Statistics in the Service of Health

Constantine DASKALAKIS
Division of Biostatistics, Thomas Jefferson University (Philadelphia, PA), USA
Section on Teaching of Statistics in the Health Sciences at the American Statistical Association.

The word statistics was first used to describe a set of aggregated data (commonly demographic observations, such as births and deaths), and later came to also denote the mathematical body of science that pertains to the collection, organization, analysis, interpretation, and presentation of data and uncertainty (Davidian & Louis, 2002; Dodge, 2006; Moses, 1986). For those interested in the historical developments in probability and statistics, there are many excellent books and reviews (Fienberg, 1992; Gigerenzer et al., 1989; Stigler, 1986). However, as John Tukey once said, “the best thing about being a statistician is that you get to play in everyone else’s backyard” (Leonhardt, 2000). Yet, there has been little systematic work on the impact of the application of statistics in various scientific disciplines.

One of the earliest such applications was in demography: John Graunt’s Bills of Mortality, a summary and analysis of births and deaths in 17th century England. Further statistical developments and applications came in astronomy (Pierre-Simon Laplace and Carl Friedrich Gauss), statistical thermodynamics (James Clerk Maxwell and Ludwig Boltzmann), quantum mechanics (Max Born), and the social sciences (Adolphe Quetelet), and later in genetics, evolutionary biology, agriculture, engineering, medicine, and economics. My objective in this review is rather modest: to discuss three historical examples when statistics (or rather, statistical principles and thinking) made a substantial contribution in advancing our understanding of health and disease.

Statistics and public health reform

Florence Nightingale was a British social reformer in 19th century England. When she was in her mid-thirties, she volunteered as a nurse during the Crimean War (September 1854 through September 1855), which was part of a wider conflict between Russia and an alliance of Britain, France, and the Ottoman Empire. Florence Nightingale arrived at the war theater in November 1854, and quickly compiled data on causes of deaths of soldiers that showed the predominance of non-battle related deaths. She attributed those deaths to lack of supplies and poor nutrition, ventilation, and sanitation, although she did not directly recognize their infectious nature.

Florence Nightingale was firmly in the camp of the miasma theory that held that many of the infectious killers of the time (cholera, typhus, dysentery) were due to environmental factors (decaying organic matter and noxious fumes) that were not passed between individuals but rather through “bad air” or “unhealthy fog.” This thesis was favored by social progressives of the time, who placed on the state the responsibility to improve the environment and living conditions of the people. In contrast, the contagion theory held that disease was passed from person to person through physical contact, and was supported by many conservatives of the time who preferred to place the focus (if not the “blame”) on individuals rather than the state. Pasteur’s experiments and the eventual rise of the germ theory in the second half of the 19th century settled the matter and miasma was discredited, but not before it spurred a push for sanitation and hygiene, bringing about substantial public health gains.

But I digress. Florence Nightingale initially placed more emphasis on nutrition and lack of supplies, although she later also focused on the importance of living conditions. She arrived in Crimea in November 1854, and a Sanitary Commission followed her in March 1855. After she returned to Britain, her presentations to politicians and civil servants were very influential, and she was instrumental in the establishment of hospitals that were sanitary and had clean and fresh air. She was also a pioneer in the training of nurses and other medical personnel. Many of her presentations and campaigns relied on inventive use of statistical summaries and graphics, and she is considered one of the first individuals to put statistics to effective use in the service of public health and health policy. Figure 1 is one of her classic summaries of the causes of death in the army in Crimea, that relies on a polar area graph (also sometimes incorrectly called “coxcomb” diagram), a type of pie chart which is particularly useful in displaying cyclical patterns.

Statistics and the polio vaccine trials

By the middle of the 20th century, paralytic poliomyelitis (with about 25,000-40,000 cases per year in the US) had emerged as one of the most dreaded childhood illnesses. In 1952, John Salk developed the inactivated polio vaccine, and soon after, plans were put in motion for a huge field trial to test the vaccine among young schoolchildren (Blume & Geesink, 2000; Meldrum, 1998). The vaccine trial was sponsored by the National Foundation for Infantile Paralysis (NFIP, later renamed the March of Dimes) and its early design called for observed controls, i.e., injecting the vaccine to consenting children, and using unvaccinated children as controls. An independent Center was set up for the trial's implementation and evaluation under the direction of virologist Dr. Thomas Francis, Jr., who then convened an external advisory group to review the trial design and implementation. Within this group, the "clinicians" panel supported the original observed controls design, while the "statisticians" panel recommended a randomized placebo controls design (Meldrum, 1998). A third "health officers" panel was divided, with most members supporting the observed controls design, but a vocal minority (including those at the more respected health departments of Massachusetts, New York, Michigan, Ohio, Illinois, and California) arguing forcefully in favor of the placebo controls design (Meldrum, 1998). Consequently, with strong backing from Dr. Francis, members of the advisory group, and outside experts (including well-known statisticians, such as Jerome Cornfield, Felix Moore, and Paul Meier), a dual design was adopted: 127 test areas in 33 states used the observed control design (consenting second graders were vaccinated, no placebo was given, and all first and third graders were used as controls), while 84 test areas in 11 states used a blinded randomized design (consenting children in grades 1-3 received injections of either vaccine or placebo and were then compared). Within a few months (October 1953 to February 1954), the scientific focus had shifted from the observed controls to the randomized placebo controls, although statistician Kenneth Brownlee would subsequently label the observed controls part of the trial as "stupid and futile" and its results "worthless" (Brownlee, 1955, p.1007). It is interesting that, 10 years later, Brownlee found himself on the losing end of the controversy regarding smoking and lung cancer (see below). The polio trials were quickly conducted from April to June 1954, outcomes were assessed through December 1954, and results reported in April 1955 (Francis et al., 1955), an amazing feat, considering that about one and a half million schoolchildren were involved.

