Working Party on Biotechnology

BASINGSTOKE MEETING:
“ESTABLISHING LINKS BETWEEN DRINKING WATER AND INFECTIOUS DISEASES”
The following policy report summarises the conclusions of the Basingstoke 2000 Expert Group Meeting, which took place in Basingstoke, hosted by the Government of the United Kingdom, on 9-11 July 2000. The text was drafted by Sarah Woodhouse and Paul Hunter with the contribution of Mike Waite, and Elettra Ronchi of the OECD Secretariat.

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TABLE OF CONTENTS

FOREWORD ............................................................................................................................................. 2

BASINGSTOKE 2000 EXPERT GROUP MEETING ON: “APPROACHES FOR ESTABLISHING LINKS BETWEEN DRINKING WATER AND INFECTIOUS DISEASES” (BASINGSTOKE, UNITED KINGDOM, 9-11 JULY 2000) .......................................................................................................................... 4

Executive Summary .......................................................................................................................... 4

THE BASINGSTOKE WORKSHOP  THE ISSUES ................................................................................... 7

  Summary of Workshop Sessions ..................................................................................................... 7
  Session 1: Surveillance of waterborne disease ................................................................................. 7
  Session 2: A system approach to Outbreak investigation ............................................................... 13
  Session 3: Use of water quality, treatment and distribution data to assess human health risk ........ 17
  Session 4: Epidemiological approaches to assessing endemic waterborne disease burden .......... 21

Tables

Table 1. Issues that might affect efficient utilisation of water and health data .................................. 5
Table 2. Issues that might affect efficient utilisation of water and health data .................................. 19
Executive Summary

Poor quality drinking water and inadequate sanitation are among the world’s major preventable causes of early mortality. According to World Health Organisation estimates, contaminated drinking water is responsible for some five million deaths each year. Risk of death is particularly high for children. A child dies every eight seconds from a preventable water or sanitation-related disease. The problem is not limited to developing countries. Even in OECD countries, waterborne outbreaks occur all too frequently, without necessarily being recognised as such. During the years 1991-98, there were 35 outbreaks of disease linked to drinking water in the United Kingdom and 113 in the United States. Yet despite the clear importance of drinking water as a cause of infectious disease, very little consideration has been given to how best to investigate the relationship between the two.

The need to achieve a better understanding of water’s role in the transmission of infectious disease was officially acknowledged by the international community in 1996 at the OECD Workshop on Biotechnology for Water Use and Conservation in Cocoyoc, Mexico. Then, in 1998, the OECD Interlaken Workshop on Molecular Technologies for Safe Drinking Water reviewed the effectiveness of drinking water plants in preventing the passage of microbial contaminants and the reliability of current indicators as means to guarantee microbiologically safe water to consumers. Recommendations from that Workshop highlighted the need for better approaches and methods to assess the safety of drinking water and to monitor and respond to adverse events.

In response, the UK Government hosted in July 2000 an OECD expert group meeting, “Approaches for Establishing Links between Drinking Water and Infectious Disease”, to address the following questions in particular:

- **What is the minimum appropriate surveillance system for Member countries to have in place to "identify outbreaks or incidents of water-related disease or significant threats of such outbreaks"?**
- **What are appropriate “indicators or technical developments to monitor system performance in preventing, controlling or reducing water-related disease” for Member countries to use?**
- **What are the “appropriate comprehensive national and local contingency plans for responses to such outbreaks” to be developed by Member countries?**

Accordingly, 26 presentations were made on four key topics:

- **Surveillance of Waterborne Disease**
- **Outbreak Investigation**
- **Use of Water Quality, Treatment and Distribution Data to Assess Human Health Risk**
- **Epidemiological Approaches to Assessing Endemic Waterborne Disease Burden**
Participants agreed on a number of important conclusions:

- They recognised that there were two main sources of data on the risk to health from drinking water: *i)* epidemiological data from surveillance systems and other studies, and *ii)* data on water quality collected by the water utility. The advantages and disadvantages of these sources differ in terms of assessing risk to health (Table 1).

<table>
<thead>
<tr>
<th>Water data</th>
<th>Health data</th>
</tr>
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<tbody>
<tr>
<td>Comprehensiveness varies between countries</td>
<td>Non-standardised</td>
</tr>
<tr>
<td>Usually geared towards statutory reporting</td>
<td>Need to maintain flexible methodological approach</td>
</tr>
<tr>
<td>Under-utilised</td>
<td>Frequently reactive</td>
</tr>
<tr>
<td>Not easily accessible to public health community</td>
<td>Lack of geographical resolution</td>
</tr>
<tr>
<td>Commercial sensitivity</td>
<td>Incomplete</td>
</tr>
<tr>
<td>Might under-estimate health risks</td>
<td>Not timely</td>
</tr>
<tr>
<td>Much data may not be timely</td>
<td>Potentially subject to significant bias</td>
</tr>
</tbody>
</table>

*Source: OECD Biotechnology Unit.*

In addressing these differences the following general considerations apply:

- Current water quality data are mainly driven by statutory standards, which may or may not relate to health risks.
- Water quality data is often comprehensive but under-utilised by the public health community.
- Data sharing between water suppliers and the public health community should be encouraged and each should take account of the other’s needs when collecting data.

In addition, in devising surveillance systems for waterborne diseases the following general criteria should be considered:

- Surveillance systems for waterborne diseases are only valuable if they lead to improved protection of public health or confirm the adequacy of current practices.
- Surveillance and outbreak investigation must inform policy so that mistakes leading to outbreaks are not repeated.
- Surveillance information should inform economic analyses of costs and benefits of changes in water treatment regimens.
- Consideration needs to be given to how the public health benefits of surveillance can be balanced with individual human rights to privacy. Countries are invited to examine approaches to improve security of data flows.
- Most surveillance systems are disease-specific or symptom-complex-specific. Appropriate additional information needed to aid linkages with water as a risk factor should be considered. The multidisciplinary nature of such systems should be recognised.

