Practical Training Exercise

ANALYZING AND MANAGING RISKS IN LIFE SCIENCES RESEARCH

Based on the article by Farooqui, A. et al. “Investigation of a community outbreak of typhoid fever associated with drinking water.” BMC Public Health. 2009; 9: 496.

AAAS

ADVANCING SCIENCE, SERVING SOCIETY

This exercise was developed by Center for Science, Technology and Security Policy at the American Association for the Advancement of Science (AAAS).

You may contact the copyright holder at:
1200 New York Ave.
Washington, DC 20002
cstspinfo@aaas.org
1-202-326-6493

This series of case study exercises was developed with input from: Lindsey Marburger, Nisreen AlHmoud, Oussama ben Fradj, Eleanor Celeste, Gwenaële Coat, Cristine Geers, Irene Jillson, Abdulaziz Kaed, Rawan Khasawneh, Fadia Maki, Kimberly Schaub, and Kavita Berger.

Developed with the support of the U.S. Department of State's Biosecurity Engagement Program.

Learning Objectives

1. Develop the skills to think critically about risks and risk mitigation strategies needed in your own scientific environment;

2. Enhance your ability to identify risk management strategies and approaches that minimize identified risks and maintain the high-quality and utility of the scientific activity; and

3. Apply the risk analysis framework to your own or your peers' scientific activities.

Participant Expectations

By the end of this exercise, you will have familiarity with:

1. The definitions of different types of risks associated with laboratory, field, and public health research.
2. The process of risk analysis—risk identification, assessment, management, and communication—including:
   - How to identify and assess risks by considering the possible likelihood and consequences of risks, and the risks versus benefits of a research activity,
   - Strategies for managing risks, and
   - Who, when, and how to communicate risks.
3. How to apply the risk analysis framework to your own scientific activities.

AAAS

Ground Rules for Participation

1. Prior to starting this exercise, participants should have read the case study article.
2. Ask the facilitator to clarify questions about the case study article.
3. Focus on understanding and analyzing the diverse risks involved in the research rather than on critiquing the methodologies or research choices of the authors.
4. Interact with one another in a way that encourages open communication and exchange of ideas. For example, listen to everyone's ideas respectfully.
5. You may want to take your own notes to enhance your ability to actively participate in the training activity.

AAAS

Biorisk Glossary

These definitions are from the WHO's *Responsible Life Science for Global Health Security: A Guidance Document*.

- Bioethics
- Biorisk
- Biorisk reduction
- Laboratory biosafety
- Laboratory biosecurity
- Dual-use life sciences research
- Research excellence

<u>Additional concepts:</u>

- Protection of human subjects
- Protection of animal subjects
- Responsible research/responsible conduct of research

AAAS

Simplified Risk Analysis Framework

Your risk review will follow these 4 stages:

1. **Risk Identification**
2. **Risk Assessment**
3. **Risk Management**
4. **Risk Communication**

1. Risk Identification

process by which researchers consider all possible internal, external, and organizational risks.

Asks the question:

- ***What are the possible risks associated with the research?***

2. Risk Assessment

process by which researchers identify needed resources and consider biosafety/biosecurity recommendations.

Also defined as the “process of evaluating the risk(s) arising from a hazard(s), taking into account the adequacy of any existing controls and deciding whether or not the risk(s) is acceptable).” (OHSAS 18001: 2007)

Asks the questions:

- ***How likely are the risks to occur?***
- ***What are the potential consequences if the risks occur?***
- ***Do the risks outweigh the benefits?***

3. Risk Management

process by which researchers consider regulations/guidelines, training, and SOP compliance issues.

Asks the question:

- ***What risk management strategies could minimize the likelihood that the risk will occur or the consequences if the risks occurred?***

Possible strategies: physical barriers, personnel training or vetting, regulations and laws, and/or alternative experiments