Table 1 summarizes the main trial results. The vaccine effectiveness can be estimated as 71% in the placebo control areas (vaccine vs. placebo groups), but only 62% in the observed control areas (vaccinated 2nd-graders vs. unvaccinated 1st- and 3rd-graders). The observed unvaccinated controls had substantially lower polio incidence than the randomized placebo controls, mainly because of complex selection (participation) biases, and statistician Paul Meier remarked that "[w]ere the observed control information alone available, considerable doubt would have remained about the proper interpretation of the results" (Meier, 1989, p.11).

Statistics and the link between cigarette smoking and lung cancer

In the early 1950s, the results of the first well-designed observational studies which suggested a strong causal association between cigarette smoking and lung cancer (Doll & Hill, 1952, 1954; Hammond & Horn, 1954) touched off a fierce debate that would last for two decades. Many (although not all) of the arguments were statistical in nature, and the fiercest early opponents of the causal link between smoking and lung cancer were famous statisticians. Joseph Berkson (1958) expressed conceptual and methodological reservations (including concerns about confounding by environmental factors, such as pollution), while Sir Ronald Fisher (1957) expressed doubts on the grounds of non-specificity of the smoking effects and favored a "constitutional" or "genetic" theory of causation (the idea that an unknown genetic factor predisposes individuals to smoking and is also involved in the causation of lung cancer).

At the same time, the list of supporters of the causal link between smoking and cancer also included prominent statisticians, such as Jerome Cornfield and Sir Austin Bradford Hill, and epidemiologists, such as William Haenszel and Sir Richard Doll. Cornfield et al. (1959) gave a particularly strong and comprehensive defense of the causal hypothesis, and by 1964, the Surgeon General's Report concluded that "[c]igarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action" (U.S. Department of Health, Education, and Welfare, 1964, p.33). Skeptics, such as Kenneth Brownlee (1965), stubbornly kept up their objections, but within a few more years, serious scientific debate was effectively over, and various educational, policy, and legislative efforts to curb smoking were being initiated.

One reason for the balance eventually tilting in favor of the causal hypothesis was the cumulative effect of well-designed observational studies which controlled for increasingly more potential confounders and which established that the estimated smoking effects were quite consistent across variations in study designs, target populations, and measurements. A second reason was that biology caught up with epidemiology, finally elucidating the biological mechanisms of smoking's diverse health effects. Finally, the skeptics themselves failed to identify any specific confounders or genetic factors that would explain the observed association, and their generic arguments that such factors could exist became increasingly unconvincing.

Conclusions

The three examples I discussed in this paper illustrate the role that statistics has played at various points in time and under different circumstances. But I think that the broader importance of those stories may lie in their implications and consequences.

Statistics became the linchpin of public health and health policy, the randomized controlled trial was established as the gold standard for evaluation of interventions, treatments, and drugs, and observational studies were accepted as valid and useful tools in the study of disease causation.

In all three examples, there was no single statistical guru, no single statistical advance, no single statistical "smoking gun" that carried the day. It was no fancy technique or analysis, but rather, basic statistical principles and thinking that shaped the direction of the scientific research and set those precedents. Various scientists (biologists, physicians, social scientists) have the subject-matter knowledge. Statistics supplies the necessary statistical toolkits, but more importantly, it anchors an entire philosophy regarding ways to attack and solve the problem at hand. It may be that this latter broader contribution of statistics is the reason behind its ever expanding reach and impact in the health sciences during the last two centuries.

Table 1

Main results of the 1954 polyomyelitis vaccine trials. *Note*. Adapted from "An Evaluation of the 1954 Poliomyelitis Vaccine Trials: Summary Report," by T. Francis, Jr., R. Korns, R. Voight, M. Boisen, F. Hemphill, J. Napier, and E. Tolchinsky, 1955, *American Journal of Public Health*, 45(5, Pt. 2).

