depending on whether the diagnosis, and hence the incubation period, is known or may be assumed.

The diagnosis is known or may be assumed

The outbreak is not finished

One approach that has proved suitable in outbreaks not yet finished is outlined in Figure 8.5. Starting with the median value for patients' illness onset, an interval is delineated backwards in time

using the maximum and minimum values for the incubation period (See Appendix 1, Food- and waterborne diseases). The time when infection occurred will often lie within this interval.

The outbreak is finished

If the outbreak has ended, the following approach may be employed (Figure 8.6): Start with the first patient and go backwards a number of days or hours corresponding to the minimum value for the incubation period. Do the same for the maximum value, starting with the last patient.

The diagnosis has not been established

Calculate the median value for the patients' illness onset. Start at this point and go backwards a number of days or hours corresponding to the interval between the first and last patient.

FIGURE 8.5 Delineation of the time of infection in an ongoing point-source outbreak

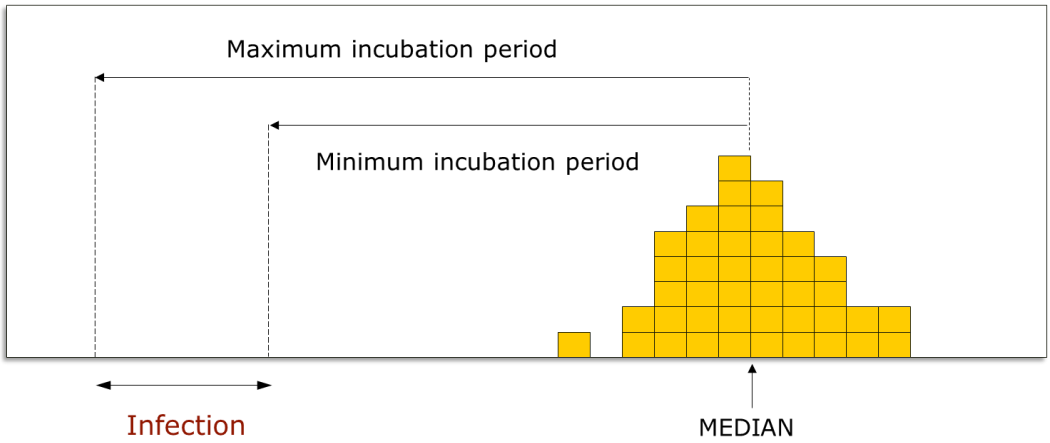
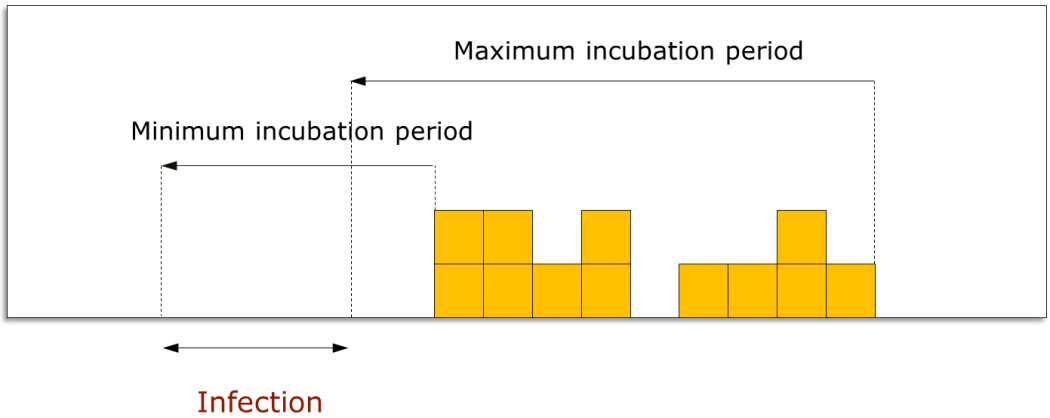


FIGURE 8.6 Delineations of the time of infection in a finished point-source outbreak



8.5 Active case finding: How many persons have become ill?

The diagnosed cases are just the tip of the iceberg

In most outbreaks, the diagnosed case-patients represent only a small part of those who have become ill. The reasons are:

- *Not everyone goes to a doctor:*

  Many people with foodborne or zoonotic diseases do not visit a doctor because they feel medical attention is not needed.

- *The doctors do not always take a sample:*

  For most foodborne and zoonotic diseases, laboratory examination of clinical samples is required to establish the etiological diagnosis and, subsequently, determine whether the patient belongs to the outbreak. However, the doctors do not always take samples for microbiological examination, mainly because they consider an etiological diagnosis is not required for treatment of the patient.

- *The laboratories do not always detect a microbial agent in the sample:*

  The results obtained by microbiological examinations depend on:

  - which agents the laboratory attempts to detect – the repertoire of diagnostic tests employed routinely (e.g. whether detection of viruses or parasites is pursued),
  - the sensitivity and specificity of the analyses employed,
  - the criteria used to determine when a given analysis is performed, unless done routinely, and
  - the methods used to collect, forward and store the samples, all of which may affect the survival and growth potential of the pathogens and thus the ability to detect them.

Consequently, many case-patients are being overlooked.

The purpose of active case finding

During the investigation of an outbreak, it may be necessary to make efforts to identify patients who have not already been found (active case finding).

The purposes are:

- Obtain an accurate estimate of the size of the outbreak and its distribution in terms of time, place and person.
- Determine the outbreak population – the population at risk (section 8.2).
- Enroll a sufficient number of patients to the investigation, e.g. to hypothesis-generating pilot interviews (section 9.2) or analytic epidemiological studies (section 10.2).
- Identify patients who need treatment.

- Identify persons who shed the pathogen and who should be excluded from high-risk situations where they may transmit the infection to others (e.g. food handlers, children and personnel in childcare facilities, employees in hospitals or nursing homes) (section 12.1).

Methods for active case finding

Unidentified patients may be identified through:

- *Enquiries to national public health authorities* requesting information from surveillance systems or reference laboratories in medical microbiology.
- *Enquiries to regional or local public health authorities, general practitioner, diagnostic laboratories or hospital departments* with questions about patients with specific diagnoses or symptoms indicative of the outbreak disease.
- *Questions to diagnosed case-patients* if they know about others who have been ill (section 4.7).
- *Enquiries to individual persons in the outbreak population* via letters, telephone surveys, e-mail or SMS, to guests (e.g. at hotels, restaurants or celebrations), participants (e.g. at sport events or festivals), attendees (e.g. at meetings or conferences), or customer records (e.g. from travel agencies).
- *General announcements through mass media, Internet or company intranets* in which people who have become ill are encouraged to make contact with the investigators (section 5.4).

8.6 Secondary cases

Secondary cases are persons who meet the case definition, but have not been exposed to the source of infection responsible for the outbreak. Instead, they have acquired their infection directly or indirectly from another case-patient who has been exposed to that source.

Secondary transmission may occur directly from person to person through the fecal-oral route, or indirectly by consumption of food, contact with utensils, cutlery or other objects that the primary cases have handled. Some microbial agents are easily spread in this manner and hence frequently cause secondary cases. This is particularly relevant for agents with a low infective dose (e.g. norovirus, EHEC, *Salmonella* Typhi and *Shigella*; see Appendix 1, Food- and waterborne diseases). Secondary transmission is not an issue in outbreaks of foodborne microbial intoxications.

The presence of secondary cases may confound interpretation of the epidemic curve. Such cases may appear after the suspected source of infection has been withdrawn from the market, thus creating a false impression that the recall was inefficient, or that the source identified was not responsible for the outbreak.

It is important to realize that secondary cases will confuse identification of the actual source of infection, since information from such cases about their exposures will be misleading. If secondary cases are included in analytic epidemiological studies (section 10.2), they will reduce the ability to

disclose a significant association between the disease and the true source. At worst, the true source may be overlooked or a wrong source identified.

Exclusion of secondary cases

Persons suspected to be secondary cases must be excluded from further investigations.

In outbreaks where two or more members of the same household are affected, it is sometimes recommended to include only the first person who developed symptoms, and exclude those with a later illness onset, since it is impossible to decide whether they have been exposed to the true source of infection or represent secondary transmission within the household.

This rule does not apply if the time interval between their illness onsets is shorter than the minimum incubation period for the disease. However, the possibility that some persons may shed the pathogen in their incubation period cannot completely be excluded. If so, the interval between the index case and a secondary case may be very short.

9 Generating hypotheses

Formulating hypotheses about the source of infection

Sections
Highlights
Introduction
9.1 Tools used to generate hypotheses
9.2 Site inspections in food businesses and premises under suspicion
9.2 The pilot interview – the hypothesis-generating interview
9.2.1 One common factor
9.2.2 Systematic pilot interviews
9.2.3 Interviews with atypical case-patients
9.2.4 Responsibilities and allocation of tasks
9.2.5 Informed consent and confidentiality
9.2.6 Pilot interview questionnaire - with user instructions
9.2.7 Analysis of data
9.2.8 Pilot interviews are not required when only one or a few meals are involved
Textbox: The pilot interview – the hypothesis-generating interview

Highlights

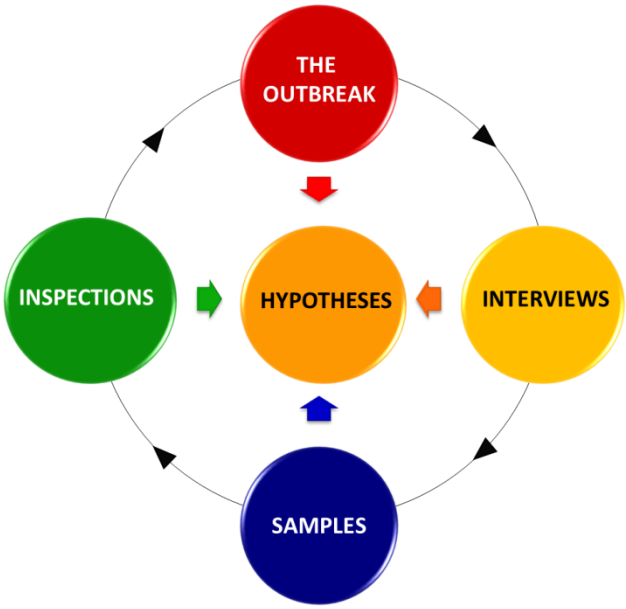
- Generation of hypotheses regarding the source of infection is a continuous and dynamic process during the investigation of an outbreak.
- Formulation of one or more qualified hypotheses is a prerequisite for being able to delimit and focus further investigations aiming at identification of the cause.
- Qualified hypotheses are made by compiling all available evidence obtained by characterization of the outbreak (chapter 8), as well as from interviews, analyses of samples, and site inspections.
- Hypotheses are continuously being tested, revised or discarded during the course of the investigation, as additional pieces of information are becoming available (chapter 10).
- Site inspections in premises where incriminated foods are produced, processed, prepared or sold are conducted to uncover failures to comply with food safety standards or identify other adverse or unsanitary conditions that may help identify the cause behind the outbreak.
- Systematic hypothesis-generating in-depth interviews of case-patients may be carried out to identify common exposures among the cases.
- These guidelines contain a template questionnaire with user instructions that may be employed for pilot interviews. The questionnaire should be edited and adapted to the current outbreak and to local conditions and food habits.

Introduction

Generation of hypotheses regarding the source of infection is a continuous and dynamic process during the investigation of an outbreak. Qualified hypotheses are made by compiling all available evidence achieved from characterization of the outbreak (chapter 8), as well as from interviews, analyses of samples, and site inspections (Figure 9.1). The hypotheses are continuously being tested, revised or discarded during the course of the investigation, as additional pieces of information are becoming available (chapter 10).

Formulation of one or more qualified hypotheses is a prerequisite for being able to focus further investigations in terms of inspections in incriminated premises, sampling and laboratory analyses, as well as interviews with case-patients.

FIGURE 9.1 Generation of hypotheses is a continuous and dynamic process



9.1 Tools used to generate hypotheses

Important tools to form hypotheses are (Figure 9.2):

- **Systematic characterization of the outbreak** (chapter 8):

  The information achieved by characterization of the outbreak may contribute to formulation of hypotheses by providing answers to the following types of questions: What has happened so far,

where does the outbreak occur, when did it begin, how does it evolve, and who are affected? What is the outbreak population? Have members of this population any common characteristics regarding demographic parameters, food or water consumptions etc.? The details are discussed in chapter 8.

- **The etiological diagnosis** (chapter 6):

  Many pathogenic microbes are associated with particular risk factors and reservoirs. Knowledge of the etiology may therefore help forming hypotheses about the most likely sources of infection and the food handling errors involved. Comparison of microbial isolates from patients and suspected sources makes it possible to confirm, support or refute the hypotheses (section 10.1).

- **Site inspections of:**
  - businesses and premises where foods under suspicion are produced, processed, prepared or sold (see section 9.2),
  - barns, other farm buildings and premises for livestock, pastures, feed mills, pet farms, zoos,
  - water works, watersheds, drinking-water distribution systems, and irrigation water supplies,
  - cultivation fields, orchards, greenhouses and other facilities for cultivation and harvesting of vegetables, herbs, fruits, berries, spices, nuts and other food of vegetable origin,
  - premises and areas where the patients have been, including childcare facilities, schools, nursing homes, hospitals, scout camps etc. and
  - any other locations or facilities at different stages in the production, processing and distribution chain for suspected foods or animals.

- **Laboratory investigations:**

  At an early stage in the outbreak investigation, it is important to collect a sufficient number of samples from patients, putative carriers, presumed sources of infection, and the environment, to ensure important evidence is not being lost (see also section 10.1). The samples may include finished food products, leftovers, wastes, raw materials, other ingredients, kitchen and production environments, animals, feedstuff, drinking water, irrigation water, manure, farmland, and any other possible or suspected source that may have contributed to transmission of the pathogenic agent. In addition to examination of specific pathogens and antibodies against them, the analyses may also entail assessment of microbial toxins and standard parameters of hygienic quality (e.g. coliforms, total bacterial counts).

- **Information and samples from food handlers:** Information and samples are collected from persons who produce, harvest, process, prepare or serve foods, or who are tending domestic animals (see section 9.2).

- **Information from individual patients in the outbreak population** about their exposures prior to illness onset, e.g. food and water consumptions, restaurant visits, travels or contact with animals. Such information may be obtained by The primary interview (Appendix 4) described in section 4.7.

- **Systematic hypothesis-generating interviews** of selected case-patients in order to identify common exposures prior to onset of their illness, using a detailed questionnaire (section 9.3).

- **Information from the reference laboratory in medical microbiology** responsible for national surveillance of the pathogen causing the outbreak. The reference laboratory may provide information on the present and previous incidence of the causative pathogen, and its subtypes, in the outbreak population.

- **Information from national reference laboratories for analysis and testing of foodborne and zoonotic agents** (e.g. the NRL-laboratories in the EU) about the prevalence of the causative microbe in foods, water, animals, feed, the environment and other nonhuman sources. They may also assess whether the pathogen has recently been detected in samples from such sources.

- **Data from national surveillance systems of communicable diseases and outbreaks.** Such systems may supply information concerning the present and previous incidence of the disease in each municipality, county and the country as a whole, and about previous outbreaks of the disease.

- **National and international literature**, including risk assessments, scientific publications and reports that are available from online databases, websites, libraries and experts. Such sources may provide research-based information e.g. on reservoirs, risk factors and sources of infection for foodborne and zoonotic diseases (See Appendix 2, Reservoirs and risk factor).

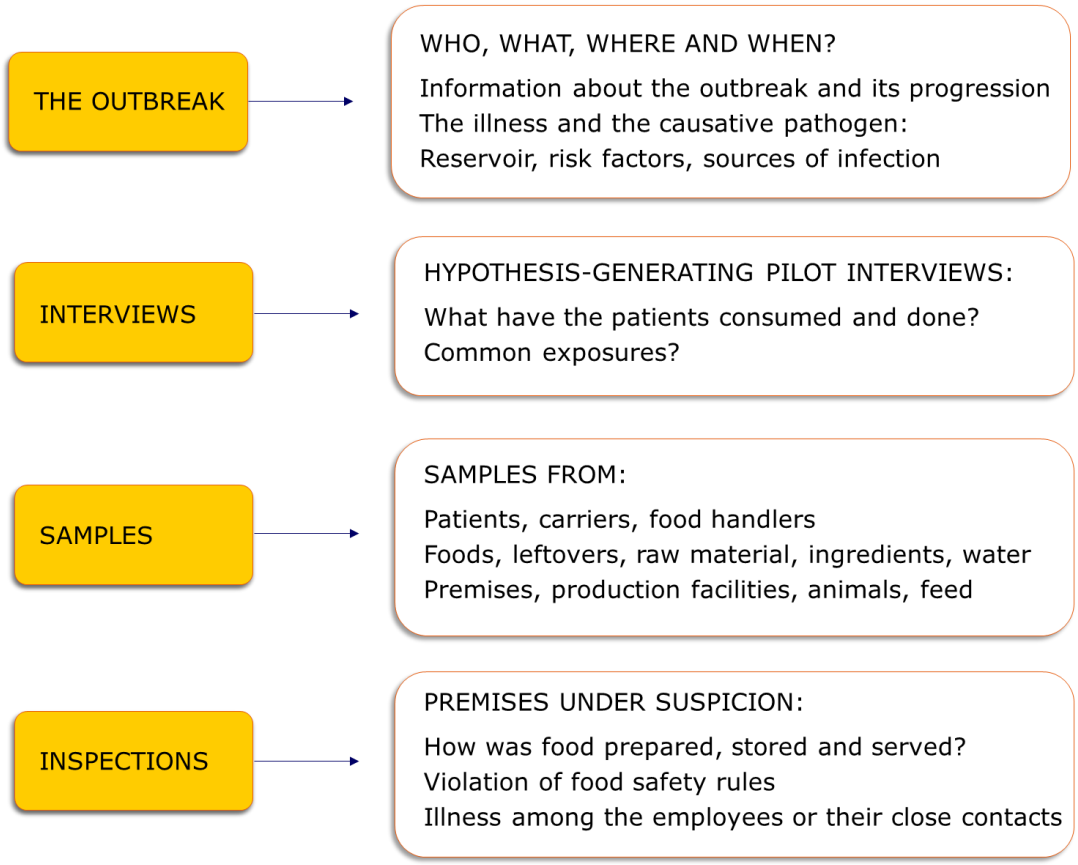
- **Information from other countries and from international authorities** on the incidence of the disease and the causative pathogen concerned. It is particularly important to ascertain whether single cases or outbreaks have recently been detected abroad. Likewise, recent isolation of the pathogen from food, water, animals or other nonhuman sources may be revealed. In this manner, a widespread international outbreak can be detected, and the countries involved may subsequently cooperate in the investigation.

- **General knowledge** about: 1) food safety, 2) presence of pathogens in the food chain, among animals and in the human population, 3) the capability of pathogens to survive, multiply and spread in foods, the food chain and in the environment, 4) sampling methods and relevant analyses, 5) knowledge about foods and their composition, production, processing, distribution, preparation and sale, and 6) production of domestic animals.

- **Special knowledge and experience** on food safety issues regarding local food businesses in the community where the current outbreak occurs.

Site inspections and pilot interviews are subject to detailed description in the next sections.

FIGURE 9.2 An overview of tools used to generate hypotheses



9.2 Site inspections in food businesses and premises under suspicion

The purpose of the site inspection is to uncover any failures to comply with food safety standards and to identify other adverse or unsanitary conditions that may help identify the cause of the outbreak. Therefore, it is important to perform the inspection as soon as possible before memory fades and important pieces of evidence are being lost.

In general, inspection in food businesses may involve all premises and processes, but during an outbreak investigation it is often useful to focus the inspection on conditions relevant for the current outbreak. If the establishment is under suspicion, and this is the reason for the inspection, the establishment should be informed appropriately.

As a part of the inspection, the employees are interviewed about procedures for production, preparation, cleaning and hygiene, including personal hygiene like hand washing, and one should observe how the routines are practiced. In establishments where foods are served (e.g. in restaurants or hotels), information is collected on what was served in the period when the outbreak occurred, how the food concerned was prepared and stored before consumption, which employees performed the work, and if there have been deviations from normal procedures and working rotas.

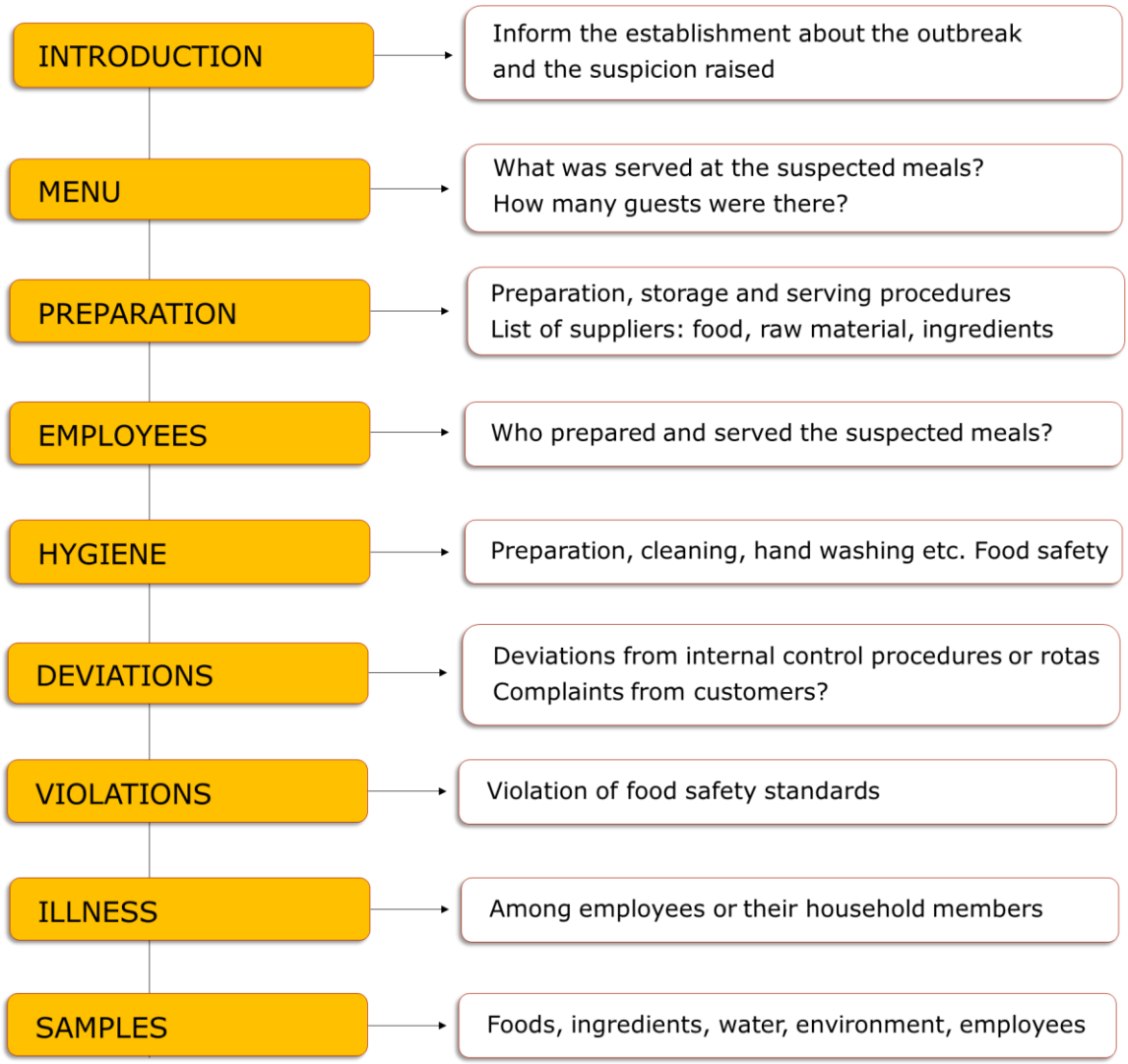
Special attention is focused on meals, dishes or particular foods that have been associated with the outbreak, in order to scrutinize how they were prepared, cooked, garnished, stored and served. Archive material from previous inspections in the establishment and deviations from the internal control system may be a valuable basis for the present inspection (Figure 9.3). To gain unbiased information, it may be an advantage to talk to staff members and their employees separately.