Outbreaks probably represent only a small proportion of cases of infectious disease caused by drinking water. Existing surveillance systems may not detect sporadic cases. Even if sporadic cases are identified by current surveillance systems, the role of drinking water may be far from clear. This is likely to be a
particular problem for emerging waterborne infectious diseases. To improve the detection of the links between sporadic cases and drinking water, the following issues should be addressed:

- Vigilance should be maintained on the surveillance of emerging and chronic infectious diseases, including disease in populations at particular risk of infection or severe outcomes of illness.
- Appropriate epidemiological tools and surrogate indicators are needed to determine levels of waterborne disease, including the potential consequences of infrequent adverse events (e.g. floods, sudden contamination, treatment failures, and conflicts).
- It is crucial to develop adequate real-time measurement or predictive models in order to understand the link between water safety and health.
- Public health protection should focus on critical control points throughout the water supply chain and on developing adequate indicators to assess the health impacts of water quality in distribution systems.
- When assessing any of the various types of studies of sporadic disease and water, it is important to acknowledge the intrinsic advantages and disadvantages of the proposed study design.
- Consideration needs to be given to how studies of waterborne disease can be adapted for use in developing countries.

Finally, participants agreed that there is great variation in the nature of surveillance systems across OECD countries, which makes country-to-country comparisons difficult and that international initiatives are urgently needed to:

- Identify the best approaches to surveillance and outbreak investigation.
- Strengthen the linkage of current international disease-based surveillance systems and environmental surveillance networks to integrate data on surveillance of waterborne diseases (the current review of the International Health Regulations should be encouraged to achieve this).
- Develop new surveillance tools, such as neural networks and Geographical Information Systems.
- Encourage data sharing on outbreaks across the OECD area, in particular to address adverse events with transboundary health and environmental impacts.
THE BASINGSTOKE WORKSHOP

THE ISSUES

Summary of Workshop Sessions

Session 1: Surveillance of waterborne disease

In order to provide a framework for considering surveillance systems, attention has to be first directed at current systems. The first session considered existing surveillance systems at the local, national and international level. To illustrate these different levels of surveillance system, experience from three countries, the United Kingdom, the United States and Sweden was discussed. In order to set subsequent discussion in a theoretical framework, the session commenced with a consideration of the theoretical principles of public health surveillance.

Principles and components of surveillance systems

For a surveillance system to be effective and to be properly evaluated, there has to be clarity about three key factors: the purpose of the surveillance system, the health problem being addressed and the target population.

Surveillance systems may serve a number of purposes:

- To enable implementation of control measures by identifying outbreaks and adverse events early and also identifying patterns of disease and risk factors.
- To evaluate the impact of prevention and control programmes.
- To project future health care needs.

The health problem to be addressed is defined by the case definition which may be based on a self-reported symptom complex or clinically suspected or laboratory proven disease. The target population may be the general population or a sub-group such as school children, occupational group, hospitalised patients or those with known high-risk exposure. The main features of a system are the data set, data flow, analysis, outputs and outcomes.

Outcomes can only be interpreted in light of the stated objectives of the system. Most importantly, the question to be answered is “Does it assist in improving the public’s health?”

The aspects of a system amenable to evaluation are its sensitivity, timeliness, representativeness, positive predictive power, acceptability, flexibility, simplicity and costs. An important issue also to consider is patient confidentiality.
Surveillance at local level

The fundamental principles of local surveillance are that it should provide useful data for local action and that these data should also feed into regional and national surveillance. It is distinct from research, although it could inform research.

In the United Kingdom local surveillance is the responsibility of the Consultant in Communicable Disease Control (CCDC) on behalf of district health authorities. A typical health authority covers on average two hospitals, three local authorities, three laboratories and a population of approximately 450 000. Environmental Health Officers (EHOs) are employed by local authorities and are also involved with surveillance. The Communicable Disease Surveillance Centre (CDSC) provides a regional as well as a national surveillance function.

Surveillance data are collected in a number of ways:

- Laboratory reporting of cases (voluntary).
- Statutory notification of specified diseases by local health providers.
- Reports of outbreaks of gastrointestinal disease from settings such as schools and nursing homes.
- Reports of incidents (for example, breaches of legislation or operational problems) by water companies.
- Reports of water quality monitoring results by water companies.

Each has strengths and weaknesses. The experience in the United Kingdom is that the statutory notification system is a weak tool for detecting cases of waterborne disease. Gastrointestinal illness is recorded as “food poisoning” when it may in fact be foodborne or waterborne.

Issues for debate and development are whether laboratory reporting should now be statutory and follow a uniform policy and how to maximise the use of electronic reporting systems and geographical information systems. It remains unclear what is the value of investigating sporadic cases and to what extent resources should be directed at this.

Surveillance at local level in the United States is more complex than that in the United Kingdom albeit with basic similarities. It is the responsibility of the state and city/county public health agencies, which have the sole authority to enforce most public health actions. There is a three-tiered reporting system with laboratories and local health providers reporting to city/county health departments, which then notify state health departments. The state departments subsequently notify Centres for Disease Control (CDC) which act in a technical advisory role.

Despite being a statutory requirement laboratory reporting is still incomplete and, in particular, waterborne outbreaks are rarely detected. The diseases that are required to be notified are specified by each state but no incentive is provided. Reporting is not timely and is mostly paper based, creating delays from days to months in some cases. The managed care approach to health care can often create disincentives to take stool samples in gastrointestinal illness, for example this was known to be an issue in the Milwaukee cryptosporidiosis outbreak.