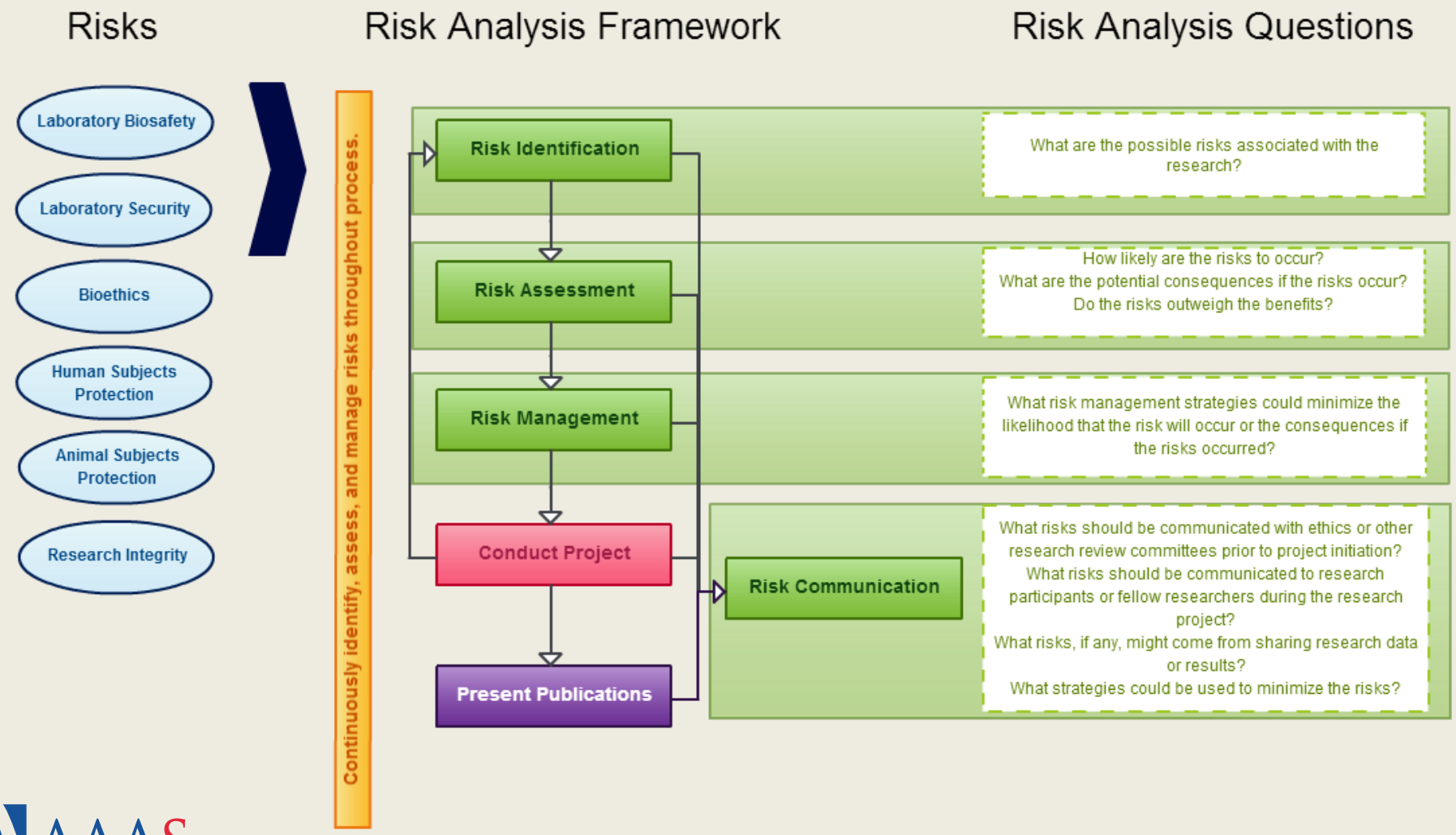
4. Risk Communication

process by which researchers consider communication strategies, non-compliance issues and approval/modification processes.

Asks the questions:

- ***What risks should be communicated with ethics or other research review committees prior to project initiation?***
- ***What risks should be communicated to research participants or fellow researchers during the research project?***
- ***What risks, if any, might come from sharing research data or results?***
- ***What strategies could be used to minimize the risks?***

Simplified Risk Analysis Chart



CASE STUDY

Investigation of a community outbreak of typhoid fever associated with drinking water

Farooqui, A. et al. “Investigation of a community outbreak of typhoid fever associated with drinking water.” BMC Public Health. 2009;; 9: 496.