It is also important to ascertain whether any of the employees or their household members is ill, or recently has been ill, with similar symptoms as the outbreak patients. Moreover, one should ask if any of the employees have recently been exposed to greater risk of infection than usual, e.g. foreign travels, contact with persons from high-endemic areas etc.

The decision to take samples from employees should always be made by, or after consultation with, the public health authorities. Such samples are forwarded to and analyzed at medical microbiological laboratories. Isolation of the causative pathogen from a food handler may indicate that the person in question has been infected from the same source as the other case-patients, and therefore belong to the outbreak. If the food handler became ill before the other patients, the possibility cannot be excluded that the person is a shedder who is the original cause of the outbreak due to insufficient hygiene routines.

It is important to consider privacy issues; all information about individual persons is strictly confidential and is subject to statutory and moral secrecy. The decision to exclude employees from situations where they can transmit the disease, and inform the establishment that an employee is a shedder, should be made by, or after consultation with, the public health service.

FIGURE 9.3 Inspection in a suspected hotel kitchen during an outbreak



9.3 The pilot interview – the hypothesis-generating interview

9.3.1 One common factor of transmission

With the exception of any secondary cases (section 8.6), the case-patients in an outbreak have usually acquired their infection by exposure to one common factor, directly or indirectly, prior to onset of their illness. Such factors may be:

- **One contaminated food item:** The source of infection is one single food, dish, beverage, or drinking water source.
- **One contaminated raw material or ingredient:** The sources of infection are several food products or dishes, all of which contain one common, contaminated raw material or other ingredient.

- **One infected food handler:** The sources of infection are several food items or dishes, all of which have been produced, prepared or served by one person shedding the pathogen.

- **One contaminated food production environment:** The sources of infection are several food items or dishes, all of which have been produced, prepared or sold in the same contaminated environment (e.g. the same restaurant kitchen, catering enterprise, deli counter, food production premise, processing plant, slaughterhouse etc.).

- **One infected animal, herd, livestock or wild animal population:** The infection has been acquired by direct contact with animals that harbor the pathogen, their droppings, urine or secretes, or indirectly through contaminated food products of animal or vegetable origin, water, equipment, farm premises and environment, and other vehicles or vectors (section 1.1).

9.3.2 Systematic pilot interviews

If one has not succeeded in forming strong hypotheses about the source of infection, such factors as those mentioned above (section 9.3.1) may be identified by systematic, hypothesis-generating, in-depth interviews of selected case-patients. The patients are queried about what they have eaten and done prior to their illness onset (i.e. in their presumed incubation period) using a detailed questionnaire (section 9.3.3). The purpose is to identify exposures that are common to all or many of the patients.

This will require interviews with ca. 5-15 case-patients who have recently been ill and who are representative for the outbreak regarding illness onset, clinical manifestations, and demographic factors. However, atypical patients may sometimes provide valuable information (see section 9.3.3, below). If there are few patients in the outbreak, everyone can be interviewed but preferably those with the most recent illness onset, since they are likely to remember their exposures better than the other case-patients.

- The interviews should be conducted as soon as possible after illness onset, before the patients forget important details.
- Therefore, the pilot interviews should be carried out in parallel with other investigations.
- Patients who are putative secondary cases must be excluded (section 8.6).
- A limited number of persons, preferably one, who is trained and motivated for the task, should conduct the interviews.
- It is recommended to perform the interviews in the patients' homes, after the interviewees have received and completed the questionnaire in advance, a procedure that has been shown to improve the quality of the answers. With this approach, the patients are encouraged to memorize their food consumptions and other exposures before a face-to-face interview is conducted.
- When the interviews are performed in the patients' households, samples of foods and the environment may be collected after the interviews have been completed, using the information revealed during the interviews as guidelines for selection of samples.

9.3.3 Interviews with atypical case-patients

Although the main principle is that the case-patients interviewed should be representative for the outbreak, one can sometimes obtain valuable clues from patients who differ from the others in terms of food preferences, age or illness onset. Some examples are given below:

- Patients who were present only a short time in an area or at a party where the infection was transmitted. Such persons may have consumed fewer food items than the other cases. For example, tourists visiting a city are more likely to remember what they ate than the residents. Hence, the source of infection may be restricted to the few meals they consumed. Tourists may be identified by being the only cases residing in a different municipality or country.
- Patients who differ by higher or lower age, by dietary requirements or food preferences, or who strictly refrain from certain foods. Such persons may have a simpler diet than other cases, thus making it easier to identify the source of infection.
- Patients who report an illness onset that is considerably earlier or later than the other cases. Although there are several explanations for this (see section 8.3) such persons may sometimes have different consumptions than the other case-patients. One example is a cook who tasted the food before or after it was served at a smorgasbord, and therefore easier recall what was eaten than the guests who had several dishes to choose from. It may also be a person who ate leftovers after a party.

9.3.4 Responsibilities and allocation of tasks regarding pilot interviews

In many countries, the responsibility for interviews with case-patients in an outbreak setting resides with the public health authorities (chapter 2). However, this responsibility does not necessarily require that they perform the task personally.

In agreement with the public health authority, the food safety personnel may conduct the interviews on behalf of the health service. There are good reasons for such an allocation of tasks:

- During pilot interviews, it is important that the interviewers are able to reason and improvise using their knowledge about: 1) food safety, 2) presence of pathogens in the food chain, animals and in the population, 3) the capability of the pathogens to survive, multiply and spread in foods, the food chain and the environment, 4) sampling methods and relevant analyses, 5) knowledge about foods and their composition, production, processing, distribution, preparation and sale, 6) production of domestic animals, and 7) local food businesses.
- When food safety personnel are conducting the interviews in the patients' homes, they can subsequently collects samples of foods, leftovers, drinking water, the kitchen environment, pets or other domestic animals. They may also record data from food packages, including the date of production, lot numbers, and other information necessary for traceback and trace-forward investigations (chapter 11). This kind of sampling belongs to the responsibility of the food safety authorities, while sampling of humans is the task of the health service.

9.3.5 Informed consent and confidentiality

Regardless of which authority performs the interviews, it is necessary to obtain informed consent from the patients before they are contacted. Normally, such consent is achieved through the patients' health care providers.

All information about individuals, healthy or sick, is strictly confidential and is subject to moral and statutory secrecy. Both the public health and food safety authorities have an independent responsibility to record, store, distribute and use personal information in accordance with the laws and regulations that are applicable in the country.

9.3.6 Pilot interview questionnaire - with user instructions

During the pilot interviews, it is advantageous to use a structured questionnaire made in advance. These guidelines contain a template questionnaire, which should be edited and adjusted to local conditions and food habits, and to the current outbreak. The principles for editing are:

- Focus attention on hypothesis that have already been made
- Emphasize known sources of infection for the disease
- Remove exposures that are not relevant
- Include foods relevant for local consumption and for the ethnic group involved
- Edit the period covered by the interview in accordance with the incubation period of the disease concerned

Alternatively, the questionnaire may be used unchanged and current hypotheses and known sources may be emphasized during the interview, to prevent an unexpected source from being overlooked.

The questionnaire collects information on personal and demographic data pertaining to the interviewees, information about their disease and the symptoms experienced, consumptions of food, beverages and water prior to their illness onset, and a variety of other exposures. The food consumption history is the main part of the questionnaire. Most questions are closed (i.e. yes, no, unsure). Closed questions activate the memory and improve the quality of the answers, as opposed to open-ended questions (e.g. "what did you eat for dinner three weeks ago?"), which are difficult to answer.

- Template questionnaire for pilot interviews (Appendix 6)
- User instructions for designing questionnaires and conducting interview (Appendix 5)

9.3.7 Analysis of data

Once the interviews have been completed, the next step is to compile, analyze and interpret the information obtained. This may be done manually by counting the number of patients who report consumption of each food item and exposure to other factors included in questionnaire.

Alternatively, the information may be entered into a computer database, which is then analyzed. If an online system for questionnaire surveys is used, a database is automatically generated. Whatever the method employed, the results should be summarized in a table presenting the numbers and percentages of patients reporting exposure to each particular food item or factor, to help in generation of hypotheses and guide further investigations.

In some outbreaks, it is suspected that the source of infection is several food products or dishes, all of which contain one common, contaminated raw material or other ingredient. One example is contaminated black pepper or another spice, or minced meat. In such cases, it may prove helpful to combine all food items containing such ingredients in broader categories and repeat the analysis.

9.3.8 Pilot interviews are not required when only one or a few meals are involved

It is not necessary to use comprehensive pilot interviews in outbreaks involving only one single or a few meals consumed by a limited number of persons – a cohort (e.g. the guest at a party or in a hotel, participants at a conference, children in a daycare facility, inhabitants of a nursing home etc.). In such outbreaks, it is preferable and possible to interview everyone who was present, both healthy and diseased. This can be done as a retrospective cohort study in which the persons who attended the suspected meals are interviewed about which food items they ate among all items listed in the menu (section 10.2).

The pilot interview – the hypothesis-generating interview

Interviewees:

- Ca. 5-15 selected case-patient, or all, preferable those with recent illness onset
- Representative for the outbreak – but atypical patients may provide valuable clues
- No control persons are included

The interview:

- Very detailed and time-consuming, includes all possible sources of infection
- Focus attention on hypothesis that have already been proposed
- Emphasize known sources of infection for the disease
- Use a structured questionnaire. The standard Template questionnaire provided in Appendix 6 may be edited and adapted to the current outbreak
- Improvisations are allowed during the interview
- Individual adjustments to each patient are also justified
- It is an advantage to conduct the interview face-to-face in the patient's home
- The patient should be encouraged to memorize what was eaten and complete the questionnaire before the interview is conducted

The interviewer:

- Preferably the same interviewer for all patients
- Has knowledge about food production, food safety and foodborne pathogens
- Is motivated and trained
- Has read the questionnaire and the user instructions in advance (Appendices 5 and 6)
- Makes hypotheses during the interview
- Collects samples based on the hypotheses generated before and during the interview

Analysis:

- Compile information in a table. Identify exposures that are common to all or many of the patients

It is necessary to obtain informed consent from the patients before being contacted for interview. Usually, this is accomplished by the patients' health care providers.

10 Testing the hypotheses

Identification of the source of infection

Section
Highlights
Introduction
10.1 Analytic laboratory investigations
- Comparisons of microbial isolates using epidemiological markers
- Submission of microbial isolates to reference laboratories
- Limitations of laboratory investigations
10.2 Analytic epidemiological investigations
- Retrospective cohort studies
- Case-control studies
- Investigation of satellite outbreaks
- Limitations of analytic epidemiology
10.3 Analysis and interpretation of analytic epidemiological studies
- Steps and procedures
- Has a causal relationship been detected?
- Computer programs
- Problems during interpretation of the result
10.4 Testing of hypotheses by tracing in the food chain
10.5 Is the evidence obtained sufficiently conclusive to discontinue the investigation?

Highlights

- Formulation, testing, revision and discarding of hypotheses are a continuous and dynamic process which goes on until it is decided to stop the investigation.
- Once hypotheses about the source of infection have been formulated, the next step is to assess their reliability by collecting supplementary evidence from interviews, analyses of samples, site inspections, and data from the ongoing outbreak. The hypotheses are reinforced, revised or discarded in accordance with the information so obtained.
- After a hypothesis has been scrutinized, and if additional evidence has been obtained in its favor, it may subsequently be tested formally using two different approaches, which should be employed in parallel: Analytic laboratory investigations and analytic epidemiology.
- Analytical laboratory investigations consist of two steps: (1) examine whether the pathogen that caused the outbreak can be detected in suspected sources of infection, and (2) compare agents isolated from patients and assumed sources.
- Analytic epidemiological studies involve interviews with healthy and sick persons from the outbreak population using concise questionnaires which focus on a limited number of hypotheses

generated in the preceding investigation. The purpose is to assess whether there are statistically significant relationships between the disease and exposures to presumed sources of infection.

- Traceback and trace-forward in the production, processing and distribution chain of the incriminated source may also contribute to testing the validity of hypotheses.
- Formal testing using analytic methods are resource intensive and may be unnecessary if the source of infection has been convincingly identified by the preceding investigations. In some outbreaks, sufficient information has been obtained to enable implementation of effective preventive measures without the need to know exactly which food was responsible.
- The decision to undertake this kind of hypothesis testing is based on a balance between available resources and the results anticipated.
- In outbreak investigation, conclusive identification of the source of infection is attained by critical assessment of all available evidence provided by several methods and from many different sources, including pilot interviews, epidemiological studies, analyses of samples, site inspections, data from the ongoing outbreak, tracing in the food chain, and evaluation of plausibility.
- If the source of infection has not been identified despite considerable efforts, it must be decided whether the investigation should be discontinued or if further exploration is justified. This decision is based on available resources, priorities, whether the outbreak has come to an end, and the outbreak's severity and consequences.

Introduction

Formulation, testing, revision and rejecting of hypotheses are a continuous and dynamic process which goes on until it is decided to discontinue the investigation. Once hypotheses about the source of infection have been generated, they are subsequently sought verified, substantiated, revised or discarded by collecting further evidence using the same tools as described in section 9.1. For instance, information obtained through pilot interviews of case-patients may elicit further inspections of food premises, perhaps in a different enterprise, and trigger the collection of additional samples from putative sources. Conversely, the results from laboratory analyses may necessitate revision of preliminary hypotheses, by conducting further interviews and inspections (Figure 9.1).

When a hypothesis has been scrutinized, and if additional evidence has been obtained in its favor, then the hypothesis graduates to the level of a theory which may be tested more formally. For a theory to be considered scientific it must be testable, which means that it must be able to make verifiable predictions.

In outbreak investigation, the reliability of the theories (the refined hypotheses) is usually ascertained by means of two different strategies (Figure 10.1): analytic laboratory investigations (as opposed to diagnostic) and analytic epidemiology. Testing of theories by tracing in the food chain is described in section 10.4. These approaches are not mutually exclusive but should preferably be used in parallel.

It needs to be emphasized, though, that in many outbreaks the demand for immediate action makes it justifiable and feasible to proceed to analytic hypothesis testing at an early stage, before supportive evidence has been obtained, so the investigation is not being delayed.

Formal testing may be unnecessary if the hypothesis is strongly supported by descriptive data, and the source of infection has been identified convincingly during the preceding investigation. In some outbreaks, the investigators feel assured that sufficient evidence has been obtained to enable implementation of effective preventive measures without the need to know exactly what food was responsible. One example is an outbreak of norovirus infection or bacterial intoxication at a hotel, in which case the operators can be imposed to improve hygiene practices in the hotel kitchen whatever the dishes that were the cause.

Nevertheless, it is always an advantage to identify the source of infection with the greatest possible degree of certainty. This is a prerequisite for tracing in the food chain in order to uncover the reason why the source was contaminated (chapter 11), and subsequently implement specific preventive measures on the basis of this knowledge (chapter 12).

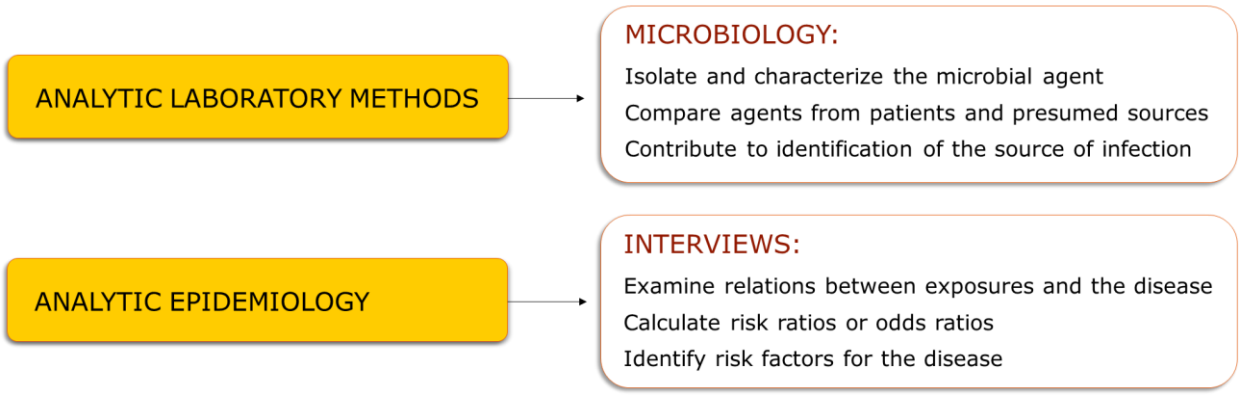
Analytic laboratory investigations

Given the presumption that the incriminated source of infections has correctly been identified, one would expect to find the causative agent in that source if it is still available for examination. This prediction can be tested by analytic laboratory methods. When used to test hypotheses during an outbreak investigation, analytic laboratory methods entail detection, characterization, and quantification of microbial pathogens or their toxins in the presumed sources of infection. Detailed characterization of the causative microbe enables comparison of pathogens isolated from patients and suspected sources, respectively. The purpose of these investigations differs from *diagnostic* laboratory analyses in which the etiological diagnosis is pursued. Analytic laboratory investigations are described in section 10.1.

Analytic epidemiology

One would expect that people exposed to the putative source are at greater risk of becoming ill than those who were not exposed. This prediction can be tested by analytic epidemiology. The aim of analytic epidemiological studies is, therefore, to ascertain whether there are statistically significant associations between exposures and the disease. To achieve this, case-patients and healthy control persons are interviewed using a concise and structured questionnaire which focuses on a limited number of hypotheses generated in the preceding investigation. Statistical analyses are then conducted to identify risk factor for the disease by calculation of risk ratios (in retrospective cohort studies) or odds ratios (in case-control studies). The basic principles of analytic epidemiological investigations are outlined in section 10.2.

FIGURE 10.1 Testing of hypotheses by analytic laboratory investigations and analytic epidemiology



10.1 Analytic laboratory investigations

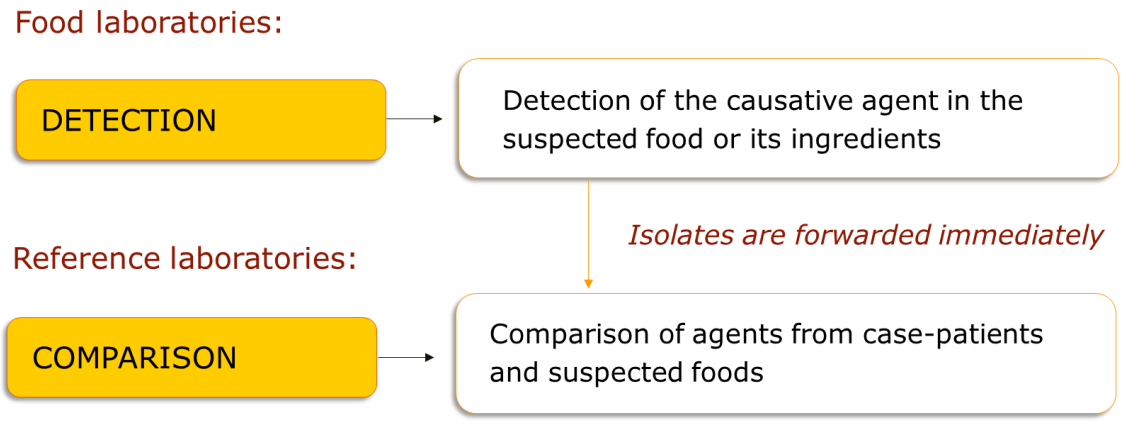
In general, laboratory methods include:

- Detection and quantification of microbial pathogens or their toxins in samples from patients, foods and the environment. For some diseases, examination of clinical samples for antibodies against the agent may be appropriate.
- Examination of the hygienic quality of suspected foods using microbiological standard parameters (e.g. coliforms, total bacterial count)
- Verification of isolated pathogens at a reference laboratory
- Typing and subtyping (differentiation into subgroups)
- Further characterization of the pathogen, e.g. virulence and antimicrobial resistance
- Comparison of isolates from patients and presumed sources of infection

In outbreaks, the aim of *analytic* laboratory investigations is to help identify the source of infection through targeted sampling of suspected foods or other sources, including potential carriers. This procedure consists of two steps (Figure 10.2):

- Examination of whether the causative microbial agent, or microbial toxins, can be detected in the incriminated source. This task is conducted by laboratories performing analyses on behalf of the food safety authorities or food businesses (food and environmental laboratories).
- Comparison of any microbial isolates recovered from case-patients and suspected sources to ascertain whether they are identical or similar, and whether they differ from control strains unrelated to the current outbreak, previously found in the area where the outbreaks occurs. This is accomplished by the relevant reference laboratory in medical microbiology which receives agents isolated from the patients.

FIGURE 10.2 Testing of hypotheses by analytic laboratory investigations



Comparisons of microbial isolates using epidemiological markers

Detection of the same pathogen (e.g. the same bacterial species) in samples from patients and suspected sources is not always sufficient to substantiate an epidemiological connection with certainty, especially if the pathogen is a variant frequently encountered in other sources as well.

In many outbreaks, therefore, effective tracing requires detailed comparison of the causative pathogen, isolates from presumed sources, and representative control isolates unrelated to the outbreak, which have previously been recovered from the outbreak area. This is accomplished using epidemiological marker analyses by which detailed differentiation of the microbial isolates into subtypes is attempted (see the textbox below). The guiding principles are:

- If the pathogenic microbe recovered from the case-patients and a suspected source of infection belongs to a rare subtype that clearly differs from the unrelated control strains, the suspicion is strengthened. It is unlikely that such an unusual type simultaneously prevails in other sources within the outbreak area.
- If the pathogenic microbe recovered from the case-patients and a suspected source belongs to a subtype that is not uncommon among the control strains, the possibility cannot completely be excluded that the outbreak was caused by a different source. The probability that the true source has indeed been found is inversely proportional to the prevalence of this subtype in the area where the outbreak occurs.
- If the pathogenic microbes isolated from the case-patients and a suspected source are distinctly different, the suspicion is disproved. However, some pathogens form heterogeneous populations consisting of several different variants, and the causative subtype may be outnumbered on the culture media. The probability of the causative subtype being overlooked depends on its prevalence in the bacterial population. To explore this, analysis of many isolates from the potential source, sometimes from the patients as well, may be necessary.

- If the pathogenic microbes isolated from the case-patients and a suspected source exhibit minor differences, the possibility exists that they represent evolutionary divergence from a common ancestor during the course of the outbreak, or that the putative source initially contained several variants. This phenomenon is particularly relevant with DNA-based analyses, some of which are capable of discerning even minor dissimilarities (i.e. their discriminatory power is high). Not infrequently, microbes displaying several DNA-profiles differing at highly variable genomic loci are detected among the patients as well as in a suspected source. Such differences may arise in vivo during the infection process, in the source, along the chain of transmission, during transport of samples, or during the cultivation procedure.
- If the isolates obtained from separate patients are dissimilar it is unlikely that there is a common-source outbreak, except in situations in which a corresponding variation can be detected in the suspected source. In many cases, however, the assumption of a common-source outbreak can be disproved on this basis.

Interpretation of results from epidemiological marker analyses should be carried out by experts, preferably persons who have research-based experience using the appropriate method for differentiating the current microbe, including knowledge of the discriminatory power of the method and, in the case of DNA analyses, the mutability of relevant genomic loci.