Surveillance capabilities vary at different levels of the system. While public health responses happen locally, the capacity for data analysis and recognition of disease clusters rests at state level. The resources are usually not available for local investigation of sporadic cases of illness. The relationship of state to
county/city health departments is often such that there is mistrust and a resulting fragmentation of the system.

Several agencies now use a method of surrogate indicator reporting to detect outbreaks, for example, monitoring over-the-counter sales of anti-diarrhoal drugs or emergency room consultations for gastrointestinal illness.

| Issues for debate and development are whether specific incentives and/or penalties should be built into the system to improve reporting and reduce delays or whether such incentive and penalties may be counter-productive. |

National surveillance for waterborne disease outbreaks

Three systems are described, one is a voluntary, mainly proactive system with annual collection of reports from local health departments (United States), the other two are reactive systems, outbreak driven (United Kingdom and Sweden). The features of the systems are described.

United States

For almost 30 years in the United States there has been a national collaborative surveillance system for waterborne disease outbreaks between CDC, the US Environmental Protection Agency (USEPA) and the Council of State and Territorial Epidemiologists (CSTE).

This is a voluntary, proactive system with annual collection of reports from state and city/county health departments. Both epidemiological and water quality data are collected. Unlike other surveillance systems in which the unit of surveillance is the individual case, this system takes the outbreak as the unit, with only two exceptions (confirmed cases of amoebic meningoencephalitis and chemical poisoning). Outbreaks associated with both drinking water and recreational water are considered.

The probability that individual cases of illness will be detected, epidemiologically linked and associated with water varies widely from one location to another due to a number of factors. It is likely therefore that the sensitivity and representativeness of this system are poor. It also does not include data for sporadic cases of disease. However, it can capture outbreaks of unknown aetiology and those associated with gastrointestinal illness, respiratory illness and dermatitis, outbreaks due to chemical poisoning and very small outbreaks.

| Box 1. Information from this system is useful for a number of purposes: |
| • To update the biology of aetiological agents and the epidemiology of outbreaks. |
| • To determine epidemiological trends. |
| • To evaluate the adequacy of current regulations for water treatment and monitoring of water quality. |
| • To establish research priorities. |
**United Kingdom**

The UK surveillance system is based on reports of suspected water related outbreaks and on the laboratory reporting system of infections, through which clusters are identified and trends in particular infections, such as *Cryptosporidium parvum*, *Giardia lamblia* and *Campylobacter spp.*, are monitored. Information on treatment failure incidents is also obtained regularly from the national Drinking Water Inspectorate. Outbreaks may be reported by Consultants in Communicable Disease Control, Medical Microbiologists, Environmental Health Officers and Regional Epidemiologists.

Reported outbreaks are investigated with a standard pro-forma to gather more information, as well as enquiries for further details and advice or assistance with investigations and epidemiological follow-up. The outbreaks are collated and reported in the PHLS publication *Communicable Disease Weekly* at six monthly intervals. The information is checked with reporters and any updates on numbers of cases or environmental investigations added when the six monthly reports are compiled. District reports on large outbreaks are also collated nationally and regionally.

National waterborne disease surveillance in the United Kingdom has an important history, but increasingly there is a need for a more innovative approach to overcome the current limitations and respond to new influences such as a “risk management” culture, the threat of newly emerging diseases, the possibility of bioterrorism and the effects of climatic change on disease patterns.

There are a number of barriers to be overcome in order to establish an ideal national system, some of which are:

- **Attributing cause** – in order to provide evidence of strength of association between illness and water it is necessary to have analytical epidemiological studies.
- **Statutory notification system** – several important diseases caused by waterborne pathogens are not notifiable in their own right, for example, *giardia*, *campylobacter*, *cryptosporidium*, *legionella* and some viral pathogens. A new system of notification is required.
- **Resources** – it becomes harder to justify surveillance and secure the necessary funding when the overall numbers of outbreaks are decreasing.
- **Caldicott guardianship** – Following the Caldicott report (a report into the confidentiality of patient identifiable data in the UK National Health Service) there have been changes to what is considered acceptable use of patient identifiable data and this has implications for local and possibly national surveillance.
- **Environmental factors** – unlike other disease surveillance systems a waterborne disease system has to take environmental factors into account requiring an integrated approach with other agencies and disciplines.

The ideal national surveillance for waterborne disease would build on the established reporting of outbreaks and develop more comprehensive surveillance providing more understanding of clusters and sporadic cases. This could be facilitated by a high profile national unit with multi-disciplinary membership and clear leadership, with access to a wide range of databases including geographical information systems (GIS), water supply areas and disease data. Links with European partners would be strengthened.
Sweden

The current Swedish system of surveillance of waterborne diseases was launched about 20 years ago. With the experience gathered, the effectiveness of the system in detecting outbreaks has improved substantially over the years, yet there are problems linked with the complexities of the reporting system. There is compulsory reporting by both laboratories and health care providers of 11 potentially waterborne diseases for example *Campylobacter spp.* and *Giardia Lamblia*. There is also voluntary reporting of diseases not covered by this list, for example, *Cryptosporidium*, caliciviruses and others.

However, the reporting system for communicable diseases both from doctors and from the laboratories seldom reveals waterborne outbreaks and if it does there is a long delay. Normally waterborne outbreaks are detected via clinical observation of increased numbers of cases of gastrointestinal symptoms or a particular illness. The timely discovery of an outbreak and its source normally involves a long series of events and contacts with different authorities, (such as County Medical Officer in Communicable Diseases, Public Health Protection Committee in the community, laboratories, water treatment plant and the Swedish Institute for Infectious Diseases Control) but one of the system’s strengths lies in the close co-operation between these different agencies.

There have been examples of waterborne outbreaks where many more people have been ill than have been reported initially and this is another important reason to investigate outbreaks. Very little information is provided by private water supplies and virtually no information is reported on sporadic cases.