Outline of Case Study

Part 1: Research Question/Hypothesis

Part 2: Background Information Overview

Part 3: Methodology

Part 4: Risk Analysis in the Research Article

Part 5: Research Results and Conclusions

Research Question/Hypothesis

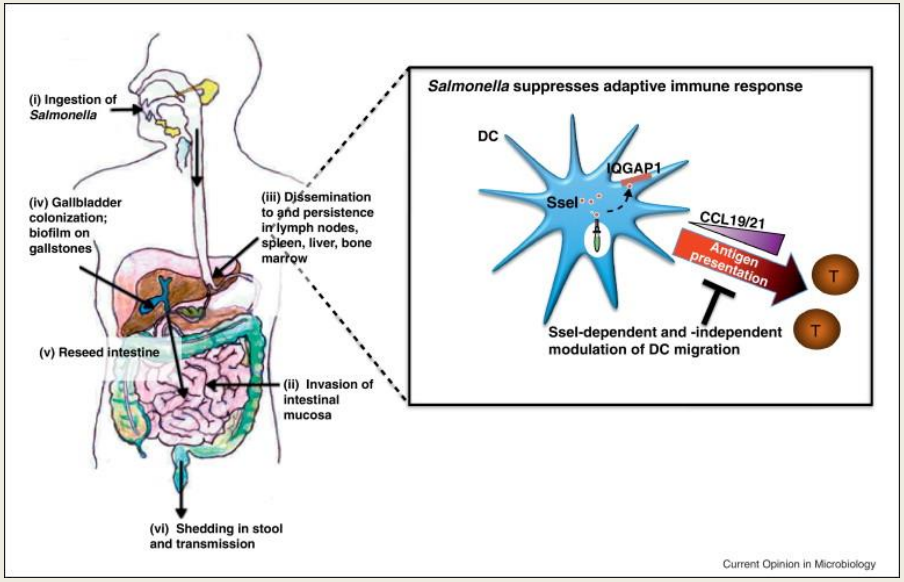
Research Statement

Water-borne diseases cause an estimated 250,000 deaths per year in Pakistan. Typhoid fever is among the leading causes.

In 2004, an outbreak of typhoid fever affected Nek Muhammad village, which is located 25 kilometers from Karachi. More than 300 people were infected and 3 people died from the infection.

The authors proposed to conduct an epidemiologic study to determine the cause of the outbreak.

Background Information Overview



Salmonella lifecycle in the human body by modulating DC migration in systemic tissues
(Monack, 2011)

Defining Typhoid Fever

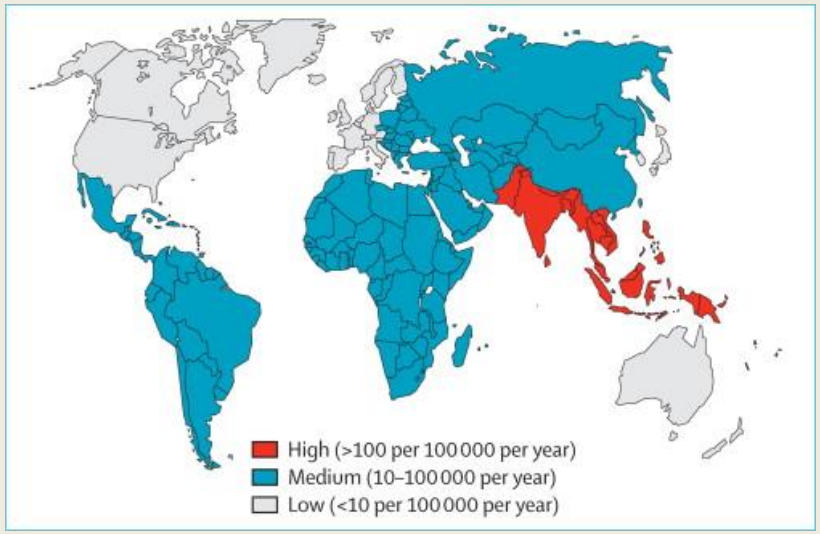
Typhoid fever is a bacterial disease caused by *Salmonella typhi.*

- Symptoms generally include high fever, headache, abdominal pain, weakness and fatigue, loss of appetite, rash, and either constipation or diarrhea. Infected individuals might become delirious and motionless after three weeks of infections.
- In 2011, approximately 70% of Salmonella typhi was resistant to common drugs, including flouroquinones (e.g., cyprofloxicin).

Background Information Overview

Typhoid Fever Transmission

- The number of cases of Typhoid fever in South and Central Asia in 2000 was approximately 9.3 million. The crude incidence was 622 per 100,000 individuals (Crump, 2004)
- Typhoid fever affects approximately 21.5 million people in developing countries.
- Salmonella typhi is transmitted through contamination of food or drinking water that has been contaminated with feces or urine of infected people.
- The bacteria is most commonly spread in parts of the world where handwashing is limited and water can be contaminated with sewage.



