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October 9 and 10, 1997
Meeting Summary

Environmental Protection Agency

WATERBORNE DISEASE WORKSHOP

October 9 and 10, 1997

Washington National Airport Hilton
Arlington, Virginia

MEETING SUMMARY

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Introduction

The Environmental Protection Agency (EPA) and Centers for Disease Control and Prevention (CDC), as recommended by the M/DBP Expedited Rule Advisory Committee resolution, co-sponsored the Waterborne Disease Workshop on October 9 and 10, 1997. The objectives of the Workshop were to:

- Provide background on the Safe Drinking Water Act mandate to conduct waterborne disease occurrence studies and develop a national estimate of waterborne disease incidence;
- Discuss how these studies fit into the larger public policy framework on providing safe drinking water;
- Discuss planned and ongoing epidemiological studies and Environmental Protection Agency & Centers for Disease Control activities related to these mandates;
- Identify data gaps, research needs, and opportunities for improved methodologies, and;
- Discuss next steps and opportunities for coordination and communication.

This report summarizes the presentations and discussion at the Workshop. It is organized in three sections. The (I.) **Background of Waterborne Disease Detection and Federal Policy Development** section includes summaries of the presentations by Agency representatives concerning the scientific and policy considerations in developing a National Estimate for Waterborne Disease Occurrence. The (II.) **Planned and Ongoing Studies of Disease Occurrence** section summarizes presentations on specific ongoing or proposed research approaches and the discussion surrounding them. The (III.) **Approaches Towards a National Estimate** section summarizes the discussion of scientific and policy considerations involved in developing the National Estimate. The presentation of the discussions throughout this summary are grouped by topic and not necessarily sequential.

I Background Of Waterborne Disease Detection And Federal Policy Development

I.1 Statutory requirements and direction of microbial drinking water regulations and EPA/CDC partnership[1]

-Presented by Stig Regli, EPA

Regli provided the regulatory background for the objectives of the Workshop, and EPA's regulatory mandate. The EPA, Regli explained, must set a maximum contaminant level goal (MCLG) for contaminants of concern. By regulation, this MCLG must be "set at a level where no known or anticipated health effects occur and which allows an adequate margin of safety." MCLG's for *Giardia* and viruses are set at zero and the EPA has formally proposed setting an MCLG of zero for *Cryptosporidium*. The MCLG is not an

[1] See attached for Stig Regli presentation notes: Attachment A.

enforceable standard but rather a benchmark used for setting the regulatory standard. EPA must set a Maximum Containment Level (MCL) or treatment technique requirements (TTR) as close to the MCLG as feasible taking costs into consideration. If the MCL or the TTR would result in an increase in risk due to other contaminants in the drinking water, EPA can set the MCL or the TTR at a level that minimizes the overall risk by balancing the risks from the different contaminants instead of setting the standard at the "feasible" level.

Regli continued that the costs associated with reducing the risks posed by waterborne disease are considered to be in the range of $100 millions to billions per year, so it is important to find a way to quantify the benefits associated with taking action. The magnitude of the risk created by taking action due to other contaminants in the drinking water (such as risks from disinfection byproducts) must be also considered. Regli pointed out that there are large uncertainties associated with quantifying each of these risks.

Responding to a question from a Workshop participant, Regli explained that EPA's current approach to regulating drinking water does not include direct measurement of pathogens. In the Surface Water Treatment Rule (SWTR) EPA required a fixed level of treatment for *Giardia* and viruses. The level of treatment was thought to be adequate for most supplies. This assumption was based on a limited amount of source water *Giardia* occurrence data. The cost and the difficulties of pathogen monitoring at the time made it infeasible to require systems to monitor their source water and to set a treatment standard based on site specific source water pathogen levels. (It is possible that future regulations will require monitoring of source water in order to establish the appropriate level of treatment.) Regli continued to explain the basis for selection of a target organism for developing the TTR. By requiring treatment to provide a certain reduction in the concentration of the target organism(s), the drinking water concentration of other less treatment resistant microbes will be reduced to acceptable levels. In the case of the SWTR, the target organisms were *Giardia* and Hepatitis A virus. The efficacy of the treatment to reduce the concentrations of the target organisms is based on laboratory bench and pilot scale studies. It is not currently feasible to base regulations on the detection of microorganisms in finished water because of the high frequency of large volume of finished water samples that would be required to ensure high probabilities of safety and detection sensitivity (1 [or less than 1] in 10,000 liters which is below currently viable technology). Indirect approaches are being considered based on prescribing appropriate levels of treatment.

EPA has redirected $1 million of the $10 million health effects research budget for FY 97 towards the CDC studies on waterborne disease occurrence. Additional funds for this purpose are expected in FY 98. EPA and CDC have not decided on a research design for the next step in this process.. Regli, as well as other EPA and CDC representatives, assured the participants that no decisions on what studies will be commissioned have been made and that the discussions at this meeting would be used to review present approaches, gather alternatives, and inform future decisions. This Workshop and the upcoming AWWARF January 1998 meeting will provide input on the types of studies

that could provide information necessary for developing the national estimate and which may be useful in developing the future microbial regulations.

I.2 Passive Surveillance, Transmission, and Serological Testing

-Presented by Dr. Jeffrey Griffiths, Tufts University[2]

Introductory remarks, and presentation of an interpretation of passive surveillance, transmission, and serological testing by Dr. Jeffrey Griffiths, Tufts University, representing the National Association of People with AIDS.

Dr. Griffiths gave a very brief overview describing some of the reasons why this workshop was being held. He related that members of the FACA committee (committee established under the Federal Advisory Committee Act to provide advice to EPA on the development of the Interim Enhanced Surface Water Treatment Ruleand Stage 1 of the Disinfectant / Disinfectant Byproduct Rule) had expressed frustration about the limits of knowledge about water borne cryptosporidiosis, and water borne diseases in general. The FACA committee had unanimously voted to ask the EPA and CDC to hold this workshop, in order to review currently funded studies on waterborne diseases, and to strategize on future studies, in the presence of an outside panel of experts in water borne diseases. He presented two flow charts describing the *Routes of Exposure* to WBD and *Spread and Infection with Waterborne Infectious Diseases*. These charts were accompanied by a review of the serological literature. Three points were made by Griffiths in these charts and the review.

1. The first is that detection of clinical cryptosporidiosis is a rare event, even in the setting of ongoing endemic widespread exposure, and that traditional passive surveillance is likely to miss more than 99.9% of the disease. [Dr. Dennis Juranek of the CDC reinforced this point in his discussion; indeed, only 12 of 250,0000 people with clinical cryptosporidiosis during the Milwaukee outbreak were detected by passive surveillance (4.8 per 100,000) during the largest known waterborne disease outbreak in the history of the United States]. (See the first chart)
2. Secondly, the issues of exposure, infection, secondary spread, and eventual detection of the disease are complex and in Griffiths' opinion, cannot be easily modeled by the equation, total GI illness x attributable fraction due to water = a national estimate of waterborne diseases. Primary reasons for this skepticism include the need to account for secondary transmission, and person-to-person spread after waterborne introduction into a community. The second chart details these transmission cycles.
3. Thirdly, extensive documentation from the literature was provided that the published seroprevalence data is likely to be an underestimate of lifetime exposure rates, perhaps by as much as two orders of magnitude, and that the duration of a serological response to parasite oocysts is short (months, not years).

[2] See attached for Jeffrey Griffiths handout: Attachment B.

I.3 Developing national waterborne disease estimates for drinking water regulations[3]

-Presented by Stig Regli, EPA

The second part of Regli's presentation described how the Agency has traditionally estimated the national level of infectious disease associated with drinking water in its regulatory impact analysis. The Agency's approach to develop this national estimate is to:

- Select target organisms (i.e., *Cryptosporidium*, *Giardia*, and viruses).
- Estimate national distribution of the target pathogen concentration levels reaching consumers. [This is done by assessing the distribution of target pathogen concentrations in the source waters nationwide and then applying a treatment reduction factor to estimate the distribution of target pathogens in the drinking water at the tap.]
- Estimate infection rates from an available dose response curve. [e.g. by extrapolation from the dose response curve for *Cryptosporidium* a person has a 0.5% likelihood of infection due to ingestion of a single oocyst.]
- Estimate (based on the above data) national illness and mortality rates.

Regli continued with a discussion of the uncertainties and issues limiting the estimate of infectious disease associated with drinking water using the methodology outlined above.

- Difficulty of measuring the source water pathogen concentration levels.
  - Source water occurrence is highly variable (many samples needed per site to get a reliable estimate.)
  - Available pathogen analytical methods have poor recovery rates (i.e. they are imprecise, and have high detection limits, they cannot yet measure viability or infectivity of pathogens).
- Difficulty in obtaining reliable treatment estimates (filtration and disinfection performance)
- Lack of data on the health effects of infection by specific pathogens:
  - Dose response curves vary by organism strain and host-derived factors including levels of immunity in the exposed individual (putting aside at this point the effect of herd immunity which affects secondary transmission.)
  - Symptomatic response of humans is not well defined.

I.3.1 Influence of national waterborne disease estimate on regulations

Regli discussed how the results of epidemiological studies that will be conducted to develop the national estimate could help define the stringency of additional microbial treatment regulations. To the extent that these studies identify the etiologic agent causing infectious disease associated with drinking water, they will help define the level of treatment necessary, i.e. there are significant differences in the effectiveness of disinfectants to inactivate different microbes, as well as differences in the effectiveness of physical removal. If studies determine that disease is associated with bacteria in the

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See attached for Regli presentation slides: Attachment A.

distribution system, then this may support limits on bacterial growth or enhanced cross connection control. However, Ron Hoffer, EPA, explained that the congressional mandate does not specifically link national estimate to any specific regulatory action. Regli continued that the Agency hopes that the national estimate will inform the discussion on the level of stringency for future regulations and on the risk factors associated with waterborne disease. This may lead to higher and/or more consistent levels of treatment for pathogens in source waters (especially for protozoa or viruses) and improvements in distribution system controls (such as limiting bacteria growth and contamination intrusions into piping.)

Regli clarified that the goal of the workshop was to hear from those persons who were involved in conducting epidemiology studies for EPA and CDC, and to listen to the comments and ideas of others with expertise or an interest in this area of research. Sue Binder, CDC, later in the meeting added that through this review and joint-deliberation the Agencies hope to improve current studies, augment understanding of waterborne disease occurrence, and expand on the idea of a portfolio of relevant research. Binder concluded that this Workshop should help EPA and CDC clarify what is missing from the current body of studies and identify next steps.

I.4 Detection of Waterborne Disease (endemic and epidemic) and inherent difficulties and limitations[4]

-Presented by Dennis Juranek, CDC

Juranek's overview of the current waterborne disease surveillance system included the CDC's objectives, an explanation of how the system works, a discussion of the sensitivity and limitations of the system, and examples of the performance of the system during outbreaks. The current system does not provide data suitable for estimating the National prevalence of waterborne disease. Juranek explained that there are many obstacles to the detection and reporting of waterborne disease outbreaks. He used the example of a Milwaukee 1993 waterborne disease outbreak. In a questionnaire survey 250,000 people were found to have had onset on watery diarrhea before local health officials were aware of a waterborne outbreak. Only 12 made it through the many obstacles that prevent cases from being recognized and reported to the local health department. Most illnesses (94%) were not recognized by the medical community because people did not seek medical assistance. Of those who sought medical care, only 6% were tested for parasites, and only 4% of those were tested for *Cryptosporidium* (12 tested positive). Thus only 1 in 24,000 cases sought and received medical care/laboratory services that resulted in their illness being reported. According to one participant, the system may not detect outbreaks of diarrhea unless more than 1% of the population gets infected. For a more complete discussion of these topics please refer to the materials that Juranek used in his presentation (attached Appendix C).

I.4.1 Current System Strengths

Juranek pointed out that the advantages of the current surveillance system are mainly a result of health departments' experience in using the system and CDC's ability to

[4] See attached for summary of presentation: Dennis Juranek, Attachment C.2.

summarize and publish data in timely fashion. The current system also provides a historical frame of reference for data and is relatively inexpensive to maintain when compared with other types of data collection systems.

1.4.2 Current System Weaknesses

Juranek also pointed out that the current system has many weaknesses that should be taken into account when quoting or interpreting the data. The system is passive (voluntary) and may miss many small-scale outbreaks. The system has trouble detecting outbreaks if physicians do not report cases to health departments or to CDC. The system is further compromised by the fact that persons with gastrointestinal illness frequently do not seek health care. In some instances physicians do not pursue the cause of illness by ordering the appropriate laboratory tests. Thus the causes of mild and moderate illnesses are often undetermined or misdiagnosed. Laboratories may not routinely test stool for pathogens transmitted by water, especially new ones like *Cryptosporidium* or *Cyclospora*. Heath Maintenance Organization (HMO) emphasis on cost reduction may further decrease requests for laboratory tests for specific pathogens in the future. There are also lengthy delays between onset of an outbreak and its detection, investigation, and reporting. This not only reduces the opportunity to take immediate corrective action to reduce the number of people who are exposed, but also reduces the chances for identifying the etiologic agent or the water treatment failure that lead to the outbreak.

1.4.3 Alternative Surveillance Approaches

Juranek then outlined some of the approaches that were suggested at a 1994 workshop at CDC to improve surveillance for *Cryptosporidium* outbreaks. The group then discussed each alternative.

1.) Make *Cryptosporidium* outbreaks reportable legally to CDC. This approach provides a baseline against which increased numbers during an outbreak may be compared. However, it does not improve diagnosis or reporting by physicians or increase routine lab testing. One participant pointed out that this approach is more likely to reflect infections in immunocompromised people or children than in the general public.