It may be difficult to detect outbreaks associated with water supplies that comply with standards. Surrogate indicators are used to aid outbreak detection, for example sales of anti-diarrhoeal medications and complaints about water quality. Compulsory reporting of outbreaks may help to improve the effectiveness of surveillance for waterborne disease.

<table>
<thead>
<tr>
<th>Box 2. Summary of Main Points</th>
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<tr>
<td>• National surveillance systems vary substantially from one country to another. There is a need to standaridise reporting of waterborne disease across nations.</td>
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<tr>
<td>• Current national surveillance systems for waterborne disease, where they exist, focus on outbreaks, and have great difficulty in detecting the impact of drinking water on sporadic disease. There is a need to develop methods for the surveillance of sporadic waterborne disease.</td>
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<tr>
<td>• Current systems tend to be disease or symptom complex based. This syndromic approach does not facilitate recognition of risk factors such as exposure to water.</td>
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<tr>
<td>• There are potential conflicts between the public health’s need for surveillance data and the individual’s right to privacy. Consideration needs to be given to the ethical issues involved in public health surveillance in regard to changing consensus on the balance between the individual and the community’s rights and responsibilities.</td>
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Surveillance at regional/international level

As with other levels of surveillance the guiding principles of international surveillance systems are that they should help protect the health of the population by providing information for action and should be shaped by the needs of those who use them. In 1993 an inventory was drawn up of the existing collaborations between European Union (EU) member states in the area of public health. Since then
strategies for further development of an “over-arching network” or “network of networks” have been devised. Important lessons can be drawn from this network. The main purpose of the network is to provide information for action through:

- The early detection of problems affecting health across several member states.
- The detection of rare events that may not be readily recognisable in surveillance systems within a single country.
- Detection of problems which require international action (*e.g.* *legionella* and *salmonella*).
- Facilitate response across member states – enable the development of a regional inventory and registry – sharing of experience.

**Box 3. Discussion points and Key Issues from Session 1**

Historically, most surveillance systems have been based on the reporting of individual disease diagnoses. Such surveillance systems usually have good specificity but fail to detect a large proportion of disease which is not adequately diagnosed because people do not seek medical advice or, if they do, the physician fails to make a diagnosis or arrange for microbiological samples to be undertaken, or neglects to report the diagnosis.

There is a general commitment, supported by international health regulations to report events of public health significance, regardless of cause. However, there are problems with syndromic surveillance as current methods have low specificity.

Current surveillance systems vary dramatically between member states with some countries still having no effective surveillance system for waterborne disease.

There is a need to:

- Improve reporting of disease and other events of public health importance in member states by looking at the introduction of appropriate rewards and penalties.
- Standardise surveillance systems between member states to allow comparison.
- Develop standardised laboratory diagnostic policies and procedures between member states to allow comparison.
- Improve timeliness of existing surveillance systems for detecting events of public health importance.
- Improve the investigation of sporadic infections that may be linked with water.
- Reduce inconsistencies between member states in the list of notifiable diseases.
- Develop ways of linking surveillance data to information on water quality.
- Develop generic systems for surveillance of emerging infectious diseases including the potential of bioterrorism.
- Improve collaboration between agencies at a national and international level.
- Improve the collection of information on possible risk factors including environmental factors, travel history, climate data, water quality monitoring and geographical location.
A series of disease specific networks is now established with operational protocols and strategic review processes for each. Their main objective is to recognise outbreaks, mount a collaborative response and provide useful data on disease trends. Other projects are also strengthening surveillance within the EU, including Euro Surveillance with weekly and monthly electronic surveillance bulletins and EPIET a training programme for service epidemiologists.

An established example of a collaborative network is SALMNET/ENTERNET, a European Union funded surveillance network for *Salmonella* and *E. coli* O157 infections, which has the potential to be developed to include all enteric diseases. There is as yet no equivalent for waterborne disease and there are issues to be resolved around how this might develop. Two important issues are how to ensure truly multi-disciplinary development and whether to let countries continue developing systems independently and get the benefits of the different approaches.

**Session 2: A system approach to Outbreak investigation**

*Figure 1. Learning from outbreaks*

**Outbreak detection**

For an outbreak to be investigated it has to be detected in the first place. Currently, outbreak detection relies on individuals monitoring routinely collected data on the number of diagnoses of particular infections. As with all systems that rely on humans to detect events such systems are not totally reliable, especially if the aim is to detect outbreaks early. Although not always easy, this routine analysis could be done automatically using various computer techniques. One such technique with considerable promise is the use of neural networks. Neural networks are computer programmes that can be trained. The use of artificial neural networks in surveillance is still in its infancy although they have been used in other fields for similar purposes, for example tornado prediction. They may have several advantages in waterborne disease outbreak detection:

- May predict an adverse event before it happens and enable prevention measures.
- More timely – using today’s data not the last four weeks.
- Handle large amounts of data that are beyond the capacity of human analysis.
- Handle variables that don’t satisfy regression rules, for example rainfall, temperature and turbidity.
They may prove useful in the following ways:

- For analysing time-series and other data to predict expected numbers of disease cases and flagging a possible outbreak when the observed numbers differ significantly from these predicted numbers.
- For detecting spatial patterns of disease distribution corresponding to a known potential outbreak source such as a water distribution network.
- For “data mining” to find previously undetected relationships between environmental or other predictive factors and increases in disease incidence, allowing the prediction of outbreaks.

However, neural network programmes need to be trained if they are to be effective. Training usually requires a very large number of data points and the provision of these may be beyond the ability of individual countries to provide.

An issue for debate and development is whether international collaboration in training of neural networks would improve the early detection of outbreaks

Epidemiological investigations – the practical issues

An outbreak of waterborne disease is likely to involve one or more large geographical areas with large numbers of people exposed. Three main practical issues are of key significance for the successful outcome of epidemiological investigations: co-ordination between agencies, selection of case-control studies, bias on self-reporting, and knowledge of potential immunity levels and endemic levels of disease in the population.