Global incidence rate for typhoid fever
(The Lancet, 2012)

Background Information Overview

Study Site: Nek Muhammad Village (2004)

- Population: 500 people, mostly between the ages of 20-45 and under 12.
- Location: 25km from Karachi, Pakistan
- Income: Relatively poor population
- Infrastructure: Limited local availability of “food, water, electricity, and health care.”
- 2004 Outbreak:
  - Within a 2-day period, more than 300 people were affected by diarrhea and/or vomiting with high grade fever
  - Infected people received medical treatment (including ciprofloxacin) from a local foundation
  - Severe cases were sent to local hospitals
  - Three individuals “lost their lives” within 5 days.
  - The only drinking well in the village was polluted with dead and decaying birds and amphibians, their fecal matter, and garbage.
  - The outbreak occurred 2 days after the well was manually cleaned.

Research Methodology

- **Epidemiologic study participants.** A total of 250 people were interviewed about onset of symptoms, general health, daily activities, education level, age, and eating habits.
- Only 100 people who met the criteria for suspected typhoid fever were selected for stool sample collection; they belonged to different age groups and families.
- Healthy individuals declined to participate in the study; it was not a controlled study.
- **Stool sample collection.** Stool was collected in a plastic container. Within 2 hours of collection, a small amount of sample was transported to the laboratory and processed.
- **Clinical sample investigation.**
  - "Stool samples were analyzed microscopically for the presence of ova and parasite(s)."
  - Standard laboratory methods were used to detect several bacteria: *Salmonella*, *Shigella*, *E. coli* 0157:H7, *Yersinia*, and *Vibrio cholera*.
  - Samples on transport swabs were used to test for the presence of Campylobacter using standard methods.

Research Methodology

- **Water sample collection**. A total of 10 well samples were collected from the contaminated well using five different water collection buckets. An additional 90 well water samples were collected from stored for different household purpose.
- **Water quality assessments.** Total aerobic bacterial count was determined using standard Pour Plate technique. The presence of coliforms (Streptococci) and fecal *E. coli* were determined using “Most Probable Number” and membrane filtration methods.
- **Food contamination assessments.** Samples were diluted in buffer; the diluted samples inoculated different culture media to test for *Salmonella*, *Shigella*, and *Campylobacter*.
- **Bacterial isolates identification.**
  - Environmental and clinical samples were processed using several standard biochemical reactions to identify bacterial isolates. AP120E strips were used to confirm the results.
  - Salmonella was identified using serotyping.
  - Susceptibility to antibiotics was assessed using standard methods.

Risk Analysis in this Research Article

While risk analysis is an important part of science, few scientific publications include in-depth descriptions of how the authors assessed and managed risk.

Today your task is to perform a risk analysis based on this research article.

To begin, answer the following question:

Based on your current knowledge of the experimental procedures or research purpose, what risks might be important to consider in designing, carrying out, or communicating this research?

Risk Identification

Investigation of a community outbreak of typhoid fever associated with drinking water

Questions
What, if any, are the potential safety risks to research staff? (Consider: clinical and environmental sample collection, transport, and laboratory testing) What, if any, security risks are posed by collecting, transporting, and testing contaminated samples?
What, if any, are the risks associated with potentially antibiotic resistant bacteria?
What, if any, are the potential risks or concerns associated with working with non-academic or governmental partners such as a local NGO? Could the partner's behavior put the research, researchers, or participants at risk in any way?
What, if any, risks are associated with enrolling people from remote villages who are affected by a devastating disease? What, if any, social or cultural risks might be associated with enrollment in the study?
What, if any, are the risks posed by conducting research in response to a rapid crisis event, such as this typhoid outbreak, where the researcher does not have the opportunity to deliberately select and screen participants?

Risk Assessment

Investigation of a community outbreak of typhoid fever associated with drinking water

Question
What types of facilities and protective equipment are necessary to safely carry out epidemiology studies such as this, which rely upon standard microbiological techniques?
What information would you need to know about the NGO partner to assess whether they are capable of and willing to uphold international best practices on treatment of human research participants? What resources are available to help you evaluate potential partners?
What are the greatest biosafety risks associated with this epidemiology study? What, if any, are the greatest biosecurity risks associated with this epidemiology study?
What are the resources, expertise, training, and tools that could be useful in assessing the risks identified for this research project?