2.) Monitor laboratory diagnoses (tests for *Cryptosporidium* in stool or serum antibodies.) Five states are currently undertaking active review of laboratory records to detect cases. One participant discussed New York City's laboratory monitoring efforts. New York City looks actively for *Giardia* and *Cryptosporidium*. According to this participant, N.Y. public health experts felt that before they started monitoring laboratories they were missing half the diagnosed cases of *Cryptosporidium* infection. In Connecticut 4-5 times more cases of *Cryptosporidium* were detected through active lab monitoring than were reported before monitoring. These cases were identified by laboratorians, but labs were failing to report all of them to the health department. Other participants pointed out that the problems with this approach are the expense of monitoring and the unreliability of monitoring for the amount of disease in the community. It was also pointed out that it is illegal for laboratories to charge for tests that are not specifically ordered by the patient or physician. Some participants pointed out, however, that blind active surveillance of fecal samples was

both possible and legal, so long as no charge is made for an unordered test. A number of participants volunteered that they have conducted or are conducting such studies.

It was pointed out by some members of the panel, that the phrase "active review" of laboratory records was in their opinion simply improving the yield of passive surveillance, and was not a substitute for true active surveillance in the estimation of cryptosporidiosis. Furthermore, these panelists pointed out that even with a doubling of the rate of passively reported cases of cryptosporidiosis, this would only alter the number of cases missed by passive surveillance from 99.95% to about 99.90%.

3.) Monitor sales of anti-diarrheal medication (indicator of infection). Juranek explained that this approach captures some of the population that does not seek further medical attention. It does not, according to one participant, distinguish between the many routes of exposure including water (drinking and recreational exposure such as swimming), food, person to person spread, or animal contact. It would, however, indicate increased incidence and permit more rapid and focused investigation.

4.) Monitor HMO and hospital logs (indicator of diarrhea). Juranek pointed out that this approach is particularly useful if medical facilities have computerized systems for logging telephone calls regarding patient illnesses. Information entered promptly into a computerized database can effectively monitor both complaints of diarrhea and severity of gastrointestinal disease in a community. One participant explained that this approach has additional power because it captures data on all medical complaints for the total population served. This can be used as a denominator for calculating an overall infection or disease rate.

5.) Monitor nursing homes for health effects associated with infection. According to one participant -- "this is a topic so complicated that it needs its own two day conference." The increased immunity of the elderly to many pathogens (because of repeated exposure to pathogens over a lifetime) was mentioned by one participant as an argument against focusing research on this population.

6.) Combine disease and water quality surveillance information for a more complete picture of the correlation between the two. Juranek mentioned that CDC and EPA will be sharing information in an effort to correlate changes in water quality with waterborne disease occurrence. Other participants agreed that this approach had the added benefit of connecting disease with water quality and pathogen source data. One participant noted that studies linking water quality and clinical gastroenteritis are already being published (e.g. Morris *et al* 1996, Schwartz *et al* 1997).

I.5 Initial Investigations: including 5-city study and CDC's Emerging Infections Program Sites[5]

-Presented by Dennis Juranek, CDC

Juranek continued the discussion by outlining the CDC and EPA activities toward developing the Congressionally mandated National Estimate of Waterborne Disease Occurrence. This presentation included a description of the March 1997 workshop at CDC, as well as a brief description of CDC's Emerging Infection Program and FoodNet Program that are monitoring the occurrences of diseases in seven sites nationally.

Juranek clarified the important questions that CDC and EPA would like to answer as part of any major effort to develop a national risk estimate.

- What populations are at greatest risk?
- What is the social and economic impact of waterborne disease?
- Which infectious agents cause waterborne disease? And what is their relative contribution?
- What are the characteristics of water systems that are more likely to lead to waterborne disease?

Juranek indicated that one approach to developing a national risk estimate was to determine how much gastrointestinal illness was occurring in the country (Total illness) and multiply that number by the percent of illness believed to be waterborne (Attributable fraction). (See formula below).

[Total cases of GI illness x Attributable fraction due to water] = National Estimate

It was pointed out by CDC personnel that the use of the Emerging Infections and FoodNet Programs might provide an inexpensive or rapid way to obtain an estimate for total cases of GI illness. However, a number of the panelists felt this approach was potentially flawed because those sites were not chosen for reasons relating to water supplies. Representatives of the water industry pointed out that a variety of sites that reflected different types of water sources would be a more rational choice. Some members of the panel felt the formula outlined above was too simplistic an approach.

I.5.1 Attributable Fraction –(Proportion of total illness due to drinking water.)
Participants agreed that this fraction, important for deriving the national estimate, is the most difficult to measure with precision. One participant suggested that it might be incorrect to assume that you can easily identify the specific proportion of waterborne illness that is related only to drinking the water. For example, it may be impossible to distinguish the initial outbreak cases who actually drank the contaminated water from those cases acquired by secondary spread from person-to-person, from food, or from other routes of infection. It was pointed out that after the Milwaukee outbreak, many secondary cases were identified that were linked to exposure to swimming pools

[5] See attached for summary of presentation: Juranek, Attachment C.1.

contaminated by children who had initially acquired infection from drinking Milwaukee tap water.

Several study designs were suggested by Juranek and discussed by the group for obtaining data on the "Attributable Fraction" of illness due to drinking water. These are outlined below. Discussions included a review of strengths and weaknesses of each study design. (For a more complete discussion of this topic please see Juranek's presentation notes, Appendix C.1.).

1) *Case - Control* (e.g. based on doctor or clinic reported cases): trying to identify the source (s) of exposures for cases by comparing their answers to questions with those of non-ill persons (controls) seen by the same doctor or at the same clinic. One caveat is that they may constitute a cohort with an increased proportion of immune subjects (from prior exposure).
2) *Cohort* (e.g. HMO based study): follow a study group of people for a year or more to see who becomes ill and then try to determine through use of a questionnaire what ill people did differently than people who remained well during the observation period.
3) *Community Intervention* (before & after comparison): use of "natural experiment" situations such as when a utility changes its treatment method. Investigators then measure changes in the occurrence of illness in the community, i.e., after a city builds and begins to operate a community water filtration plant, is the illness rate in the community lower than it was before filtration was used.
4) *Household Intervention* (controlled trial): randomly assign one group of households drinking water made as microbe-free as possible while a control group of households in the same area receives the same quality of drinking water as they normally would from their tap.

Juranek also reviewed some of the major types of study bias, confounding, and sample size issues that are inherent in some of the study designs.

1.5.2 Design Issues

- *Case ascertainment bias* (or who gets included in the study group.) – Case ascertainment bias is most likely to have a negative impact on Case-Control and Cohort studies. Participants discussed the difficulties of choosing cases in a "case-control" study that are representative of the entire population. According to some participants, severe cases of illness are more likely to be detected and counted. This includes persons with immuno-compromising illnesses and children. People who do not have easy access to health care or who have different health care seeking behaviors are unlikely to be counted. Other sources of bias mentioned by participants were the differences between populations in behaviors that affect risk such as consumption of tap versus bottled water and uncertainty that the distribution of risks for infection is the same for comparable groups in different cities.
- *Confounding Variables* (Confounding is a distortion in the association between an exposure variable and a outcome variable due to some other variable.) – Confounding is most likely to have a negative impact on Case-Control and Cohort studies. Many

participants brought up the difficulties in trying to eliminate confounding. For example bottled water users may appear to be at lower risk for gastrointestinal illness than tap water drinkers, but the lower risk may be a false impression, i.e. it is possible that bottled water drinkers as a group are more health conscious about everything they do. Thus they may have lower illness rates because in addition to drinking bottled water, they also tend to wash their hands well, avoid the types of fast foods that are often implicated in food-borne outbreaks, etc. Their income level and access to health care may differ from the general population. Confounding is not a problem in study designs, such as a household intervention study, where participants are randomly placed in one of the study groups.

Sample size (or the number of participants needed to show that differences in illness rates are not due to chance alone). In addition, the number of people in the study needs to be large enough so that a negative study is meaningful. Participants discussed the sample size needed from both a technical and political perspective. According to Juranek, if we believe that drinking tap water caused no more than 1% of gastrointestinal illness, we would need to study over 50,000 people to prove it. The need for such large sample sizes reduces the feasibility (i.e. cost and logistics) of successfully completing a study. Based on "best guesses" and limited published data, the current estimate of the attributable fraction of mild gastrointestinal illness associated with drinking tap water may be in the 10% to 30% range (Use this estimated range to calculate the population sizes needed to implement the various types of study designs described above). Based on this analysis, the household intervention study design was identified as the design that would enable investigators to test the lowest level of attributable fraction with the smallest number of participants (sample size). Some participants had doubts about the utility of a household intervention study in enabling a national estimate of waterborne disease to be generated.

During the course of the Workshop Juranek, as well as Regli and Susan Binder of CDC, gave overviews of approaches to the National Estimate. Discussion continued throughout the Workshop on how the Agencies should answer these questions. These discussions are broken down into specific decision points and are summarized in the **Approaches Towards a National Estimate** section of this report.

1.6 Incidence of Gastrointestinal Illness – Cross Sectional Studies[6]
-Presented by Thomas Navin, CDC

The final portion of Navin's presentation was an overview of the use of cross-sectional studies to determine the incidence of gastro-intestinal illness. Navin reviewed sources of baseline data on gastrointestinal illness, emerging infection detection programs in the US, and the use of FoodNet surveys (part of the Emerging Infections Program). Navin concluded by mentioning studies of HIV populations and concerns with this, and other, immuno-suppressed sub-populations.

[6] See attached for summary of presentation: Juranek, Attachment C.3.

The discussion of this presentation concerned the role of immuno-compromised sub-populations in the national estimate and the types of health outcomes (infection with specific pathogens versus general gastrointestinal illness) that should be the focus of these studies. The discussion points are included in the **Approaches Towards a National Estimate** section of this report.

II Planned And Ongoing Studies Of Disease Occurrence

II.1 A Randomized, Triple-Blinded, Placebo-Controlled Trial of the Feasibility of Household Drinking Water Intervention Studies[7]

-Presented by Jack Colford, University of California, Berkeley

Jack Colford presented a proposed study design to test the effectiveness of blinding in household drinking water intervention studies. Health data would also be collected and the study continued in years 2 and 3 if the study design is found to be appropriate. Colford began with an overview of the characteristics of the study's design and purpose: (For a more complete discussion please see Colford presentation notes in Appendix 2.D.).

- *Randomized & placebo-controlled*: Participants are randomly assigned to receive either water treated at home by special devices or usual water passing through a sham device.
- *Triple blinded*: Knowledge of the group (active device vs. sham device) to which a participant is assigned will not be known by the participant, the investigators, or the statistical team. The households are to be divided into two groups:
- "Intervention" groups - households using the devices to treat drinking water. "Placebo" groups - households using inactivated devices that resemble active devices in every visible external characteristic
- *Duration*: 4 to 6 months in the first year, ideally the study would continue for 12 months for each participant in years 2 and 3.
- *Devices and Arms of the Study:* (choice between point of entry or point of use device has not been made). The researchers are still contemplating different points of entry of the device into the homes:
  - Arm 1A: **Point of entry** (to home) device including joint use of filter and ultraviolet (UV) light enclosed in a locked cabinet that cannot be opened by the homeowner (tamper seal).

    versus
  - Arm 1B: **Placebo device** resembling the point of entry device in all visible respects except that no filter will be present, the UV source will be disabled and the entire device will be encased in a locked cabinet that cannot be opened by the homeowner (tamper seal).

  - Arm 2A: **Point of entry** device including the joint use of filter and UV light on two faucets in a household (tamper seal).

    versus
  - Arm 2B: **Placebo device** resembling the point of use device on every faucet in the household enclosed in cabinet that cannot be opened by participant (tamper seal).
- *Outcomes* to be measured are divided between year 1 and years 2 and 3. Year 1 focuses on the effectiveness of the study design including; costs (of conducting a fullscale study), laboratory outcomes (occurrence of infection with specific pathogens), and effectiveness of recruitment strategies and retention. Researchers

[7] See attached for summary of presentation: Colford, Attachment D.

will use estimates of health and lab-confirmed outcomes obtained during year 1 to generate appropriate sample sizes for the studies in years 2 and 3. Years 2 and 3 expand the study with respect to the number of communities and households per community.

After Colford's description Workshop participants discussed the advantages and disadvantages of the study design and some of the ethical issues raised by the study design.

II.1.1 Advantages

- Randomized, placebo-controlled design widely used in clinical and experimental sciences to address controversial questions. The question "does drinking tap water increase risk of measurable human disease?" is politically controversial because studies concerning it are likely to attract public, political, and media attention.
- Randomization provides the strongest control for "confounding" factors.
- In FDA evaluations of drugs, multiple randomized trials are mandated before a new drug is made available to the public. This study subjects drinking water to this level of scrutiny.
- Results of a (properly conducted) randomized, controlled trial are considered the most defensible evidence in both scientific and legal terms.

II.1.2 Disadvantages

- High cost.
- Labor intensive.
- Requires much more time to conduct than other studies because of the need to recruit participants and obtain permission from (multiple) institutional review boards (human subjects committees).
- Only provides data from one site during one particular time period, and therefore will not be generalizable in the effort to provide a national estimate of waterborne disease.
- Does not control for waterborne exposures outside the home.

II.1.3 Ethical issues

- Do investigators have "equipoise"? (a state of scientific uncertainty about the answer to a research question, or the relationship between outcome and factors tested that precludes certainty in making a widespread recommendation.)
- Is it ethical for corporate or municipal entities to claim that home drinking water is either healthy or unhealthy in the face of conflicting evidence from uncontrolled, non-randomized studies?
- If the issue under consideration is of widespread public health importance, is it ethical to omit the most scientifically defensible design from the suite of designs put forth to address the question?

II.1.4 Discussion

Following his presentation Colford addressed questions and comments from other Workshop participants. He indicated that the pilot first year study was not designed to be large enough to detect small health effect differences between two groups. This study is

most useful as a pilot to gauge the effectiveness of this type of study (in particular the ability to blinding and if blinding is necessary), but health outcomes will be measured in the first year as well. Colford suggested that the study should be helpful in deciding if it is worthwhile doing more blinded intervention studies in future and help clarify what types of studies should be included in the National Estimate "portfolio".