Epidemiological marker analyses include:

- *Phenotypic analyses* like serotyping, biotyping, phagetyping and characterization of antimicrobial resistance.
- *Genotypic analyses* based on analysis of the microbial genome, e.g. DNA or RNA profiles.
- *Analysis of virulence,* either by phenotypic analysis like enterotoxin assays, or by detection of genes encoding virulence factors.

In outbreak investigations, analyses of epidemiological markers are used to compare microbes recovered from case-patients, isolates from putative sources, and unrelated control strains, to help identify the source of infection.

Submission of microbial isolates to reference laboratories

During outbreaks of foodborne or zoonotic diseases, it is important that laboratories performing analyses of possible sources of infection, routinely forward any isolates they recover to the reference laboratory in medical microbiology responsible for verification and characterization of clinical isolates from the case-patients (Figure 10.2).

The aim is to ensure that pathogens from non-human sources can quickly be compared with the clinical isolates. Therefore, the isolates should be forwarded immediately, directly from the laboratories performing primary analyses of the samples, so the investigation is not being delayed.

Limitations of laboratory investigations

In many outbreaks, laboratory investigations are not sufficient to enable conclusive identification of the source of infection. This is due to:

- **Sample material is not available.** There is nothing left to sample because the suspected food has been consumed, discarded or sold. Although this problem may arise in any outbreak, it is particularly relevant in point-source outbreaks (section 8.3) in which the food is consumed only in a limited time interval, for instance one single meal or a product that has been sold in a short period. In such outbreaks, it is likely that the outbreak is finished when the investigators arrive.

- **Relevant methods are not available:** Samples are obtainable but analytic methods for detection of the causative agent have not been implemented at the laboratory in charge, for instance methods for detection of parasites or viruses in food and water.

- **False-negative results:** Samples and relevant analytic methods are available but the results are negative even though the agent was present when the food was consumed. This may be due to:
  - The sensitivity of the method is insufficient to enable detection of the low number of microbes that still exists in the sample, but which nevertheless was high enough to cause disease.
  - The pathogenic microbes have been sub-lethally impaired, reduced in number, decimated or completely exterminated during storage or transport of the sample. Accordingly, attempts to uncover them by cultivation are unsuccessful. Nonetheless, dead microbes may be detected by DNA-based methods (see below).

- **Thermostable toxins:** In outbreaks caused by bacterial intoxication, the bacteria may have been killed by heat treatment of the food during production, processing or cooking and they are consequently not cultivable. However, pre-formed, thermostable toxins have retained their activity and are amenable for detection provided relevant methods are accessible.

- **The agent is detected by a DNA-based method but not by confirmatory cultivation:** Culture-independent methods are increasingly being implemented at microbiological laboratories. In some outbreaks, the laboratory is unable to verify a DNA-positive result by reflexive, conventional culture methods. The reason may be:
  - the DNA analysis is more sensitive than cultivation,
  - the DNA method has insufficient specificity, leading to a false-positive result, or
  - the microbes are dead or sub-lethally injured, but are nevertheless detectable by DNA analysis.

  Most DNA analyses are unable to distinguish live and dead microbes. In case a positive DNA result cannot be verified by cultivation, the question arises whether the microbe was alive when the food was eaten or whether it was killed before consumption during production, processing or cooking. Some DNA methods are tailored to detect virulence genes considered diagnostic for certain pathogens. Occasionally, such genes may be present also in apathogenic bacteria or in

free-living bacteriophages in the same environment, without the presence of the causative pathogen, a problem encountered for instance by analysis for Shiga-toxin producing *E. coli* (STEC).

- **False-positive results:** The results are false-positive because the specificity of the analytic method is suboptimal, or because initially negative samples have become contaminated secondarily due to an error at the laboratory. Unfortunately, this is not a hypothetical incident; laboratory contamination has occurred several times.

- **The outbreak strain is encountered in other sources:** Although the pathogen causing the outbreak is detected in the suspected source of infection, epidemiological marker analyses show that it belongs to a common variant encountered in other sources as well. Hence, the possibility that a different source is involved cannot completely be excluded (see the discussion on epidemiological markers above).

- **The package with the incriminated food has been opened in a household with a shedder:** If a sample, which later tests positive, is taken from a food package that has been opened in a household where there is one or more case-patients, the question arises whether the food was contaminated secondarily by a food handler who sheds the pathogen. Although this possibility may seem fairly modest, it is not improbable in certain settings like childcare facilities, private homes, and even in hotel kitchens.

- **Laboratory analyses may be time-consuming and labor-intensive:** If the source of infection has not been identified, explorative analyses of large number of samples may be required. Moreover, if the causative pathogen is unknown, it may be necessary preform multiple assays for each sample. Furthermore, culture-dependent methods may involve long-term enrichment steps, sometimes for several weeks, followed by an identification procedure. Verification of the results and epidemiological marker analyses at a reference laboratory will require additional time.

Limitations of laboratory investigations

- There is nothing left to sample – all foods have been eaten, thrown away or sold
- Relevant analytic methods are not available
- False-negative or false-positive results
- DNA-positive results are not verified by cultivation
- The causative agent is a common variant encountered in several sources
- The food package has been opened in a household where there is a shedder
- Laboratory procedures may be time-consuming and labor-intensive

10.2 Analytic epidemiological investigations

Analytic epidemiological investigations may enable identification of the source of infection independent of laboratory analyses. In many outbreaks, analytic epidemiology is the most efficient, sometimes the only possible, approach because of the limitations of laboratory methods (section 10.1). Such studies should be initiated as soon as possible in parallel to other investigations, before the case-patients forget important information.

Analytic epidemiological studies should preferably be conducted in cooperation with or by guidance from central authorities experienced in the field. Some countries offer on-the-spot assistance by an outbreak investigation team that is trained in analytic epidemiology.

Information enabling identification of individual persons is strictly confidential and must always be treated in accordance with the prevailing laws and regulations.

The principle is:

Case-patients and healthy control persons enrolled from the outbreak population are interviewed using a concise and structured questionnaire focusing on a limited number of hypotheses previously generated during the investigation. The aim is to uncover any statistically significant associations between the disease and exposures to presumed sources of infections.

There are mainly two types of studies that are relevant in outbreak investigation: Retrospective cohort studies and case-control studies. Other epidemiological investigations, as case-cohort studies, will not be discussed here.

Retrospective cohort studies

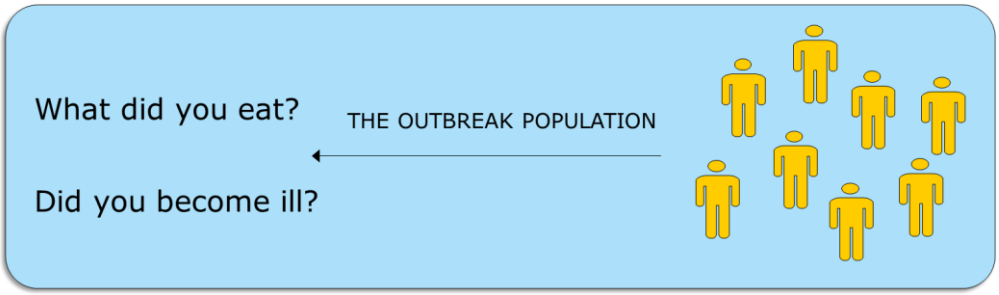
In outbreaks involving only one single or a few meals consumed by a limited number of persons – a cohort (e.g. the guest at a party or in a hotel, participants at a conference, children in a daycare center, patients in a nursing home etc.), it is possible and preferable to interview everyone who was present, both healthy and diseased. If the cohort is large, a random selection of the population may be interviewed.

This can be conducted as a retrospective cohort study in which the persons who attended the suspected meals are queried about which food items they ate, based on the menu. For each food item being served, the proportion that became ill (the attack rate) among exposed and non-exposed, respectively, is compared. Risk factors are then identified by calculation of risk ratios (relative risks) with confidence intervals and p-values. It is not necessary to know in advance who became ill, since this is explored by separate queries in the questionnaire (Figure 10.3).

These guidelines contain a template questionnaire for use in cohort studies. The questionnaire is also available in Word format to facilitate adaption to the current outbreak by entering the food items that was served. The accompanying user instructions describe how to develop questionnaires, conduct interviews, and perform data analyses:

- Template questionnaire for cohort studies (Appendix 8)
- User instructions for design, conduct and analysis (Appendix 7)

FIGURE 10.3 Retrospective cohort study



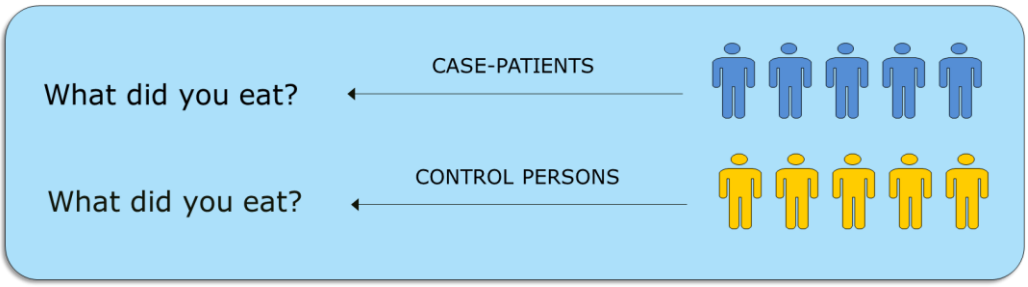
Case-control studies

If the outbreak population is large, for instance the residents in a municipality, a county or the whole country, it is obviously impossible to interview everyone. In such outbreaks, the method of choice is a case-control study in which selected case-patients and healthy control persons enrolled from the outbreak population are interviewed (Figure 10.4).

Since it is unknown how many persons became ill and how many were exposed to each factor, attack rates and risk ratios cannot be calculated. Instead, risk factors are identified by calculation of odds ratio, which is a fairly good estimate of risk ratio in most outbreaks. For each suspected food item, the exposure frequencies among the selected cases and controls are compared and odds ratios with confidence intervals and p-values are computed (Figure 10.5).

Case-control studies require a pre-determined strategy for identification and selection of cases and controls and this kind of investigation is, therefore, more complicated than cohort studies. Likewise, the data analyses are more demanding, especially when cases and controls are matched (e.g. on factors like age, gender, and residence), a recommended strategy in many such outbreaks. In most outbreaks, therefore, case-control studies require guidance from national or regional agencies, unlike cohort investigations which can readily be performed by local authorities. Furthermore, it is not possible to provide a template questionnaire since the hypotheses to be tested vary substantially between outbreaks, whereas in cohort studies the enquiries are based on all food consumptions during one single or a few suspected meals.

FIGURE 10.4 Case-control study



Investigation of satellite outbreaks

During an outbreak in a large «open» population, for example the residents in a municipality or the whole country, it may simultaneously occur one or more satellite outbreaks caused by the same agent affecting a small subpopulation like the guests at a party, restaurant or hotel, meeting participants etc. Such persons have eaten a limited number of food items or dishes during the short time when they were present and, therefore, easier remember what they consumed than the remaining case-patients who are interviewed for their entire incubation period.

In satellite outbreaks, it may be possible to obtain a list of all foods and dishes that were served, as well as detailed records on all raw materials, ingredients and garnish. Hence, a retrospective cohort study can be conducted using a questionnaire based on this list. This is an effective approach for identification of the source of infection that may supplement or sometimes even replace a comprehensive case-control study.

Also, traceback in the food chain may be fairly easy in such outbreaks because restaurants and other catering establishments will be able to identify the suppliers from which they received foods and raw materials (chapter 11).

Limitations of analytic epidemiology

Analytic epidemiology cannot be used if:

- everyone in the outbreak population became ill (the attack rate is 100 percent), in which case there are no healthy control persons to compare with,
- everyone in the outbreak population ate each food item or dish that was served, so there are no unexposed controls to compare with, or
- the number of cases or controls is insufficient to enable identification of statistically significant difference – the statistical power is too low.

I some outbreaks in which everyone in the outbreak population ate each food item or dish, it may still be possible to establish a significant linkage between exposure and disease if it turns out that those who became ill ate or drunk larger amounts of the contaminated food than the healthy ones.

One example is a waterborne outbreak in which everyone used tap water from the same source, but the interviews reveal that the cases drunk water more frequently or in larger quantities.

Other problems associated with analytic epidemiological studies are:

- **Bias:** Bias is due to systematic errors in design, conduct or analysis of the investigation resulting in incorrect estimation of the relation between an exposure and the disease. At worst, the true source of infection is being overlooked, or a wrong source identified. For example, a bias may be introduced if the probability of becoming enrolled in the investigation depends on exposure (for instance, if patients are more likely to be enrolled if they ate a particular food), or if the interviewers encourage and reward positive answers on a food they suspect. A number of other sources of bias are described below, including incorrect classification or selection of cases and controls, and recall bias.
- **Confounding:** Confounding occurs when the effects of two associated exposures have not been separated, resulting in the false interpretation that the effect is due to one variable rather than the other. For example, certain foods may be identified as risk factors by statistical analysis without even being the cause of the outbreak, because they are associated with real source of infection. This phenomenon is called confounding and may, for instance, occur if two food items are served together in the same dish. Both items will then appear as risk factors although only one is contaminated. Confounding may be explored by multivariable analyses to determine which factors are independently related to disease (section 10.3).
- **Cross-contamination to other food items:** Some of the case-patients ate a different food item that was cross-contaminated from the real source of infection. One example is lettuce contaminated from raw meat due to insufficient food safety routines in a restaurant kitchen. During the interviews, case-patients who consumed the cross-contaminated food items, but not the initial source, will correctly deny having eaten the suspected food, and the statistical association between the source of infection and the disease will consequently be diluted.
- **The source of infection may be several foods or brands** containing the same contaminated raw material or ingredient, handled by the same infected person, or produced or prepared in the same contaminated production environment (see section 9.2). One example is contaminated black pepper or another spice, which was used in many different products. Hence, the number of persons who ate each particular product may be insufficient to enable identification of statistically significant risks. It may prove helpful to combine all food items containing such ingredients in broader categories and repeat the analysis. Another case is a food handler who transmitted norovirus to several dishes prepared in a hotel kitchen. Since the number of cases reporting consumption of each contaminated food item will be fairly low, the ability to detect statistically significant correlations is reduced. In some small outbreaks, e.g. among the guests at a lunch buffet, the statistical analyses may fail to incriminate any of the food items, a finding which in itself might indicate that several dishes are contaminated.
- **Problems recalling past exposures:** It is conceivable that the interviewees may have problems recalling what they ate weeks ago. Moreover, they may have consumed the suspected food without being aware of it, for instance one particular lettuce item among several components in a green salad, or bean sprouts used as garnish.

If the presumed source of infection has been disclosed in the media or during the interview, the case-patients are inclined to erroneously report such exposure even though they have not eaten the food in question, while their controls may underreport exposure to the suspected source, leading to biased comparison with resultant overestimation of risk.

One approach to counteract this kind of recall bias is to ensure that the questionnaire contains several related products (such as several types of salads or brands of meat products), not just the food that is suspected, thus avoiding disclosure of the hypothesis. This is comparable to the police's witness interrogation when they ask the witnesses to identify the criminal among a panel of photos or persons with similar appearance.

Another type of recall bias may occur because patients remember better what they have eaten than the control subjects. Many patients who have gastroenteritis are aware that their disease may be due to food or water. They have therefore tried to recall what they ate before their disease started. They tend to suspect the last meal, foods they perceive themselves as risk products, or potential sources of infection that are revealed. Even though they often are wrong, they have nevertheless activated their memory. The controls, in turn, are unprepared for the questions about what they ate often several weeks ago. This applies both to case-control and cohort investigations. Such differential recall can be enhanced if some patients have undergone a pilot interview, possibly also a follow-up interview, where the interviewer has asked them to memorize everything they may have eaten before the disease. Strategies to reduce this type of recall bias are: (1) Exclude patients who have undergone a pilot interview from the investigation. (2) In order to give the controls a better chance of remembering, they can be interviewed for the period just before they fill out the questionnaire, while the patients are interviewed for the period before their illness started. (3) A third option is to select the controls among patients with gastroenteritis caused by another agent, who became ill at the same time as the patients in the outbreak.

- **Inclusion of patients who are not eligible cases:**
  - **Secondary cases:** By definition, secondary cases have not been exposed to the source of infection but have acquired their infection secondarily from other case-patients (section 8.6). If secondary cases are unintentionally enrolled in analytic epidemiological studies, the ability to identify a significant association between the disease and the true source will be reduced.
  - **Cases that have not been verified:** Non-verified cases may encompass patients not belonging to the outbreak. If possible or probable cases are included, the validity of the investigation may be diminished (section 7.4). Information from such patients is irrelevant and misleading, with the possible consequence that the source of infection is not being identified or, at worst, a wrong source is appointed.
  - **Endemic cases:** If the endemic background level of the disease is considerable, the possibility exists that patients not belonging to the outbreak are accidentally enrolled in the investigation. The probability is proportional to the endemic incidence in the outbreak area. Since endemic cases have not been exposed to the source of infection, they will confuse the analysis.

- **Inclusion of ineligible controls:** There are mainly two types of ineligible controls: undiagnosed cases and persons not belonging to the outbreak population. If such persons are inadvertently enrolled as controls they will obscure the linkage between the disease and the source of infection. Inclusion of controls who are undetected cases may be prevented by excluding persons with symptoms suggestive of the outbreak disease.

- **Statistical coincidence without causal connection:** An association detected by analytic epidemiology may be a statistical coincidence without causal relationship to the disease. The more factors included in the questionnaire, the greater the likelihood that one or more foods will become associated with the disease by pure chance.

Limitations of analytic epidemiology

- No healthy controls available: Everyone in the outbreak population became ill
- No unexposed controls available: Everyone ate each food or dish that were served
- The number of cases or controls is insufficient to enable identification of statistically significant differences
- Systematic errors in design, conduct or analysis leading to biased comparisons
- Confounding: the effects of two associated exposures have not been separated
- Cross-contamination to other food items during preparation
- Several food items are contaminated (e.g. containing the same ingredient, handled by one infected person etc.)
- Problems recalling past exposures
- Inclusion of secondary cases, non-verified cases, or endemic cases
- Enrollment of ineligible controls
- Statistical coincidence without causal connection

10.3 Analysis and interpretation of analytic epidemiological studies

Steps and procedures

The statistical analyses of data collected by analytic epidemiological studies attempt to identify which food consumptions or other exposures that are associated with increased risk of disease. The analyses consist of the following steps:

- *Descriptive analysis and validation of data*

  Descriptive analysis enables assessment of the validity of the results by determining how representative the cases and controls are for the outbreak population. This may be done by comparing the enrollees with the outbreak population regarding demographic variables (e.g. age, gender and residence). In a case-control-study, the enrolled patients are compared with all verified cases, while the control persons are compared with the population from which they have been selected. In a cohort-study, the enrollees are compared with the whole cohort.

  Descriptive analyses also contribute to validation of consistency and quality of the data record by uncovering obvious misclassifications and inconsistent coding of variables.

  The information collected provides an opportunity to describe the medical consequences of the outbreak in terms of clinical manifestation of the disease. Likewise, the economic impact may be outlined (e.g. number of medical visits, treatments, hospitalizations, sick leaves etc.). The data obtained may also contribute to basic knowledge about the disease and the causative agent, as detailed in section 1.3.

- *Univariable analyses*

  Univariable analyses are performed for each of the food consumptions and other exposures included in the questionnaire, and for any combinations of such exposures. It may be necessary to combine food items containing the same ingredients in broader variables to uncover statistical significant associations with the disease. Retrospective cohort-studies entail calculation of risk ratios (relative risks) by comparing attack rates among exposed and unexposed interviewees, while case-control-studies involve calculation of odds ratios in order to disclose any differences in their exposures, as shown in Figure 10.5. To ascertain whether any differences detected can be ascribed statistical significance, confidence intervals and p-values should be computed.

- *Multivariable analysis*

  Finally, multivariable analyses may be required to identify which exposures are independently associated with increased risk of disease. For instance, certain foods may be identified as risk factors by the univariable analysis without even being the cause of the outbreak, because they are associated with the real source of infection. This phenomenon is called confounding and may occur e.g. if two food items are served together in the same dish (see section 10.2).

FIGURE 10.5 Calculation of risk ratios and odds ratios

Ate sausages	Became ill		Attack rates
	Yes	No	
Yes	**A**	**B**	R+ = A / (A+B)
No	**C**	**D**	Ro = C / (C+D)

Risk ratio (RR) = R+ / Ro Odds ratio (OR) = A:C / B:D = AD/BC

In Figure 10.5, consumption of sausage is used as an example. Similar analyses must be performed for all exposures tested. If RR of OR is significantly greater than 1, and this is approved by the confidence interval, the presumed association between sausage consumption and disease is reinforced.

On the other hand, if RR or OR is not significantly different from 1 the association cannot be substantiated on this background. However, the failure to demonstrate a significant association does not decisively disprove that such a relationship might exists. Rather, the explanation may be that the risk is not particularly high or the number of enrollees is insufficient to attain statistical significance. It may be necessary to recruit more cases and controls (it is more effective to increase the number of cases than the number of controls) and repeat the analysis in order to ascertain whether the food in question is related to increased risk or not. Whatever the result, identification of the source of infection does not depend on analytic epidemiology alone. In outbreak investigation, the conclusion is drawn by critical assessment of all available evidence (section 10.5).

Has a causal relationship been detected?

It needs to be emphasized that the statistical associations detected do not necessarily reflect a causal relationship. They may also be due to:

- statistical coincidence without causal relationship to the disease,
- systematic errors in design, conduct or analysis leading to biased comparisons (section 10.2), or
- confounding (section 10.2).

The probability that a causal relationship has been detected increases if (see also section 10.5):

- The result is consistent with other evidence obtained during the investigation, for example laboratory results, site inspections and tracing in the food chain (internal consistence).

- The relationship is biologically and technologically plausible, i.e. the result is in agreement with current knowledge about the disease and the agent, and the production, processing and cooking methods used are conducive for growth or survival of the pathogen (external consistence).
- Alternative sources of infection have been assessed and ruled out.
- The explanation is simple, without requiring additional premises or non-verified presumptions.
- The risk estimate is high and displays a narrow confidence interval.
- The association is statistical significant in a multivariable analysis.
- A great majority of the case-patients report exposure to the identified source of infection.
- In some outbreaks, a dose-response relationship may be demonstrated (e.g. the risk estimate increases with the quantity of food consumed).

Computer programs

A number of free software packages suitable for registration and analysis of data from analytic epidemiological studies are available. Two examples are given below:

- *EpiData*

  The free software program EpiData may be used to develop questionnaires, enter data directly into the questionnaire form during an interview, and conduct analyses. The program can be downloaded from www.epidata.dk. The European Centre for Disease Control (ECDC) has provided a toolkit for investigation and response to food- and waterborne outbreaks affecting several EU member states, in which the use of EpiData is explained.

- *OpenEpi*

  The free software program OpenEpi contains statistical routines enabling direct online calculation of risk ratios and odds ratios with confidence intervals and p-values by entering data for each exposure into two-by-two tables as in Figure 10.5. The program is available on www.openepi.com

Multivariable analyses will require programs such as Stata, SPSS or EpiData.

Problems during interpretation of the result

Some case-patients maintain that they did not eat the incriminated food item

Possible explanations:

- Recall problems: They have forgotten that they ate the food.
- They ate the food without having noticed it (e.g. a special type of lettuce included in a green salad along with other components, or sprouts or berries used as garnish).

- The patient is a child who ate the food item in a childcare facility, with friends or grandparents without the parents being aware of it.
- They ate a different food item that was:
  - cross-contaminated from the incriminated food,
  - contaminated from the same source as the suspected food, for example by a food handler or in a contaminated kitchen or production environment, or
  - containing the same contaminated raw material or ingredient as the putative source of infection.
- The patients concerned had longer incubation periods than the others. They consumed the causative food in the days before the period covered by the interview.
- They are secondary cases who acquired their infections directly or indirectly from a case-patient, without exposure to the source of the infection responsible for the outbreak (section 8.6). This is particularly relevant for agents with a low infective dose, which are readily transferred from person to person.
- The patients represent the endemic background level of the disease and do not belong to the outbreak.
- The suspected food is not the cause of the outbreak. The association detected is due to statistical coincidence, systematic error (bias), or confounding (section 10.2).