Co-ordination

Co-ordination of the investigation is vital, especially having a clearly identified lead individual and also good relationships between the agencies involved. It is also necessary to have access to relevant information about the exposed population and their water supply, resources such as computer mapping and statistical packages and the necessary personnel for tasks such as interviewing and data entry.

Case control studies

In investigating the cause of an outbreak it may be a difficult decision whether to perform a case control study or to rely on descriptive epidemiology alone. There is a groundswell of opinion that case control studies have limited value in the investigation of waterborne disease outbreaks. This is because there can be bias (selection, interviewer and recall bias) and the studies often do not have the necessary power to significantly associate the illness with the causative exposure. Recall bias is a particularly important issue and may be influenced by cases’ differential recall of exposures due to having been ill, publicity about an outbreak and the introduction of “boil water” advice.
**Immunity levels**

Immunity levels in the population affect the power of study to make the association between the cause and the illness. If there is above approximately 20% immunity, the number of cases required giving statistical power dramatically increases. Misclassification of cases, for example counting secondary cases as primary cases in an outbreak is also likely to reduce the power.

| Issues for debate and development include how epidemiological studies in the investigations of outbreaks of waterborne disease can be improved to reduce problems with bias, especially recall bias. Also whether there is a need for an international standard for determining the strength of evidence in favour of an outbreak being waterborne. |

**Environmental and engineering aspects of waterborne disease investigations**

Environmental investigations complement epidemiological investigations and although there will be some overlap they are more likely to take place after the outbreak. Operational water company data can be analysed retrospectively to identify weaknesses that may have existed in the past to allow the organism to survive.

Water supply practice relies on a key concept, that of a multiple barrier which provides a number of critical control points to monitor the integrity of the system if it has been breached leading to contamination. There is very rarely one single reason for an outbreak but rather several problems occurring together. The investigation therefore relies on the systematic examination of all aspects of the multiple barriers. The main lessons learned from recent waterborne outbreaks have been:

- There must be an assumption that pathogens are always present in raw water.
- It is important to recognise every stage of the multiple barrier concept.
- There is a need to optimise the filtration process to remove particulate matter.
- It is important to recognise the link between turbidity fluctuations and the passage of particulate material through the treatment process.
- Water systems need to establish stringent treatment goals for microbial protection.

Federal regulations in the United States require that a “sanitary survey” be undertaken every five years. Although useful information from these surveys may be available during an outbreak there is evidence that it may not always be used.

**Clinical/microbiological investigations**

To illustrate the importance of clinical and medical microbiological investigations the workshop considered the experience in two specific areas; cryptosporidiosis in the United Kingdom and viral gastroenteritis in Finland.

*Cryptosporidium* is the main pathogen causing waterborne disease outbreaks in the United Kingdom and understanding its epidemiology can lead to strategies for reducing disease. Work has been done at the PHLS Central Public Health Laboratory to elucidate the different genotypes responsible for human disease.
Using a stepwise approach a monoclonal antibody and Western blotting typing were developed and applied to many faecal samples. A sensitive PCR protocol was then developed and applied to over 2,000 samples.

Three genotypes were found: *C. Parvum* genotypes 1 and 3 were found only in humans and genotype 2 in humans and animals. Genotypes 1 and 2 showed different seasonal and regional distributions and type 1 was more frequently associated with foreign travel. Analysis of outbreaks associated with both drinking water and swimming pools showed that both main genotypes can be involved, type 1 being associated with human sewage contamination and type 2 being associated with contamination from animal sources. Mixed infections with two types were more frequently associated with swimming pool than drinking water outbreaks, perhaps suggesting more than one infected individual as the source. This methodology furthers understanding of the epidemiology of sporadic, family and waterborne outbreaks and will be followed with sequencing and micro-satellite work.

Human caliciviruses (and especially Norwalk-like viruses) can cause large food and waterborne outbreaks and are also easily spread by direct contact. They are the most abundant human viruses that are excreted into and contaminate the environment. They might therefore be considered useful indicators for monitoring drinking water for sewage contamination.

The detection and identification of these viruses is based on a sensitive PCR method, which was developed to amplify a stretch of the viral genome. This has been successfully used in the investigation of four waterborne outbreaks in Finland where a similar NLV was isolated from both the water supply and patient samples. Further work is underway to assess the contamination risk of surface water by measuring the amount of these viruses in sewage.

In both these cases, important information can be provided by the detailed microbiological analysis of samples from human patients. Characterisation of strains will enable better epidemiological linkage of human cases to each other and to suspect environmental factors if such strains can be isolated from environmental samples. The isolation and characterisation of pathogens from human and environmental sources is increasingly becoming reliant on the use of novel molecular methods.

Geographical information

A key factor in identifying the relationship between drinking water and human disease is the ability to demonstrate geographical clustering of cases within areas supplied by single water distribution systems. Geographical information systems (GIS) are having a major impact on the investigation of both outbreaks and sporadic waterborne disease. GIS enables the investigator to observe the distribution of cases of a particular infection in relation to water supply systems. Furthermore, complex numerical analyses can be done to further show the relationship between human illness and water supply.

Firstly the relevant databases must be collected. These are epidemiological data, information on water supply structure and spatial data (for example, address co-ordinates, postcodes and water service areas). In Germany, where the method is under development, examples indicate that epidemiological data is compiled from health insurance company data and from cases of disease notified to the local health departments. Water companies supply information on water supply zones, sample points etc. With all GIS, databases need to be maintained and updated regularly.
Spatial and statistical analyses can both be carried out and the statistical analysis may be descriptive or analytic. There are a number of possible applications:

- Demonstrating graphically links between illness and water source during investigation of outbreaks and sporadic cases.
- Probability mapping to demonstrate risk of illness in geographical areas.
- Survey of population’s water drinking habits.
- More detailed statistical analysis and evaluation.
- Potential use in routine surveillance to improve outbreak detection.