In response to a question Colford explained that the study will use telephone interviews coupled with laboratory measurements to determine the incidence of diarrhea but that his team is looking into other ways of gathering data. This is especially important in the case of people with underlying medical conditions. Colford responded to a question on the ethical obligation of researchers to report illness and that if specific infections are detected through the laboratory testing, patients will be notified and advised to contact their personal health care providers. Colford added, however, that there should not be further ethical issues in administering the filter and sham devices. All the water will meet current regulations. Some of it will then be treated further. What degree of extra treatment is still undecided. Water will not be degraded.

One difficulty pointed out by a few Workshop participants is finding a device that would not change chlorine and taste. A dose of UV will change the quality of the water (i.e. raise ozone and change taste). One participant recommended that "taste testing" be conducted because it is likely that participants will taste if their water was treated with UV light. Even in sham devises there is a likelihood of changing the drinking water quality. Additional questions raised on this topic were: how researchers will ensure that the water coming out of devices is cleaner than tap water? To what extent the device further treats the water? And, how will the study account for elevated risk if the device or sham is not properly maintained?

One participant suggested that this study design only focused on household tap water and that integrated studies are necessary in the same community while this study is going on. To accomplish this the ongoing FoodNet survey could be intensified in that area. Participants pointed out that tying FoodNet survey system to these studies severely limited the sites where linked studies could be done, and pointed out that the choice of sites for studies of waterborne diseases should be made on the basis of the water supply, not the presence of a FoodNet survey system.

Selection of families with children and the elderly was another issue discussed. The elderly population could be viewed as immuno-compromised (although they may also have high resistance to some pathogens). Studying the elderly has the design advantage that they take most of their water at home.

The topic of timing and prioritization of research was also considered. One Workshop participant criticized this design because although the study design might be fine from an epidemiological standpoint, the results will not be available for another year. This question concerned the amount of data that the study would collect. This participant suggested that the effort should be on low cost studies using retrospective data. Another comment was that retrospective studies could usefully be complementary or additional,

rather than an alternative approach. Another question presented was whether the present focus should be on studies that give indications of incidence of disease.

In response to concerns about the study design one Workshop participant noted that participants at the March 1997 workshop had favored the household intervention study design (like the one presented by Colford). Data collected would include signs and symptoms of gastrointestinal illness, water consumption, collection of clinical specimens (including stool, sera, saliva), and monitoring of water quality indicators.
At the end of Colford's presentation, Workshop participants made some additional comments on the proposed household intervention study design;

- The device itself, if not maintained, may add to risk – not reduce it – because it provides more surface area for bacteria to grow.
- Most people drink most of their water away from home. A participant asked; how can you identify and then capture in the study people who only drink water from the home without then selecting a group who are elderly or immuno-compromised. homebound people.
- There is a need to look into doing these studies in multiple sites because differences between sites might be more important than other confounding factors.
- It would also be a good idea to investigate using a less expensive design because it could be used at more sites.

In the discussion of the household intervention design one participant suggested an alternative approach based on a "community" intervention with randomization by community (not individual household). A presentation and discussion of this study design was added to the next day's agenda.

II.2 Community Enteric Study[8] -- Study Design Model
-Presented by Rebecca Calderon, EPA

Rebecca Calderon presented EPA's efforts to study rates of enteric disease using a longitudinal study – following 300 families with children between 2 and 10. The study integrates surveillance (clinical lab results, HMO/nurse hotlines, and cross sectional survey) and indirect measures of illness (nursing home surveillance, hospital admissions, antidiarrheal sales, and school absenteeism) to compare with symptom reporting in the families. Researchers could use utilities that are currently planning on making changes in their water source, treatment, or distribution systems (either in response to EPA regulations or not) and use them as opportunities to do "natural" before/after experiments. (For a more complete discussion please see Calderon presentation notes in Appendix 2.D.).

Calderon presented the four objectives of the study;

- Determine the enteric disease rates in various communities across the country.
- Determine the relative source contribution of environmental factors associated with enteric disease.

[8] See attached for summary of presentation: Calderon, Attachment E.

- Determine etiologic agents associated with enteric disease.
- Evaluate methods of surveillance.

II.2.1 Discussion Points

Calderon explained that this effort began with site identification, looking for communities that would be useful because they were changing their water treatment systems – a natural time series experiment. This task was harder than expected and she spent two years identifying unfiltered utilities changing to filtered treatment systems. Many of the unfiltered plants were not aware that EPA regulations required them to install filtration. Calderon has currently identified 5 plants that are upgrading to filtered water treatment systems. Calderon also found that many other plants are changing – i.e. groundwater to surface water, treatment technology, etc. One participant commented that this is great opportunity to do comparative before/after epidemiology studies.

Dr. Calderon explained that in her experience gaining trust in a community is the hardest part of doing a community-based study. Especially concerning the collection of blood. Calderon had done sero-surveys previously with success in other communities. In those communities the Red Cross helped in collecting blood samples. In this study the Red Cross was not used and citizens were reluctant to give blood samples. The solution was to test local college students. They were happy to give blood for money ($25), they also returned so they could be monitored over time. For the serum testing Calderon chose a college with mostly local students so they were not traveling as much as students from other regions during breaks. Students would have to remain in an area through different seasons, because of the variability of water quality during different seasons. Participants noted difficulties with using Red Cross sera, as they do not represent the population as a whole, and voiced the same concerns about college students. Other specific populations of interest identified included children and parents of young children.

According to Calderon, one of the current challenges to understanding WBD occurrence is the lack of surveillance. Calderon suggested that if studies were continued over time researchers could gain experience and have a much better idea of what is going on. An advantage of this study design is that it is an integrated approach that could easily become part of a surveillance system.

II.3 A Paired City Study -- Study Design Model[9]
-Presented by Floyd Frost, Lovelace Institute

Floyd Frost presented his work on a completed "paired city" study comparing Las Vegas and Albuquerque. The study looks at infections among residents of both cities. The study used infection as an endpoint because a very small percentage of infections result in illness (estimated 1/100 to 1 /1000) and even fewer cases of illness result in a report to CDC (estimated 1/100,000 to 1/million). The study investigated serum response to *Cryptosporidium* in individuals and used a benchmark of 35% to represent a "serum-positive". This number was chosen because few baselines were above this number. The

[9] See attached for results from paired city survey: Frost, Attachment F.

duration of serum response (IgG – up to one year) makes it possible to identify recent infections with high rates of confidence. Two years after an outbreak in Las Vegas (LV), Nevada, responses for two *Cryptosporidium*-specific antigen groups were evaluated for 200 LV and 200 Albuquerque, New Mexico blood donors to determine if endemic *Cryptosporidium* infection was elevated in LV. LV participants had higher mean responses to the 15/17 kDa marker. However, for late September-early October, 1996, Albuquerque participants had higher mean responses for both markers, corresponding to an increase in the point prevalence of cryptosporidiosis cases in New Mexico and several other states. More LV participants used bottled water or had a home water filter system, but these precautions were not associated with lower serological response to either marker. Washing food with bottled water was associated with an increased response for the 15/17 kDa marker. These results suggest that the contribution of LV drinking water to infection during this time might be modest.

II.3.1 Discussion Points

The discussion following Dr. Frost's presentation centered on the confounders that could complicate the drawing of conclusions from data collected in an epidemiological study. Eating vegetables has been shown to have protective effect for illness. However, is this because of curative/preventative vegetables or increased exposure/immunity?

- A study in an area of Ecuador where water - because of its scarcity and expense - was being reused by multiple children for washing themselves and for washing vegetables found that the more people used the contaminated water, the more likely they got infected.
- Bottled water users may have other risks -- washing vegetables with bottled water by not doing as good of a job as washing them under running tap water.
- Life style and health consciousness may be the primary confounders.

II.4 Randomized Community Trial -- Study Design Model

-Presented by Dana Flanders and Robert Gilman

Both Flanders and Gilman presented an outline of the Randomized Community Trial study design. The goal of the study is to determine an estimated reduction of infection due to increased treatment (i.e. filtration, UV, chlorination, Ozone) at a community level. This study design has the benefits of a large sample size. It allows researchers to collect blood or stool specimens door to door (if indicators miss disease symptoms they still detect incidence of infection), look at broader community-wide indicators such as growth and school attendance of children (most susceptible sub-population), and collect data through mortality rates and sewage surveillance.

II.4.1 Method

1) Identify approximately 30 communities:
   - Homogeneous or matched pair: not too dissimilar in baseline rates of infection and/or disease, type of water source/treatment/distribution system, population characteristics such as size and age distribution.

- At least 6 communities would be studied per intervention group. The sample size would be relatively large (# people in community * # of communities).

2) Identify households in each community

- Distance from treatment plant (to identify effects of distribution system). Possibly over-sample those near the source so that effects of the distribution system might be minimized for this subgroup
- High-risk sub-populations (children or immuno-compromised).

3) Measure baseline infection or disease rates.

4) Randomly select some communities for control. One group will receive early intervention, the other late intervention -- all will eventually get water quality improvements.

5) Measuring effects:

- -Stool collected once per week (regardless of presence of symptom) and tested for pathogens.
- -Serum collected - use of finger stick could reduce some of the public's resistance.
- Other data points and collection techniques:

-vomiting --	telephone
-doctor visits --	telephone
-birth weight --	telephone
-absenteeism --	telephone (school/work)
-growth --	hospital visits
-mortality --	reported

- Use hooks to convince people to cooperate: monitoring of children for free for anemia, growth, etc.

6) Outcomes:

- Time to time variation within community -- prevalence/incidence between years, natural waxing and waning within one community would be measured (this natural variation is important to understand for National Estimate. It measures the noise of random variation between years.)
- Time-to-time variation of household versus outside (office/school) exposure. Meaningful because of randomization.
- Outcomes would take 2 years (to account for variation in time and season)
- Intervention studies present problems -- however, randomization solves many of these problems.
- Baseline and post-treatment: you get two years of "before and after" data.
- Infection: studying infection is much more sensitive than looking for symptoms (diarrhea).
- Check stool weekly whether or not there is diarrhea. Dr. Calderon's experience showed that people are willing to provide samples.
- Get diarrhea rates by phone: collects both infection and diarrhea rates which is another correlation the study would be collecting data on (disease rate / infection).
- Incidence: you can compare directly those communities with good and bad water.
- Interventions –Installation of filter at utility- study could still be randomized because of large amount of plants making changes. Scientifically credible

because you know and can account for the quality of water sources in communities you are comparing.

7) Cost :

- Many of the components of this study could be subcontracted out to reduce costs. (Laboratory testing should cost around $3 / sample).
- Infection costs could be reduced by sub-contractors (visit 1 time per month)
- Testing for *Cryptosporidium* and viruses could be inexpensive if you leave out the few pathogens that are particularly difficult and expensive to detect.
- Cost to community of adding extra treatment for 10,000 is roughly 1 million dollars.
  -Lots of cities are currently putting in filtration/ozone -- 100s of communities are currently making changes, many are also remaining untreated, however;
  -There may be other important differences between communities that choose to change/upgrade their treatment methods and those that do not. It is feasible to take list of communities making changes and randomize on this list -- this keeps randomization with the bounds set by those making changes and those that are not.

II.4.2 Discussion

In summary this study design:

- Uses and established epidemiological design, intervention at community-wide level.
- Responds to the fact that there is no single method that will get attributable fraction number -- you need a mosaic, i.e. numbers of estimated waterborne disease cases vary greatly.
- Is inexpensive in comparison to the cost of changing technology to add observational studies in changes that are already going on -- these communities making technology changes are natural experiments that can be used for this study.

Workshop participants offered the following comments:

- The fundamental research question should be: what is the impact of drinking water on GI illness and compare with water of little or no risk? The study would then use "pristine" water and look at the absolute risk of drinking tap water.
- This study answers the question of relative risk between different treatment approaches.
- It is also hard to eliminate problems of post-treatment reintroduction of pathogens. Just knowing the treatment technology (as unit of comparison between communities) does not guarantee quality of water.

The issue of whether and how to blind people in the study was discussed at length. One participant suggested that the following criteria are used to determine when blinding is necessary: 1) blinding is necessary for the success of a study, and 2) blinding adds no appreciable risk. Another participant stated that an open issue is how much will blinding effect the results of the study? Gilman and Flanders responded that researchers, laboratory and analysts must be blind -- but it is questionable whether it is necessary or even possible to blind the community. It is not clear whether the public will care or change their behavior if they do know. In contrast to this view, one participant felt that a

study on this scale would attract the media and political attention. In the case of household treatment units it was pointed out that the taste of water will change and people are likely to figure out which water has been treated and which is sham.

Another observation was that avoiding blinding of the community addresses many of ethical considerations of epidemiological studies. A non-blinded study means communities have a choice. One participant pointed out that if community that is not getting intervention still gets equal medical care (i.e. baseline is not diminished) then there are not ethical problems with an intervention study. For example, utilities make changes all the time without public notice. However, another participant noted that the EPA Administrator recently announced an effort to increase the public's "right to know" about changes in water treatment methods by utilities.

II.5 Time Series -- Study Design Model

-Presented by Robert Morris, Tufts University

Robert Morris presented a Time Series design as a waterborne disease occurrence study design. This approach evaluates the association between day to day changes in community health indicators and changes in water quality over time in the same community. Data on turbidity, presence of pathogens, and other water quality indicators would be compared with community health indicators that are readily available in a computerized form such as emergency room visits as recorded in medical billing data or anti-diarrheal sales. These data could be used to determine if short-term changes in water quality are associated with increases in these indicators of gastrointestinal illness. This approach eliminates all confounders except those that vary in time with water quality. Thus, the list of confounders is relatively short and is primarily limited to factors that demonstrate the same temporal variability as water quality. Morris explained that the sample size could be as large as an entire city, depending on the data set used as an indicator of gastroenteritis in the community.
Estimating attributable fraction using this method would require two steps. First, the time series method would be used to estimate the association between water quality and a given health indicator. Then, the relationship between the specific health indicator and the incidence of disease in the community could be examined. Finally, this information could be combined to estimate disease risk in the community.

Coupling this method with planned cohort and intervention studies would provide important information valuable information on the relationship between health indicators based on computerized data bases and rates of infection and disease among individuals in the community. This information could help in the interpretation of time series studies, particularly with respect to attributable fraction.