The analysis shows that two, or more, food items are related to increased risk of disease

Possible explanations:

- The food items were all contaminated from the same source, for example by a food handler or in a contaminated kitchen or production environment.
- They contain the same contaminated raw material or ingredient.
- They were cross-contaminated from the original source during preparation or serving.
- Confounding: Although only one item is contaminated, two or more foods appear as risk factors, because they are served together in the same dish (section 10.2). Multivariable analysis should be implemented to sort out the effects and determine which food is the real source.

The analysis reveals that one, or several, foods are associated with *reduced* risk of disease

Possible explanations:

- Menu effect: In many catering enterprises, the guests are allowed to choose among several dishes or food items, for instance in a restaurant or at a smorgasbord. Those who happen to choose dishes that do not contain the contaminated food have made a choice that protects them from becoming exposed to the source of infection. Such dishes will, therefore, be associated with

reduced risk in the analysis. For example, if one component in a meat dish is contaminated, those who ate fish will appear as protected.

- It is theoretically possible that certain foods may contain an antibacterial substance causing a genuine protective effect.

No statistically significant association are detected in the analysis

Possible explanations:

- The number of cases and controls is insufficient to enable detection of significant differences (i.e. the statistical power is too low).
- The source of infection is something you have not asked about.
- Your hypotheses are wrong.

10.4 Testing of hypotheses by tracing in the food chain

Before the source of infection has been conclusively identified, tracing may contribute to test hypotheses about the cause of the outbreak. Tracing is performed forward and backward in the production, processing and distribution chain of the suspected food and for all its ingredients and raw materials.

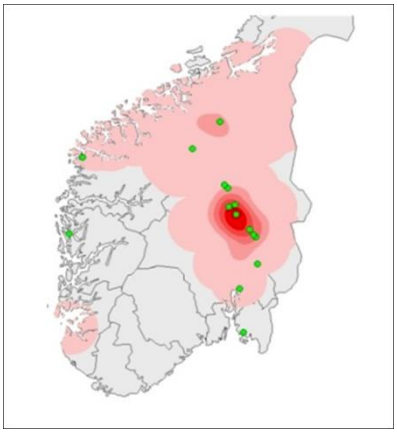
Trace-forward

By trace-forward investigations it may be possible to answer the following question:

- Does the sales distribution pattern of the suspected food coincide with the geographical distribution of the patients? If the answer is yes, the hypothesis is reinforced.

In some outbreaks, the suspected food has been sold over a wide area while the patients are distributed regionally. Although it is tempting to discard the hypothesis on this basis, further investigations may disclose that the contamination is restricted to one or a few production series or lots with limited distribution corresponding to the area where the patients live (Figure 10.6).

Figure 10.6 Correlation between sales pattern and the geographic distribution of patients



The area where a particular lot of the incriminated food was sold is shown in red; the darkness of the color indicates the amount purchased. Patients are displayed by green dots (adapted from Petter Hopp).

Traceback

Traceback investigations in the food chain may help answer the following questions:

- Which raw materials and ingredients does the suspected food source contain?
- How is the food produced, processed, prepared and served? Does this support or disprove the suspicion?
- Is the suspicion biologically and technologically plausible?

In some outbreaks, the source of infection was initially regarded implausible. Nevertheless, the pathogenic microbe was later recovered from the suspected food, and other investigations provided further evidence substantiating the conclusion that the true source had indeed been found.

Two outbreaks that occurred in Norway may serve to illustrate this point:

- In 1987, an outbreak of *Salmonella* Typhimurium infection was traced to chocolate bars from one factory where the chocolate was routinely processed at 95 °C, a temperature which usually is considered sufficient to kill *Salmonella*. Yet, the pathogen was isolated from several brands of chocolate bars and, surprisingly, laboratory experiments showed that the bacteria survived in chocolate heated to 95 °C, presumably because they were protected by the high fat content and the absence of water in the chocolate (Kapperud G et al. J Clin Microbiol 1990; 28:2597-2601).

- In 2001, a processed fish product was incriminated in an outbreak caused by *Salmonella* Livingstone. Although *Salmonella* was recovered from an unopened package from a patient's home freezer, it was still a puzzle how infection could have been possible, since the product requires cooking at more than 220 °C for about 45 minutes. However, interviews with case-patients disclosed that they had departed from the established procedure, for instance by cooking in a microwave oven or in a frying pan (Hasseltvedt V et al. Eurosuveillance Wkl 2001; 14).

The lesson is that one should not rule out a suspected source of infection that initially appears implausible.

10.5 Is the evidence obtained sufficiently conclusive to discontinue the investigation?

The public, journalists included, have the impression that an outbreak has not been solved unless the causative pathogen has been recovered from the presumed source of infection. To them, this represents the final proof, without which the investigation must be deemed inconclusive; other results are considered circumstantial evidence, only.

Although it is always reassuring to find the causative pathogen in a suspected food, the discussion presented earlier in this chapter demonstrates the fallacy of such arguments and strongly underlines that every method used in outbreak investigation is afflicted by problems and pitfalls, laboratory analyses not the least.

In outbreak investigation, the conclusion is drawn by critical scrutiny of all evidence provided by several methods and from many different sources, including pilot interviews, epidemiological studies, analyses of samples, detailed characterization of the agent, site inspections, data from the current outbreak, tracing in the food chain, and evaluation of plausibility. Like scientists, outbreak investigators are vulnerable to confirmation bias: the tendency to look for and see only evidence that confirms what they already believe. It is essential, therefore, to perform an overall assessment of all available evidence to ensure that the source of infection is identified with the highest possible certainty. After all, outbreak investigation is not an exact science, such as theoretic mathematics and axiomatic physics, in which a definite proof is achievable. Hence, uncertainty is inevitable and wrong conclusions may accidentally be drawn. The same is true in science. It is to be noticed that even in a court of law, direct eyewitness evidence or convincing forensic findings is not always necessary. Sometimes the indirect evidence becomes so massive that there is no room for reasonable doubt anymore. From a philosophical point of view, nothing can be proved beyond a shadow of doubt, neither in outbreak investigation, science nor in detective work. What is the issue is evidence beyond any reasonable doubt.

The conclusion reached is based on logical reasoning using available evidence which culminates in an explanation of why the outbreak occurred. The validity of the explanation depends on *the degree* with which a series of criteria (epistemic values) are satisfied, among others:

- Simplicity: Is the explanation simple and easily understood without requiring additional premises or presumption that have not been substantiated (i.e. the principle of parsimony)?
- Falsification of competing explanations: Have contrastive explanations been ruled out ("why this and not that")?
- Testability: Is the explanation able to make testable predictions and has testing been attempted?

- Internal consistency: Are the observations and results obtained by different methods in accordance with the explanation (i.e. does evidence from independent, unrelated sources converge to a strong conclusion, even when individual pieces of evidence are not very strong on their own)?
- External consistency and consilience: Is the conclusion in agreement with current knowledge, as for instance known properties of the disease and the pathogenic agent (i.e. the biological and technological plausibility of the explanation)?
- Explanatory power: Is exposure to the identified source able to explain the majority of the cases?

Outbreak investigation differs from the scientific process in which results and conclusions are subject to continuous criticism through a cycle that can never be declared completed. In outbreak investigation, practical, pragmatic and emergency considerations must be taken into account. First of all, immediate implementation of control measures may be necessary to prevent further spread of a serious outbreak, even in a situation when the available evidence is strongly suggestive but not absolutely conclusive.

If the source of infection has not been identified despite considerable efforts, it must be decided whether the investigation should be discontinued or if further exploration is justified. This decision is based on available resources, priorities, whether the outbreak is finished, and the severity and consequences of the outbreak.

There are several situations in which it is warranted to discontinue an investigation:

- The source of infection has been identified with a high degree of certainty. The outbreak has come to an end (the number of new cases has returned to the background level), either spontaneously without intervention or due to implemented control measures.
- A source of infection has been designated, but it is still doubted whether the correct source has been found. However, the responsible authorities are confident that sufficient evidence has been obtained and it is felt that further investigations are unnecessary for practical and priority reasons.
- All efforts to identify the source of infection have been unsuccessful but available resources and priorities do not warrant continued investigations (section 4.4). Such a decision may be necessary even when the outbreak is not finished. In other words the investigators give up.

Even when a source of infection has been identified, the investigation should not be considered completed until attempts have been made to uncover the reason why the food source was initially contaminated. This is the subject of the next chapter.

11 Tracing

Traceback and trace-forward in the food chain

Sections
Highlights
11.1 Tracing – one of the most important tasks in outbreak investigation
11.2 Traceback and trace-forward in the food chain
11.3 Steps in the traceback investigation
11.4 Sources of information
11.5 Tracing requires cooperation with food businesses

Highlights

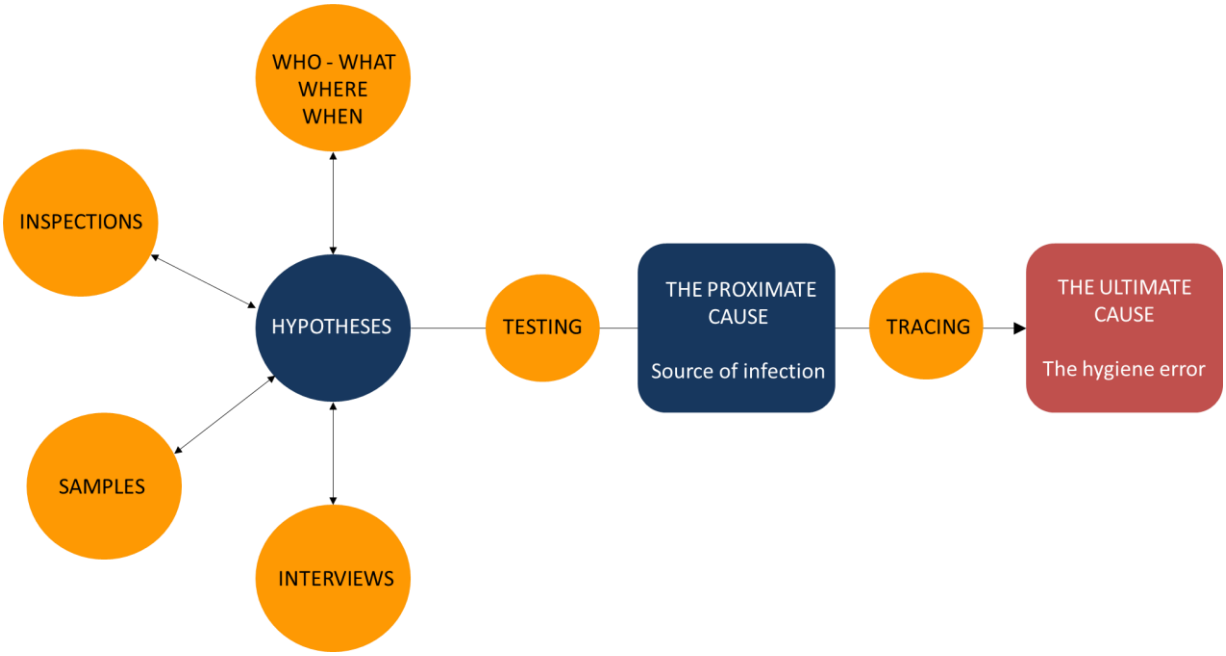
- Once the source of infection has been conclusively identified it is important to disclose the original reason why the source was contaminated, in order to correct the food handling errors which was the ultimate cause the outbreak. This task is accomplished by traceback investigations through all stages of the production, processing and distribution chain.
- Unless the initial causative factor becomes identified and corrected, new outbreaks may emerge, perhaps with greater consequences than the current outbreak. Tracing is, therefore, one of the most important steps in the outbreak investigation, and the investigation should not be considered completed unless efforts have been invested to uncover the ultimate cause.
- If the source of infection is still in sale it will be necessary to perform targeted withdrawal of the specific products, brands, lots or production series that are contaminated, and issue an accurate warning to the consumers. The information required is pursued through trace-forward investigations.
- Traceback in the food chain consists of five steps: (1) Identify the last stage in the chain which is common to the case-patients, (2) starting at this point, map out all stages backwards in the chain for the incriminated product and all its raw materials and other ingredients, (3) identify critical points where the contamination most likely occurred and scrutinize these points by site inspection including sampling and interviews with food handlers, and (5) implement preventive measures in accordance with the results.
- In most outbreaks, tracing will require close cooperation between the food safety authorities and the businesses which import, produce, process, prepare or sell the incriminated food or its ingredients.
- The regulations in the European Union make traceability compulsory for all food and feed businesses. This requires that all operators implement special traceability systems.

11.1 Tracing – one of the most important tasks in outbreak investigation

When the source of infection has been conclusively identified it is important to uncover the original reason why the source was contaminated, in order to correct the food handling error that was the ultimate cause of the outbreak. Unless the initial causal factor is identified and corrected, new outbreaks may emerge, perhaps with greater consequences than the current outbreak.

This is task is accomplished by traceback investigations in the food chain. Traceback is, therefore, one of the most important steps in the outbreak investigation, and the investigation should not be considered completed unless efforts have been invested to uncover the original cause.

FIGURE 11.1 Traceback is required to identify the ultimate cause of the outbreak



Moreover, if the implicated source of infection is still in sale, it will be necessary to withdraw it from the market to prevent contaminated products from reaching consumers, and issue a warning to the public to prevent more persons are becoming infected (see also chapter 12, about Implementing control and preventive measures). To achieve this, trace-forward explorations are conducted to identify the specific products, brands, lots, or production series that are contaminated, and to delineate the outlets and areas where it still can be purchased.

Hence, once the source of infection has been pointed out, the tracing has two purposes:

- Disclose the reason why the source initially became contaminated, in order to correct the food safety violation that made the contamination possible.

- Provide information enabling targeted withdrawal of the particular products, brands, lots, or production series that are contaminated, and issue a specific warning to the consumers.

11.2 Traceback and trace-forward in the food chain (Figure 11.2)

Trace-forward

Trace-forward investigations in the production, processing and distribution chain for the source of infection are performed to answer the following type of questions:

- Where has the incriminated food product been distributed and where is it still in sale (e.g. in which food stores or restaurants, and within which geographical area)?
- Is the contamination restricted to certain brands, specific products, lots, or production series?

Such information may help the food businesses perform targeted withdrawal of exactly the products concerned, and any warning issued to the consumers may be limited to a few goods or production series, thereby minimizing disruption of trade and reducing economic impact.

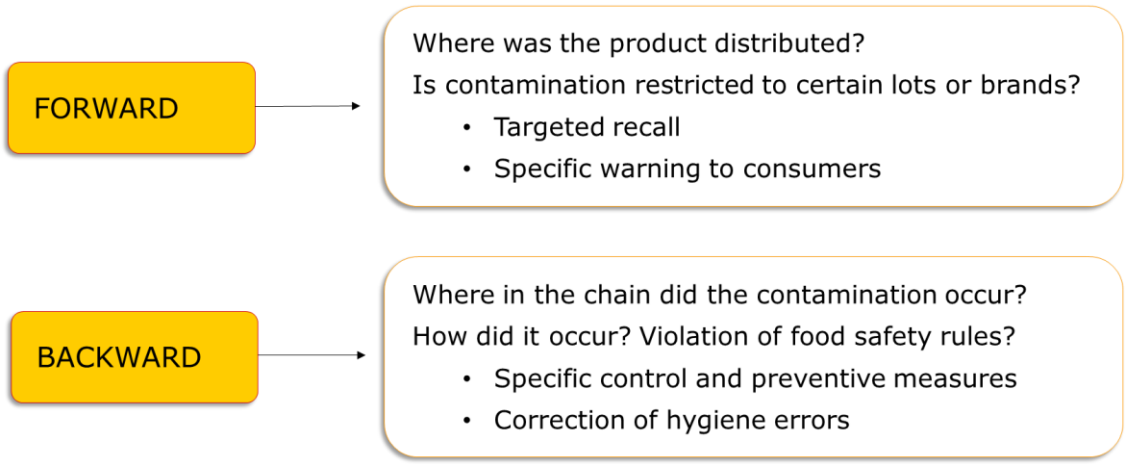
Traceback

Traceback investigations are conducted backwards (against the product flow) in the production, processing and distribution chain, not only for the incriminated food itself, but also for all its ingredients and raw materials, in order to answer the following questions:

- At which stage in the chain was the incriminated food or its ingredients contaminated?
- Which food safety violations or hygiene failures made the contamination possible?

The information so obtained enables implementation of specific control and preventive measures to correct the errors and, hence, prevent further cases and outbreaks.

FIGURE 11.2 Trace forward and backward in the food chain



11.3 Steps in the traceback investigation

In outbreaks caused by contaminated food, it is often necessary to trace the underlying reason for the contamination through several stages in the production, processing and distribution chain for the source of infection as well as for all ingredients and raw materials it contains. Such systematic tracing may be very resource-intensive and complicated, and may involve many participants. Although an outbreak is confined to inhabitants in one single municipality, the traceback efforts may nevertheless involve businesses in other parts of the country, and sometimes also abroad.

When imported products are incriminated, the contribution from agencies and authorities in all countries where the foods are produced and distributed is required, and the results may have considerable consequences for economy and trade policy. Frequently, food businesses such as importers, companies and food industry organizations may launch their own investigations.

Traceback in the food chain commences with information from the patients about where they consumed or purchased the incriminated food and, if necessary, continues all the way back to the first stage in the chain, from table to farm. Information obtained at one stage should be sought verified at the next one.

Traceback in the food chain consists of four steps (Figure 11.3):

- *Identify the last stage in the chain which is common to the case-patients:*

  Use the information obtained during the outbreak investigation to identify the last stage in the chain (i.e. closest to consumption) that is common to the case-patients. Have everyone been at the same restaurant, attended the same party, consumed food from the same production unit, or bought food in the same store or deli counter? Identification of such a location is a strong indication that the incriminated food was contaminated either at this location or at an earlier stage in the chain.

- *Map out the chain:*

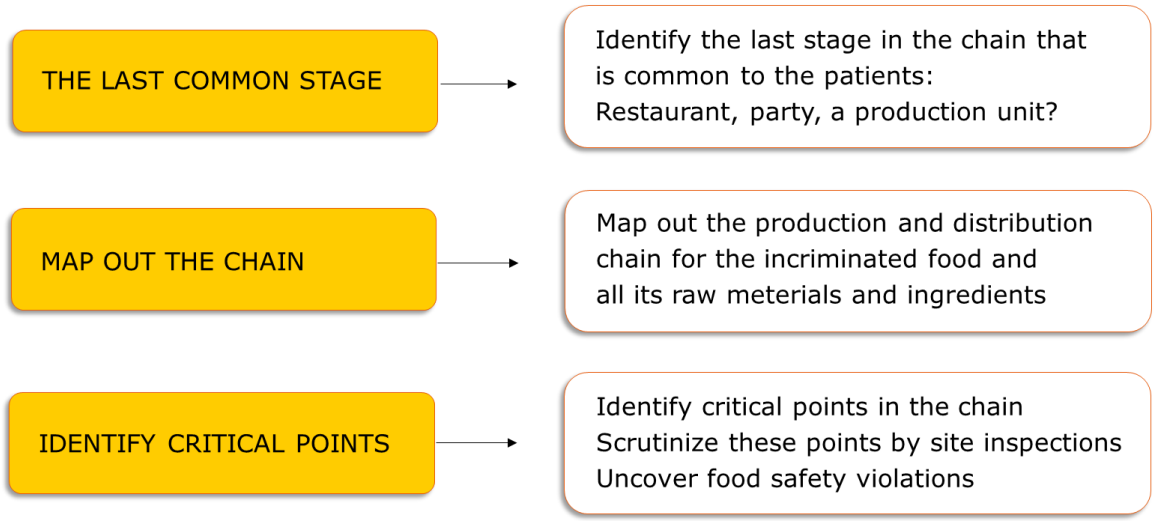
  Starting at the last stage common to the patients, make a detailed map of all stages backwards (against the product flow) in the production, processing and distribution chain for the incriminated food and for all its ingredients, including raw materials and spices, as well as for any food producing animals, animal feed, fertilizers, and irrigation water. To aid interpretation, a flow chart may be drawn to illustrate the elements in the chain.

- *Identify critical points:*

  Identify critical stages in the chain where the contamination most likely have occurred, and scrutinize these stages by site inspection, including interviews with employees and analyses of samples, to uncover food safety violations or other adverse conditions that may serve to explain why the contamination happened. One example is inadequate kitchen hygiene in a restaurant or failures to comply with standard food safety routines in a production facility. In outbreaks involving raw vegetables, fruits or berries, potentially critical points include irrigation water quality, manure treatment, and hand washing routines among the pickers.

- *Implement preventive measures* in accordance with the results, as detailed in chapter 12.

FIGURE 11.3 Steps in the traceback investigations



11.4 Sources of information

Information relevant to tracing may be collected from:

1. The case-patients
2. Food businesses in which the incriminated food was sold, cooked or served (e.g. restaurants and retail outlets)
3. Suppliers, distributors, wholesalers, and importers

4. Food businesses responsible for the primary production or initial processing, including farms, factories, processing units, slaughterhouses etc.

1. The patients may contribute information on (see also sections 4.7 and 9.2):

- Where and when the product was consumed or purchased
- Which brand or type that was eaten
- If the food items was bought fresh, refrigerated, frozen or cooked, or was homemade
- If the food was pre-packed from the producers or wrapped by the retailer, for example at a deli counter
- The size, volume or weight of the package
- Lot-number, expiration date and best-before-date (if the patient has kept the packaging)
- How the food was stored and prepared

2. Businesses in which the food was sold, cooked or served may provide information on:

- Name of suppliers, distributers, wholesalers or importers from which the product or its ingredients was purchased
- Date when the food was received and quantity
- The size and weight of the package and what kind of wrapping that was used
- Lot-numbers, production series and other codes
- Best-before-date, expirations date, date of production or outlet dates
- How the food was handled, stored, packed or processed
- How the food was prepared, cooked or served, including food safety and hygiene conditions
- Raw materials, other ingredients and garnish used when cooking or processing
- Other information from available documents and internal records in the enterprise

3. Suppliers, distributors, wholesalers, and importers may provide information on:

- Name of customers who received the incriminated product, when it was distributed and the quantity sold
- Name of subcontractors and importers from which the product was purchased, when they received the product and the quantity received
- Name of producers including farms, factories, processing units, slaughterhouses etc.
- How the product was handled, stored and packaged, including food safety and hygiene conditions
- Other information from available documents and internal records in the company

4. Businesses responsible for the primary production or initial processing may give information on:

- Name of customers who received the incriminated product, when it was distributed and the quantity sold
- Dates of production or processing, expiration dates, best-before-dates etc.
- Technical and hygienic details pertaining to production and processing
- Which raw materials and other ingredients that were used, and the suppliers of these goods
- Where farms and other primary production units are localized
- Details on harvesting, irrigation, fertilization, use of manure, housing of livestock, feeding, grazing, maintenance of pastures, slaughtering etc.
- How products were handled, stored and packaged, including food safety and hygiene issues

11.5 Tracing requires cooperation with food businesses

In most outbreaks, tracing will require close cooperation between the food safety authorities and the businesses that import, produce, process, prepare or sell the incriminated food. Private enterprises and public authorities may have coinciding interests and motives, albeit not always. At an early stage of the outbreak, it is important to inform food businesses that their products are under suspicion, and how the outbreak investigation advances. They can provide valuable information that is vital to the tracing, and they are obliged to disclose such information. Food businesses may apply considerable economic constraints on subcontractors and manufacturers to correct adverse conditions (e.g. by changing to another supplier). Sometimes, economic arguments are more effective than measures implemented by the authorities.