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<tr>
<th>Box 4. Discussion Points and Key Issues from Session 2</th>
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<tr>
<td>• The investigation of outbreaks associated with drinking water is a highly technical process involving experts from several professional backgrounds.</td>
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<tr>
<td>• The increasing complexity of waterborne disease outbreak investigation is a challenge to surveillance systems since there are not many experienced personnel with adequate practice. Many countries appear to lack public health individuals with skills in management of waterborne outbreaks.</td>
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<tr>
<td>• It would, however, not be cost effective to train local individuals in each discipline required to investigate waterborne outbreaks. A better model is to develop a team with particular skills that can then be deployed to waterborne outbreaks over a wider geographical area. There may be a role for international co-operation in developing necessary skills.</td>
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<tr>
<td>• Both human and environmental samples should be taken at the beginning of an outbreak since this may enable identification of unusual events affecting water quality, which may have significant implications for public health and the water industry.</td>
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<tr>
<td>• Outbreak investigations are often costly. Lessons should be learned from previous outbreaks and there may be value in developing larger (international) data sets, as these are more likely to predict future outbreaks than national surveillance databases.</td>
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Session 3: Use of water quality, treatment and distribution data to assess human health risk

In this third session the information that may be held primarily by the water industry and regulators and relevant to the public health community was discussed.

Progress report on the WHO/OECD guidance document “Improving microbiological safety of drinking water”

The need to achieve a better understanding of water’s role in the transmission of infectious disease was officially acknowledged by the international community in 1996 at the OECD Workshop on Biotechnology for Water Use and Conservation in Cocoyoc, Mexico. Then, in 1998, the OECD Interlaken Workshop on Molecular Technologies for Safe Drinking Water reviewed the effectiveness of drinking water plants in preventing the passage of microbial contaminants and the reliability of current indicators as means to guarantee microbiologically safe water to consumers. Recommendations from that Workshop highlighted the need for better approaches and methods to assess the safety of drinking water and to monitor and respond to adverse events.
In particular, the 1998 Interlaken OECD workshop “Molecular technologies for safe drinking water” produced three main recommendations:

- Development of a guidance document on microbiological testing of drinking water.
- International co-ordination and promotion of molecular methods in the field of drinking water microbiology.
- International co-ordination for improved surveillance and outbreak detection.

The first of these has been addressed with a co-operative effort between WHO and OECD producing a guidance document “Improving microbiological safety of drinking water”. The basic concept of this document is a system approach to the issue of safe drinking water, the need for effective information management and for guidance on the available technology to respond to these needs.

Management of drinking water has to be extended to include the whole system, from testing of source water, followed by evaluation of the efficiency of the available treatments for pathogen removal to ultimately end product testing. Each step of this system requires appropriate performance control strategies.

The document addresses selection of methods, both conventional and molecular, that would most appropriately achieve the best results at each step of this system and discusses their relative sensitivity, selectivity, robustness and cost-effectiveness. It also provides detailed information on treatment processes, methods to assess distribution system integrity and methods for outbreak investigations. There is also a visionary statement that reinforces two important messages:

- New improved methods are needed to ensure drinking water safety.
- Research in biotechnology may offer significant solutions to satisfy these needs.


Water System deficiencies and Water Source

Lessons have been learned in the last decade in the United States about waterborne disease outbreaks. The most common cause of outbreaks associated with community water supplies has been contamination of the distribution system by a number of mechanisms such as contamination from cross-connections, back-siphonage, corrosion, or during construction or repairs of the distribution system (Table 2). The remainder has been associated with inadequate treatment of water or undetermined causes.

In contrast, in non-community systems the large majority of outbreaks have been due to consumption of untreated or inadequately treated groundwater, though a small number have been due to distribution deficiencies or undetermined causes.
Table 2. Waterborne outbreaks and deficiencies in public water systems in the United States, 1991-1998

<table>
<thead>
<tr>
<th>Type of contamination</th>
<th>Community systems</th>
<th>Non-community systems</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outbreaks</td>
<td>Percent</td>
</tr>
<tr>
<td><strong>Surface water</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated surface water</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inadequate or interrupted disinfection</td>
<td>4</td>
<td>9.1</td>
</tr>
<tr>
<td>Inadequate or interrupted filtration</td>
<td>4</td>
<td>9.1</td>
</tr>
<tr>
<td>Distribution system contamination</td>
<td>9</td>
<td>20.5</td>
</tr>
<tr>
<td>Inadequate control of chemical feed</td>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td>Miscellaneous/Unknown</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td><strong>Total surface water</strong></td>
<td>22</td>
<td>50.0</td>
</tr>
<tr>
<td><strong>Groundwater</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated groundwater</td>
<td>5</td>
<td>11.4</td>
</tr>
<tr>
<td>Inadequate or interrupted disinfection</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td>Inadequate or interrupted filtration</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Distribution system contamination</td>
<td>8</td>
<td>18.2</td>
</tr>
<tr>
<td>Inadequate control of chemical feed</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td>Miscellaneous/Unknown</td>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Total groundwater</strong></td>
<td>22</td>
<td>50.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>44</td>
<td>100</td>
</tr>
</tbody>
</table>

Source: Gunther F. Craun – Basingstoke 2000.