	Paralytic Polio		
	N	*n*	*Rate (per 100,000)*
Placebo controls trial			
Vaccine	200,745	33	16.4
Placebo	201,229	115	57.1
Not vaccinated (non-participants)	338,778	121	35.7
Observed controls trial			
Vaccinated (2nd grade)	221,998	38	17.1
Not vaccinated (2nd grade)	123,605	43	34.8
Not vaccinated (1st & 3rd grades)	725,173	330	45.5

Figure 1

Example of polar area graph drawn by Florence Nightingale, summarizing the number of deaths due to preventable diseases (in green), wounds (in orange), and other causes (in brown), during the Crimean War, 1854-1856. The graph was published in *Notes on Matters Affecting the Health, Efficiency, and Hospital Administration of the British Army* and sent to Queen Victoria in 1858.

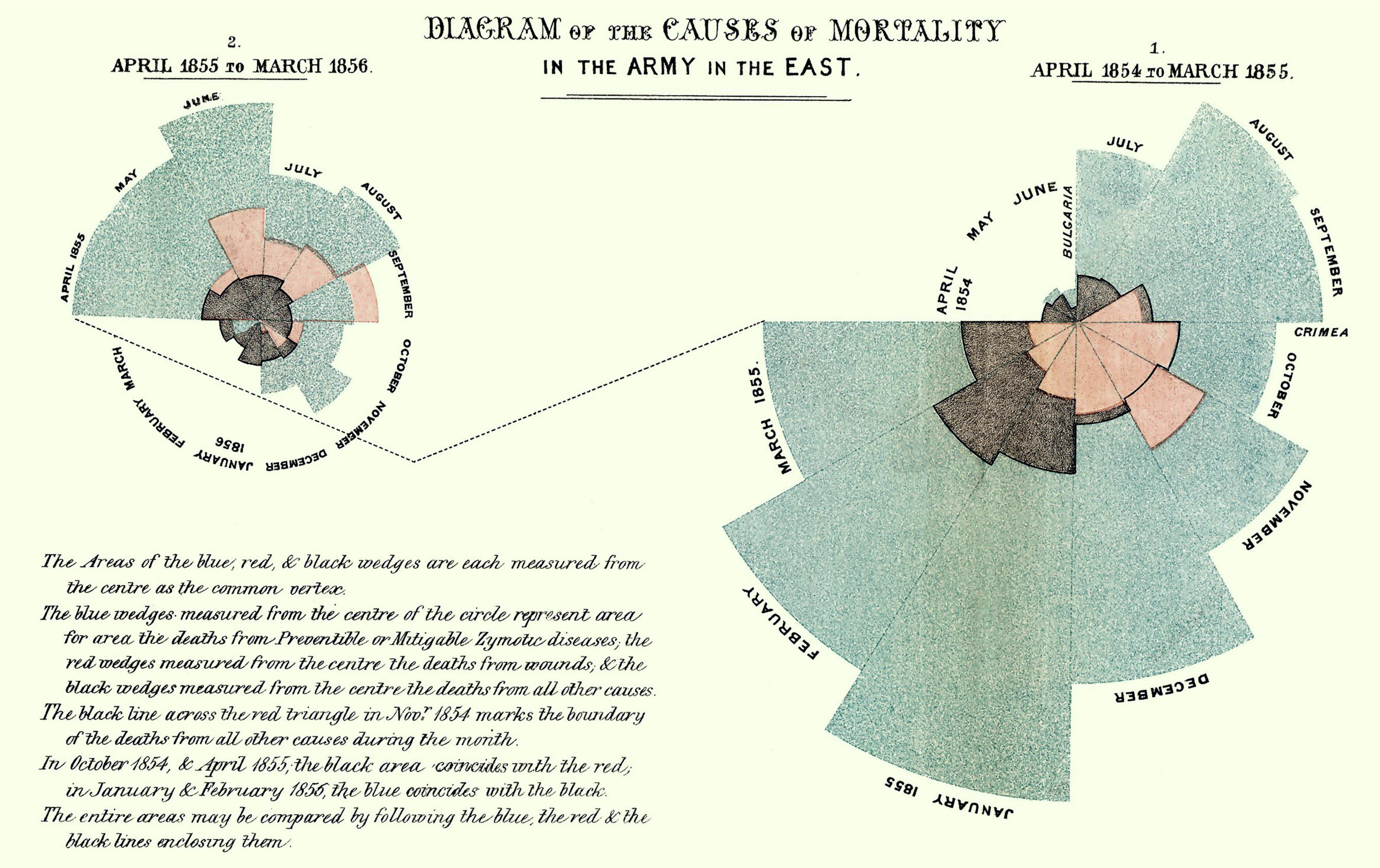

DIAGRAM OF THE CAUSES OF MORTALITY
IN THE ARMY IN THE EAST.