It is essential that the food businesses have confidence the authorities will notify them once a suspicion arises, and treat the entrusted information confidentially. On the other hand, they must be made aware that the authorities cannot refrain from taking preventive and control actions (chapter 12) if the investigation reveals conditions that may constitute a health hazard, and the enterprise does not promptly take the responsibility imposed on them (e.g. withdraw the product voluntarily).

The regulations in the European Union make traceability compulsory for all food and feed businesses. The food establishments must be able to identify where their products have come from and where they are going. They are imposed an independent responsibility to identify and delineate which products are associated with risk, at which production plant they are manufactured, and where the product units have been distributed.

All food businesses have a statutory obligation to implement special traceability systems enabling tracing of raw materials, ingredients, other constituents, and the final products at least one step forward and one step backward in the distribution chain (exception: from retail sale to consumers). The competent authorities in the member states monitor production, processing and distribution of food and feed to ensure that operators have traceability systems in place.

Detailed requirements relevant for tracing of foods of animal origin, food-producing animals, and feedstuff are laid down in regulation 931/2011.

Therefore, it is necessary to request information describing the company's own internal traceability system for identification and tracking of lots and consignments and, when applicable, marking of animals, carcasses and herds. The distribution chain often involves repacking and therefore also re-registration - and such procedures must be uncovered.

12 Measures

Implementing control and preventive measures

Section
Highlights
12.1 Short-term measures
- The responsibility of the food businesses
- Exclusion of patients and carriers from situations where they can transfer infection
12.2 Long-term measures

Highlights

- The outbreak investigation is not completed unless control and preventive measures are implemented and it is ensured that these measures are followed up in an efficient manner.
- There are two types of measures: Short-term actions intended to stop or reduce the spread of the current outbreak, and long-term measures aimed at preventing future cases of disease.
- Using the precautionary principle, control measures may be implemented at an early stage in the investigation based on preliminary results, in order to stop the outbreak or prevent further spread of the disease. More specific measures are effectuated when the source of infection has been conclusively identified.
- Food businesses are imposed an independent responsibility to immediately withdraw unsafe food, which may constitute a health hazard, from the market. They are also obliged to warn the consumers if the product has been sold. Moreover, they are required to inform the food safety authority of the risk and the action taken.
- The food safety authorities ensure that the food businesses comply with their compulsory duties. If the businesses do not promptly take the responsibility imposed on them, the authorities will take appropriate actions to secure safe food.

12.1 Short-term measures

In order to stop or reduce the spread of an ongoing outbreak it is necessary to eliminate the source of infection or break the chain of transmission. Using the precautionary principle, the competent authorities may implement control and preventive measures at an early stage in the investigation based on preliminary results to ensure a high level of protection, pending more evidence are becoming available. More specific measures are effectuated when the source of infection has been conclusively identified.

Factors that should be considered before precautionary measures are implemented:

- The severity of the disease
- The consequences of the outbreak
- The probability with which the responsible source of infection has been identified (see sections 10.3 and 10.5).
- The principle of proportionality: Ensure proportionate balance between the restriction imposed by a corrective measure and the expected outcome of the measure (i.e. balance between ends and means).

Short-term measures include:

- Information and advice to the consumers, such as avoiding specific products (section 5.4).
- Withdrawal of products from the market, food seizure
- Destruction, confiscation, closing of premises, sales prohibition, import bans
- Requirements imposed on food businesses to perform remediation, washing or disinfection
- Re-deployment of premises and reorganization of work
- Prompt improvement of hygiene and control routines
- Exclusion of patients and carriers from situations where they can transfer infection (see below)
- Vaccination (e.g. hepatitis A, typhoid fever, cholera) or passive immunizations (hepatitis A).

The responsibility of the food businesses

According to the legislation in European Union, food businesses are imposed an independent responsibility to immediately withdraw unsafe food, which may constitute a health hazard, from the market. If the product has been sold, they are also obliged to warn the consumers. Moreover, they are required to inform the food safety authority of the risk and the action taken.

The food safety authority (i.e. the competent authority) ensures that the food businesses comply with their compulsory duties. If the businesses do not promptly take the responsibility imposed on them, the authorities will take appropriate measures to secure safe food.

Exclusion of patients and carriers from situations where they can transfer infection

Local regulations may have different rules or recommendations regarding exclusion of patients and carriers from situations where they can transmit infection. When an enteric pathogen has been isolated from a patient with diarrhea, the patient must be regarded capable of transmitting the pathogen as long as the diarrhea persists. During this period, the potential for spreading the infectious agent is large. Such patients should therefore, regardless of the agent, usually be excluded from situations where they constitute a considerable risk of disease dissemination. Once the symptoms have resolved, the patient may for a period be a carrier who sheds the pathogen in the

stools and consequently still be capable of transmitting the disease. The length of the carrier period varies with the patient as well as the agent. Usually, asymptomatic carriers pose a significantly lower risk of transmission than patients with diarrhea. Nevertheless, restrictions in terms of exclusion from situation where they can spread the infection may still be relevant if they belong to one of the following high-risk groups:

1. Persons who produce, process, prepare or serve foods, especially persons who handle foods to be consumed without further heat treatment (e.g. ready-to-eat foods).
2. Health care professionals who have direct contact (including food preparation) with patients who are particularly susceptible to infectious diseases, or for whom an infection may have serious consequences (e.g. employees in hospitals, nursing homes and senior centers).
3. Children and staff in kindergartens, childcare facilities and other institutions for pre-school children.
4. Persons who have problems in maintaining a satisfactory personal hygiene.

Such persons should be excluded from their high-risk situations until they no longer shed the pathogen. The number of negative samples recommended varies with the agent and with the high-risk group to which the person belongs. For some diseases, however, the restrictions can already be repealed two days after the symptoms have resolved, without the need for control samples, as is the case with for instance viral gastroenteritis.

Persons belonging to a high-risk group who are not ill themselves but have household members or other very close contacts with *Salmonella* Typhi, *Salmonella* Paratyphi, *Shigella dysenteriae* 1 or EHEC infection should also be excluded from their high-risk situations until they have submitted negative control samples.

When the symptoms have resolved, it may still be relevant to exclude persons from work or other situations, even though they do not belong to one of the high-risk groups above, if the disease in question is particularly severe. Such a decision should be based on an assessment of the risk for transmission in each case.

12.2 Long-term measures

Long-term measures are aimed at preventing future cases of disease. An important purpose of the outbreak investigation is to provide information enabling correction of the food handling errors that was the original cause of the outbreak (chapter 11). If the initial causal factor is not being identified and corrected new outbreaks may emerge, perhaps with greater impact than the current outbreak. Long-term measures to achieve this include:

- Permanent changes in production processes, working procedures or receipts
- Improvement of food safety practices and routines
- Adjustment of control routines, including internal control plans

- Technical improvements: Rebuilding of premises, upgrading of equipment and facilities, acquisition of new equipment etc.
- Change of suppliers or re-negotiation of contracts with stricter requirements to food safety standard of the products
- Training of personnel in food businesses
- Information and educational campaigns directed towards the general public or against food businesses
- Modification of information to consumers (for instance by instructions on the label)
- Strengthening or implementation of surveillance activities aimed at detection of outbreaks
- Strengthening of procedures for investigation and control of outbreak, including joint exercises for all responsible authorities
- Revision of contingency plans for rapid investigation and control, collaboration protocols or agreements, notification procedures, and other routines for coordination of authorities at local, regional and national level
- Improvement of legislation, regulations and guidelines
- Initiate or encourage research and risk assessments that will contribute to prevention of similar outbreaks

Follow-up control of imposed measures

Ensure that imposed measures are effective and are being complied with. The outbreak investigation is not completed until control and preventive measures have been implemented, and it has been confirmed that corrective action are carried out in an efficient manner.

13 The final report

Writing a final outbreak report and evaluating the investigation

Finally, the results obtained during the investigation, and implementation of control measures, should be communicated to all agencies and authorities concerned, and to any food businesses involved in the outbreak. This should be accomplished by a final outbreak report. The report should:

- Provide information about the outbreak, its geographical distribution and progression, as well as its medical and economic consequences
- Describe the investigation, the results achieved, the measures implemented, and the impact of these measures

In larger outbreaks, it is also relevant to inform the general public through the media (see section 5.4). Moreover, it may be appropriate to inform individual persons affected by the outbreak, and thank those who have contributed particularly to the investigation.

The final outbreak report should form a basis for evaluation of how well the investigation and the cooperation proceeded, often in the form of a meeting between the agencies involved. It should be discussed whether it is necessary to revise contingency plans, collaboration protocols or agreements, notification procedures, and other routines for coordination of authorities at local, regional and national level.

The report should not convey information enabling identification of individuals. Confidential information about operating conditions or production routines in food businesses must not be revealed. However, the reports are basically open documents and should not evade the public unless there is a legal basis for this. The report should reveal all information required to prevent similar errors committed in the future, and it is therefore relevant to explain what went wrong. It is important that all facts are disclosed.

The final report should highlight unresolved questions and pinpoint research needs identified during investigation of the current outbreak.

The final outbreak report should be shared with colleagues, on websites, or by publications in scientific journals and collegiate periodicals, so others can learn from the experiences harvested. The report must give due credit to all contributors.

Once the outbreak investigation has been discontinued, and prior to completion of the final report, one should make a last update of the information notified to national authorities, especially regarding the number of case-patients identified, etiological agent, source of infection, and contributing causal factors.

The purpose of the final outbreak report

- Convey information about the outbreak, its extent and progression, as well as its medical and economic impact
- Describe the investigation, the results achieved, the measures implemented, and the impact of these measures
- Form the basis for implementation of long-term preventive measures (chapter 12)
- Make it possible for others to learn from the experience obtained
- Form the basis for evaluation of the investigation and the cooperation
- Form the basis for revision of contingency plans, collaboration protocols or agreements, notification procedures, and other routines for coordination of the authorities
- Highlight unresolved questions and research needs
- Give due credit to all contributors

Suggestions for the development of an outbreak investigation report have been provided by the European Centre for Disease Prevention and Control:

- Structure of an outbreak investigation report

Suggested reading

- Centers for Disease Control and Prevention (CDC). Investigating outbreaks. http://www.cdc.gov/foodsafety/outbreaks/investigating-outbreaks/index.html
- Centers for Disease Control and Prevention (CDC). Principles of epidemiology in public health practice. An introduction to applied epidemiology and biostatistics. Self-study course SS1978. 3rd Edition, 2012. https://www.cdc.gov/ophss/csels/dsepd/ss1978/ss1978.pdf
- European Centre for Disease Prevention and Control (ECDC). Toolkit for investigation and response to food- and waterborne disease outbreaks with an EU dimension. http://ecdc.europa.eu/en/healthtopics/food_and_waterborne_disease/toolkit/Pages/index.aspx
- European Centre for Disease Prevention and Control (ECDC).Outbreak investigations. Field epidemiology manual – a set of core training materials for intervention epidemiologists. https://wiki.ecdc.europa.eu/fem/w/wiki/outbreak-investigations
- Giesecke J. Modern infectious disease epidemiology. 2nd edition. London: Arnold Publishers, 2002.
- Gregg MB, ed. Field epidemiology. Oxford: Oxford University Press, 1996.
- Heymann DL, ed. Control of communicable diseases manual. 19th edition. Washington: American Public Health Association, 2008.
- Krauss H et al, ed. Zoonoses. Infectious diseases transmissible from animals to humans. 3rd edition. Washington: ASM Press, 2003.
- World Health Organization. Foodborne disease outbreaks: Guidelines for investigation and control. WHO, 2008. http://www.who.int/foodsafety/publications/foodborne_disease/outbreak_guidelines.pdf

Background information and questionnaires

Chapters
Background information
1. Food- and waterborne diseases – an overview
2. Reservoirs and risk factor for selected diseases
Questionnaires with user instructions
The primary interview
3. The primary interview – user instructions
4. The primary interview: Information collection form
The hypothesis generating pilot interview
5. User instructions for designing questionnaires and conducting interview
6. Template questionnaire
Cohort study of food- and waterborne outbreaks
7. User instructions for design, conduct and analysis
8. Template questionnaire

1. Food- and waterborne diseases

An overview of selected diseases that may cause food- and waterborne outbreaks

Agent	Infektive dose	Incubation period	Symptoms [a]	Duration of illness
1. Bacterial intoxications caused by preformed toxin in foods				
Staphylococcus aureus	(Enterotoxin)	1-8 hours	N A V (D F)	8-24 hours
Bacillus cereus (emetic type)	(Enterotoxin)	1-6 hours	N V	6-26 hours
Clostridium botulinum	(Neurotoxin)	12-72 hours	Neurological	Days - months
2. Bacterial infections where enterotoxins are produced in the intestinal lumen without adherence to the epithelium				
Bacillus cereus (diarrheic type)	10^5 - 10^7	6-24 hours	A D	12-24 hours
Clostridium perfringens	10^7 - 10^8	6-24 hours	A D N (F)	16-24 hours
3. Bacterial infections with adherence to the epithelium and enterotoxin production				
Aeromonas spp.	10^6 - 10^8	6-48 hours	D A (F)	1-3 days
Escherichia coli ETEC	10^5 - 10^8	10-72 hours	D (A V F)	1-5 days
Escherichia coli EHEC/STEC/VTEC	< 10^3	3-8 days	D AB (renal failure)	Days - weeks
Vibrio cholerae	10^8 - 10^{10}	2-5 days	D A (V)	4-6 days
4. Invasive enteric bacterial infections				
Campylobacter jejuni/coli	< 10^3	1-10 days	F A D B	2-10 days
Salmonella [b]	10^3 - 10^6	1-7 days	D A F (V)	2-7 days
Shigella spp.	< 10^3	1-7 days	A F D B (N V)	4-7 days
Escherichia coli EIEC	10^6 - 10^8	1-3 days	A F D (B)	4-7 days
Vibrio parahaemolyticus	10^6 - 10^{10}	4-30 hours	A D N V F B	1-7 days
Yersinia enterocolitica	10^6 - 10^7	3-10 days	F D A (V)	7-21 days
5. Systemic bacterial infections				
Listeria monocytogenes	10^7 - 10^8	Days - weeks	Systemic	Weeks
Salmonella Typhi / Paratyphi [b]	< 10^3	10-21 days	Systemic	Weeks

Agent	Infektive dose	Incubation period	Symptoms [a]	Duration of illness
6. Viral infections				
Norovirus	< 100	6-48 hours	N V D (A F)	1-3 days
Hepatitis A virus	< 100	15-50 days	F N Icterus	Weeks
7. Parasitic diseases				
Taenia saginata		Days - years	Varies	Prolonged
Trichinella spiralis		5-45 days	Varies	Prolonged
Giardia spp.	< 100	3-25 days	D A	Prolonged
Cryprosporidium spp.	< 100	1-12 days	D M (F O N)	Prolonged
Toxoplasma gondii		1-4 weeks	Varies	Prolonged
Other parasites		Miscellaneous	Miscellaneous	Prolonged
8. Special intoxications				
Poisonous mushrooms		Varies	Varies	Varies
Biogenic amines		Minutes – hours	Varies	A few hours
Diarrheic shellfish poisoning		30 min - hours	N V D	Several days
Paralytic shellfish poisoning		30 min - hours	Neurologic	Days - weeks
Mycotoxins		Varies	Varies	Varies
Heavy metals (Cd, Cu, Ti, Zn)		1-60 minutes	N V A D	Varies

[a] The symptoms are shown in the order they often occur. However, it needs to be emphasized that the nature, sequence and duration of the symptoms varies considerably with the patient and the microbial strain.

B: Bloody diarrhea D: Diarrhea
F: Fever N: Nausea
V: Vomiting A: Abdominal pain

[b] *Salmonella* Typhi og Paratyphi may sometimes cause gastrointestinal symptoms without systemic infection, especially in children.

The clinical manifestations of foodborne and zoonotic diseases are rarely so specific that the diagnosis can be ascertained solely on this basis, although the nature, sequence and duration of the symptoms might enable formulation of hypothesis about the etiology. For a majority of the diseases, detection of the causative agent in clinical samples is required to establish the diagnosis. More information, including a complete list of diseases, is available in Heymann DL (ed.). Control of communicable diseases manual (CCDM). 19th edition. Washington: American Public Health Association, 2008.

Reservoirs and risk factors for selected foodborne and zoonotic diseases are presented in a separate table:

- Reservoirs and risk factor (Appendix 2)

2. Reservoirs and risk factor

An overview of selected foodborne and zoonotic agents

Agents	Reservoirs	Risk factors
Campylobacter	Wild birds Poultry Sheep, cattle and pigs Dogs and cats	• Food safety violation (cross-contamination) when preparing raw poultry meat • Food safety violation (cross-contamination) during barbecues • Consumption of raw, rare or undercooked poultry products • Drinking untreated water • Unsanitary contact with pets and livestock (dogs, cats, poultry, cattle, sheep) • Consumption of unpasteurized milk and products thereof • Eating other foods contaminated from animal or human shedders [a]
Salmonella (non-typhoid)	Domestic animals Wild birds Imported reptiles Hedgehogs	• Food safety violation (cross-contamination) when preparing raw meat • Consumption of raw, rare or undercooked meat products • Eating other foods contaminated from animal or human shedders [a] • Drinking untreated water • Unsanitary contact with reservoir animals • Travel to endemic areas
Salmonella Typhi and Paratyphi	Humans	• Direct fecal-oral transmission from human shedders • Consumption of food or water contaminated from human shedders [a] • Drinking untreated water • Travel to endemic areas
Shigella spp. ETEC, EIEC, tEPEC	Humans	• Direct fecal-oral transmission from human shedders • Consumption of food or water contaminated from human shedders [a] • Drinking untreated water • Travel to endemic areas
Yersinia enterocolitica	Swine	• Consumption of raw, rare or undercooked pork products • Food safety violation when preparing raw pork (cross-contamination) • Eating other foods contaminated from porcine or human shedders [a] • Drinking untreated water • Unsanitary contact with pigs
Listeria monocytogenes	Ubiquitous	• Consumption of processed, ready-to-eat, meat and fish products with long shelf-lives at refrigeration temperature (e.g. cold cuts, smoked fish, fermented fish) • Eating soft cheeses • Eating product made of unpasteurized milk

Agents	Reservoirs	Risk factors
Zoonotic, enteric *E. coli* (EHEC/STEC and aEPEC)	Cattle Sheep and goats	• Consumption of raw, rare or undercooked beef, lamb or mutton products • Food safety violation when preparing raw beef or lamb (cross-contamination) • Consumption of unpasteurized milk and products thereof • Eating other foods contaminated from animal or human shedders [a] • Drinking untreated water • Bathing in contaminated water • Unsanitary contact with cattle, sheep or human shedders
Francisella tularensis	Small rodents Hare, beaver Vectors: Mosquitos, ticks	• Handling sick or dead reservoir animals, or contact with their droppings • Bitten by vectors or by reservoir animals (e.g. lemmings) • Inhalation of dust contaminated with feces or carcasses from reservoir animals (e.g. in hay barns, woodsheds, wood stacks) • Consumption of untreated water contaminated by dead or sick reservoir animals (e.g. wells, brooks, creeks)
Staphylococcus aureus *Bacillus cereus* *Clostridium perfringens*	Ubiquitous	*Violation of elementary food safety principles:* • Keeping hot food warm at too low temperatures (< 60°C) • Insufficient or too slow cooling of food • Prolonged storage of food at room temperature • Inadequate heating of previously cooked foods *For S. aureus, the following is also relevant:* • Consumption handling of food contaminated from the skin, nostrils or wounds of infectious persons or animals • Contact with animal carriers (livestock and pets)
Clostridium botulinum	Ubiquitous	• Eating homemade fermented fish • Eating homemade cured meats • Infant botulism: Consumption of honey, exceptionally other products
Norovirus	Humans	• Direct infection by feces or vomit from human shedders • Contact with objects contaminated from human shedders (e.g. cutlery, utensils, tableware, toys, doorknobs, faucets) • Eating foods contaminated by feces or vomit from shedders • Drinking untreated water
Hepatitt A virus	Humans	• Direct infection by feces from human shedders • Contact with objects contaminated from shedders • Eating foods contaminated by feces from shedders [a] • Drinking untreated water
Puumulavirus and other hantanviruses	Small rodents	• Inhalation of dust contaminated with feces, urine or carcasses from reservoir animals (e.g. in cabins, cottages, hay barns, woodsheds, wood stacks) • Drinking untreated water

Agents	Reservoirs	Risk factors
Toxoplasma gondii	Cats (primary host) Other mammals and birds (secondary hosts)	• Eating raw, rare or undercooked meat • Contact with feces from cats, for instance when cleaning the cat tray or while gardening • Eating unwashed raw vegetables, herbs, fruits or berries • Inadequate cleaning of kitchen utensil after being used with raw meat
Cryptosporidium spp.	Cattle, especially calves Sheep and goats Humans	• Drinking untreated water • Direct or indirect contact with feces from human or animal shedders • Eating foods contaminated by feces from human or animal shedders [a]
Giardia duodenalis/lamblia	Humans Exceptionally, other mammals	• Drinking untreated water • Direct or indirect contact with feces from human shedders • Eating foods contaminated by feces from human shedders, exceptionally from animals [a] Usually, the infection is not zoonotic.

[a] Including unwashed raw vegetables, herbs, sprouts, fruits and berries.

For a more complete and exhaustive presentation of reservoirs, sources, modes of transmission and associated foods, specific control measures and occurrence, it is referred to the WHO publication: Foodborne disease outbreaks: Guidelines for investigation and control. WHO, 2008. www.who.int

The primary interview – the first contact with an informant

User instructions for conducting interviews

General practitioners, the public health service and the food safety authorities are occasionally contacted by persons who believe they have become ill from something they have eaten or drunk. It may be convenient to have at hand an information registration form or questionnaire to fill out while talking to the informant, in order to systematically record the details entrusted. The data so collected may be sufficient to raise the suspicion that an outbreak is in progress.

Persons who contact their health care provider, the public health service or food safety authority, are not always aware that they are involved in an outbreak. Although they know about other people with similar symptoms, they do not necessarily mention this spontaneously.

Thus, it is important to ask the informant if others have been ill at the same time with a similar disease, to disclose whether an outbreak is ongoing.

Information collection form

These guidelines contain a template information registration form, which may be edited and adapted to local conditions:

- The primary interview – template questionnaire (Appendix 4)

It is important to systematically record the following information:

- WHAT: What is the informant's problem? (e.g., description of the symptoms, whether a doctor was contacted, if a sample was taken etc.).
- WHEN: When did the affected person become ill, and what was the duration of the illness?
- WHO: Did other persons become ill with the same or similar symptoms? When did they become sick? Note name, age and contact information
- WHY and HOW: What does the informant believe is the cause of the disease? What has the affected person eaten and done in the time period before the disease started? What have other sick or healthy people eaten?

Below is an overview of the type of questions included in the form:

- Whom am I talking to?
- When did you become ill?
- What kind of symptoms did you have?
- Did you go to a doctor? Was a sample collected?
- Do you know about other persons who were ill with similar symptoms?
- What did you eat and drink prior to the onset of your illness?
- Did you visit a restaurant or did you eat food from another catering establishment?
- Were you in contact with wild or domestic animals or birds?
- Did you drink untreated water?
- What do you believe is the reason for your illness?
- Do you work with production, processing, preparation or serving of food?
- Do you work in a hospital, childcare facility, nursing home or care facility for the elderly? (or in another institution where infections may have serious consequences)
- Did you travel abroad?
- Do you have food allergy, intolerance or chronic gastrointestinal problems? (to exclude other conditions that might explain the symptoms)
- How can I get in touch with you later? (e.g. phone, e-mail)
- Thank you for calling me!