One participant pointed out that, though turbidity may not be the best indicator of water quality, it could be coupled with other information collected on pathogens and other tested criteria. However, regulations are presently based on turbidity and so associations between turbidity and health have direct relevance to these water quality standards.

Morris then outlined the advantages and disadvantages of the Time Series study design.

Advantages:

- Low cost (can look at many cities).
- Short time to completion (could use historical data).
- Can directly relate to indicators used in standard setting (could use changes in turbidity or other indicators that are regularly measured).
- May provide tool for long term surveillance (not expensive to maintain information collection system once it is established).
- Could extrapolate findings to National Estimate if method were validated by detailed study in a few cities and then employed in a larger number of cities.
- Confounders would have to be connected with water quality (temporal changes).
- Can be used to study factors related to water source and water quality that influence the association between monitoring data and disease.
- Lots of things will cause GI illness but these studies should pick up those that are correlated specifically with drinking water quality.
- Analysis of the specific time lag between changes in water quality and changes in a health indicator may be related to the incubation period for the infectious agent and may be useful in identifying the responsible pathogen.

Disadvantages:

- Does not relate individual exposure to outcome.
- May be difficult to isolate effects of the distribution system. Stratification of the population by distance from treatment plant might give some indication of this effect. (Note that this is not the only study design that has this problem).
- Rare events difficult to analyze.
- Stage I rule may reduce efficacy of current surrogates for water quality such as turbidity.
- You need several years of data to deal adequately with seasonal effects in the data.

III Approaches Towards A National Estimate

Ron Hoffer, EPA, summarized the topics covered on the first day of the Waterborne Disease Workshop in an effort to organize the discussion and to help participants understand its scientific and policy context. Discussion then focused on the individual study designs and extrapolation to the national estimate. The following section is organized around the outline presented by Hoffer and discussed at the Workshop.

III.1 Causative Factors & Site Selection

III.1.1 General

- A participant noted that the National Estimate would not be helpful unless it included information on the source or cause of contamination. He suggested that one way to obtain this data is stratification of households by other variables such as distance from treatment center (i.e. if the source of contamination is in the distribution system – either due to bacterial growth or exogenous pathogens – then the likelihood of being exposed to contamination may be less closer to the plan).
- According to one participant the dispersal of the pathogens in water is a central and not very well understood component in estimating the risk of waterborne disease. "This is a universe of distributions," these pathogens are not evenly distributed in the water. Also, there is wide intra-population variability of resistance of humans and in the virulence of pathogens. Another participant pointed out that there appears to be disagreement of predicted risks versus measured concentrations of pathogens in groundwater.

III.1.2 Source Water (Surface/Ground)

- One participant noted that viral contamination had been documented in groundwater sources and that future epidemiological studies should be sited in communities using ground water.
- This participant also suggested that the criteria for selecting water supplies for study should be made explicit.
- A participant explained that *Cryptosporidium* has been noted in groundwater (including in a supply associated with an outbreak in the UK.)

III.1.3 Treatment Method/Technology

- Another participant suggested that a consideration in evaluating the type and number of studies should be on an understanding of the distribution and characteristics of different types of water supplies and treatment/distribution systems including their vulnerability to contamination.
- More than one participant suggested that the utility industry would play a crucial part in identifying the types of treatment that were being used and in helping researchers choose which should be the focus of study.

III.1.4 Reportability and Compliance

- One participant explained that reportability of suspected waterborne illness – for those cases that are reported on clinical suspicion – food borne infection is often used

as general heading. This heading should reflect more specific separation among water and food as the source.

- This participant continued that because *Cryptosporidium* and *Giardia* are hard to identify without a laboratory test, physicians should be encouraged to recognize their symptoms and order tests for them when encountered.

III.1.5 Site Selection

- One participant suggested basing site selection decisions on information about current risk. What characteristics present highest risk (what types of source, treatment, distribution, etc.). However, countered another participant, highest risk areas make up a very small percentage of the water systems in the US. Small community systems are often least adequate, but they also serve a small population.
- In response to a question an EPA representative pointed out that there are many questions of practicality in how to measure water quality or identify contamination in source water. It would be ideal to have at least one study in each category of water source and treatment technique, but they have limited resources. In an environment of limited resources, the economics of the situation dictate that the Agency must try and achieve the "greatest bang for the buck."
- The unit of organization is not clear – By water source, watershed, community, city or sub-population. How do we find representative groups? Can we generalize criteria used in one situation to others (i.e. one type of system or sub-population?) How do we characterize watersheds? -- Need basis for broader representation.
- Issues of site selection also involve criteria imposed by epidemiological study design issues.

III.1.6 Choice of System and System Size

- Levels of contamination and types of contamination (i.e. relation between turbidity and pathogens) vary greatly between individual systems and by season and other variables such as weather conditions.
- Other participants mentioned their concern that the studies not focus exclusively on large city systems. They noted the common assumption that large systems account for most infection, and pointed out the bias towards picking up outbreaks in large systems. There may be correlation between system size, water source, the population's immunity, and access to medical care, physician's ability to detect, and likelihood of reporting an outbreak.
- Federal regulations differ for large and small systems and it may make sense from both a policy and science perspective to separate consideration of them. One participant suggested that focus should be put on the system characteristics that serve the largest percentage of the population. Another suggestion was to define simple categories of sites. One participant suggested using either a weighted average (in proportion to the number of people in each category) or taking a random sample of the population by selecting individual characteristics (by source of water) and using random matched pair comparisons.
- An EPA representative pointed out that EPA has work to do before deciding how to prioritize between water systems for the next set of studies.

III.1.7 Number and Types of Sites Needed for Portfolio

- One participant suggested that ultimately 20 to 25 sites (not just the 5 mandated by Congress) should be studied, once you start looking at different characteristics of water systems there are many different characteristics you must consider: size, source, treatment method, distribution system. Dr. Juranek explained that the CDC will probably take more than the mandated number of five sites because a wider portfolio is needed. The national estimate is not the endpoint of the CDC/EPA effort.
- It is crucial to obtain the help of experts from the water industry to understand what types of water systems and which communities it would be useful to study.
- One participant felt that there should not be one National Estimate number; "this estimate should change over time -- going down as the amount of uncertainty decreases and water quality improves."
- This participant continued that a related goal is the development of tools and criteria that are low cost and generalizable. Hoffer explained that EPA and CDC have responded to this concern through their goal of creating a portfolio of studies and approaches as a basis for a national estimate.
- There is no single study that will come up with an acceptable risk estimate number. The question, according to another participant, should be: what would be the suite of studies that would be most helpful in arriving at national estimate?

III.1.8 Indicators of Exposure to Pathogens and Disease

- Another major point of discussion concerned the health endpoint that should be measured. Participants discussed specific questions on which and how to measure exposure to pathogens, immune response, infection, or disease directly and whether to use indicators such as symptoms, medication sales, or behavior.
- Many participants felt that pathogen specific testing offers the greatest confidence in the results because it is able to test for stool positivity and serum antibody response for suspected pathogens. Other participants, however, explained that this approach is not entirely practical. It misses many cases of infection because only approximately 10% of people suffering with gastrointestinal illness see a doctor and less than 3% have stool tested for parasites or viruses. Also, no tests currently exist for many waterborne pathogens.
- One participant relayed their experience that it can be difficult to obtain the specimens of blood needed for testing – especially from children. This participant, as well as others are currently investigating the use of saliva as an alternative.
- Specific pathogens, according to a participant, present individual problems in monitoring. For instance, cryptosporidiosis is a relatively common infection. The role of immunity affects our ability to study it. People at highest exposures and risk of spreading infection often have lowest illness rates -- visitors to an area may get sick while immuno-competent residents (exposed regularly) are immune. This participant explained that in this case, intervention studies could draw the wrong conclusions (if trying to detect risk of infection). Looking for illness could be the wrong place to look for exposure or risk of drinking water. This is further complicated because we do not know how long immunity persists or the distribution of *Cryptosporidium* in the drinking water systems.

- We are looking at many pathogens with differing levels of understanding of their virulence, symptoms, and health effects.
- This participant suggested that *age-restriction* of the study population would make wider sampling more feasible. The only criteria to limit the number of specimens required that made sense was age-restriction -- those below the age of 10 have 60% of the cases of infection of *Cryptosporidium* and those above 65 have very few cases. Therefore, efforts should be concentrated on looking at children.

III.1.9 Distribution Systems

- Another concern brought up was the issue of pathogens coming from within distribution systems. According to one participant it is imperative to understand the source of pathogens in drinking water to truly understand and address drinking water risk.
- A number of participants brought up the concern that the focus on water sources was missing other contributing factors within the distribution systems (i.e. pipe contamination). The characteristics of the water distribution system and water supply are crucial. Therefore the studies must ultimately identify the source of the risk and focus on intra-system problems. Participants also discussed the potential role of biofilms as a contributor to contamination.

III.1.10 Specific Pathogens

- One participant related that the FACA Committee had suggested concentrating more effort on pathogen specific studies.
- Need to add *Cyclospora* to list of pathogens of interest

III.1.11 Immuno-Compromised Sub-Populations

- According to Dr. Juranek a major question surrounding the choice of a study population concerns the focus on monitoring the drinking water risk on immuno-compromised (such as AIDS or recent chemotherapy patients) and immuno-competent persons. Some participants felt that the immuno-compromised sub-population is at greatest risk for severe infection and therefore may not be representative of a national estimate. Others suggested that the best approach is to determine the sensitivity of immuno-compromised persons and utilize them as target or indicator populations. Other parties countered that focusing efforts on this population may lead to policy implications limited to immuno-compromised population.
- There was a concern that the studies include sub-populations at highest risk in the National Estimate in a meaningful way.

III.2 Societal Impact

III.2.1 Health Issues

- What is the focus of studies; do they measure severe illness, mortality, or chronic health effects?

- Are studies sensitive to secondary effects: such as developmental issues or organ dysfunction associated with infection that are not accompanied by acute effects (i.e. diabetes associated with viral infection)?
- Are the studies looking at endemic occurrence of WBD or outbreaks?

III.2.2 Economic Issues

- Health Care Costs
- School or Workdays Lost
- Unemployment
- Lost Tourism Revenue; a participant mentioned that dollars lost due WBD outbreaks cost the entire economy money (not just region). This study found that there is a national net loss of economic gain from an outbreak (cancelled vacations)
- Decreased Consumer Confidence
- Avoidance costs (costs of switching to other water sources such as bottled water).
- Administrative Costs of outbreak
- A CDC representative mentioned that CDC is currently involved in an effort to study the costs associated with WBD outbreaks.

III.2.3 Equity/Justice Issues

- Access is limited to alternative sources of drinking water (home bottled or filtered water) because of high costs. These effects may be compounded because the same communities may have limited access to health care as well.
- Who should the regulations protect and how should society protect immuno-suppressed sub-populations.

III.3 Methods

III.3.1 General

- A participant suggested that for very little extra cost you could expand on-going studies to get useful epidemiological data. You may be able to get information on specific pathogens for little extra cost once you are doing other monitoring. For instance, time series studies could be *add-ons* to the other studies. It is likely that expensive studies will become the "gold standard" for developing, but would be enhanced by cheaper studies in the same places to broaden knowledge on the many variables involved.
- Many participants recognized Dr. Calderon's effort to identify utilities that were changing water sources or treatment methods and opportunities that should not be missed to do "natural" experiments.

III.3.2 Case Control

- The case-control design involves identification of cases with infections that are potentially waterborne and controls who do not have the disease. The exposures of the groups are then compared to determine if the cases have a higher likelihood of a given exposure.
- Example: Persons with laboratory diagnosed cryptosporidiosis would be identified together with a group of controls of the same age, race and sex from the same

community. They would then be interviewed concerning their patterns of water use. One might then be able to ask the question: Were persons with disease more likely to have consumed tap water than persons without disease?

III.3.3 Prospective Cohort

- The cohort design involves identification of a group of persons who have different levels of exposure to the risk factor of interest, in this case tap water. The cohort is then followed over time to determine if the persons with the exposure are more likely to become infected and/or develop disease.
- Example: A sample of persons living in a community is identified and interviewed concerning their patterns of tap water consumption at home and at work. Over the following year, they are asked to record any events during which they experience symptoms related to gastroenteritis. At the end of the year, the rates of symptoms among persons using exclusively bottled water is compared to those using exclusively tap water.

III.3.4 Household Intervention

- A set of households is randomly assigned to receive water that has undergone a higher level of treatment than the tap water in those homes. These households are then followed over time. At the end of the follow up period, members of households with this treated water are compared to members of households without the treatment with respect to measures of infection and/or disease.
- Example: A group of households is randomly assigned to receive either a in-home membrane filter or a box resembling the membrane filter. Over the following year, they are asked to record any events during which they experience symptoms related to gastroenteritis. At the end of the year, the rates of symptoms among persons using home water filters is compared to those without home water filters.

III.3.5 Community Intervention

- This is similar to the household intervention except communities are randomized to receive improved treatment rather than households.
- Ten similar communities are identified and 5 are randomly selected to receive improved water quality treatment. These communities are then followed for one year to determine the incidence rates of gastroenteritis.

III.4 Study Scale – for National Estimate

- The problem with looking for data on a national level is that it is extremely difficult to extrapolate from one city to another because of the variability of drinking water, variability of water, and demographic and other host factors.
- Taking a national approach also limits other uses of data – smaller scale studies add to our understanding and are useful in public health surveillance.
- One participant suggested that the most efficient way of doing the national estimate would be a national scale study that would randomly select sites from specific regions. This study would not be useful for extrapolating down to more specific data on a regional level, but it might be the best way of avoiding the issues of site and sub-population selection.

- One participant felt that intervention and analysis may be better at community level. One drawback is that you would need a larger number of communities to obtain meaningful data. The number needed would depend on the amount of illness.