The Areas of the blue, red, & black wedges are each measured from the centre as the common vertex.

The blue wedges measured from the centre of the circle represent area for area the deaths from Preventible or Mitigable Zymotic diseases; the red wedges measured from the centre the deaths from wounds; & the black wedges measured from the centre the deaths from all other causes.

The black line across the red triangle in Novr. 1854 marks the boundary of the deaths from all other causes during the month.

In October 1854, & April 1855, the black area coincides with the red; in January & February 1856, the blue coincides with the black.

The entire areas may be compared by following the blue, the red & the black lines enclosing them.

References

Berkson, J. (1958). Smoking and lung cancer: Some observations on two recent reports. *Journal of the American Statistical Association*, *53*(281), 28-38. DOI: 10.1080/01621459.1958.10501421

Blume, S., & Geesink, I. (2000). A brief history of polio vaccines. *Science*, *288*(5471), 1593-1594. DOI: 10.1126/science.288.5471.1593

Brownlee, K. A. (1955). Statistics of the 1954 polio vaccine trials. *Journal of the American Statistical Association*, *50* (272), 1005-1013. DOI: 10.1080/01621459.1955.10501286

Brownlee, K. A. (1965). A review of "Smoking and Health". *Journal of the American Statistical Association*, *60*(311), 722-739. DOI: 10.1080/01621459.1965.10480823

Cornfield, J., Haenszel, W., Hammond, E. C., Lilienfeld, A. M., Shimkin, M. B., & Wynder, E. L. (1959). Smoking and lung cancer: Recent evidence and a discussion of some questions. *Journal of the National Cancer Institute*, *22*(1), 173-203.

Davidian, M., & Louis, T. A. (2012). Why statistics? *Science*, *336*(6077), 12. DOI: 10.1126/science.1218685

Dodge, Y (ed). (2006). *The Oxford dictionary of statistical terms* (6th ed.). Oxford, UK: Oxford University Press.

Doll, R., & Hill, A. B. (1952). A study of the aetiology of carcinoma of the lung. *British Medical Journal*, *2*(4797), 1271-1286. DOI: 10.1136/bmj.2.4797.1271

Doll, R., & Hill, A. B. (1954). The mortality of doctors in relation to their smoking habits: A preliminary report. *British Medical Journal*, *1*(4877), 1451-1455. DOI: 10.1136/bmj.1.4877.1451

Fienberg, S. E. (1992). A brief history of statistics in three and one-half chapters: A review essay. *Statistical Science*, *7* (2), 208-225.

Fisher, R. A. (1957). Dangers of cigarette-smoking. *British Medical Journal*, *2*(5039), 297-298. DOI: 10.1136/bmj.2.5039.297

Francis, T., Jr., Korns, R., Voight, R., Boisen, M., Hemphill, F., Napier J, & Tolchinsky, E. (1955). An evaluation of the 1954 poliomyelitis vaccine trials: Summary report. *American Journal of Public Health*, *45*(5, Pt. 2), 1-50.

Gigerenzer, G., Swijtink, Z., Porter, T., Daston, L., Beatty, J., & Kruger, L. (1989). *The empire of chance. How probability changed science and everyday life*. New York, NY: Cambridge University Press.

Hammond, E. C., & Horn, D. (1954). The relationship between human smoking habits and death rates: A follow-up study of 187,766 men. *Journal of the American Medical Association*, *155*(15), 1316-1328. DOI: 10.1001/jama.1954.03690330020006

Leonhardt, D. (2000, July 28). John Tukey, 85, statistician; Coined the word 'software.' *The New York Times*. Retrieved from http://www.nytimes.com/

Meier, P. (1989). The biggest public health experiment ever: The 1954 field trial of the Salk poliomyelitis vaccine. In J. Tanur, F. Mosteller, W. H. Kruskal, E. L. Lehmann, R. F. Link, R. S. Pieters, & G. R. Rising (Eds), *Statistics, a guide to the unknown* (3rd ed.). San Francisco, CA: Holden Day, 1989.

Meldrum, M. (1998). "A calculated risk": the Salk polio vaccine field trials of 1954. *British Medical Journal*, *317* (7167), 1233-1236.

Moses, L. E. (1986). *Think and explain with statistics*. Addison-Wesley Publishing Company.

Stigler, S. M. (1986). *The history of statistics: The measurement of uncertainty before 1900*. Cambridge, MA: Harvard University Press.

U.S. Department of Health, Education, and Welfare. (1964). Smoking and health. Report of the advisory committee to the surgeon general of the public health service. Washington, DC: U.S. Government Printing Office. Public Health Service Publication No. 1103.