The interviewer should refer to the patient's health care provider for collection of clinical samples, medication, and other medical issues.

All information about individuals, healthy or sick, is strictly confidential and is subject to moral and statutory secrecy. Information enabling identification of persons must always be treated in accordance with the prevailing laws and regulations.

It should be emphasized that the form is intended mainly to serve as a reminder that makes it easier to remember all information it is important to obtain. The informant should be allowed to speak freely without unnecessary interruption. This, however, does not preclude that the interviewer should try to steer the conversation to ensure all relevant data are being collected.

The primary interview is not meant to replace the comprehensive hypothesis generating pilot interview which is an in-depth interview aiming at the identification of common exposure among the patients involved in an outbreak that has already been recognized (section 9.3). The primary interview, on the other hand, is intended for collection of information from people who initially cannot be linked to any known outbreak.

Implementation of measures to prevent that an outbreak will emerge

Information obtained from one single person may trigger immediate implementation of measures in order to prevent eruption of an outbreak. This is particularly important if the informant have an occupation that entails increased risk of transmitting infections:

- Persons who handle foodstuff, including production, processing, preparation and serving of food (for instance in a restaurant kitchen).
- Employees in hospitals, nursing homes and long-term care facilities for the elderly, as well as children and staff in kindergartens and daycares, where the clients are more susceptible to infection and for whom an infectious disease may have more serious consequences than for others.

Such persons should be excluded from their work until they no longer shed the pathogen (see details in section 12.1). Informants, who present with gastrointestinal symptoms and belong to one of the high-risk groups above, should be encouraged to seek medical attention in order to examine if they are shedding a pathogenic microbe.

Information collection form

The questionnaire is available in Word-format to facilitate adaption to the current outbreak and to local conditions and food habits.

The primary interview Questionnaire.docx

(See section 4.7 for theoretical background)

The primary interview – the first contact with an informant

Name of interviewer: ..... Date of interview: .....

■ Personal data about the informant

Name:	
Age:	
Occupation:	
Address:	
Telephone, email:	

■ Information about the disease

When did you become ill?	Date / time	
For how long time were you ill?	Days / hours	No. of sick-leave days:

What kind of symptoms did you have? Please specify when the symptoms started (date, time) and how long they lasted (no. of days or hours)

Symptoms	Yes	No	Unsure	When did the symptoms start? Duration?
Nausea	☐	☐	☐	
Vomiting	☐	☐	☐	
Abdominal pain	☐	☐	☐	
Diarrhea	☐	☐	☐	No. of loose stools per day?
Bloody stool	☐	☐	☐	
Fever (subjective or measured?)	☐	☐	☐	Temperature?
Other symptoms, incl. neurological	☐	☐	☐	

Did you contact a doctor?	☐	☐	☐	Name of doctor?
Was a stool sample collected?	☐	☐	☐	Diagnosis?

Refer to the patient's health care provider regarding treatment and other medical issues.

■ Information about other ill persons

Do you know other persons who became ill with similar symptoms?

Yes ☐ No ☐ Unsure ☐	If yes, record their name(s), age, telephone - and when their illness stared:

Are any of these persons a member of your household?	Yes ☐ No ☐
Did they eat food at the same place as you?	Yes ☐ No ☐
If yes, where?	
Did any of these persons contact a doctor?	Was a stool sample collected?

■ Information about the possible source of infection

What do you believe is the cause of your illness? Do you suspect a particular meal, dish, foodstuff, drinking water or animal? Why? Do you know how the suspected food was prepared?

Are there any leftovers of the suspected food?	Yes ☐ No ☐	What kind?
Arrange delivery or pickup of samples:	When? How?	Ask the patient to keep wrappings or packages!

Other information	Yes	No	
Do you work with production, preparation or serving of foods?	☐	☐	
Do you work in a hospital, nursery home, or childcare facility?	☐	☐	
Did you travel abroad prior to your illness onset? Where? When?	☐	☐	
Did you eat at a restaurant or other catering enterprise? Where/when?	☐	☐	
Did you drink untreated drinking water?	☐	☐	
Were you in contact with animals? *	☐	☐	
Do you have a food allergy or intolerance?	☐	☐	
Do you suffer from a chronical bowel disorder?	☐	☐	

* If direct transmission from animals is suspected, ask what kind of animals the patient was in contact with, where, and when.

■ Information about foods eaten prior to illness onset

If the informant does not suspect a particular food, meal or dish, which you think is a reasonable explanation of the illness, it may be relevant to request a list of everything the person remember having consumed prior to the illness onset. Keep in mind that many persons, often wrongly, suspect the last meal consumed before they became ill, or products that have received negative publicity in the media.

Record all foods and beverages the informant remembers having consumed in the period before the illness started. If the symptoms indicate an infection: the last 3-4 days prior to illness onset; if microbial intoxication is suggested: the last 24 hours. If the diagnosis is known, use the incubation period for the disease in question (see Appendix 1: Food- and waterborne diseases).

If more than one person reportedly has been ill with similar symptoms, make a record of which meals or foods they shared, as well as where and when the food was consumed.

(Continued on next page)

Date	Breakfast	Lunch	Dinner	Other

Date	Breakfast	Lunch	Dinner	Other

How can I contact you later?

Thank you for calling me!

5. The pilot interview – user instructions

The pilot interview – the hypothesis-generating interview

User instructions for designing questionnaires and conducting interview

Sections
Highlights
When should pilot interviews be conducted?
The questionnaire
Conducting the interview
- Face-to-face interviews
- Online survey systems
- Telephone interviews
The interviewees
The period covered by the interview
Advice to the interviewers
- Before the interview
- During the interview
Request detailed information
Collection of samples
Follow-up interviews
Confidentiality

Highlights

- In outbreaks where one has not succeeded in forming strong hypotheses about the source of infection, systematic, hypothesis-generating, in-depth interviews of selected case-patients may be conducted.
- The patients are queried about what they have eaten and done prior to their illness onset (i.e. in their presumed incubation period) using a detailed questionnaire. The questionnaire may be edited and adapted to local conditions and to the current outbreak
- The purpose is to identify exposures that are common to all or many of the patients.
- This will require interview with ca. 5-15 patients who have recently been ill and who are representative for the outbreak. However, atypical patients may sometimes provide valuable information.
- If there are few patients in the outbreak, everyone may be interviewed but preferably those with the most recent illness onset, since they are likely to remember their exposures better than the others.

- The interviews should be conducted as soon as possible after illness onset, before the patients forget important details. The pilot interviews should therefore be carried out in parallel to other investigations.
- It is recommended to perform the interviews face-to-face in the patients' homes. This approach allows collection of food and environmental samples after the interviews have been completed, using the information revealed during the interviews as a basis.
- Alternatively, telephone interviews or online survey systems may be used, but they are suboptimal compared with face-to-face interviews.
- It is advantageous to give the questionnaire to the patients in advance and encourage them to fill out the form before the interview is conducted, thus granting the patients an opportunity to refresh their memory beforehand.
- Collect detailed information about each of the food items the patients remember having eaten. Likewise, similar details should also be recorded if the patients are unsure about their consumption of a particular food item, since such consumptions cannot be ruled out.

When should pilot interviews be conducted?

Hypothesis- generating pilot interviews are conducted in outbreaks where one has not succeeded in forming plausible hypotheses about the source of infection and, therefore, all possibilities must be kept open. The purpose of such interviews is to identify exposures that are common to all or many of the case-patients. The reliability of hypotheses so obtained may subsequently be assessed by collecting further evidence using analytic microbiology, analytic epidemiology, site inspections, and tracing in the food chain, as explained in chapter 10.

The theoretical basis for the pilot interviews is presented in section 9.2.

The interviews should be conducted as soon as possible after illness onset, before the patients forget important details. The pilot interviews should therefore be carried out in parallel to other investigations.

It is not necessary to use comprehensive pilot interviews in outbreaks involving only one single or a few meals consumed by a limited number of persons – a cohort (e.g. the guest at a party or in a hotel, participants at a conference, children in a daycare center, inhabitants of a nursing home etc.). In such outbreaks, it is preferable and possible to interview everyone who was present, both healthy and diseased. This can be done as a retrospective cohort study in which the persons who attended the suspected meals are interviewed about which food items they ate, based on the menu (section 10.2). If the number of persons involved is very low, and a cohort study is consequently not feasible for statistical reasons, it may still be useful to conduct interviews with patients in the cohort in order to generate hypotheses about the source of infection. The questionnaire is then used in the same way as in hypothesis-generating pilot interviews (section 9.3), but the queries are restricted to the few dishes or food items that were served.

The questionnaire

It is advantageous to use a structured questionnaire made in advance. The scheme provided in these guidelines is a template that may be implemented to elaborate questionnaires for the hypothesis-generating pilot interviews. The template questionnaire should be edited and adapted to local food habits and conditions, and to the

current outbreak. The principles for editing are outlined in section 9.3.6. For instance, it is possible to take into account any hypotheses already generated and emphasize known sources of infection for the disease.

Alternatively, the questionnaire may be used without alterations, and current hypotheses and known sources can then be emphasized while the interview is ongoing, to prevent an unexpected source being overlooked. Nevertheless, exposures that are not relevant should be excluded, for example enquiries about drinking water in outbreaks where it is obvious that the patients do not share a common water supply.

If the incubation period of the disease is longer or shorter than one week (which is default in the enclosed form) the period covered by the interview should be edited accordingly. This is relevant for diseases such as hepatitis A, typhoid fever and listeriosis, and for bacterial intoxications.

The questionnaire is available in Word format enabling editing and adaption to the current outbreak:

- Template questionnaire for pilot interviews (Appendix 6)

The questionnaire does not provide an exhaustive list of all possible foods, beverages or other exposures. Instead, several common examples in each category are included to activate the patients' memory and facilitate recall of similar food items. The interviewer should ask supplementary questions as the interview advances. Therefore, it is an advantage if the interviewers have knowledge about foods and their composition so they can reason and improvise during the interview.

The free software program EpiData may be used to develop questionnaires, enter data directly into the questionnaire form during an interview, and conduct analyses. The program can be downloaded from www.epidata.dk. The European Centre for Disease Control (ECDC) has provided a toolkit for investigation and response to food- and waterborne outbreaks affecting several EU member states, in which the use of EpiData is explained.

Conducting the interview

The interview will take at least one hour, usually more time. Hence, it is advantageous to perform the interview in a comfortable and relaxed setting in which the patients are allowed to take the time they need to memorize what was eaten. Similarly, the interviewer should be provided ample time to make hypotheses and ask supplementary and explorative questions based on the information revealed during the interview.

It is recommended to submit or send the questionnaire to the patients **in advance** and encourage them to fill out the form before the interview is conducted. This procedure has been shown to improve the quality of the answers. With this approach, the patients are allowed to memorize their food consumptions and other exposures at leisure before the interview takes place. Often the easiest way is to send the questionnaire by email.

Face-to-face interviews

It is recommended to perform the interviews face-to-face **in the patients' homes**, but other places where the interview will be uninterrupted may be appropriate, for example workplace etc.

One advantage with conducting the interview in the patients' households is that this approach allows collection of food and environmental samples after the interviews have been completed, using the information obtained as a

basis. The interviewer should also take care of food wrappings and packages on which important traceback information is found (chapter 11). Together with the patient, the interviewer can explore what are the foods and leftovers in the refrigerator, freezer and kitchen cabinets, and ask if any of those items may have been eaten before the illness started.

Online survey systems

The questionnaire may be uploaded in a web-based survey system. If the patients are asked to complete the form online without the presence of an interviewer, the quality of the information will be reduced, and it will be impossible to detect and correct misconceptions and to collect supplementary information about issues not directly mentioned in the questionnaire. Most notably, the interviewer will be unable to explore ideas and hypotheses generated while the interview is ongoing, and the patients are inclined to fill out the form in a hurry.

The interviewer may complete the form online while talking to the patient, either in the patient's home or on telephone. While such a procedure may seem effective and appealing, it is likely to disturb the relaxed atmosphere required. Moreover, in many outbreaks, the coordinators of the outbreak investigation will arrange a joint meeting or telephone conference with the interviewers to discuss the results. In such situations, it is convenient to have the completed scheme in front of you. Unfortunately, most online survey systems do not provide a printer-friendly version of the results unless each page is printed separately during the process. It is better, then, to fill out the form and make notes while talking to the patient, and enter the data online afterwards. Although time-consuming, this process grants the interviewer an extra opportunity to rethink and memorize the information collected and, thus, prepare for a joint assessment with the other interviewers.

One advantage with most online survey systems is that they automatically generate a database ready for subsequent descriptive analyses. Hence, the results can rapidly be summarized in a table presenting the numbers and percentages of patients reporting exposure to each particular food item or factor, to help in formulation of hypotheses and guide further investigations (section 9.3.6).

Telephone interviews

Telephone interviews may sometimes seem attractive. This approach allows rapid collection of data, and the interviewer can correct any misinterpretations while talking to the respondent, thus improving the quality of the information, as is the case with face-to-face interviews. On the other hand, simultaneous collection of samples is not possible, and the atmosphere is likely to be less relaxed and focused than with a face-to-face interview.

The interviewees

The pilot interviews require participation of ca. 5-15 patients who have recently been ill and who are representative for the outbreak regarding illness onset, clinical manifestations, and demographic factors. However, atypical patients may sometimes provide valuable clues (see section 9.3.3). If there are few patients in the outbreak, everyone may be interviewed but preferably those with the most recent illness onset, since they are likely to remember their exposures better than the others.

As a rule, each patient should be interviewed in person, but for some patients it may be necessary to approach a parent or guardian because of high or low age (usually < 16 years), disease, mental problems, or death. If the

patient has passed away, the interview will require great caution and empathy, but may still be justifiable if the outbreak is serious and it is necessary to identify the source of infection in order to prevent further cases and deaths. In case of language problems, one may consider using an interpreter.

The period covered by the interview

Patients are interviewed about exposures in the period before they became ill, i.e. the number of days or hours preceding their illness onset, which corresponds to the presumed incubation period of their disease:

- For foodborne infections: the last week before illness onset, with emphasis on the last three days, with the exception of diseases with significantly longer incubation such as listeriosis, typhoid fever, and hepatitis A.

- For microbial intoxications: the last 24 hours before the illness started, with emphasis on the last eight hours. It is notable, though, that most outbreaks caused by microbial intoxications involve only one single or a few meals consumed by a limited number of persons – a cohort. In such outbreaks it is appropriate to conduct a retrospective cohort study, not requiring extensive pilot interviews (see above).

- Even if the etiological diagnosis is unknown it may still be possible to distinguish infections from intoxication by means of the clinical manifestations of the disease, as described in section 6.3.
  Information on incubation periods is provided in Appendix 1: Food- and waterborne diseases

Advice to the interviewers

Before the interview:

- Make sure informed consent has been obtained from the patients before they are being contacted. Such consent is normally achieved through the patients' health care providers (section 9.3.5).
- Read section 9.3 in these guidelines where the theoretical basis of the pilot interviews is described.
- Prepare yourself for the interview: Read about the disease and its reservoirs, sources of infection, and risk factors, or talk with experts.
- **Carefully read through the questionnaire and the present user instructions.**
- If necessary, edit the questionnaire so that it is adapted to local conditions and the current outbreak. Make sure that the period covered by the interview is in accordance with the incubation period of the disease in question.
- Bring or send the questionnaire to the patients **in advance** and encourage them to fill out the form before the interview is conducted, a procedure which has been shown to improve the quality of the answers. Often the easiest way is to send the questionnaire by email.
- If the patient is a child, tell the parents or an attendee that they respond on behalf of the child. When it says YOU in the questionnaire, it refers to the child's food consumptions.
- Ask the patients or a guardian to take care of all foods, beverages and leftovers the patients may have consumed prior to their illness onset (i.e. in a period corresponding to the presumed incubation period, usually one week). Also, ask them to keep any wrappings or packages, even from the trash. Many persons are inclined to throw away everything when there has been illness in the family.

- Make an appointment for the interview. It is recommended to perform the interviews face-to-face **in the patients' homes**, but other places where the interview will be uninterrupted may be appropriate, for example workplace etc. (The suitability of telephone interviews and online survey systems are discussed above).
- The first time you take contact, give the patients an oral or written explanation describing the purpose of the interview, and tell them the interview will require **at least one hour**, usually more time (see the three first bullet points below).
- Show particular caution and respect if there is a serious illness, death, or other social or human factors that will make the interview demanding. You may need to consult the patient's health care provider beforehand.

During the interview:

- Present yourself and explain which agency you come from.
- Describe the purpose of the interview. Explain that it is important to identify the source of infection in order to stop the outbreak and prevent further cases of illness. The information provided by the patient during the interview is essential to achieve this.
- Emphasize that participation is voluntary and that all information entrusted will be treated confidentially.
- Be friendly but professional. Show that you are interested in the patient's illness. However, this is not a medical consultation. Refer to the patient's health care provider regarding treatment and other medical issues.
- Be systematic but flexible. During the pilot interview, improvisations are allowed (unlike the situation with analytic epidemiological studies in which testing of hypotheses is pursued, and in which all interviewees must be treated equally to prevent information bias (section 10.2)).
- Avoid medical terminology, jargon and abbreviations.
- Take into account the patient's age, occupation and education. In pilot interviews, individual adjustments are allowed.
- Be careful and diplomatic about sensitive issues, such as kitchen hygiene, which may make the patient feel uncomfortable or guilty.
- Ask the patient to find an almanac or diary where appointments and events have been recorded. This will make it easier to remember what happened and what was eaten in the period covered by the interview. If such records are not available, show the patient a calendar where you have highlighted the interview period. ("This is the date when you became ill - I am interested in what you ate in the week before").
- Record the information in the questionnaire. Print out the scheme on the front page of each sheet with a blank backside where you can note supplementary information if more space should be needed.
- For each food item the patients remember having eaten, it is required to obtain detailed information about the product, as described below. Such information should also be requested in case the patients are unsure about their consumption of a particular food item, since such consumption cannot be ruled out.
- Together with the patient, explore what are the foods and leftovers in the refrigerator, freezer and kitchen cabinets, and ask if any of these items may have been eaten before the illness started.

- Use the information above and from the pilot interview to guide **collection of samples** from the household (see details below).
- If the patient has eaten food in a childcare facility, with relatives or friends, in a restaurant or other catering establishment, it may be necessary to contact such places to obtain details about what was served and how the food was prepared, and collect samples of foods, raw materials, other ingredients and leftovers there.
- Explain how the patients may contact you later if they have questions or supplementary information, and ask if you may be allowed to contact them once more if further questions or clarifications are needed.
- Thank the patients for their valuable help. They have provided important information to the outbreak investigation!
- After the interview, you can use the completed form to memorize what happened and consider all information in context to facilitate generation of hypotheses about the source of infection. If you feel more information is needed to elucidate what the patient ate, or if you forgot mentioning some details, do not hesitate to contact the patient once more.

Request detailed information

Below is a list of details, which should be requested for every food or beverage the patient remember having consumed, if relevant. The same information should be obtained even if the patients are unsure about their consumption of a particular food item, since such consumption cannot be ruled out:

- Was the food purchased in a store, in a restaurant, hotel, canteen or other catering facility – or was it homemade?
- Where and when was the food item bought? Where and when was it consumed?
- Which brand or type was eaten? What was the approximate size, volume or weight of the package?
- Was the food fresh, refrigerated, frozen or cooked when it was purchased?
- If the food was bought in a store, was it pre-packed by the producer or wrapped by the retailer (e.g. sliced cold cuts from a deli counter)?
- Has the patient retained the wrapping or package? (Take care of it. Note the brand, serial number, lot-number, expiration date, best-before-date etc.).
- If the wrapping is not available, ask the patients if they remember other details about the product or the package. Every detail, even if it seems insignificant, may later prove useful (e.g. the color of the package).
- Are there any leftovers of the food? Consider whether it is appropriate to take a sample.
- How was the food stored and prepared? Is cross-contamination to or from other foods a possibility?
- What kind of ingredients was used when the food was cooked?
- What kind of accessories and garnish was the food served together with?

Collection of samples

In principal, everything that was eaten in the period prior to illness onset may potentially be a source of infection. However, it is necessary to give priority to:

- foods under special suspicion due to evidence obtained in the preceding investigation or information revealed during the interview,
- known sources of infection for the disease in question, and
- perishable foods and foods in which the pathogenic microbe is capable of growth or survival.

Apart from this, the decision to take a sample or not should be based on knowledge about food safety and about foods and their composition, production, processing and preparation. Although not every specimen will be examined at once, samples from all potential sources should be collected and stored appropriately (usually refrigerated) pending information from other pilot interviews and further evidence from the outbreak investigation. Otherwise, important evidence may be lost. Capacity problems at the laboratory may also imply that some samples must be stored before being forwarded and analyzed. Therefore, the laboratory should always be alerted prior to collection and submission of samples.

Follow-up interviews

After the questionnaires have been collected and the results are compiled, one or more foods may appear interesting because many of the patients remember having eaten them. It may be necessary to perform a follow-up interview to obtain detailed information about such foods. Although details have already been requested during the pilot interview, it may be necessary to confirm and supplement the information. Such follow-up interviews can be conducted on telephone, preferably by the same person who performed the pilot interview.

Confirm consumption of the suspected food

The primary purpose is to confirm or refute that patients have eaten the suspected food. It may be advantageous to contact all patients again, including those who initially did not remember eating the food in question, to ascertain whether they may still have eaten the food you suspect. One approach to increase the validity of the information so obtained, is to incorporate several related products in the query (such as different types of salads or brands of meat products), not just the food that is suspected, thus avoiding disclosure of the hypothesis. If the case-patients understand which food item is suspected, they are inclined to erroneously report such exposure even though they have not eaten the food in question (see section 9.3). This is comparable to the police's witness interrogation when they ask the witnesses to identify the criminal among a panel of photos or persons with similar appearance.

Identify the brand and perform trace-back investigations

An important purpose of the follow-up interview is to obtain information that makes it possible to identify which brand or type that was consumed, and thus determine where the food was produced or prepared. Such information enables the Food Safety Authority to conduct trace-back investigations to identify the ultimate source of infection and implement preventive measures accordingly.

Although the patients do not remember exactly which brand or type, it is important to obtain as many details as possible, including the size of the package, type of packaging, color or other details that make it possible to identify the manufacturer. If the patients do not remember what brand they ate, or did not take care of the wrapping, it is especially helpful to ask them about the store in which the foods were bought and when it was purchased. Using this information, the Food Safety Authority can contact the relevant food store with questions concerning which brands were on sale during the relevant period. Likewise, if the food was a dish eaten at a restaurant, the Food Safety Authority may contact the restaurant with questions about which ingredients and raw materials were used and the names of the suppliers.

Note that some companies or food businesses produce several brands of the same kind of food (e.g. different brands of salami). Such products likely contain the same raw materials or other ingredients (e.g. spices), or they may simply be the same product that is labeled differently. In EU and EEC, the wrapping of meat, fish and dairy products display a traceability mark identifying the producer.

Sometimes, the sources of infection are several different foods or dishes that are all manufactured, prepared or sold in the same contaminated production environment (for example in the same shop, deli counter, restaurant, catering business, production company, farm environment, or handled by the same infected person etc.). The ultimate source may also be one contaminated commodity used in several different food items (see section 9.3). During compilation and interpretation of the information from the pilot interviews, it may be useful to merge all foods containing the same raw materials or ingredients into larger categories when analyzing the results. It may also be appropriate to merge products that are manufactured, prepared or sold in the same place.

Confidentiality

All information enabling identification of individuals are subject to moral and statutory secrecy and should be treated in accordance with prevailing laws and regulations.

6. Pilot interview – Template questionnaire

The questionnaire is available in Word-format to facilitate adaption to the current outbreak and to local conditions and food habits.