Waterborne outbreaks and Routine Coliform Monitoring

When water quality data from the aforementioned outbreak investigations was assessed, only a small minority of supplies had violated the USEPA coliform limits in the previous 12 months. This raises questions about the value of coliform standards as an indicator of a system’s potential for an outbreak. Possible chief reasons for the failure to correlate are timing and location of water sample collection. For example, water samples may not be collected until two to four weeks after the beginning of an outbreak and are not always collected from the distribution system.
Preventing waterborne cryptosporidiosis in England and Wales

The United Kingdom is the first country to now have specific regulations regarding cryptosporidium oocysts in public water supplies and this has arguably been hailed as a major advance in public health protection. In England and Wales new cryptosporidium monitoring and reporting regulations have been introduced following the acquittal of a water company of charges of causing an outbreak, when the epidemiological evidence on which the case rested was ruled inadmissible. The conclusion was that if epidemiological evidence of the consequences of failure to treat adequately was not to be admissible in Court, new regulations were required to make failure to achieve a treatment standard an offence in itself. Prior to the new regulations there was no legal requirement to monitor for Cryptosporidium and the only standard was the “catch-all” requirement that water should “not contain any organism (other than a parameter) at a concentration that would be detrimental to public health”. In respect of outbreaks of disease it was, and is, an offence to supply water unfit for human consumption but whether water was unfit has to be determined by the Courts.

The new regulations which came into force in April 2000 require that water entering the supply must contain less than an average of one cryptosporidium oocyst in ten litres of water based on daily sampling at average 40 litres/hour. It establishes a new criminal offence of allowing the presence of excessive numbers of cryptosporidium oocysts in treated water leaving a treatment works.

Continuous sampling (except for the time required each day to remove the filter for analysis and replace with a new one) for cryptosporidium must take place at all water treatment works where there is a significant risk that water leaving the works will contain oocysts. Criteria are laid down for some works where continuous sampling is known to be needed and all other works require a risk assessment to be carried out based on guidance from the UK Drinking Water Inspectorate (DWI). These are then reviewed by the DWI to check their thoroughness and compatibility.

There has only been one breach of the standard in the first six months since the regulations came into force. There is much debate about the value of this treatment standard as it is not yet known what the public health implications are of a breach of this standard, but it is providing invaluable data regarding the baseline exposure to cryptosporidium in drinking water. It will also ensure that in the event of a future suspected waterborne outbreak there will be data on the level of cryptosporidium oocysts in treated drinking water at the time when it was suggested that people became infected.

Water industry data sources- developing an integrated system of health and technical data

Water industry information can be classified under three main headings, regulatory monitoring (to comply with statutory standards of water quality), process/operational monitoring (sampling done by a water company to enable it to manage water treatment and distribution, and research and development (as may be the case when developing new analytical tools or monitoring novel water treatment processes).

The water industry has data that are comprehensive and complex but under-utilised, especially by the public health community. In contrast, it was argued that the corresponding health data are relatively unstandardised, reactive and limited in relation to identifying risks relating to waterborne disease. A vision for the future is an integrated system of both health and technical data that may be applied to evidence based risk assessment and active case searching.

A model for this might be EPISYS, a system being experimented in the north east of England as a collaboration between the health sector and the water industry. This uses technical data and health care outcome data in a collaborative effort. The aim is for the health data to be real time, with multiple inputs,
This system is in the second year of operation and has so far been found to detect the traditional episodes, track non-notifiable illness and detect episodes where there is otherwise no data. Further developments might be including other data sources such as environmental and geographical, use in damage limitation and developing predictive models.

Box 5. Discussion points and Key Issues from Session 3

- Indirect health indicators, such as pharmacy sales of antidiarrhoeal agents or calls to telephone advice lines, may help in detecting outbreaks.
- There is a need to develop a better understanding of the relationship between the detection of pathogens such as *cryptosporidium* in water and the subsequent risk to health. Most instances where *cryptosporidium* is detected in water are not followed by any observable increase in infections.
- There is a need to develop predictive models, for both outbreaks and endemic disease. Thus, there may be a case for having different indicators and indices for monitoring the quality of water in the catchment, during treatment and distribution.
- Real time monitoring of water quality is currently not predictive of health risk but it can provide valuable information.
- WHO’s current guidelines, which rely on end product standards, are being reworked with requirements to undertake risk analysis at all stages of water supply. The current emphasis is on critical control points hazard assessment, *i.e.* on verifications for each control point, procedural and process audit.
- Surveillance is not predictive or preventive and must be used together with engineering information. This further underscores the need to integrate water quality surveillance with disease surveillance.
- Surveillance of waterborne disease should not be limited to a few pathogens as this would not allow detection of newly emerging diseases or syndromes.

Session 4: Epidemiological approaches to assessing endemic waterborne disease burden

Whilst outbreaks are the most obvious manifestation of waterborne disease, they probably represent only a small proportion of the total burden of disease associated with water, even in western nations with effective disease surveillance systems. One of the major challenges facing epidemiologists is to describe the epidemiology and causes of waterborne disease which is not correlated to outbreaks, *i.e.* of assessing endemic waterborne disease burden. Unlike the situation with outbreaks, sporadic disease may be overlooked and dismissed as part of the general background of illness. In this fourth session, attention
turned onto the issue of sporadic waterborne disease and various strategies for determining the contribution of water.

Using existing surveillance based data

In the United Kingdom detection of waterborne disease outbreaks is relatively effective because of the routine detection of pathogens by laboratories, routine reporting to a national surveillance system and local monitoring of cases by consultants in communicable disease control. This allows a rapid response to a local increase in reported cases. Integration of epidemiological, microbiological and reference investigations further contributes to a good local system for establishing the causes of an outbreak, controlling it and reporting it nationally. However, because risk factors are rarely included in this surveillance system, it is difficult to use this data to determine levels of waterborne disease. Nevertheless such data is amenable to further analysis which can begin to provide additional information. Factors such as seasonal and geographical variation can provide some clues to possible epidemiology as can the use of information technology to identify small clusters of infection that may otherwise be missed.

