Learning Objectives

Through participation in this case study, students should be able to:

1. Discuss how this case illustrates the evidence-based problem solving approach.
2. Use evidence presented in this case to illustrate how inductive logic can be used to generate hypotheses from data.
3. Define and apply the criteria for establishing contributory cause and efficacy.
4. Explain how population comparisons, case-control studies, cohort studies and randomized controlled trials contribute to establishing cause and effect and efficacy.
5. Interpret the meaning of and use of statistical significance and confidence intervals.
6. Interpret the meaning of relative risk and percent efficacy as measures of the strength of a relationship.
7. Explain basic ethical principles used in randomized controlled trials.

Preparatory Materials

Please read An Introduction to Evidence-based Problem Solving, available at:
http://www.aacu.org/stirs/casestudies/index.cfm
**Introduction- About Neural Tube Defects**

Neural tube defects (NTD) are congenital birth defects that result from the failure of closure of the spinal column and skull or cranium. This closure normally occurs at approximately one month after conception. This is before most women recognize that they are pregnant. The most severe form of NTD is anencephaly – which is partial or complete absence of the brain – and uniformly results in fetal deaths after 20 weeks or death soon after birth.

![Spina Bifida](http://www.cdc.gov/ncbddd/spinabifida/facts.html)

Figure 1. Spina Bifida


Spina bifida (see Figure 1) is incomplete closure of the spinal column. In the most serious form of spina bifida the unfused or open portion of the spinal column allows the spinal cord to protrude through an opening in the overlying vertebrae. The protruded nerves are usually damaged prior to birth resulting in some degree of paralysis and loss of sensation below the level of the spinal cord defect. Many individuals experience bowel and bladder problems as well. Until recently spina bifida occurred in approximately 1 in 1,000 births in the United States. The rate of anencephaly, including fetal deaths after 20 weeks or soon after birth, was approximately two-thirds the rate for spina bifida. The chance of recurrence in a subsequent pregnancy once an NTD has occurred is approximately 5%.

**Preventing Spina Bifida and Other Neural Tube Defects**

In recent years a great deal has been learned about the causes of neural tube defects. As is often the case in health research, the earliest studies used basic approaches and generated hypotheses. As knowledge accumulated, investigators designed more complex studies to test hypotheses.

In 1974 a study (Leck 1974) found that there was a substantial increase in neural tube defects (spina bifida and anencephaly) among those from lower socioeconomic groups compared to those in higher socioeconomic groups. This group association led investigators to suspect a range of causes including nutritional factors.
In 1976 a case-control study (Smithhells 1976) was published comparing pregnant women who gave birth to offspring with neural tube defects to a control group of pregnant women whose offspring were healthy. Red blood cell folate levels of all study participants were measured during pregnancy, at least one month after conception. Folate (or folic acid) is a B-vitamin found naturally in some foods such as beans and dark leafy vegetables; red blood cell folate is considered the best measurement of folate levels. The investigation demonstrated that the mothers of offspring with neural tube defects had substantially lower red blood cell folate levels compared to women whose offspring were healthy; this difference was statistically significant.

In 1981 a prospective cohort study (Smithhells 1981) was reported from five British health centers among women who had given birth to one or more infants with neural tube defects and were planning to become pregnant in the near future. All women were offered folic acid supplementation and chose whether or not to take the supplements. Women were divided into fully supplemented, partially supplemented and unsupplemented based upon their reported self administration of folic acid. Of the fully supplemented women, 1 of 200 had a NTD recurrence compared to 0 of 50 recurrences among partially supplemented women and 13 recurrences among the 300 unsupplemented women. The data were adjusted to take into account the differences between the groups, including the number of previous NTDs, maternal age, and social class.

Two randomized controlled trials were published in 1991 and 1992. In the first investigation (MRC Vitamin Study Research Group 1991) women with a previous NTD were randomized to receive either 4 mg of folic acid supplement per day or placebo pills. The occurrence of NTDs was 6 among the approximately 600 women randomized to folic acid supplementation, versus 21 among the approximately 600 randomized to the placebo or comparison group. This difference in NTD rates was statistically significant.

In the second randomized controlled trial (De Wals 1992), women planning a pregnancy (in most cases their first) were randomly assigned to receive folic acid or alternatively to receive a trace element supplement not containing folic acid. Pregnancy was confirmed in 4753 women. There were 6 cases of NTD in those assigned to trace element supplement as compared to none among those assigned to the vitamin supplement group (P=0.029).