Pilot Interview Questionnaire.docx

Interview survey – foodborne disease outbreak

Name of interviewer: ..... Date the questionnaire was completed: .....

Information about the patient	
Name:	
Date of birth:	
Profession:	
Workplace / school / daycare:	
Address:	
Telephone / e-mail:	

If the patient is a child (or is unable to answer for other reasons): Who respond on behalf of the patient? ……

Questions about your disease

1. **What kind of symptoms did you have?**

Please specify when the symptoms started (date, time) and how long they lasted (no. of days or hours)

	Yes	No	Unsure	When did the symptoms begin? Duration?
Nausea	☐	☐	☐	
Vomiting	☐	☐	☐	
Abdominal pain	☐	☐	☐	
Diarrhea (how frequent?)	☐	☐	☐	
Bloody stools	☐	☐	☐	
Fever	☐	☐	☐	
Joint pain	☐	☐	☐	
Other symptoms (what kind?)	☐	☐	☐	

If the fever was measured: How many degrees?	

2. **When did you become ill?**

Date / time:	(Date when you first noticed symptoms)

3. **How long lasted your illness?**

Days / hours:	Are you still sick?

4. **Do you know other persons who had similar symptoms in the week before or the week after the day when your illness started?**
If the answer is yes, did the person(s) become ill before or after your illness began?

Yes ☐ No ☐ Unsure ☐	If yes, note when the illness approximately started:

Are any of these persons a member of your household?	Yes ☐	No ☐	
Did they eat at the same place as you?	Yes ☐	No ☐	Unsure ☐
If yes, where?			

Most questions in the rest of the questionnaire are about what you ate and what you did in the last week before you became ill

Please answer ALL questions: Tick YES if you most likely ate the food, check NO for the foods you most likely did not eat.

If in doubt, check the UNSURE

Please write down as many details as possible about each food item

Travels – foreign and domestic

5. Were you abroad during the last week before you became ill? (Also include shopping trips)

Yes ☐ No ☐ Unsure ☐	
What country?	When?

6. Were other persons in your household abroad during <u>the last month</u> before you became ill?

Yes ☐ No ☐ Unsure ☐	
What country?	When?

Did the person(s) become ill with the same symptoms as you, while being abroad or shortly after return home?	
Yes ☐ No ☐ Unsure ☐	When did the illness start?

7. Did you travel within your own country during the week before illness onset? (Also include weekend trips)

Yes ☐ No ☐ Unsure ☐	
Where?	When?

8. Did you attend dinners, parties, meetings, seminars, conferences, sports competitions, festivals, or other events?

Yes ☐ No ☐ Unsure ☐	
Where?	When?
Did you eat there?	Yes ☐ No ☐ Unsure ☐
What did you eat? (Details will come later in the questionnaire)	

Drinking water

9. What kind of water supply do you have in your household?

Does the water come from a water work or do you have a private water supply for just your household?

	Yes	No	Unsure	Details (for instance name of the water work):
Water work for at least 20 households	☐	☐	☐	
Water work for fewer than 20 households	☐	☐	☐	
Private water supply for just your household	☐	☐	☐	

If you have a private water supply for just your household, or if you receive water from a water work for fewer than 20 households: What kind of source does the water come from?

	Yes	No	Unsure	Details:
Lake, river or brook	☐	☐	☐	
Borehole, groundwater well	☐	☐	☐	
Dug well	☐	☐	☐	

10. Is your drinking water treated (disinfected with chlorine or UV)?

Yes ☐ No ☐ Unsure ☐ If yes, what kind of treatment?	

11. Did you drink tap water, either at home or elsewhere, during the week before you got sick?

Also include water used to make juice, lemonade or ice cubes

At home: Yes ☐ No ☐ Unsure ☐ If yes, how many glasses per day? (1-2, 3-5 eller >5):	

Elsewhere: Yes ☐ No ☐ Unsure ☐ If yes, how many glasses per day? (1-2, 3-5 eller >5):	
Where?	What kind of water supply? (see question 9)

12. Did you drink water directly from a lake, pond, river or brook? (for instance while hiking, camping or hunting)

Yes ☐ No ☐ Unsure ☐	If yes, where?

13. Did you drink any water from a well or cistern? (for instance at a holiday cabin or tourist cabin)

Yes ☐ No ☐ Unsure ☐	If yes, where?

14. Did you drink bottled water or water from a container?

Yes ☐ No ☐ Unsure ☐	If yes, what kind of water?

Food from a catering business

15. Did you eat food from a catering business or another commercial kitchen during the week before your illness?

	Yes	No	Unsure	Where? When?
Restaurant	☐	☐	☐	
Hotel	☐	☐	☐	
Hamburger / fast food restaurant	☐	☐	☐	
Pizza restaurant	☐	☐	☐	
Kebab stand, take-away, snack bar	☐	☐	☐	
Other street-vended food	☐	☐	☐	
Roadside cafe, gas station	☐	☐	☐	
Kiosk, hotdog stand	☐	☐	☐	
Cafeteria, café, patisserie, bar, pub	☐	☐	☐	
Tourist cabin	☐	☐	☐	
Canteen – at work or school	☐	☐	☐	
Hospital, nursing home	☐	☐	☐	
Senior center, retirement home	☐	☐	☐	
Daycare facilities for children	☐	☐	☐	
Food brought on the door	☐	☐	☐	
Planes, trains, ferries	☐	☐	☐	
Other	☐	☐	☐	

Poultry

16. Did you eat poultry?

How was the food when purchased: (1) raw but not frozen, (2) raw and frozen, (3) fried or grilled, (4) from a restaurant or catering?

	Yes	No	Unsure	Where / when / type / store / restaurant / catering
Chicken, gourmet chicken	☐	☐	☐	
Chicken filets	☐	☐	☐	
Chicken wings, drumsticks	☐	☐	☐	
Marinated chicken	☐	☐	☐	
Other chicken products	☐	☐	☐	
Hens	☐	☐	☐	
Turkey, turkey filets	☐	☐	☐	
Duck, goose	☐	☐	☐	
Grouse, pheasant, pigeon	☐	☐	☐	
Minced poultry meat	☐	☐	☐	
Cold cuts made of poultry meat	☐	☐	☐	
Sausages made of poultry meat	☐	☐	☐	
Stew or casserole with poultry meat	☐	☐	☐	
Chicken or turkey salads	☐	☐	☐	
Other foods with poultry meat	☐	☐	☐	

Eggs and egg products

17. Did you eat eggs or food made with eggs? (Bakery, pastry, desserts etc. with eggs will come later in the questionnaire)

	Yes	No	Unsure	Where / when / type / store / restaurant / homemade?
Raw eggs	☐	☐	☐	
Soft-boiled eggs	☐	☐	☐	
Hard-boiled eggs	☐	☐	☐	
Fried eggs	☐	☐	☐	
Omelet, scrambled eggs	☐	☐	☐	
Eggnog	☐	☐	☐	
Egg cream	☐	☐	☐	
Mayonnaise, remoulade	☐	☐	☐	
Béarnaise sauce	☐	☐	☐	
Tasted raw dough with eggs	☐	☐	☐	
Other foods with eggs	☐	☐	☐	

Red meat and red meat products

18. Did you eat red meat, or products made of red meat?

How was the meat when purchased: (1) raw but no frozen, (2) raw and frozen, (3) fried or grilled, (4) from a restaurant or catering?

Do not include canned food. (Cold cuts and cured meats will come later in the questionnaire)

	Yes	No	Unsure	Where / when / type / store / restaurant / homemade
Beef:				
Steaks	☐	☐	☐	
Entrecote, rib eye, tenderloin, sirloin	☐	☐	☐	
Roast beef	☐	☐	☐	
Liver	☐	☐	☐	
Casseroles or stews with beef	☐	☐	☐	
Other foods with beef	☐	☐	☐	
Pork:				
Ham, pork roast, pork steaks	☐	☐	☐	
Salted ham roasts	☐	☐	☐	
Bayonne ham, smoked ham	☐	☐	☐	
Ham strips, ham cubes, pulled pork	☐	☐	☐	
Pork chops, cutlets	☐	☐	☐	
Pork tenderloin, sirloin	☐	☐	☐	
Ribs, barbecue ribs, spareribs	☐	☐	☐	
Pulled pork	☐	☐	☐	
Bacon	☐	☐	☐	
Pork tongue, liver	☐	☐	☐	
Pork knuckle	☐	☐	☐	

	Yes	No	Unsure	Where / when / type / store / restaurant / homemade
Casseroles or stews with pork	☐	☐	☐	
Other foods with pork	☐	☐	☐	
Mutton and lamb:				
Roasted lamb, lamb steaks	☐	☐	☐	
Lamb chops, lamb cutlets	☐	☐	☐	
Lamb ribs	☐	☐	☐	
Casseroles or stews with lamb	☐	☐	☐	
Ragu	☐	☐	☐	
Other foods with lamb or mutton	☐	☐	☐	
Game:				
Elk, moose, reindeer	☐	☐	☐	
Deer, red deer, roe deer	☐	☐	☐	
Hare, rabbit	☐	☐	☐	
Minced meat, hamburgers of game	☐	☐	☐	
Casseroles or stews with game	☐	☐	☐	
Other foods with game	☐	☐	☐	
Food made of minced meat or forcemeat:				
Beef tartar	☐	☐	☐	
Meatballs, patties	☐	☐	☐	
Hamburgers, beef burgers	☐	☐	☐	
Stuffing	☐	☐	☐	
Meatloaf	☐	☐	☐	
Beef Lindstrom	☐	☐	☐	
Cabbage rolls, other meat rolls	☐	☐	☐	
Fried minced meat	☐	☐	☐	
Casseroles / stews with minced meat	☐	☐	☐	
Other foods with minced meat	☐	☐	☐	
Sausages:				
Grilled sausages, bacon grill	☐	☐	☐	
Hot dogs, frankfurters	☐	☐	☐	
Smoked sausages	☐	☐	☐	
Casseroles or stews with sausage	☐	☐	☐	
Other sausages / food with sausage	☐	☐	☐	
Other foods with or without meat:				
Pizza with meat or sausage	☐	☐	☐	
Pizzas without meat	☐	☐	☐	
Kebab, wraps	☐	☐	☐	
Pies, spring rolls, pirogues, calzone	☐	☐	☐	
Tapas	☐	☐	☐	
Taco, fajitas, burritos etc.	☐	☐	☐	
Sauces: Salsa, guacamole etc.	☐	☐	☐	

	Yes	No	Unsure	Where / when / type / store / restaurant / homemade
Lasagna, tortellini, ravioli etc.	☐	☐	☐	
Spaghetti, macaroni – with meat?	☐	☐	☐	
Other pasta with meat	☐	☐	☐	
Other pasta without meat	☐	☐	☐	
Pasta sauces, pesto etc.	☐	☐	☐	
Noodle, finished dishes with noodle	☐	☐	☐	
Moussaka etc.	☐	☐	☐	
Risotto, dishes with rice and meat	☐	☐	☐	
Schnitzel, beef Stroganoff, goulash	☐	☐	☐	
Soups with meat	☐	☐	☐	
Soups without meat	☐	☐	☐	

Ready-made meals

19. Did you eat ready-made meals or dishes, which were bought in a store? (please include both chilled, frozen and hot dishes)

How was the dish or meal when purchased: (1) chilled, (2) frozen, or (3) hot, for instance bought at a deli counter.

	Yes	No	Unsure	Where / when / type / store
Ready-made dinners	☐	☐	☐	
Ready-made porridges, puddings	☐	☐	☐	
Ready-made stews or casseroles	☐	☐	☐	
Ready-made sauces or dressings	☐	☐	☐	
Ready-made desserts	☐	☐	☐	
Other ready-made meals or dishes	☐	☐	☐	

Homemade meat and fish dishes

20. Did you eat homemade any meat or fish dishes, which were made from scratch in your own household or in another private kitchen?

	Yes	No	Unsure	Where / when / type
Homemade hamburgers, meatballs	☐	☐	☐	
Homemade stews or casseroles	☐	☐	☐	
Homemade fish products	☐	☐	☐	
Homemade rolls, pâtés, cold cuts	☐	☐	☐	
Taco, pizza, lasagna, pasta dishes	☐	☐	☐	
Other homemade meat of fish dishes	☐	☐	☐	

Were spices or seasoning added to these dishes while cooking?

Yes ☐ No ☐ Unsure ☐	
If yes, what kind of spice?	

Raw, rare or undercooked meat

21. Did you eat meat of any kind that was raw, rare or undercooked?

(Red at the bone, red inside the steak, pink meat juice etc.)

	Yes	No	Unsure	When / where / type / store / restaurant / homemade
Mutton, lamb	☐	☐	☐	
Pork	☐	☐	☐	
Beef	☐	☐	☐	
Poultry	☐	☐	☐	
Hamburgers	☐	☐	☐	
Meatballs, patties	☐	☐	☐	
Minced meat or forcemeat products	☐	☐	☐	
Marinated meat	☐	☐	☐	
Sausages or hot dogs that were cold	☐	☐	☐	
Other	☐	☐	☐	

22. Did you taste or nibble raw meat, raw minced meat or stuffing while preparing food?

Yes ☐ No ☐ Unsure ☐	If yes, what kind?

23. Did you eat sausages, hot dogs, hamburgers or other meat or fish products straight from the package without heating?

Yes ☐ No ☐ Unsure ☐	If yes, what kind?

Cold cuts and cured meats

24. Did you eat cold cuts, lunchmeats, sandwich meats, cooked meats, sliced meats, cold meats, or deli meats?

If yes, was the product: (1) sliced in the store (for instance at a deli counter), (2) pre-sliced and pre-packaged at the factory, (3) purchased in whole pieces, (4) served on a smorgasbord, (5) on ready-to-eat sandwiches, rolls or baguettes, or (6) was it homemade?

	Yes	No	Unsure	Brand / type / sliced in the store / pre-sliced / homemade
Ham, smoked ham cold cuts	☐	☐	☐	
Meat rolls, pork roll, bologna etc.	☐	☐	☐	
Mortadella, meat loaf, olive loaf	☐	☐	☐	
Beef or roast beef cold cuts	☐	☐	☐	
Chicken or turkey cold cuts	☐	☐	☐	
Other cold cuts	☐	☐	☐	

25. Did you eat salted or cured meat products?

If yes, was the product: (1) sliced in the store (for instance at a deli counter), (2) pre-sliced and pre-packaged at the factory, (3) purchased in whole pieces, (4) served on a smorgasbord, (5) on ready-to-eat sandwiches, rolls or baguettes, or (6) was it homemade?

	Yes	No	Unsure	Brand / type / sliced in the store / pre-sliced / homemade
Salami	☐	☐	☐	
Pepperoni, chorizo	☐	☐	☐	
Other salted or cured sausages	☐	☐	☐	
Cured ham, gammon	☐	☐	☐	
Parma ham, serrano ham	☐	☐	☐	
Other salted or cured meat products	☐	☐	☐	

Pâtés and salads

26. Did you eat pates, mayonnaise salads, potato salad, other salads etc.?

If yes, was the product: (1) made in a store (for instance at a deli counter), (2) ready-made and pre-packed in a factory, (3) served on a smorgasbord, (4) on ready-to-eat sandwiches, rolls or baguettes, or (6) was it homemade?

	Yes	No	Unsure	Brand / type / made in a store / factory made / restaurant
Liver pate	☐	☐	☐	
Other pates	☐	☐	☐	
Aspic	☐	☐	☐	
Caesar salad, pasta salad	☐	☐	☐	
Chicken salad, turkey salad	☐	☐	☐	
Other salads with meat or seafood	☐	☐	☐	
Potato salad	☐	☐	☐	
Waldorf salad	☐	☐	☐	
Coleslaw etc.	☐	☐	☐	
Fruit salad, strawberry salad	☐	☐	☐	
Other salads	☐	☐	☐	

Fish, fish products and other seafood

27. Did you eat any kind of fish or fish products? (Do not include canned products)

	Yes	No	Unsure	Where / when / brand / type / store / restaurant
Fresh fish (whole, filets, slices)	☐	☐	☐	
Frozen fish (whole, filets, slices)	☐	☐	☐	
Fish fingers, fish sticks etc.	☐	☐	☐	
Other frozen fish products	☐	☐	☐	
Products made of minced fish	☐	☐	☐	
Fish au gratin	☐	☐	☐	

	Yes	No	Unsure	Where / when / brand / type / store / restaurant
Other processed fish products	☐	☐	☐	
Bacalao, stockfish	☐	☐	☐	
Fish soup, ready-made	☐	☐	☐	
Fish soup, homemade				
Other soups or casseroles with fish	☐	☐	☐	
Smoked salmon	☐	☐	☐	
Smoked mackerel, eel or herring	☐	☐	☐	
Other smoked fish or fish products	☐	☐	☐	
Gravlax, cured fish	☐	☐	☐	
Half-fermented fish	☐	☐	☐	
Sushi or raw fish	☐	☐	☐	
Roe - raw or cooked	☐	☐	☐	
Caviar	☐	☐	☐	
Herring, salted or pickled	☐	☐	☐	
Anchovies (not canned)	☐	☐	☐	
Tuna salad, salmon salad	☐	☐	☐	
Other salads with fish	☐	☐	☐	
Other food items with fish	☐	☐	☐	

28. Did you eat shellfish, mussels or snails? (Do not include canned products)

	Yes	No	Unsure	Where / when / brand / type / store / restaurant
Shrimps with shell	☐	☐	☐	
Peeled shrimps	☐	☐	☐	
Shrimps on sandwich or baguettes	☐	☐	☐	
Shrimp salad, crayfish salad etc.	☐	☐	☐	
Crabsticks	☐	☐	☐	
Scampi, prawns	☐	☐	☐	
Crabs, lobster	☐	☐	☐	
Crayfish	☐	☐	☐	
Mussels, scallops, oyster, clams	☐	☐	☐	
Snails, squids	☐	☐	☐	
Paella etc.	☐	☐	☐	
Salads with shellfish or mussels	☐	☐	☐	
Other food with shellfish or mussels	☐	☐	☐	

Milk and milk products

29. Did you eat or drink any of the following milk products?

	Yes	No	Unsure	Where / when / brand / type / store / restaurant
Unpasteurized milk	☐	☐	☐	
Food made of unpasteurized milk	☐	☐	☐	
Chocolate milk etc.	☐	☐	☐	
Cream, whipped cream	☐	☐	☐	
Milk shake, banana split	☐	☐	☐	
Soft ice	☐	☐	☐	
Ice-cream, wrapped	☐	☐	☐	
Ice-cream, scooped	☐	☐	☐	
Ice-cream, homemade	☐	☐	☐	
Yoghurts	☐	☐	☐	
Yoghurt dressing, tzatziki o.l.	☐	☐	☐	
Sour milk, kefir, buttermilk etc.	☐	☐	☐	
Sour cream, crème fraiche	☐	☐	☐	
Sour cream dressing or dips	☐	☐	☐	

Bakery, pastry and cakes

30. Did you eat any of the following bakery, pastry or cakes?

If yes, was the food: (1) bought in patisserie, restaurant or another catering business, (2) bought in a grocery store, (3) or was it homemade? Specify the kind of fill and topping on the cakes.

	Yes	No	Unsure	Where / when / brand / type / store / homemade
Sweet rolls with fill, topping or cream	☐	☐	☐	
Danish pastry	☐	☐	☐	
Cream cake, layer cake	☐	☐	☐	
Swiss rolls, apple strudel	☐	☐	☐	
Cheesecakes, chocolate cakes	☐	☐	☐	
Other cakes with filling or icing	☐	☐	☐	
Muffins, chocolate biscuits, brownies	☐	☐	☐	
Biscuits with filling	☐	☐	☐	
Other cakes or biscuits	☐	☐	☐	
Waffles, pancakes	☐	☐	☐	
Store-bought cake mix / batter	☐	☐	☐	
Store-bought waffle mix / batter	☐	☐	☐	
Store-bought pancake batter	☐	☐	☐	
Ready-to-eat rolls, bagels	☐	☐	☐	
Ready-to-eat baguettes, sandwiches	☐	☐	☐	

Cheeses

31. Did you eat any soft cheeses?

	Yes	No	Unsure	Hvor / når / merke / type / butikk
Blue Castello, Danablue, stilton etc.	☐	☐	☐	
Roquefort, gorgonzola etc.	☐	☐	☐	
Other blue mold cheeses	☐	☐	☐	
Camembert, brie etc.	☐	☐	☐	
Other white mold cheeses	☐	☐	☐	
Dessert cheeses	☐	☐	☐	
Spiced soft cheeses	☐	☐	☐	
Feta, fetina	☐	☐	☐	
Mozzarella	☐	☐	☐	
Cottage cheese, kesam, quark, curd	☐	☐	☐	
White goat cheese	☐	☐	☐	
Other soft cheeses	☐	☐	☐	
Salads with cheese	☐	☐	☐	
Cheese soufflé, cheese pie	☐	☐	☐	

Were any of the cheeses made from unpasteurized milk?	
Yes ☐ No ☐ Unsure ☐	What kind of cheese?

Were any of the cheeses produced abroad?	
Yes ☐ No ☐ Unsure ☐	What kind of cheese?

Did you eat sliced, grated or shredded cheese, which was bought in a store?	
Yes ☐ No ☐ Unsure ☐	What kind of cheese?

Spices and herbs

32. Did you eat any foods with dried spices or dried herbs?

Please note if the spices were added before or during heat treatment or after the food was finished.

	Yes	No	Unsure	Where / when / brand / type / store
Black pepper, black pepper mixtures	☐	☐	☐	
Paprika / pepper powder	☐	☐	☐	
Chili powder, ground dried chili	☐	☐	☐	
Barbecue spices, pizza spices etc.	☐	☐	☐	
Spices for tacos, fajitas, burritos etc.	☐	☐	☐	
Curry	☐	☐	☐	
Cumin, turmeric	☐	☐	☐	
Other dried spices or spice mixtures	☐	☐	☐	

	Yes	No	Unsure	Where / when / brand / type / store
Cinnamon, cinnamon sticks	☐	☐	☐	
Nutmeg, ginger, cloves, caraway	☐	☐	☐	
Cardamom, vanilla, saffron	☐	☐	☐	
Dried chives, parsley, dill	☐	☐	☐	
Dried basil, oregano, thyme	☐	☐	☐	
Laurel leaves, juniper berries	☐	☐	☐	
Other dried herbs	☐	☐	☐	

33. Did you eat any food with fresh (not dried) herbs?

Also include fresh herbs used in salads and as garnish for hot dishes, toppings, sandwiches and baguettes.
Did you eat the herbs raw (without heat treatment) or were they heat-treated (for instance added to a casserole, stew or soup)?

	Yes	No	Unsure	Where / when / brand / type / store / eaten raw?
Parsley, leaf parsley	☐	☐	☐	
Chives	☐	☐	☐	
Dill, coriander	☐	☐	☐	
Oregano, basil, thyme, mint	☐	☐	☐	
Rosemary, sage	☐	☐	☐	
Lemongrass	☐	☐	☐	
Exotic herbs - imported	☐	☐	☐	
Other fresh herbs	☐	☐	☐	

Lettuce and sprouts

34. Did you eat lettuce or sprouts?

Also include lettuce and sprouts used in salads and as garnish for hot dishes, toppings, sandwiches and baguettes etc.