III.4.1 Scientific and Policy Credibility

- The question of how the EPA extrapolates risk estimates of low levels of exposure was asked by a number of participants. Regli explained how this estimate was the result of "fitting" a dose response curve down to zero based on the available dose response data points from different studies. One participant pointed out that although it is understood that exposure to a single oocyst can lead to health effects, there are huge intra-population differences in resistance to pathogens, different in the virulence of pathogens and effects of exposure.

III.5 Next Steps

The final presentation of the WBD Workshop was by Emerson Lomaquahu from the American Water Works Association Research Foundation (AWWARF) on a January 1998 meeting AWWARF and EPA are sponsoring on epidemiological studies related to the development of a national estimate and possibilities for research funding. In closing CDC and EPA representatives discussed how they would move forward with the development of the national estimate.

III.6 American Water Works Association Research Foundation

Emerson Lomaquahu gave a description of the American Water Works Association Research Foundation's upcoming waterborne disease workshop. AWWARF is a private, non-profit organization primarily supported by drinking water utilities, as subscribers, that contribute to a centralized research program. AWWARF also collaborates with other organizations such as EPA. One example of this collaboration is the Microbial/Disinfection By-Product Council. This council has met annually over the last two years to determine research needs and projects. It has allocated approximately $2 Million per year for research to support regulatory mandates. One project planned for 1998 is a workshop that will convene a multi-disciplinary group of experts to review study designs of epidemiologic studies to estimate endemic diseases associated with drinking water. The study designs will serve as a basis for possible future funding. Lomaquahu closed by noting that the AWWARF would take nominations for candidates to participate in the expert workshop.
Emerson Lomaquahu can be reached at AWWARF (303/347-6114).

III.7 Additional Site selection considerations and closing remarks

Fred Hauchman, EPA, proposed using a decision tree approach to answering the questions surrounding the national estimate, in particular how to approach possible differences in drinking water quality (and any associated disease) based on a number of factors. The group also discussed the development of a study site selection matrix based on broad categories of source water contamination (high/low) versus level of microbial treatment (no/limited/excellent treatment). Information on source water quality and treatment will become available within the next two years from the results of the

Information Collection Rule, EPA's supplemental *Giardia* and *Cryptosporidium* surveys, and through an AWWARF/M/DBP Research Council project on the source water quality variability. The AWWARF project involves the collection of frequent (daily) samples for pathogens and water quality indicators. Participants discussed the feasibility of selecting epidemiological study sites where treatment and water quality information would be collected.

National Waterborne Disease Occurrence Estimate Decision Tree

Water Source (*surface/ground*) → System Size (*large/small*) → Treatment Technique (*filtration, chlorine, UV, etc.*)

Considerations: study design, etiologies, water quality, demographics, seasonality, region, etc.

The meeting concluded with representatives from EPA and CDC thanking the participants for their hard work and cooperation in making the Workshop a success. According to one participant, the meeting had helped EPA and CDC identify new ideas to ponder and put "different spins on old ideas."

WATERBORNE DISEASE WORKSHOP
October 9 and 10, 1997

Meeting Summary

Attachments

Presentation Notes

A. Stig Regli Presentation Notes: Statutory Requirements

B. Jeffrey Griffiths Handout: Routes of Exposure / Spread and Detection of Waterborne Infectious Disease

C. Dennis Juranek Presentation Notes:
   1. National Estimate of Waterborne Disease Occurrence
   2. Ongoing CDC Surveillance Systems Related to Water 1996
   3. Incidence of Gastrointestinal Illness

D. Jack Colford Presentation Notes: Toward a National Estimate of Waterborne Diseases: A Randomized, Triple-Blinded, Placebo-Controlled Trial of the Feasibility of Household Drinking Water Intervention Studies

E. Rebecca L. Calderon Presentation Notes: Community Enteric Study – Enteric Disease Study
   Phase I – site selection
   Phase II – site evaluation
   Phase III - pilot (full scale)

F. Floyd Frost Presentation Notes: Survey Results from Paired City Study

Meeting Information

G. Agenda

H. Participant List

Attachment A

Stig Regli Presentation Notes:

Statutory Requirements

Statutory Requirements Pertinent to Microbial DW Regulations

- Must set maximum contaminant level goal (MCLG) for contaminants of concern
  - set at level at which no known or anticipated health effects occur & which allows adequate margin of safety
  - Current MCLGs under SWTR :
    - Giardia = 0, viruses=0
  - Proposed MCLGs under IESWTR
- Cryptosporidium = 0

Statutory Requirements Con'd

- Must set MCLs or Treatment Technique Requirements as close to MCLG as feasible (considering costs)
- Additional Considerations
  - may be set at level other than feasible if
    - feasible level results in increase risk of other contaminants in drinking water
    - level of treatment shall minimize overall risk (balance risk) that may result from treatment technique or MCL
  - must be sensitive to cost/benefit analysis

Overview of Current Regulations

- Surface Water Treatment Rule (SWTR)
  - systems using surface water must maintain
    - >= 99.9 percent removal/inactivation of Giardia
    - >= 99.99 percent removal/inactivation of viruses
    - turbidity monitoring & performance criteria
    - disinfectant residual in distribution system
  - unfiltered systems meet watershed control & source water quality criteria
- Total Coliform Rule
  - applies to all systems
    - all systems must monitor for coliforms
    - < 5% measurements can be positive

Possible Interim Enhanced SWTR Criteria

- applies to systems with >10,000 people
- all filtered systems must achieve >=99 percent removal of Cryptosporidium
  - tighter filtration performance criteria
  - monitoring of individual filters
- systems changing disinfection practice to comply with Stage 1 D/DBP rule must maintain exisiting levels of disinfection
  - exceptions allowed through state approval

Regulatory Strategy for Controlling Pathogens

- Develop criteria to adequately address source water pathogen concerns
  - control pathogens associated with causing waterborne disease
  - specify criteria that control for pathogens most resistent to treatment
- Develop criteria to adequately address distribution system concerns

Approach to Developing National Risk Estimates

- select target organism
  - Cryptosporidium, Giardia, viruses
- estimate national distribution of concentration levels reaching consumer
  - national source water distribution
  - national level of treatment distribution
- estimate infection rates from available dose response curves
  - e.g., by extrapolation, person ingesting 1 oocyst has 2% likelihhood of being infected
- estimate illness and mortality rates

Attachment B

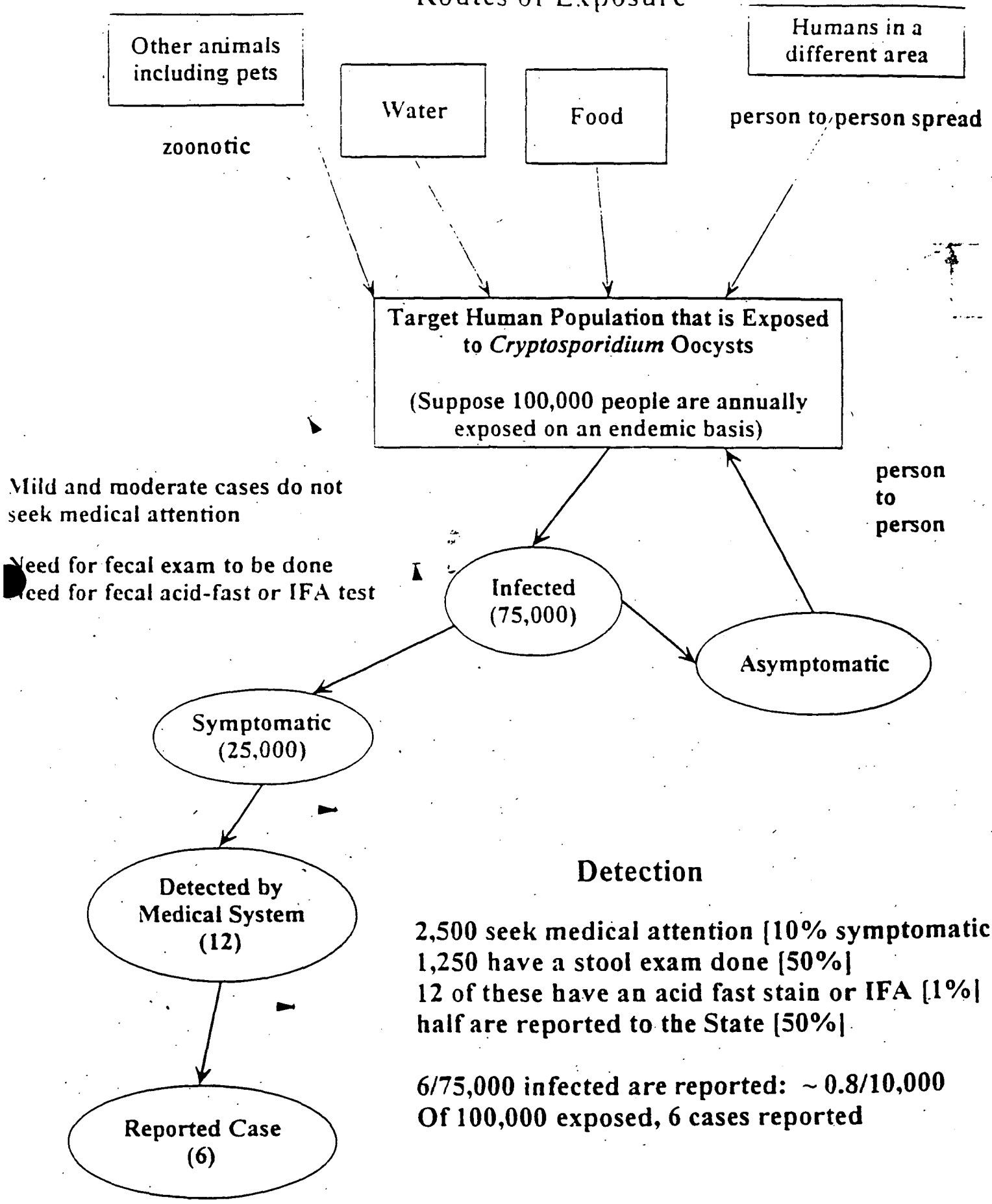
Jeffrey Griffiths Handout:

Routes of Exposure /

Spread and Detection of Waterborne Infectious Disease

JKG. RDM
TUSM: 10/5/97

Routes of Exposure



Detection

2,500 seek medical attention [10% symptomatic]
1,250 have a stool exam done [50%]
12 of these have an acid fast stain or IFA [1%]
half are reported to the State [50%]

6/75,000 infected are reported: ~ 0.8/10,000
Of 100,000 exposed, 6 cases reported

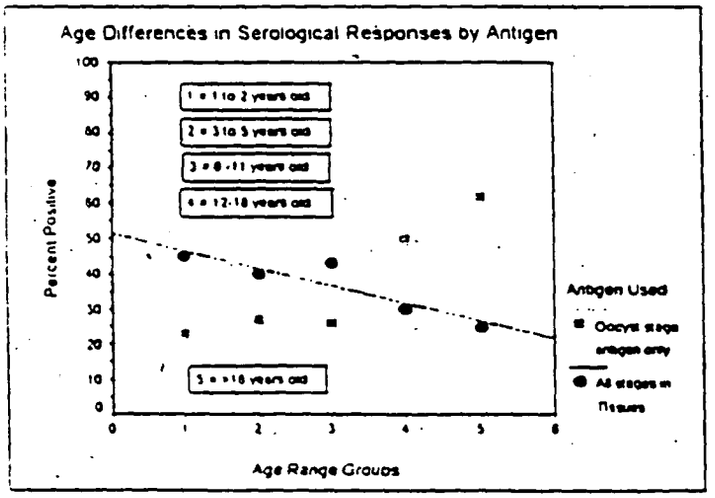
A POTENTIAL BIAS IN THE LITERATURE IS THE BELIEF THAT SEROPREVALENCE TO THE TRANSMISSION (OOCYST) STAGE EQUATES TO THE CUMULATIVE TOTAL OF PRIOR INFECTIONS.

- Ungar et al[1] (1986) found that only 3 of 4 people immunologically competent people with known C. parvum developed IgG to oocyst antigens, and the duration of response was ≤ 4 months. In contrast, people with AIDS and persistent infection had persistently (+) IgG.
- Mead *et al*[2] found that serum antibody to sporozoites using Western blots decreased markedly over 5 months after infection with C. *parvum* in immunocompetent people.
- Moss *et al*[3] obtained acute (3-week) and convalescent (10 and 28 weeks) serum from Coast Guard personnel with cryptosporidiosis after the 1993 Milwaukee outbreak. They tested for antibody using Western blots of oocysts. IgA, IgM, and IgG to anti-oocyst antibody diminished markedly over time, and were usually gone by 28 weeks.
- Groves *et al* (1994)[4] showed that anti-oocyst antibody peaks 3-6 weeks after documented infection, and falls to baseline within a few months.
- DuPont *et al* have infected human volunteers with CR.[5] None of their seronegative volunteers developed persistent IgG anti-oocyst antibody after infection, and only 40% developed any IgG antibody reaction to oocyst antigens after a second infection (C. Chappell, pers comm; presentations to the EPA).
- This same transience of anti-oocyst antibody has been noted in other mammals.[6]

No study has demonstrated that antibody to C. parvum, using oocyst antigen, is persistent except in chronically infected people with AIDS. ***In all studies that have examined this issue, antibody responses (as measured with oocyst antigen) have been transient in the general population.***

ANTIBODY TO TISSUE STAGES. Individuals are only exposed to tissue stages (trophozoites, schizonts, and gametes) during infection, and so antibody to the tissue stages could be markers for infection. Two published studies, and one abstract, have tested for serum antibody to tissue stages.

- Tzipori and Campbell in Scotland (1981)[7] found ~ 86 % of adult blood bank serum samples diluted 1:10 had antibody to tissue stages using an indirect immunofluorescent (IIF) assay, where serum is reacted with tissue stages in cryostat sections of infected animal intestine.
- Campbell and Current (1983) reported that after known infection, 12/12 immunocompetent people were tissue antibody (+) using IIF.[8] 7/7 were positive at 60-90 days, and 5/5 were still positive at 360-400 days. Here they used dilutions of ≥ 1:40 to exclude any false positives.
- Miron *et al* at Rhode Island Hospital[9] prospectively found ~ 45% of normal children aged 1-4 were tissue antibody (+), matching the known pattern of infection in populations (Meinhardt *et al* 1996),[10] and that this rate decreased with age, while antibody to oocysts increased with age.