In 1992 the United States Public Health service recommended that all women of childbearing age increase consumption of folic acid to reduce spina bifida and anencephalus. Follow-up public health surveillance studies found little change over the next few years in the level of red blood cell folate among women of childbearing age. In 1996 the FDA authorized low level fortification of all cereal grain products with folic acid. Fortification, which is very inexpensive, became mandatory in both the United States and Canada in 1998.

The following graph plots the changes that occurred in spina bifida incidence rates in the United States based upon birth certificate data between 1991 and 2005 (Centers for Disease Control and Prevention 2013)

A study in Canada (De Wals 2007) before and after fortification was introduced looked at the incidence rates of NTD. A total of 2446 births with neural-tube defects were recorded among 1.9 million births between 1993 and 2002. The incidence of neural-tube defects decreased from 1.58 per 1000 births per year before fortification to 0.86 per 1000 births per year during the full-fortification period, a 46% reduction (95% confidence interval, 40% to 51%).

**Key Questions**

**Question #1** What other hypotheses besides a nutritional cause for NTDs might be suggested by the group association between social-economic status and neural tube defects found by Leck? Also, please discuss some possible limitations of the study by Leck.

**Question #2** What conclusions can you draw from the case-control investigation in terms of the definitive criteria for contributory cause? To support your answer, examine in turn each of the three criteria for contributory cause and discuss whether or not you think the Smithhells et al. results supports each criterion.
Question #3 What conclusions can you draw from the cohort investigation in terms of the definitive criteria for contributory cause? Has a dose response relationship been demonstrated based upon this data?

Question #4 What conclusions can be drawn from the first randomized controlled trial that go beyond those obtained from the previously described investigations? How can you measure the magnitude of the impact of folic acid supplementation on the development of NTD in this investigation?

Questions #5 What conclusions can be drawn from the second randomized controlled trial that go beyond the conclusions that can be drawn from the first randomized controlled trial? Was it ethical to withhold folic acid supplementation for those in the trace element supplement group in this investigation?

Question #6 What conclusions about effectiveness can you draw from the data on folic acid food supplementation in both the United States and Canada? How do you think food supplementation compares to in terms of effectiveness to encouraging women of childbearing age to take vitamins to supplement dietary folic acid? Explain

Question #7: What other issues would you want to consider when making recommendations to reduce the frequency of NTD in the United States and Canada? Explain

References:


About the Author

Richard Riegelman is Professor of Epidemiology & Biostatistics, Health Policy and Medicine at the George Washington University. He is Founding Dean of the George Washington School of Public Health and Health Services. Dr. Riegelman has been a leader in the Educated Citizen and Public Health initiative in which AAC&U is collaborating with public health educational organizations to integrate public health into liberal education utilizing the AAC&U's LEAP framework.

Richard Riegelman is working closely with AAC&U on the STIRS initiative including the development of the STIRS framework and the STIRS case studies project. Dr. Riegelman teaches undergraduate courses and frequently utilizes the types of case studies that are the focus of the STIRS case studies project.

Supplemental Materials- Answer the following multiple choice questions indicating the one best answer.

1. Which of the following is LEAST likely to have a cause and effect relationship with NTD?
   A. Nutritional deficiencies
   B. Nutritional excesses
   C. Method of delivery
   D. Genetic factors

2. Which of the following conclusions can most reliably be drawn from the case-control investigation of red blood cell folate in pregnant women, with and without a fetus with NTD?
   A. A cause and effect relationship exists between NTD and red blood cell folate
   B. Low red blood cell folate levels are associated with NTD at the individual level
   C. NTDs are the result of low red blood cell folate levels
   D. No association exists between red blood folate and NTD

3. Lower socio-economic groups were found to have a higher incidence of NTD in the 1974 population comparison before any intervention was known to reduce the incidence of NTD. Which of the following possible differences between socio-economic groups is LEAST likely to explain the higher incidence in lower socio-economic groups?
   A. Differences in nutrition
   B. Differences in access to health care
   C. Differences in the physical environment
   D. Differences in number of pregnancies