Time series to assess endemic waterborne disease burden

The increasing use of on-line measurements for assessing and monitoring drinking water quality and the ability to store and analyse computerised data have facilitated the use of time-series studies to assess the waterborne disease burden.

Before model fitting, attention has to be paid to the choice of the step of time and to the design of the indicators in order to fit as closely as possible the nature and the dynamics of infection. This is because the available indicators of health effects, for example gastrointestinal symptoms, and exposure to pathogens, are both indirect indicators. In order to avoid false positive correlation due to confounding effects, seasonal variations have to be filtered out of target variables as well as trend and auto-correlation. Only high frequency events are taken into account in the calculation of the relative attributable risk. This leads to an underestimation of risk and may also result in false negative outcomes.

The advantages of time studies are their low cost and the improvement of communication between public health and water company professionals, leading to improved risk management.

Case control studies for assessing endemic waterborne disease burden

Case control studies have a role in the assessment of endemic waterborne disease burden, particularly in the case of rare diseases. However, they are limited by their very nature, since they can only address diseases caused by a single organism, which may represent a small proportion of all potential disease. In addition, because of possible biases inherent in the methodology, particularly the reporting of drinking water consumption, they should be interpreted with caution. Caution should be particularly applied when dealing with low odd ratios of less than 2. Case-control studies have a role in supplementing randomised-controlled trials. Randomised-controlled trials are useful to assess the general burden of disease resulting from a variety of pathogens. When specific pathogens are being examined however, they can be inconclusive or negative because of a lack of power. Case-control studies are then a useful adjunct.

Prospective epidemiological studies

Prospective epidemiological studies can be used in the assessment of endemic waterborne disease burden. There are few examples but a recent one is the Epidemic and microbial risk assessment (EMIRA)
study carried out in the French Alps from October 1998 to June 1999. This combined a daily epidemiological follow-up of participants from four different water supplies for gastro-intestinal symptoms with microbiological surveillance of drinking water.

Its main provisional findings were that protozoan and enteric virus markers were often present in water in the absence of bacterial indicators and that there is an association between protozoan markers and gastrointestinal illness.

In designing prospective studies careful consideration needs to be given to the following factors:

- Range of pathogens is potentially unlimited so microbial indicators need to be selected.
- Health outcomes are uncommon.
- Participant selection: whether the general population or susceptible groups such as children or immunocompromised are chosen for study and whether a representative sample of the study group or volunteers are used).
- Case definition and ascertainment.
- Exposure assessment.
- Data analysis.

These studies are difficult for hazard identification and there is a need for real life epidemiological studies to confirm the experimental studies.

_Prospective epidemiological studies of waterborne disease in developing countries_

Water-related illness contributes a substantial proportion of the total global burden of disease. Furthermore, diarrhoeal diseases remain a leading cause of illness and death in the developing world. When waterborne disease burden is studied in developing countries there are many issues to take into account that are different from those in developed countries.

The main issue in these countries is shortage of water and this has implications for use of water generally and hygiene measures in particular. In many parts of the developing world, drinking water is collected from unsafe surface sources outside the home and is usually transported and then held in storage vessels. Thus, drinking water may be easily contaminated at collection, during transport and storage in the home. A basic assumption is that improvements in water quality result in improved health and this cannot always be demonstrated, possibly because of methodological limitations or effects of other transmission routes. Providing safe drinking water sources may fail to reduce diarrhoea because transmission continues through food-borne or person-to-person routes.

_Sero-epidemiological studies – Identifying immunity levels in populations_

Much useful information has been obtained from serological studies in different countries. These were based on sera from blood donors or from people who have contributed blood for other tests. The main findings from recent studies of the sero-epidemiology of Cryptosporidiosis have been that infection is common. In addition, separate markers were identified and that signal recent infection or longer-term response. The immune response increases with increasing age and people aged 20 to 50 may therefore be the most informative to study in the future. A prior response may prime future responses but this may only give slight protection. However, the exact role of immunity in preventing subsequent illness due to Cryptosporidium is still not clear.
Studies on *cryptosporidiosis* in the United States indicate that drinking water is likely to be the most important risk factor for infection in certain communities. For example, consumers of contaminated surface water may be commonly infected.

**Box 6. Some unresolved questions are:**

- If infection is common, why is disease rare?
- What is the sensitivity of a stool parasite examination?
- Will treatment of home drinking water reduce the risk of infection?
- What level of sero-conversion is associated with illness?
- What is the duration of serological response?
- Are the people who do not respond at higher or lower risk of infection and illness?

*Intervention studies*

The use of intervention studies to evaluate the level of endemic waterborne disease in a population is uncommon. Their use has usually been limited to monitoring the effect on health of a new or improved water supply or demonstrating the effectiveness of various sanitation procedures. They have also been used, with limitations, in developing countries to demonstrate the impact on health of water treatments.

As water quality improves it becomes more difficult to design and implement intervention studies that are robust and do not require prohibitively large cohorts. Although a similar study in Melbourne has demonstrated no health effect due to unfiltered clean surface waters, the particular nature of the water supply means that the results are unlikely to be comparable.

These studies are effective tools with which to evaluate the level of preventable waterborne illness in a population, but need to be carefully designed to exclude bias and confounders. They are more expensive than some other study designs but when compared with numerous smaller and less expensive studies that yield inconclusive results and costly outbreak investigations, they may prove cost effective in the longer term.

**Box 7. Discussion points and Key Issues from Session 4**

- There is value in surveillance of sub-groups of populations such as elderly, children, immunosuppressed – since it may be possible to see trends in these groups that are not obvious in the general population.

- Water is usually only one of several risk factors each of which can affect the risk for other factors. This adds to the complexity of assessing waterborne disease.

- When used in conjunction with outbreak investigation data, sero-epidemiology may be very important for assessing burden of disease.