	Yes	No	Unsure	Where / when / brand / type / store / restaurant
Leaf lettuce, head lettuce	☐	☐	☐	
Iceberg lettuce, Chinese cabbage	☐	☐	☐	
Ruccola / rocket lettuce	☐	☐	☐	
Raddichio rosso	☐	☐	☐	
Heart lettuce, frieze, rapid, lollo	☐	☐	☐	
Fresh spinach	☐	☐	☐	
Baby spinach, baby leaves	☐	☐	☐	
Sliced or shredded lettuce	☐	☐	☐	(Store-bought)
Ready-made salad with lettuce	☐	☐	☐	(Store-bought)
Other kinds of lettuce	☐	☐	☐	
Bean sprouts, alfalfa sprouts, cress	☐	☐	☐	
Other sprouts	☐	☐	☐	
Salad dressings	☐	☐	☐	
Did you eat food from a salad bar?	☐	☐	☐	

Vegetables and mushrooms

35. Did you eat vegetables or mushrooms?

Please also include raw vegetables and mushrooms used in salads or as garnish for hot dishes, toppings, sandwiches, baguettes and rolls. Did you eat the vegetables/mushrooms raw or were they heat-treated (for instance boiled, wok-fried, added to a casserole, stew or soup)? (Do not include canned products)

	Yes	No	Unsure	Where / when / brand / type / store Eaten raw?
Tomato	☐	☐	☐	
Cucumber	☐	☐	☐	
Pepper, paprika	☐	☐	☐	
Broccoli, cauliflower	☐	☐	☐	
Carrots, radishes	☐	☐	☐	
Cabbage, Brussel sprouts	☐	☐	☐	
Sauerkraut, pickled cabbage	☐	☐	☐	
Rutabaga, turnip, beets	☐	☐	☐	
Celery sticks, celery root, parsley root	☐	☐	☐	
Sugar peas, sugar snaps	☐	☐	☐	
Beans, green beans	☐	☐	☐	
Corn, corn on the cub, mini maize	☐	☐	☐	
Onion, garlic, shallot, leek	☐	☐	☐	
Pumpkins	☐	☐	☐	
Ginger	☐	☐	☐	
Fennel, asparagus, artichoke	☐	☐	☐	
Chili, Spanish pepper, horseradish	☐	☐	☐	
Avocado, squash, aubergine	☐	☐	☐	
Frozen vegetables	☐	☐	☐	
Frozen vegetable mixtures	☐	☐	☐	
Mushrooms, chanterelles etc.	☐	☐	☐	
Other vegetables or mushrooms	☐	☐	☐	
Vegetables from a family garden	☐	☐	☐	
Pickled onion, pickled cucumber etc.	☐	☐	☐	
Pickled beets	☐	☐	☐	
Fried onion, onion rings	☐	☐	☐	
Capers	☐	☐	☐	
Dried tomatoes	☐	☐	☐	
Dried tomatoes in olive oil	☐	☐	☐	
Olives	☐	☐	☐	
Pickled olives	☐	☐	☐	
Filled grape leaves, dolmades	☐	☐	☐	
Chestnuts	☐	☐	☐	

Fruits and berries

36. Did you eat any fruits?

Please also include fruits used in fruit salads, vegetable salads, or as garnish on warm or cold dishes, or as topping on cakes or sandwiches? Did you eat the fruits raw, or were they heat-treated? (Do not include canned products)

	Yes	No	Unsure	Where / when / brand / type / store Eaten raw?
Apples, pears, plums	☐	☐	☐	
Bananas	☐	☐	☐	
Grapes	☐	☐	☐	
Oranges, mandarins, clementines	☐	☐	☐	
Grapefruit, lemon, lime	☐	☐	☐	
Melons, cantaloupe, honeydew	☐	☐	☐	
Peaches, nectarines, apricots	☐	☐	☐	
Kiwi, mango, papaya, pineapple	☐	☐	☐	
Passion fruit, pomegranate	☐	☐	☐	
Physalis, carambola, litchi	☐	☐	☐	
Other fruits	☐	☐	☐	
Fruits picked on the ground	☐	☐	☐	
Rhubarb	☐	☐	☐	
Jam with fruits, store-bought	☐	☐	☐	
Jam with fruits, homemade	☐	☐	☐	
Marmalades	☐	☐	☐	
Chutney	☐	☐	☐	
Honey	☐	☐	☐	

37. Did you eat any berries?

Please also include berries eaten together with other food, for instance in salads, or on cakes or with ice cream. (Do not include canned products). Did you eat the berries raw or were they heat-treated?

	Yes	No	Unsure	Where / when / brand / type / store Eaten raw?
Strawberries	☐	☐	☐	
Raspberries	☐	☐	☐	
Cherries	☐	☐	☐	
Red or black currants, gooseberries	☐	☐	☐	
Boysenberries, blackberries	☐	☐	☐	
Blueberries	☐	☐	☐	
Lingonberries	☐	☐	☐	
Cloudberries, cranberries	☐	☐	☐	
Other berries	☐	☐	☐	
Frozen berries, store-bought	☐	☐	☐	
Dried berries, store-bought	☐	☐	☐	
Jam with berries, store-bought	☐	☐	☐	
Jam with berries, homemade	☐	☐	☐	

Nuts, dried fruits, sweets and snacks

38. Did you eat nuts, dried, fruits, sweets or snacks?

	Yes	No	Unsure	When / where / brand / type / store
Nuts, kernels and seeds:				
Hazelnuts	☐	☐	☐	
Walnuts	☐	☐	☐	
Peanuts	☐	☐	☐	
Almonds, almond flakes	☐	☐	☐	
Cashews	☐	☐	☐	
Pecans, pistachio, macadamia	☐	☐	☐	
Nut mixes	☐	☐	☐	
Pine nuts	☐	☐	☐	
Sunflower seeds, melon seeds	☐	☐	☐	
Coconuts, minced coconut	☐	☐	☐	
Sesame seeds, linseeds	☐	☐	☐	
Other nuts, kernels or seeds	☐	☐	☐	
Cereal / muesli with nuts or seeds	☐	☐	☐	
Halva, tahini, hummus etc.	☐	☐	☐	
Dried fruits:				
Raisins, Corinthians	☐	☐	☐	
Dates, figs	☐	☐	☐	
Prunes	☐	☐	☐	
Dried apricot, candid fruit peels	☐	☐	☐	
Other dried fruits	☐	☐	☐	
Cereal / muesli with dried fruits	☐	☐	☐	
Cereal / muesli with dried berries	☐	☐	☐	
Other cereals or muesli	☐	☐	☐	
Sweets and candy:				
Chocolates, confectionary	☐	☐	☐	
Marzipan	☐	☐	☐	
Caramels	☐	☐	☐	
Sweets, candy, tidbits	☐	☐	☐	
Licorice	☐	☐	☐	
Turkish delight, jelly tops	☐	☐	☐	
Other sweets	☐	☐	☐	
Snacks:				
Potato chips, crisps, shrimp chips	☐	☐	☐	
Popcorn	☐	☐	☐	
Croutons, grissini, breadsticks	☐	☐	☐	
Other snacks	☐	☐	☐	
Dips or sauces for chips and crisps	☐	☐	☐	
Mustard, ketchup etc.	☐	☐	☐	

	Yes	No	Unsure	When / where / brand / type / store
Nut toppings and sweet toppings:				
Peanut butter	☐	☐	☐	
Hazelnut butter	☐	☐	☐	
Chocolate spread	☐	☐	☐	
Other	☐	☐	☐	

Desserts and sweet sauces

39. Did you eat sweet puddings, sauces, creams or compotes?

If yes, was the product: (1) bought at a restaurant or other catering establishment, (2) bought ready-to-eat in a store or (3) was it homemade?

	Yes	No	Unsure	Where / when / brand / type / store
Chocolate pudding, almond pudding	☐	☐	☐	
Caramel pudding, other puddings	☐	☐	☐	
Crème brûlée, fromage, mousse	☐	☐	☐	
Sorbets, jelly	☐	☐	☐	
Caramel sauce, chocolate sauce	☐	☐	☐	
Custard, vanilla cream, egg custard	☐	☐	☐	
Chocolate cream	☐	☐	☐	
Strawberry sauce, raspberry sauce	☐	☐	☐	
Other sweet sauces or creams	☐	☐	☐	
Prune compote, fruit compote	☐	☐	☐	
Other compotes or desserts	☐	☐	☐	

Juices and sweet beverages

40. Did you eat or drink any of the following products?

	Yes	No	Unsure	Where / when / brand / type / store
Orange juice	☐	☐	☐	
Apple juice, apple cider	☐	☐	☐	
Pear juice	☐	☐	☐	
Grape juice	☐	☐	☐	
Other fruit juices or ciders	☐	☐	☐	
Carrot juice	☐	☐	☐	
Other vegetable juices	☐	☐	☐	
Other juices or lemonades	☐	☐	☐	
Ice tea, ice coffee (store bought)	☐	☐	☐	
Smoothies etc.	☐	☐	☐	

Organic foods

41. Did you eat any organic vegetables, fruits, milk, cheese, meat, eggs, or other organic foods?

Yes ☐ No ☐ Unsure ☐	
If yes, what kind of products?	

Natural medicines and dietary supplements

42. Did you use natural or organic medicines, naturopathy, slimming products or dietary supplements?

Yes ☐ No ☐ Unsure ☐	If yes, what kind of products?

Foods purchased abroad

43. Did you eat meat or other foods, which were purchased abroad? (Do not include canned products)

	Yes	No	Unsure	Where / when / brand / type / store / country
Poultry (chicken, turkey, hens)	☐	☐	☐	
Pork	☐	☐	☐	
Beef	☐	☐	☐	
Lamb, mutton	☐	☐	☐	
Hamburgers, meat balls	☐	☐	☐	
Minced meat, forced meat	☐	☐	☐	
Hot dogs, sausages	☐	☐	☐	
Cold cuts	☐	☐	☐	
Salami, salted or cured sausages	☐	☐	☐	
Other salted or cured meats	☐	☐	☐	
Pates, pies etc.	☐	☐	☐	
Soft cheeses, other cheeses	☐	☐	☐	
Chocolate, sweets, snacks etc.	☐	☐	☐	
Fruits	☐	☐	☐	
Vegetables, herbs, mushrooms	☐	☐	☐	
Spices	☐	☐	☐	
Other foods purchased abroad	☐	☐	☐	

Foods with unpleasant taste, smell or color

44. Did you eat any food with unpleasant taste, smell, color or appearance?

Yes ☐ No ☐ Unsure ☐	If yes, what kind of food?

Foods that had passed the expiration date

45. Did you eat any food, which had passed the expiration date or best-before-date?

Yes ☐ No ☐ Unsure ☐	If yes, what kind of food?

Food stores

46. Did you eat food purchased in a delicatessen store or deli-counter?

Yes ☐ No ☐ Unsure ☐ If yes, what kind of foods - and in which stores were they purchased?

47. In which stores were foods you ate in the week before your illness purchased?

Groceries:	
Meat and fish:	
Vegetables and fruits:	
Other fresh foods:	
Delicatessen:	
Other foods:	

Other foods

48. Did you eat any other foods that we have not mentioned so far?

Yes ☐ No ☐ Unsure ☐ If yes, what kind of foods - and in which stores were they purchased?

Contact with animals

49. Did you have contact with animals or birds, or with their droppings or feed?

	Yes	No	Unsure	Where? When?
Livestock and pets:				
Dog	☐	☐	☐	
Cat	☐	☐	☐	
Cattle	☐	☐	☐	
Pig	☐	☐	☐	
Sheep, goat	☐	☐	☐	
Horse, pony	☐	☐	☐	
Chicken, hens, turkeys, ducks, geese	☐	☐	☐	
Cage bird	☐	☐	☐	
Rabbit, guinea pig, hamster	☐	☐	☐	
Mouse or rat – as pets	☐	☐	☐	
Aquarium fishes	☐	☐	☐	
Turtles, snakes, reptiles	☐	☐	☐	
Other livestock or pets	☐	☐	☐	
Wild-living animals:				
Seagulls	☐	☐	☐	
Small birds, bird feeders, bird tables	☐	☐	☐	
Grouse, ptarmigan, pheasant				
Other wild-living birds	☐	☐	☐	
Wild mice, mouse droppings	☐	☐	☐	
Elk, moose, deer, reindeer, roe deer	☐	☐	☐	
Fox, wolf, bear	☐	☐	☐	
Hare, rabbit, beaver	☐	☐	☐	
Hedgehogs	☐	☐	☐	
Other wild-living animals or birds	☐	☐	☐	
Are there birds in your garden?	☐	☐	☐	
Did you feed the birds?	☐	☐	☐	
Other animals in the garden?	☐	☐	☐	
Did you feed them?	☐	☐	☐	
Visiting a farm or a zoo:				
Did you visit a zoo?	☐	☐	☐	
Did you visit a farm with animals?	☐	☐	☐	
Did you buy milk there?	☐	☐	☐	
Did you by cheese or other food?	☐	☐	☐	
Did you drink water or juice there?	☐	☐	☐	
Were you hunting for food or sport?	☐	☐	☐	

Bathing and swimming

50. Did you bathe or swim in the seas, in a lake or in a pool?

	Yes	No	Unsure	Where? When?
In the sea	☐	☐	☐	
In a lake, river or brook	☐	☐	☐	
Outdoor pool, hot tub, outdoor spa	☐	☐	☐	
Indoor pool, indoor spa, whirlpool	☐	☐	☐	

Closing questions

51. Did you eat any food that was not eaten by other, healthy, members of your household?

Yes ☐ No ☐ Unsure ☐	If yes, what kind of food?

52. Do you have any leftovers of the food you ate in the last week before your illness onset?

Do not dispose of leftovers or the packaging – keep everything in the fridge, even from the trash.

Yes ☐ No ☐ Unsure ☐	If yes, what kind of food?

53. What do you think is the cause of your disease? Do you suspect a particular food item, meal or dish? Why?

Please note how the suspected food was prepared, stored, served or purchased (if this is known):

Thank you for your help!

Medical and socioeconomic impact questionnaire (used if needed)

Medical and socioeconomic impact and underlying diseases

How many days or hours were you ill?

Days or hours of illness duration:	
Have your symptoms resolved now?	Yes ☐ No ☐ Unsure ☐

How many days did you stay home from work or school due to your illness?

If the patient is a child (or a person needing attention for other reasons): How many days did the parents or other guardians stay home from work or school to care for the sick child?

Number of lost workdays / schooldays:	

Did you contact a doctor for this disease?

Number of medical visits:	
Number of telephone calls to a doctor:	
Was a stool sample collected?	Yes ☐ No ☐
Were other samples taken?	Yes ☐ No ☐ What kind?
Did you get a sick leave note?	Yes ☐ No ☐ For how many days?
Did you receive antibiotics?	Yes ☐ No ☐ What kind?
Did you get any other presciption / treatment?	Yes ☐ No ☐ What kind?

Were you admitted to hospital because of this illness?

Yes ☐ No ☐	
When were you hospitalized?	Date:
For how many days were you hospitalized?	Number of days:
Did you receive antibiotics there?	Yes ☐ No ☐ What kind?
Did you receive intravenious fluid?	Yes ☐ No ☐ For how many days?
Did you get any other medication / treatment?	Yes ☐ No ☐ What kind?

Did you take any other medicines or drugs for this disease?

Medicines againts pain or fever	Yes ☐ No ☐ What kind?
Medicines against diarrhea	Yes ☐ No ☐ What kind?
Natural or organic medicines	Yes ☐ No ☐ What kind?
Alternative therapy	Yes ☐ No ☐ What kind? (e.g. homeopathy)

Do you suffer from any chronic diseases?

	Yes	No	Unsure	Comments:
Gastric ulcers, gastritis	☐	☐	☐	
Dyspepsia, gastric acid reflux symptoms	☐	☐	☐	
Chronic diarrhea	☐	☐	☐	
Ulcerative colitis, Crohn's disease	☐	☐	☐	
Celiac disease	☐	☐	☐	
Lactose intolerance	☐	☐	☐	
Other food allergies or intolerances	☐	☐	☐	
Other gastrointestinal problems	☐	☐	☐	
Diabetes	☐	☐	☐	
Liver disease	☐	☐	☐	
Rheumatic disease	☐	☐	☐	
Immunodeficiency	☐	☐	☐	
Other chronic diseases	☐	☐	☐	

Did you take any medicines during the month before your illness started? (Check the glass or package)

	Yes	No	Unsure	What kind? Do you take this medicine regularly?
Antibiotics	☐	☐	☐	
Medicines against gastric ulcer	☐	☐	☐	
Anta vids, medicines against gastric acid	☐	☐	☐	
Insulin – against diabetes	☐	☐	☐	
Cortisone, steroids	☐	☐	☐	
Other immune-suppressive medicines	☐	☐	☐	
Food supplements, vitamins	☐	☐	☐	
Organic or natural medicines	☐	☐	☐	
Other medicines	☐	☐	☐	

7. Retrospective cohort study - Instruction

User instructions for design, conduct and analysis

Designing questionnaires

The scheme provided in these guidelines is a provisional template, which may be used to elaborate a questionnaire in retrospective cohort studies. Cohort studies are appropriate in outbreaks in which only one single or a few meals have been consumed by a limited number of persons – a cohort (e.g. the guest at a party or in a hotel, participants at a conference, children in a daycare center, inhabitants of a nursing home etc.) as explained in section 10.2. In such outbreaks, it may be possible to obtain a list of every meal, dish and food item, which was served, for instance in terms of a menu. Hence, the template questionnaire can be edited according to that list.

The questionnaire is available in Word format enabling adaption to the current outbreak by entering the food items and dishes that was served:

- Template questionnaire for cohort studies (Appendix 8)

Conducting interviews

The questionnaire should preferably be forwarded to all members of the outbreak population (i.e. the cohort - everyone who was present), regardless of whether they became ill or not. It is not necessary to know in advance who became ill, since this is explored by separate enquiries in the questionnaire. If the cohort is large a random selection of the outbreak populations may be interviewed, but the statistical power of the ensuing analyses will be reduced proportionally.

If the number of persons in the outbreak population is very low, and a cohort study consequently is infeasible for statistical reasons, it may still be useful to conduct interviews with patients in the cohort in order to generate hypotheses about the source of infection. The questionnaire is then used in the same way as in hypothesis-generating pilot interviews (section 9.3), but the queries are restricted to the few dishes or food items that were served.

An introductory letter that explains the reason for the enquiry and motivates the recipients to respond (see below) should accompany the questionnaire. The questionnaire and the introductory letter can be conveyed by mail or, more conveniently, by email. If the inquiry is forwarded by mail, it should be accompanied by prepaid and pre-addressed return envelope.

Telephone interviews may sometimes be convenient. Although this approach is labor-intensive, rapid collection of data is possible, and the interviewer can correct misinterpretations while talking to the respondent, thus improving the quality of the information. Moreover, it is not necessary to send a reminder to non-responders since everyone is contacted directly.

The questionnaire may be uploaded in an online survey system and subsequently sent by email to members of the cohort together with an introduction. In outbreaks where employees in an enterprise or institution are affected, the company's intranet can be used. When telephone interviews are conducted, the interviewer can enter data directly into the questionnaire form.

Analysis

Results may be entered manually into a database, which is then analyzed. Most online survey systems will automatically generate a database that is ready for subsequent analysis.

The free software program OpenEpi contains statistical routines enabling direct online calculation of risk ratios and odds ratios with confidence intervals and p-values by entering data for each exposure into two-by-two tables as shown in Figure 10.5 (section 10.3). The program is available on www.openepi.com

The free software program EpiData may be used to develop questionnaires, enter data directly into the questionnaire form during an interview, and conduct analyses. The program can be downloaded from www.epidata.dk. The European Centre for Disease Control (ECDC) has provided a toolkit for investigation and response to food- and waterborne outbreaks affecting several EU member states, in which the use of EpiData is explained.

If there is doubt whether a person is a case (for example, people with non-specific symptoms), he or she must be excluded from all analyses. Persons who are unsure whether they have eaten or drunk one or more foods items, must be excluded from the analysis of these particular foodstuffs, but are included for all other exposures.

The introductory letter

The respondents should be informed that they are part of an important and exciting outbreak investigation, and that their contribution is essential to identification of the source of infection. It is also necessary to emphasize that participation is voluntary and that all information will be treated strictly confidential.

In the introductory letter, it is required to underline that information from those who did not become ill are crucial in order to allow comparison of their consumptions with what the patients ate. This is frequently misunderstood; many people believe that only those who were ill are encouraged to participate in the survey.

Confidentiality

All information enabling identification of individuals are subject to moral and statutory secrecy and should be treated in accordance with prevailing laws and regulations.

More information about cohort studies and case-control studies are presented in section 10.2.

8. Cohort study – Template questionnaire

The questionnaire is available in Word-format to facilitate adaption to the current outbreak and to local conditions and food habits.

Cohort Questionnaire.docx

COHORT INVESTIGATION OF A FOODBORNE OUTBREAK

Date the questionnaire was completed: ☐

■ Information about the respondent

Name:	
Date of birth:	
Address:	
Telephone, e-mail:	

Did you attend [insert name of party, meal etc. and date]? Yes ☐ No ☐

If the answer is NO, you need NOT answer the remaining questions, but please submit the questionnaire.

During the week after the [insert name of party, meeting, meal] did you develop vomiting, diarrhea, abdominal pain or other stomach symptoms?

Yes ☐ No ☐ Unsure ☐ Comments:

If the answer is NO, skip the remaining questions on this page, but please answer the questions on the following two pages.

■ Questions to be answered by those who became ill, only

What kind of symptoms did you have?

Please specify when the symptoms started (date, time) and how long they lasted (no. of days or hours)

	Yes	No	Unsure	When did the symptoms start? Duration?
Nausea	☐	☐	☐	
Vomiting	☐	☐	☐	
Abdominal pain	☐	☐	☐	
Diarrhea	☐	☐	☐	
Bloody stools	☐	☐	☐	
Fever	☐	☐	☐	Temperature?
Other symptoms	☐	☐	☐	

When did you become ill? Date and time:	
Are you still sick?	Yes ☐ No ☐ Unsure ☐
If no, how long lasted your disease? No. of days or hours:	
Did you visit a doctor?	Yes ☐ No ☐

■ **Questions to be answered by everyone, regardless of whether you became ill or not**

Below is a list of all food items that was served [insert food items from the menu).

Please answer ALL questions:

Tick «yes» if you most likely ate the food, check «no» for the dishes you most likely did not eat.

If in doubt, check the «unsure».

Did you eat any of the warm dishes?

[Fill in dishes from the menu]	Yes	No	Unsure	Comments:
Dish 1	☐	☐	☐	
Dish 2	☐	☐	☐	
Dish 3	☐	☐	☐	
Dish 4	☐	☐	☐	
Dish 5	☐	☐	☐	
Dish 6	☐	☐	☐	

Did you eat any of the cold meat dishes?

	Yes	No	Unsure	Comments:
Dish 1	☐	☐	☐	
Dish 2	☐	☐	☐	
Dish 3	☐	☐	☐	
Dish 4	☐	☐	☐	
Dish 5	☐	☐	☐	
Dish 6	☐	☐	☐	

Did you eat any of the cold dishes with fish or shellfish?

	Yes	No	Unsure	Comments:
Dish 1	☐	☐	☐	
Dish 2	☐	☐	☐	
Dish 3	☐	☐	☐	
Dish 4	☐	☐	☐	
Dish 5	☐	☐	☐	
DIsh 6	☐	☐	☐	

Did you eat any of the vegetable salads or other salads?

	Yes	No	Unsure	Comments:
Dish 1	☐	☐	☐	
Dish 2	☐	☐	☐	
Dish 3	☐	☐	☐	
Dish 4	☐	☐	☐	
Dish 5	☐	☐	☐	
Dish 6	☐	☐	☐	

Did you eat any desserts, cheeses or fruits?

	Yes	No	Unsure	Comments:
Item 1	☐	☐	☐	
Item 2	☐	☐	☐	
Item 3	☐	☐	☐	
Item 4	☐	☐	☐	
Item 5	☐	☐	☐	
Item 6	☐	☐	☐	

Which beverages did you drink?

	Yes	No	Unsure	Comments:
Item 1	☐	☐	☐	
Item 2	☐	☐	☐	
Item 3	☐	☐	☐	
Item 4	☐	☐	☐	
Item 5	☐	☐	☐	
Item 6	☐	☐	☐	

Thank you for your help!