4. Which of the following provides the LEAST amount of information about the strength of a relationship found in a randomized controlled trial?
   A. A P-value comparing the study and control groups
B. A relative risk of 3.5 and 95% confidence intervals comparing the study and control groups
C. An odds ratio of 3.6, used as an approximation of relative risk, and 95% confidence intervals comparing the study and control groups
D. A difference of 15/600 between the study and control groups

5. In the second well designed and well conducted randomized controlled trial, women planning a first pregnancy were randomly assigned to receive a daily vitamin supplement containing a low dose of folic acid or alternatively assigned to receive a daily vitamin supplement not containing folic acid. Pregnancy was confirmed in 4753 women. There were 6 cases of NTD in those assigned to the control supplement, and none among those assigned to the folic acid containing vitamin supplement group (P=0.029).

Based on this description of the investigation, which of the following is the most accurate statement about the impact of the intervention under practice conditions?

A. The absence of cases of NTD among those assigned to receive folic acid supplementation helps ensure that folic acid supplementation will eliminate NTD when used in practice
B. The P value of 0.029 ensures that folic acid supplementation will eliminate NTD when used in practice.
C. The inclusion of women who were planning a pregnancy helps ensure that the study population is similar to the group for whom low dose folic acid supplementation is intended to be used in practice.
D. The small number of cases of NTD among those in the control group helps ensure that folic acid supplementation will reduce NTD when used in practice.
Questions 6, 7 & 8 utilize Figure 1

Figure 1 displays the U.S. incidence rate of spina bifida prior to and after the 1992 USPHS recommendation that women of childbearing age should increase their consumption of folic acid. It also displays the data during and after the introduction of food supplementation which occurred between 1996 and 1998.

![Figure 1. Spina bifida rates, 1991–2005](image)

Figure 2. Spina bifida rates 1991-2005

6. Which of the following conclusions can be drawn most reliably from this data?
   A. The incidence rates of spina bifida fell during and after introduction of food fortification in 1996 and remained lower during subsequent years
   B. Pregnant women with higher levels of folic acid intake are at lower risk of spina bifida
   C. The recommendation to increase folic acid caused an increase in spina bifida rates in 1993 and 1994
   D. The increased consumption of folic acid among women of child bearing age has no predictable relationship to the incidence of spina bifida
7. Which of the following is the most serious limitation of the way Figure 1 is constructed?
   A. The confidence intervals (CI) do not provide any additional information
   B. The use of straight lines to connect the yearly data is misleading
   C. The use of rates per 100,000 per year is not a standard measure of risk
   D. The Y axis has a gap in the range of possible values leading to potential misinterpretation.

8. Which of the following provides the LEAST likely explanation for the reduced incidence of spina bifida after the requirement for food fortification between 1996 and 1998 but not after the recommendation for increased intake of folic acid among women of childbearing age in 1992?
   A. Food supplementation reaches a larger number of individuals at risk of NTD
   B. Use of vitamin supplements requires difficult to achieve behavioral change
   C. Increased intake of folic acid through food requires a substantial change in type of food consumed
   D. No cause and effect relationship exists between folic acid consumption and NTD

9. Imagine that a cohort investigation compared the impact of prescribing folic acid supplements to a study group of non-pregnant women with a previous NTD child compared to a control group of non-pregnant women without a previous NTD child. The investigators followed these women every month over a two year period using a standard protocol. The study group had a 20 times greater risk of having a pregnancy with a clinically important NTD. The results were statistically significant. Which of the following study design issues is most likely to explain the findings in this investigation?
   A. This is a cohort study which provides less information than a case-control study
   B. Women who have had a child with a previous NTD are more likely to report taking the folic acid supplement.
   C. Women who have had a child with a previous NTD are more likely to recall taking the folic acid supplement.
   D. Comparing groups with and without a previous NTD child is likely to produce an important difference between groups that is likely to affect the outcome of the investigation.

10. Which of the following best describes the role that randomized controlled trials can potentially play in the investigation of a new intervention such as prescribing high dose folic acid to prevent spina bifida for women with a previous history of a child with spina bifida?
   A. Randomized controlled trials are the gold standard for establishing that an intervention improves outcome in a research setting
   B. Randomized controlled trials are the gold standard for establishing that an intervention results in minimal harms in a research setting
   C. Randomized controlled trials are the gold standard for establishing that an intervention is effective in practice
   D. Randomized controlled trials are the gold standard for establishing that an intervention is safe when used in practice.