In cryostat sections of intestine, *all* the life cycle stages of the parasite are present. This means that all of the antigens associated with infection are available, not just those present in the oocyst stage. Thus the Miron *et al* study compares the age-related occurrence of positive *C. parvum* antibody to a) the oocyst stage, and b) all the life cycle stages.

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Attachment C

Dennis Juranek Presentation Notes:

1. **National Estimate of Waterborne Disease Occurrence**
2. **Ongoing CDC Surveillance Systems Related to Water 1996**
3. **Incidence of Gastrointestinal Illness**

Waterborne Disease Workshop
October 9-10, 1997

- **National Estimate of Waterborne Disease Occurrence**
- **Ongoing CDC Surveillance Systems Related to Water 1996**
- **Incidence of Gastrointestinal Illness**

Dr. Dennis Juranek
Center for Disease Control

National Estimate of Waterborne Disease Occurrence

A Daunting Task

Congressional Mandate

- EPA and CDC conduct studies in at least five cities to derive a national estimate of waterborne disease occurrence.
- Interpretation - Concentrate on microbiological constituents in water, both well-know and "emerging" bacteria, viruses, and protozoa.

Important Questions

- What populations are at greatest risk?
- What is the impact of waterborne disease?
- Which infectious agents cause waterborne disease? What is their relative contribution?
- What are the characteristics of water systems that are more likely to lead to waterborne disease?

Workshop - March 1997

- Purpose - to discuss the design and management of waterborne disease occurrence studies
- Attendees - specialists from:
  - CDC
  - EPA
  - State Health Departments - Emerging Infections Programs (EIP)

Emerging Infection Programs

- 7 sites - CN, NY, MD, GA, MN, OR, CA
- Competitively chosen
- Existing resources - FoodNet - surveillance for enteric pathogens and GI illness
- Funding considerations

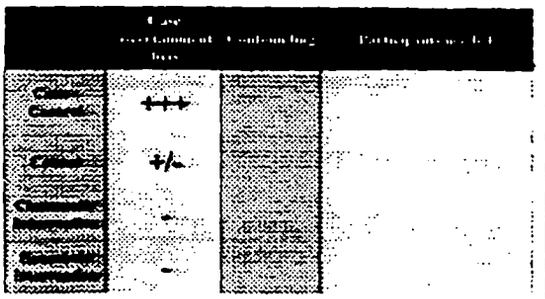
Study Population

- HIV positive
  - Greatest risk for severe infection
  - Not representative
  - Policy implications only for immunocompromised
- Immunocompetent
  - More representative - severity, demographics
  - Broader policy implications

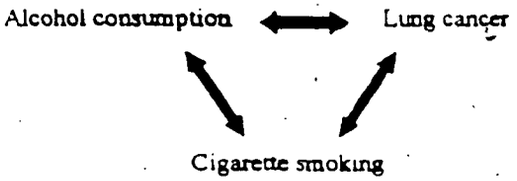
Case Ascertainment Bias

- Who gets included as a case? Are cases representative?
  - Severe cases
  - Immunocompromised populations
  - Health care access or behaviors

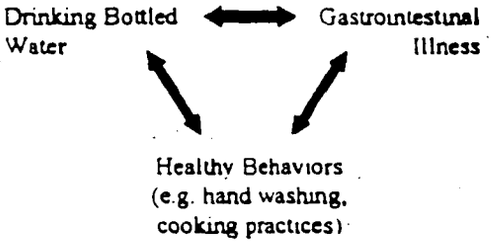
Study Characteristics



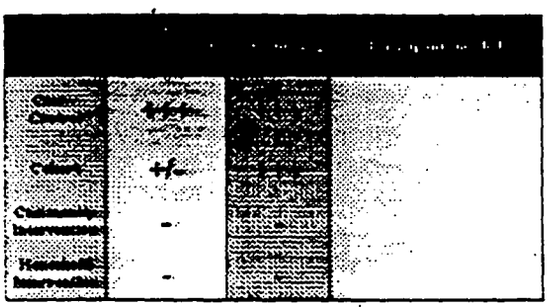
Confounding - Distortion



Confounding



Study Characteristics



Number of Participants Needed

- When is a negative study meaningful?
- If we believed that drinking tap water caused no more than 1% of GI illness we would need to study over 50,000 people to prove it
- Assumption - the attributable fraction of GI illness due to drinking tap water may be between 10% and 30%

First Steps

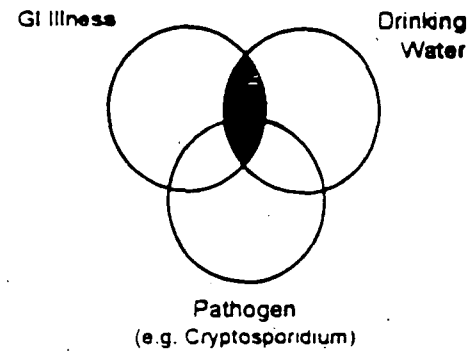
- Cross-sectional studies using EIP sites
- Feasibility study of household interventions to assess:
  - Blinding to intervention
  - Effectiveness of the intervention device
  - Point of entry vs. point of use
  - Identify logistic obstacles
  - Data collection tools
  - Accessing human specimens

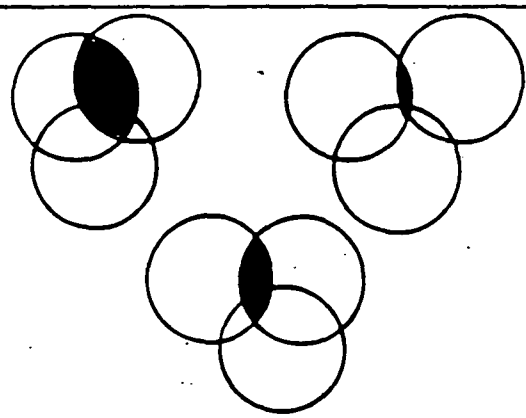
Selection of First Site

- Municipality of > 100,000 persons
- Surface water source
- Evidence of fecal contamination of source
- Conventional water treatment (coagulation, flocculation, sedimentation, filtration)

Representativeness?

- Different populations
- Source waters (ground vs. surface)
- Levels of contamination
- Types of pathogens
- Treatment technologies
- Distribution systems





Gaining Understanding and Clues

- Attributable fraction
- Incidence/impact of GI illness
- Etiologic agents
- Association of water quality indicators and GI illness
- Water consumption habits

Ongoing CDC Surveillance Systems Related to Water 1996

- Water-Borne Disease Outbreaks
- *Cryptosporidium*

CDC

Water-Borne Disease Outbreak Surviellance
CDC's and EPA's Objectives

- Characterize epidemiology of waterborne disease outbreaks (WBDOs)
- Identify etiologic agents of WBDOs and determine why WBDOs occurred
- Identify types of water systems associated with WBDOs
- Train public health personnel how to detect and investigate WBDOs
- Collaborate with local, state, federal, and international agencies on initiatives to prevent waterborne diseases

CDC

Waterborne Disease Outbreak Surveillance involves

systematic
- collection
- analysis
- interpretation
- dissemination

of health related data.

CDC

Water-Borne Disease Outbreak Surviellance

- Passive system with annual solicitation of reports
- State and Local Health Dept's collect data
- Voluntarily share data with CDC
- EPA provides supplemental water treatment data

CDC

Limitations

- Passive system:
- Sensitivity: probably low
  - Actual number of WBDOs unknown
  - Primary cause of under-reporting probably under-recognition
- Lengthy delays in recognizing & reporting

CDC

Factors that affect whether WBDOs are recognized and investigated:

- Size of outbreak
- Severity of disease caused by outbreak
- Public awareness that an outbreak may be occurring
- Investigator's interest in studying the etiologic agent
- Health department resources
- Routine laboratory testing for pathogen

CDC

Approaches to Cryptosporidiosis Surveillance

- Make Cryptosporidiosis Reportable
- Monitor Laboratory Diagnoses (Cryptosporidium)
- Monitor Sales of Antidiarrheal Medication (diarrhea)
- Monitor HMO and Hospital Logs (diarrhea)
- Monitor Nursing Homes (diarrhea)
- Combined Disease and Water Quality Surveillance

CDC

Surveillance for *Cryptosporidium*

- December 1994: CSTE recommends that *Cryptosporidium* be made a nationally notifiable disease
- 36 states make *Cryptosporidium* a notifiable disease
- January 1995: States begin notification

CDC

Make Cryptosporidiosis Reportable

Strengths:

- Establishes estimate of minimum number of cases
- Serves as a baseline against which increased numbers may be compared

Weaknesses:

- Does not improve diagnosis or reporting by physicians
- Does not increase routine lab testing
- Most likely to reflect infections in immunocompromised

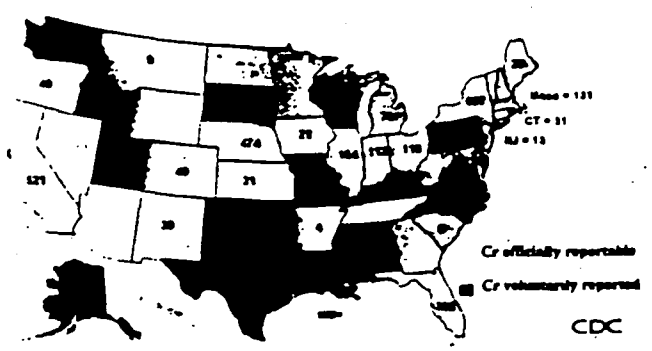
CDC

1995 National Survey of Laboratories:
Cryptosporidium Testing Indications and Practices

- 94 Labs contacted in 36 States
  - Test all O&P stools routinely: 5
  - Test some stools: 74
    - At the request of a physician: (74)
      (35 labs tested only at physician request)
    - All HIV+ persons: (8)
    - All liquid stools: (7)
  - Do not test : 15

CDC

Number of *Cryptosporidium* cases reported to CDC by state, US, 1995



CDC

Current Surveillance Systems

Strengths:

- In place and operational
- Health depts. experienced in using them
- Inexpensive to maintain
- Data are summarized and published in timely fashion
- Data provide a historical frame of reference

Weaknesses:

- Passive (voluntary) systems are insensitive - miss many smaller outbreaks
  - Can't detect outbreaks if cases are not reported
  - Persons with gastrointestinal illness frequently do not seek health care
  - Many causes of illness not considered by physician, e.g. Crypto, E. coli
  - Causes of mild to moderate illness often undiagnosed/misdiagnosed
  - Laboratory may not routinely test for organism, esp. new ones
    - MHC emphasis on cost reduction may decrease requests of lab tests
- Lengthy delays in detecting outbreak
- Does not provide an estimate of national risk from drinking water

CDC

Incidence of Gastrointestinal Illness

Cross-sectional Studies

Cleveland, Ohio 1948-1957

- 443 persons in 86 middle and upper class families
- 1.34 episodes of diarrhea and/or vomiting per person per year

Tecumseh, Michigan 1965-1971

- Non-random sample of 4905 persons in 850 young families
- 0.98 episodes of vomiting and/or diarrhea per person per year
- 1.9 episodes per year in children < 5 years
- Garthright et. Al. - Age-adjusted national estimate of 0.62 episodes per person per year

Household Intervention Studies Payment et. al.

- Tap water drinkers
- Age groups # of episodes per year
  - 0-5 years 1.54
  - 6-20 years 0.78
  - 21-49 years 0.68
  - 50 + years 0.23

Emerging Infection Programs

14.7 million people; 6% of the U.S. population

FoodNet Surveys

- 1996 - five sites - CA, OR, MN, GA, CT
- Random digit dial surveys
- Diarrheal illness (≥ 3 loose stools in 24 hour period)
- 750 interviews per month; > 9000 per year

Attachment D

Jack Colford Presentation Notes:

Toward a National Estimate of Waterborne Diseases: A Randomized, Triple-Blinded, Placebo-Controlled Trial of the Feasibility of Household Drinking Water Intervention Studies

Waterborne Disease Workshop
October 9-10, 1997

Toward a National Estimate of Waterborne Diseases:

A Randomized, Triple-Blinded, Placebo-Controlled Trial of the Feasibility of Household Drinking Water Intervention Studies

Dr. Jack Colford
University of California, Berkeley
School of Public Health

Toward a National Estimate of Waterborne Diseases:

A Randomized, Triple-Blinded, Placebo-Controlled Trial of the Feasibility of Household Drinking Water Intervention Studies

Participating Institutions/Agencies/Individuals

- University of California, Berkeley (UCB), School of Public Health (Jack Colford, Art Reingold, Judy Rees, Asheena Khalakdina)
- California Department of Health Services and Emerging Infections Program (EIP), (Duc Vugia)
- California Department of Health Services, Office of Drinking Water (Cliff Bowen)
- University of California San Francisco (UCSF), School of Medicine (Joan Hilton)
- Environmental Protection Agency (EPA), (Rebecca Calderon)
- Centers for Disease Control and Prevention (CDCP), (Bill Mackenzie)

Study Design: Overview

Randomized, placebo-controlled: Participants are randomly assigned to receive either:

- ❖ water treated at home by special devices (see below)

OR

- ❖ their usual water passing through a sham treatment device

Triple-blinded: Knowledge of the group (active device vs. sham device) to which a participant is assigned will not be known by: 1) the participant (single-blinding); 2) the investigators (double-blinding); nor 3) the statistical team (triple-blinding).

Intervention groups: Households using devices to treat home drinking water

Placebo groups: Households using inactivated devices that resemble the active device in every visible external characteristic

Duration: 4-6 months in year 1; ideally 12 months for each participant in years 2/3.