Risk Management

Investigation of a community outbreak of typhoid fever associated with drinking water

Question
How could researchers in this or a similar project minimize possible biosafety and biosecurity risks without changing the scientific question or quality?
What approaches, if any, could minimize any of the identified risks associated with the epidemiology study?
What strategies can you use to minimize the risks from working with outside partners? In addition to being a source of risk, can having outside NGO partners be a strategy to reduce risks? If so, how?
What, if any, are the specialized competencies, skills, and training needed to carry out this epidemiological study?
Researchers were unable to collect samples from healthy individuals, who would have served as the study control. What strategies, if any, could the researchers use to better engage the community to improve the experimental analyses and study results?

Research Results and Conclusions

Results

- The total viable bacterial count in the water samples exceeded the standard limits for untreated potable water. The predominant types of viable bacteria in the water were coliforms.
- All well water and 65% of household water tested positive for *Salmonella enterica* serovar Typhi, versus only 2% for food samples.
- The *Salmonella enterica* serovar Typhi was resistant to ampicillin, chloramphemicol, and co-trimoxadole/trimethoprim, but not to ciprofloxacin and nalidixic acid.
- A total of 22 samples (out of 100 tested) tested positive for multidrug resistant strains of *Salmonella* Typhi. The authors state that this number might be an underestimate because participants had received antibiotic treatment.
- *Shigella*, *E. coli* O157:H7, *Yersinia*, *Vibrio cholera*, and *Campylobacter* were isolated from the stool samples.

Conclusions

- The outbreak of typhoid fever in the Nek Muhammed village was a caused by the presence of *Salmonella enterica* serovar Typhi contaminated water the village's only well.
- The "rapid spread of MDR [multidrug resistant] infection in [a] small community like [the] Nek Muhammad Village can provide a niche for the spread of antibiotic resistant strain[s] among [the] larger population."
- The authors state that the villagers were vulnerable to the outbreak because of the "contaminated and uncovered well, consumption of un-boiled water, poor sanitary and domestic hygiene."

Risk Communication

Investigation of a community outbreak of typhoid fever associated with drinking water

Question
What are the risks that should be communicated during this research? To whom?
What information is needed to communicate the risks and risk mitigation approaches to institutional review boards or ethics committees prior to initiation of the epidemiology study? What, if any, challenges are associated with having to provide the information in a very short time scale?
What steps could be taken to de-identify data and make it anonymous before it is shared with other researchers during the study, at conferences, or upon publication?
What strategies could be used to communicate findings and recommendations with the typhoid-affected community and other stakeholders to prevent similar outbreaks in the future?
What, if any, biosafety and biosecurity risks are associated with communicating the study results in open literature? Do the risks change with results describing multidrug resistant bacteria in an unprotected area?

Final Exercise: Risk in Your Own Research

Perform a risk analysis of your own research. Choose one past, ongoing, or future research project to analyze:

1. Identification: What are the primary risks you face in your research? Think about the risks to you and other researchers and technicians in the field, clinic, and/or lab, the general public, the environment and economy, your institution, and human and animal subjects.
2. Assessment: What are the consequences of the identified risks if they occur? How likely are they to occur? Based on your assessment of the potential consequences, are there are there any risks that could harm people, animals, crops, or the economy? What resources, capabilities, and skills are needed to mitigate these risks?
3. Management: What strategies could you use or resources you could refer to minimize or mitigate these risks? (These strategies should not decrease the quality of the research.) For ideas of possible strategies and resources, consider those discussed in this practical exercise and from your own experiences. Are there any risks associated with your research that cannot be adequately mitigated?
4. Communication: What risks, if any, are associated with communicating your research during the design or conduct of the research? What risks, if any, are associated with communicating the research results at scientific conferences and in publications? What strategies could you use to mitigate the risks? Are there any stakeholders with whom you must share or should share the risks of your research? Your findings?