Study Design: Specific Outcomes to be Measured

Year 1

- blinding effectiveness (can patients correctly identify the group to which they are assigned). If not, a blinded trial is not possible and this study design is not be appropriate for future work. Blinding specifically to be quantitated using a previously published index from the clinical trial literature.
- costs of conducting the trial (i.e. is it likely the trials can be conducted at other (at least 5) sites at a reasonable cost
- health outcomes: nausea, vomiting, diarrhea, days lost from work, visits to physicians, "highly credible gastrointestinal illness" (HCGI) index used by Payment
- laboratory outcomes: goal is to obtain blood, stool, and saliva (using a home nursing agency) from all subjects during episodes of illness. Specimens to be sent for testing to EPA/CDC.
- recruitment and retention effectiveness (participant enrollment and dropout rates)

Years 2/3

- expand the study with respect to the number of cities/towns under investigation (to meet Safe Drinking Water Act mandate)
- use estimate of health and lab-confirmed outcomes obtained during year 1 to generate appropriate sample sizes for the studies in years 2-3.

Study Design: Advantages and Disadvantages of a Randomized Trial (cont.)

Disadvantages of this design

- Cost
- Labor intensive
- Require much more time to conduct because of the need to recruit participants, obtain permission from (multiple) Institutional Review Boards (human subjects committees),

Study Design: Intervention Devices and Groups

Comment: Preliminary bids received for grant preparation; final bidding process to be conducted with EPA / CDCP guidance

Sample size: 38 families in each of the four groups (152 total) powered to detect effectiveness of participant blinding

Study Design: Intervention Devices and Groups (cont.)

Comparisons to be made

- Note: In a properly randomized and conducted trial, any difference between two groups is attributable to a difference in the controlled exposure (in this case the exposure is the drinking water used at home by the participants)

- Comparison #1 (Effectiveness of point of entry devices)
  - ❖ Rate (cases / person / year) of disease in Arm 1A versus Rate of disease in Arm 1B

- Comparison #2 (Effectiveness of point of use devices)
  - ❖ Rate of disease in Arm 2A versus Rate of disease in Arm 2B

Study Design: Participants

Eligibility criteria

- household consisting of at least one adult and one child age 2-10 detailed informed consent completed
- household does not currently use bottled or specially filtered water at home (nor have plans to begin use during the study)
- type of drinking water used outside the home is NOT of concern (such water consumption will be recorded in our data but in a randomized trial is not likely to differ between the treatment group and the placebo group)

Recruitment Strategies

- randomly identified and recruited by telephone by a CDC contractor
- $50 payment after initial enrollment and informed consent
- $10 credit for each of the next 15 weeks
- whether subjects are permitted to keep devices at the end of the trial is a debated point

Study Design: Sites

Process

- interaction between primary study team, EPA, and CDC to identify sites in California with the following characteristics:

  - ❖ water supply currently meets all drinking water standards
  - ❖ moderate to large urban area (>100,000 population)
  - ❖ reasonable distance from principal study team (to minimize travel budget)
  - ❖ preferably within the area of the California Emerging Infections Program (pre-existing close working relationship with these county health departments)
  - ❖ potential for logical expansion of the study at this site in years 2/3

FAQs: (Frequently Asked Questions)

What about the participants' consumption of drinking water outside their homes?

- unlikely to differ between two randomly allocated groups of participants
- introduces a "conservative bias" (i.e. any results obtained are likely to underestimate the magnitude of the difference)

What about specific infections?

- specific viruses, parasites, and bacteria will be studied to the extent that funding is arranged to test the specimens collected during the study

More FAQs: (Frequently Asked Questions)

What about generalizability to other communities throughout the US?

- all scientific evidence needs to be replicated (regardless of study design)
- one outcome of this study could be a standardized approach for responsibly examining the health effects of drinking water in communities across the US

Are the costs of the study unreasonable?

- What are the costs of not properly addressing the question of drinking water safety?
- On the scale of costs faced by local utilities in making decisions about water safety, the costs of properly conducted trials are far below the radar.

Background

- Workshop on Design of Waterborne Disease Occurrence Studies (Atlanta, March 12-13, 1997) sponsored by USEPA and CDCP (R. Calderon, F. Hauchman, R. Hoffer, S. Binder, W. Mackenzie)

- Workshop on Drinking Water and the Risk of Cryptosporidiosis (Atlanta, June 1996) sponsored by the American Water Works Association Research Foundation (AWWARF) (D. Juranek–CDC and S. Leonard--SF Water Dept)

- Canadian trials of household drinking water intervention (randomized but not blinded) (P. Payment et al.)

- Safe Drinking Water Act (1996) charge to EPA/CDC:
  - *within 2 years after the date of enactment of this section, conduct pilot waterborne disease occurrence studies for at least 5 major US communities or public water systems*

Attachment E

Rebecca L. Calderon Presentation Notes:

Community Enteric Study – Enteric Disease Study

- **Phase I – site selection**
- **Phase II – site evaluation**
- **Phase III- pilot (full scale)**

COMMUNITY ENTERIC STUDY

Rebecca L. Calderon

Epidemiology & Biomarkers Branch

NHEERL

USEPA

ENTERIC DISEASE STUDY

- Phase I - site selection
- Phase II - site evaluation
- Phase III - pilot (full scale)

RATES OF ENTERIC DISEASE

- **Longitudinal study** – daily diary

  - ▸300 families
  - ▸children between 2 and 10

- **Surveillance**

  - ▸Nursing home surveillance
  - ▸Hospital admissions
  - ▸Clinical lab reporting
  - ▸Antidiarrheal sales
  - ▸Cross section serosurvey
  - ▸HMO/nurse hotlines
  - ▸(School absentees)

COMMUNITY ENTERIC DISEASE STUDY

Goal: Obtain information on enteric disease rates in the United States. Enteric disease rates are needed to determine environmental health policy and management strategies for environmental sources of microorganisms.

Objectives:

Determine the enteric disease rates in various communities across the country.

Determine the relative source contribution of environmental factors associated with enteric disease.

Determine etiologic agents associated with enteric disease.

Evaluate methods of surveillance.

Background:

Microbial organisms that cause enteric disease and their sources are a major concern for EPA. To conduct risk assessments or determine environmental health policy, information is needed on the level of disease, factors that influence that level, specific microbial organisms that cause illness, and possible sources of those organisms. Approximately 50% of food and waterborne disease outbreaks are of unknown etiology. Current surveillance programs do not provide adequate information on background rates of enteric illness and the relative source contribution of environmental sources of organisms that cause disease. In addition, current surveillance does not provide information on the effectiveness of environmental policy or management decisions in lowering exposure or reducing disease.

Proposal:

This project will conduct an enteric disease study in several communities across the United States looking at various ranges in environmental parameters. These studies would determine endemic levels of disease in the community and determine the relative source contribution of known environmental factors. In addition, assess efforts to identify etiologic agents (known and unknown) responsible for symptomatology.

Studies will examine alternative surveillance methods versus longitudinal studies as means to obtain information for trend analysis.

Site selection. To vary environmental ranges of environmental factors, communities of different geographic location, size, drinking water sources and drinking water treatment have been identified. Ideal communities would be those served by utilities that are about

Attachment F

Floyd Frost Presentation Notes:

Survey Results from Paired City Study

Waterborne Disease Conference
October 9-10, 1997

Dr. Floyd Frost
Lovelace Medical Foundation
Center for Health and Population Research

Ground Water-Albuquerque

1: What is your age?		Greater than 35% of Positive Control(%)			
Age	Frequency	27H	27A	17H	17A
< 30	19	15.79	10.53	10.53	10.53
31-40	60	36.67	23.33	25	13.33
41-50	68	39.71	25	22.06	16.18
51-60	40	27.5	17.5	25	12.5
61+	11	54.54	36.36	54.54	36.36
p=		0.41	0.68	0.44	0.36
2: What is your sex?					
Sex	Frequency	27H	27A	15/17H	15/17A
Male	99	37.37	28.28	27.27	15.15
Female	101	31.68	15.84	20.79	14.85
p=		0.32	0.07	0.45	0.89
3: What is your race?					
Race	Frequency	27H	27A	15/17H	15/17A
White	160	35	23.13	23.75	15.63
Black	2	0	0	0	0
Asian	3	33.33	0	0	0
Hispanic	27	37.04	25.93	25.93	14.81
Other	8	25	0	37.5	12.5
p=		0.82	0.42	0.64	0.83
4: Are you married?					
Married	Frequency	27H	27A	15/17H	15/17A
Yes	140	37.14	23.57	27.14	15.71
No	60	28.33	18.3	16.67	13.33
p=		0.22	0.46	0.19	0.65
5: Are you an Albuquerque resident?					
Resident	Frequency	27H	27A	15/17H	15/17A
Yes	165	34.54	21.21	22.42	13.94
No	35	34.29	25.71	31.43	20
p=		0.92	0.56	0.39	0.42
6: Length of residence (years)					
Length	Frequency	27H	27A	17H	17A
1-4	33	35.29	25	26.47	16.18
5-9	25	32	20	20	20
10-14	31	40.63	21.88	28.42	18.75
15-24	30	34.48	24.14	24.14	6.9
25+	46	30.43	17.39	19.57	13.04
p=		0.97	0.94	0.60	0.29
7: Where does your household water come from?					
Source	Frequency	27H	27A	15/17H	15/17A
City Water	166	35.54	23.49	22.29	13.86
Pvt. Well	1	0	0	0	0

Other	11	18.18	9.09	27.27	18.18
City w/filter	13	38.46	30.77	38.46	23.08
Pvt.Well/Strm	8	37.5	0	37.5	25
Not sure	1	0	0	0	0
p=		0.76	0.46	0.58	0.89

8: Do you work or got to school in a different city?

Work/School	Frequency	27H	27A	15/17H	15/17A
Yes	33	30.30	18.18	30.3	24.24
No	167	35.33	22.75	22.75	13.17
p=		0.72	0.50	0.33	0.16

9: Do you regularly drink bottled water?

Bottled	Frequency	27H	27A	15/17H	15/17A
Yes	39	33.33	20.51	20.51	15.38
No	161	38.92	26.09	29.19	19.87
p=		0.59	0.85	0.23	0.64

10: Do you use bottled water to make ice?

Ice	Frequency	27H	27A	17H	17A
Yes	8	50	37.5	37.5	37.5
No	192	33.85	21.35	23.44	14.06
p=		0.38	0.29	0.33	0.08

11: Do you use bottled water to wash food?

Wash	Frequency	27H	27A	17H	17A
Yes	2	50	50	50	50
No	198	34.34	21.72	23.74	14.65
p=		0.67	0.35	0.37	0.18

12: Do you have children in your household under age 5?

Children	Frequency	27H	27A	15/17H	15/17A
Yes	29	37.93	27.59	31.03	17.24
No	171	33.92	21.05	22.81	14.62
p=		0.74	0.44	0.27	0.41

13:In the past 12 months, have you had a child in your house attend day care?

Day Care	Frequency	27H	27A	15/17H	15/17A
Yes	23	39.13	34.78	39.13	26.09
No	177	33.9	20.34	22.03	13.56
p=		0.67	0.12	0.05	0.14

14:In the past 12 months, have you handled a child with diapers?

Diapers	Frequency	27H	27A	15/17H	15/17A
Yes	79	29.11	18.99	21.52	15.19
No	121	38.02	24.00	25.62	14.88
p=		0.30	0.66	0.72	0.73

15:In the past 12 months, have you cared for someone with diarrhea?

Cared For	Frequency	27H	27A	15/17H	15/17A
Yes	29	41.38	24.14	37.93	27.59
No	171	33.33	21.64	21.64	12.87
p=		0.45	0.44	0.04	0.01

16:In the past 12 months, have you handled pets (cats, dogs)?

Pets	Frequency	27H	27A	15/17H	15/17A
Yes	172	32.56	20.35	22.09	15.12
No	28	46.43	32.14	35.71	14.29
p=		0.18	0.17	0.22	0.84

17:In the past 12 months, have you handled young pets (less than 1 year old)?

Young Pets	Frequency	27H	27A	15/17H	15/17A
Yes	75	38.67	28	28	18.67
No	125	32	18.4	21.6	12.8
p=		0.27	0.12	0.36	0.35

18:In the past 12 months, have you handled livestock or zoo animals?

Livestock	Frequency	27H	27A	15/17H	15/17A
Yes	37	35.14	21.62	29.73	16.22
No	163	34.36	22.09	22.7	14.72
p=		0.90	0.99	0.46	0.84

19:In the past 12 months, have you drunk untreated water from lakes, streams?

Drunk	Frequency	27H	27A	15/17H	15/17A
Yes	11	45.45	27.27	45.45	36.36
No	189	33.86	21.69	22.75	13.76
p=		0.46	0.75	0.07	0.05

20: In the past 12 months, have you swum in a lake, stream, or public pool?

Swum	Frequency	27H	27A	15/17H	15/17A
Yes	88	37.5	26.14	29.55	18.18
No	112	32.14	18.75	19.64	12.5
p=		0.36	0.22	0.11	0.20

21:In the past 12 months, have you traveled out of the United States?

Traveled	Frequency	27H	27A	15/17H	15/17A
Yes	42	50	35.71	38.1	23.81
No	158	30.38	18.35	20.25	12.66
p=		0.02	0.02	0.03	0.10

22: In the past 2 months, have you had diarrhea (3 or more loose bowel movements a day) lasting 4 or more days?

Diarrhea	Frequency	27H	27A	15/17H	15/17A
Yes	7	57.14	42.86	0	0
No	192	33.85	21.35	25	15.63
Not sure	1	0	0	0	0
p=		0.21	0.17	0.14	0.25

SURFACE WATER

~~Ground Water~~- Las Vegas, NV

1: What is your age:

		Greater than 35% of Positive Control (%)			
Age	**Frequency**	**27H**	**27A**	**17H**	**17A**
<30	30	30	20	26.67	20
31-40	50	48	44	38	36
41-50	72	41.67	33.33	40.28	33.33
51-60	34	52.94	44.12	47.06	35.29
61+	14	35.71	35.71	57.14	57.14
p=		0.37	0.21	0.32	0.19

2: What is your sex?