Example Risk Analysis Strategy

Communicate

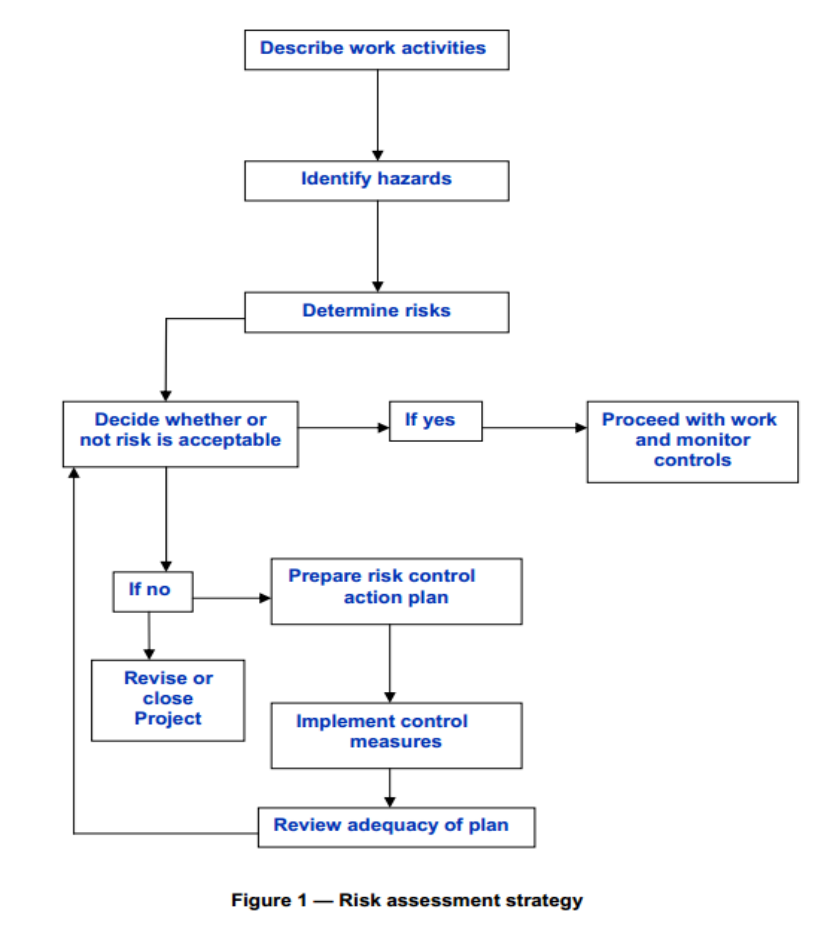


Figure 1 — Risk assessment strategy

"Laboratory risk management." CWA 15793: 2011

Reference List

Background Information

Centers for Disease Control and Prevention. "Diseases/Pathogens Associated with Microbial Resistance." Updated September 30, 2013. Available at: http://www.cdc.gov/drugresistance/diseasesconnectedar.html.

Center for Disease Control and Prevention. "Typhoid Fever: General Information." March 14, 2013. Available at: http://www.cdc.gov/nczved/divisions/dfbmd/diseases/typhoid_fever/.

Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull WHO*. 2004;82:346–353.

Dewan AM, Corner R, Hashizume M, Ongee ET (2013) Typhoid Fever and Its Association with Environmental Factors in the Dhaka Metropolitan Area of Bangladesh: A Spatial and Time-Series Approach. PLoS Negl Trop Dis 7(1): e1998. doi:10.1371/journal.pntd.0001998

Farooqui, A. et al. "Investigation of a community outbreak of typhoid fever associated with drinking water." BMC Public Health. 2009; 9: 496.

Water and Sanitation Program (WSP). "Water and Sewerage Services in Karachi." Citizen Report Card: Sustainable Service Delivery Improvements. December 2010. Available at: https://www.wsp.org/sites/wsp.org/files/publications/WSP_CRC_Press.pdf

Mayo Clinic. "Typhoid fever symptoms." August 22, 2012. Available at: http://www.mayoclinic.com/health/typhoid-fever/DS00538/DSECTION=symptoms.

World Health Organization. "Typhoid fever." Available at: http://www.who.int/topics/typhoid_fever/en/.

World Health Organization, Responsible Life Science for Global Health Security: A Guidance Document. 2010; http://whqlibdoc.who.int/hq/2010/WHO_HSE_GAR_BDP_2010.2_eng.pdf.

Diagrams and Images

European Committee for Standardization (CEN). CEN Workshop Agreement: CWA 15793. "Laboratory biorisk management." Ref. No: CWA 15793:2011 D/E/F. September 2011: 17. Available at: ftp://ftp.cenorm.be/CEN/Sectors/TCandWorkshops/Workshops/CWA15793_September2011.pdf.

Monack, Denise M. *Salmonella* persistence and transmission strategies. Current Opinion in Microbiology, Volume 15, Issue 1, February 2012, Pages 100–107.

Maurice, J. "A first step in bringing typhoid fever out of the closet." The Lancet, Vol. 379. 25 February 2012. www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60294-3.