Sex	**Frequency**	**27H**	**27A**	**17H**	**17A**
Male	89	34.83	30.34	34.83	26.97
Female	111	49.55	40.54	44.14	39.64
p=		0.04	0.14	0.18	0.06

3: What is your race?

Race	**Frequency**	**27H**	**27A**	**17H**	**17A**
White	180	42.22	36.11	39.44	33.33
Black	6	66.67	50	50	50
Hispanic	2	0	0	50	50
Asian	10	50	30	50	40
Other	2	50	50	0	0
p=		0.53	0.74	0.72	0.71

4: Are you married?

Married	**Frequency**	**27H**	**27A**	**17H**	**17A**
Yes	105	40.95	35.24	40.95	38.09
No	95	45.26	36.84	38.95	29.47
p=		0.54	0.81	0.77	0.20

5: Are you a Las Vegas resident?

Resident	**Frequency**	**27H**	**27A**	**17H**	**17A**
Yes	187	42.24	35.29	39.15	33.33
No	13	53.85	46.15	46.15	38.46
p=		0.41	0.43	0.64	0.73

6: Length of residence (years)

Length	**Frequency**	**27H**	**27A**	**17H**	**17A**
1-4	48	35	31.67	40	33.33
5-9	42	38.09	33.33	33.33	28.57
10-15	20	64	48	62.5	52
16-24	35	48.39	45.16	41.94	35.48
25+	42	42.86	30.95	33.33	28.57
p=		0.27	0.58	0.42	0.63

7: Where does your household water come from?

Source	**Frequency**	**27H**	**27A**	**17H**	**17A**

City Water	143	41.26	34.97	35.66	28.67
Pvt. Well @ pond	1	100	100	100	100
City w/filter	33	54.54	45.45	51.51	45.45
Pvt. well	8	50	25	37.5	37.5
Other	7	42.86	42.86	71.43	71.43
Not sure	8	12.5	12.5	37.5	37.5
p=		0.26	0.35	0.19	0.07

8: Do you work or go to school in a different city?

Work/school	Frequency	27H	27A	17H	17A
Yes	15	46.67	46.67	40	33.33
No	185	42.7	35.14	40	34.05
p=		0.77	0.37	1.0	0.95

9: Do you regularly drink bottled water?

Bottled	Frequency	27H	27A	17H	17A
Yes	100	46	38	40	32
No	100	40	34	40	36
p=		0.39	0.56	1.0	0.55

10: Do you use bottled water to make ice?

Ice	Frequency	27H	27A	17H	17A
Yes	38	34.21	26.31	42.1	34.21
No	162	45.06	38.27	39.51	33.95
p=		0.22	0.17	0.77	0.98

11: Do you use bottled water to wash food?

Wash	Frequency	27H	27A	17H	17A
Yes	9	66.67	44.44	88.88	66.67
No	191	41.88	35.60	37.7	32.46
p=		0.14	0.59	0.002	0.03

12: Do you have any children in your house under age 5?

Under 5	Frequency	27H	27A	17H	17A
Yes	28	42.86	39.29	39.29	35.71
No	172	43.02	35.47	40.12	33.72
p=		0.99	0.70	0.93	0.84

13: In the past 12 months, have you had a child in your house attend day care?

Day Care	Frequency	27H	27A	17H	17A
Yes	19	52.63	52.63	47.37	47.37
No	181	42	34.25	39.23	32.6
p=		0.37	0.11	0.49	0.20

14: In the past 12 months, have you handled a child with diapers?

Diapers	Frequency	27H	27A	17H	17A
Yes	73	43.84	35.62	45.21	39.73
No	127	42.52	36.22	37	30.71
p=		0.86	0.93	0.25	0.19

15: In the past 12 months, have you cared for someone with diarrhea?

Cared	Frequency	27H	27A	17H	17A

Yes	30	36.67	33.33	33.33	26.67
No	170	44.12	36.47	41.18	35.29
p=		0.45	0.74	0.42	0.36

16: In the past 12 months, have you handled pets (cats, dogs)?

Pets	Frequency	27H	27A	17H	17A
Yes	162	43.83	37.65	38.89	33.95
No	38	39.47	28.95	44.74	34.21
p=		0.63	0.31	0.51	0.98

17: In the past 12 months, have you handled young pets (less than 1 year old)?

Young pets	Frequency	27H	27A	17H	17A
Yes	56	51.79	39.29	48.21	42.86
No	144	39.58	34.72	36.81	30.56
p=		0.12	0.55	0.14	0.10

18: In the past 12 months, have you handled livestock or zoo animals?

Livestock	Frequency	27H	27A	17H	17A
Yes	10	30	30	30	30
No	190	43.68	36.31	40.53	34.74
p=		0.39	0.69	0.51	0.34

19: In the past 12 months, have you drunk untreated water from lakes, streams?

Drunk	Frequency	27H	27A	17H	17A
Yes	10	30	30	30	20
No	190	43.68	38.33	40.53	34.74
p=		0.39	0.69	0.51	0.34

20: In the past 12 months, have you swum in a lake, stream, or public pool?

Swum	Frequency	27H	27A	17H	17A
Yes	72	100	83.33	66.67	66.67
No	128	41.24	34.54	39.18	32.99
p=		0.02	0.05	0.35	0.19

21: In the past 12 months, have you traveled out of the United States?

Traveled	Frequency	27H	27A	17H	17A
Yes	33	41.67	27.78	37.5	30.56
No	167	43.75	40.63	41.41	35.94
p=		0.87	0.09	0.67	0.50

22: In the past 2 months, have you had diarrhea (3 or more loose bowel movements a day) lasting 4 or more days?

Diarrhea	Frequency	27H	27A	17H	17A
Yes	11	54.54	36.36	36.36	36.36
No	180	41.11	34.44	38.89	32.78
Not Sure	9	66.67	66.67	66.67	55.56
p=		0.70	0.59	0.70	0.69

Attachment G

AGENDA

Environmental Protection Agency
and
Center for Disease Control

WATERBORNE DISEASE WORKSHOP

October 9 and 10, 1997

Waterborne Disease Occurrence Workshop
October 9-10, 1997

Washington National Airport Hilton
2399 Jefferson Davis Highway
Arlington, Va. 22202
703/418-6800

Agenda

Workshop Objectives:

- *provide background on the Safe Drinking Water Act mandate to carry out waterborne disease occurrence studies and develop a national estimate of waterborne disease incidence;*
- *discuss how these studies fit into the larger public policy framework on providing safe drinking water;*
- *discuss planned and ongoing epidemiological studies and EPA/CDC activities related to these mandates;*
- *identify data gaps, research needs, and opportunities for improved methodologies; and*
- *discuss next steps and opportunities for coordination and communication.*

Thursday, October 9, 1997

8:30-8:45 Welcome, introductions, review agenda — A.Arnold, RESOLVE/ E.King, EPA

- Introductions
- Review meeting objectives, agenda, groundrules, and logistics

8:45-11:30 Overview on Background of Waterborne Disease Detection and Federal Policy Development *(Presentation and discussion)*

8:45-9:30
- Statutory requirements and direction of microbial drinking water regulations and EPA/CDC Partnership, S. Regli, EPA

- Developing national waterborne disease estimates for drinking water regulations, S. Regli, EPA

9:30-10:05
- Detection of waterborne disease (endemic and epidemic) and inherent difficulties and limitations, D. Juranek, CDC

10:05-10:25 Break

Friday, October 10, 1997

9:00-10:45 Approaches Towards A National Estimate, *(breakout group report and plenary discussion). (Each breakout group will report out the Thursday day afternoon answers to the four questions and then the plenary group will discuss the four questions).*

Are there other potentially viable approaches that ought to be considered in developing a national estimate?

Are there additional studies that ought to be considered to develop a national estimate?

Are there other current and relevant techniques that ought to be considered?

While developing a national estimate, what additional questions about microbial contamination of drinking water and public health need to be answered to most effectively protect public health?

10:45-11:00 Break

11:00-12:30 Next Steps

- Workshop highlights and identification of unresolved questions
- Are there any technical, coordination, or other issues that ought to be raised?
- Report on AWWARF 1998 Workshop, E. Lomaquahu, AWWARF
- Closing comments

12:30 p.m. Adjourn

Attachment H

PARTICIPANT LIST

Environmental Protection Agency
and
Center for Disease Control

WATERBORNE DISEASE WORKSHOP

October 9 and 10, 1997

Waterborne Disease [redacted]rkshop, Oct. 9-10, 1997
PARTICIPANT LIST

First Name	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisa	Almodon	OM / OST / HECD (4304)	401 M Street, SW		Washington	DC	20460	202/260-1310
Arthur	Ashendorff	New York City Department of Environmental Protection	59-17 Junction Boulevard	3rd Floor Low-Rise	Corona	NY	11368	718/595-5340
Lonnie	Backer	NCEH	4770 Buford Hwy, NE	MSF-46	Atlanta	GA	30341	770/488-7603
Philip	Berger	US EPA	401 M Street, SW		Washington	DC	20460	202/260-7006
Susan	Binder	DPD/NCID/CDC, MS F22	4770 Buford Highway, NE		Atlanta	GA	30341	770/488-7793
Valerie	Blank	US EPA-OGWDW	401M Street SW	Room 1219 ET	Washington	DC	20460	202/260-8367
Tom	Bonacquisti	Fairfax County Water Authority	8560 Arlington Blvd.		Merrifield	VA	22116-0815	703/698-5600 x476
Tracy	Bone	US EPA (MC 4607)	401 M Street, SW	Waterside Mall	Washington	DC	20460	202/260-2954
Brenda	Boutin	U.S. EPA - (NCEA-CIN)	26 W. Martin Luther King Drive		Cincinnati	OH	45268	513/569-7532
Lynn	Bradley	Association of State and Territorial Public Health Laboratory Directors	1211 Connecticut Avenue, NW	Suite 608	Washington	DC	20038	202/822-5227
Rebecca L.	Calderon	U.S. EPA, Epidemiology and Biomarkers Branch	MD-58A		Research Triangle Park	NC	27711	919/966-0617
David	Casemore	Public Health Lab. / PHLS Cryptospordium Reference Unit	Glan Clwyde District General Hospital	Rhyl Denbigshire	Wales		LL18 5UJ	011 441 1745-583737
Keith	Christman	Chlorine Chemistry Council	1300 Wilson Boulevard		Arlington	VA	22209	703/741-5935
Jack	Colford	School of Public Health	UC Berkeley	140 Warren Hall	Berkeley	CA	94720	510/643-1076
Peter L.	Cook	NAWC	1725 K Street, NW	Suite 1212	Washington	DC	20006	202/833-8383 x20
Gunther	Craun	Gunther Craun and Associates	101 West Fredrick Street	Suite 104	Staunton	VA	24401	540/886-1939
John	Cromwell	Apogee Research, Inc.	4350 East-West Highway	Suite 600	Bethesda	MD	20814	301/652-8444
Cora	Dones	WSSC	Rt. 1, House # 11	Farmington Road West	Accokeek	MD	20607	301/206-7401
Steve	Edberg	Yale University School of Medicine	Department of Labor Medicine	PO Box 3333	New Haven	CT	06510	203/785-2457
Laura	Ehlers	National Research	2101 Constitution Avenue, NW		Washington	DC	20418	202/334-3423
Mary Ann	Feige	US EPA	26 West Martin Luther		Cincinnati	OH	45268	513/569-7944

Waterborne Disease Workshop, Oct. 9-10, 1997
PARTICIPANT LIST

First Name	Last Name	Organization	Address	Address 2	City	State	Zip Code	Phone Number
Vernon	Land	City of Norfolk Department of Utilities	6040 Waterworks Road	Division of Water Production & Quality	Norfolk	VA	23502	757-441-5678
Mark	LeChevallier	American Water Works Service Co., Inc.	1025 Laural Oak Road		Voorhees	NJ	08043	609/346-8281
Steve	Leonard	San Francisco PUC	1155 Market Street	4th Floor	San Francisco	CA	94103	415/554-0792
Emerson	Lomaquahu	AWWA Research Foundation	6666 West Quincy Avenue		Denver	CO	80235	303/347-6114
Robin	Massengale	NAPWA	1413 K Street NW, Suite 700		Washington	DC	20005	202/898-0414
Karl	Mavian	Louis & Harrison	122 C Street, NW	Suite 740	Washington	DC	20001	202/393-3903
Maureen	McClelland	US EPA - Region I	JFK Federal Bldg. - (CCT)		Boston	MA	62203	617-565-3543
Jennifer	McLain	US EPA - OGWDW	401 M Street, SW		Washington	DC	20460	202/260-0431
James R.	Miller	NYC Dept. of Health-Parasitic Disease Surveillance	125 Worth Street	Room 326, Box 22A	New York	NY	10013	212/788-9638
Christine	Moe	Dept. of Epidemiology	School of Public Health University of North Carolina at Chapel Hill	CB-7400, McGavran-Greenberg Hall	Chapel Hill	NC	27599-7400	919/968-1420
Robert D.	Morris	Dept. of Family Medicine & Community Health	Tufts University Medical School	136 Harrison Ave.	Boston	MA	02111	617/636-1374
Tom	Navin	CDC	4770 Buford Hwy	Mail Stop F-22	Atlanta	GA	30341	770/488-7766
Diana	Neidle	Consumer Federation of America	2129 Florida Ave., NW	Apt. 401	Washington	DC	20008	202/667-9280
James V.	O'Conner	AU	3102 Starner Court		Kensington	MD	20895	
Erik	Olson	Natural Resources Defense Council	1200 New York Avenue, NW		Washington	DC	20005	202/289-2360
Steve	Potts	US EPA	OGWDW	401 M Street SW	Washington	DC	20460	202/260-5015
Stig	Regli	US EPA Office of Groundwater and Drinking Water	East Tower, Room 935D	401 M Street (4603), SW	Washington	DC	20460	202/260-7379
Alan	Roberson	American Water Works Association	1401 New York Avenue, NW	Suite 640	Washington	DC	20005	202/628-8303
Crystal C.	Rodgers	US EPA	401 M Street SW East Tower, Room 11136	MC 4607	Washington	DC	20460	202/260-0676