Probabilistic thinking and evaluation of therapies: an introductory overview

Ulrich Tröhler

Institute of Social and Preventive Medicine, University of Berne, CH-3012 Bern, Switzerland
Corresponding author: Ulrich Tröhler. Email: ulrich.troehler@ispm.unibe.ch

This article is in our series on probabilistic thinking and the evaluation of therapies, 1700-1900

Collecting and comparing data

In this first pandemic year of an infectious disease (COVID-19), it seems particularly apt to recall that the foundations for controlling and eventually eradicating another devastating infectious disease – smallpox – began during the 18th century.

I can draw on a vast secondary literature to briefly recount this history. It is relevant, for it will deploy this important early example of probabilistic thinking in the history of evaluation of a medical measure, and how this thinking was related to quantification.

Between 1715 and 1721, smallpox had killed one-fourteenth of the population of London. Variolation – the inoculation of smallpox lymph into the skin of healthy people as a preventive measure against small-pox (Miller, 1957a)[1,2] – was an oriental and North African practice (Boylston, 2012). In Europe, it was first used in Britain in the 1720s. Thomas Nettleton (b.1683; Boylston, 2010), a physician in Halifax and one of the earliest to carry out mass smallpox inoculation, calculated the outcomes in terms of death rates: the death rate of naturally acquired smallpox was 'near one fifth' (636 out of 3405) whereas it was none out of 61 inoculated persons (Nettleton, 1722). This was an unconsciously expressed probabilistic statement.

James Jurin (b.1684), Secretary of the (London) Royal Society, and a Cambridge MA and MD with a good mathematical education, was motivated by Nettleton's observations to solicit reports of personal and professional experiences with variolation from readers of the *Philosophical Transactions of the Royal Society*. From 1721, he received over 60 replies from physicians and surgeons and summarised them in a series of annual pamphlets (Bird, 2018; Jurin, 1724). Jurin's analysis concluded that the chance of death from variolation was roughly 1 in 50, while the chance of death from naturally contracted smallpox was 1 in 7

or 8 (Bird, 2017, 2018). This was a further example of an unconsciously expressed informal probabilistic statement, implying a mode of probabilistic thinking.

After Jurin's death, the revolutionary technique of systematic collection and computation was continued in London by a Swiss, Johann Caspar Scheuchzer (b.1702), who presented his data in tabular form (Scheuchzer, 1729). Similar tabular data were also produced by an American, Zabdiel Boylston (b.1679; Boylston, 2008a; Boylston and Williams, 2008), who, in his 40s, had travelled from Boston to present them to the Royal Society in 1725! Such actuarial data were published in the *Philosophical Transactions* and widely circulated throughout Europe, but they did not end controversies over the propriety and efficacy of smallpox inoculation. Dependence on data collected was doubted: Could one trust in numbers? More data were needed. But there was also opposition of other kinds: concerns about contagiousness of inoculated persons were raised; and religious fatalists saw inoculation as a blasphemous attempt to escape God-sent providence.[2]

Eventually, however, inoculation became widely adopted during the 18th century.[1] By the end of the century, calculation had been used to evaluate the results of controlled clinical trials (Boylston, 2008b), and mathematics had even been deployed to guide contact tracing and prevent spread of the disease (Haygarth, 1784, 1793). Vaccination (inoculation with cowpox) had been identified as an even safer way of protecting people from the disease (Boylston, 2012). Using these approaches developed in the 18th century, smallpox was eventually eradicated 200 years later.

These 18th-century numerical evaluations of healthcare interventions led to a fundamental debate on the applicability of a formal calculus of probabilities in decisions related to medical treatments.

Applying the calculus of probabilities

Probability had been a branch of mathematics before 1700 (Hacking, 1975, 2006). The notions of 'opinion' and 'belief' had been used to express the meaning of certainty for centuries (and sometimes still are). However, these notions of *emotional certainty* of belief could be seen in reality as unconscious probabilistic reasoning. This became clear in the 17th century when mathematisation began to deal with games of chance[3] and probability became designated 'the doctrine of chance'.

In his book *Ars conjectandi* (The art of conjecturing, published posthumously in 1713), Jacob Bernoulli (b.1654), professor of mathematics in Basel, included works of mathematicians such as Christiaan Huygens, Gerolamo Cardano, Pierre de Fermat, Blaise Pascal and Gottfried Leibniz. As an additional motive for furthering the theory of probability, Bernoulli called for rational action at a time when passion, pride and prejudice conditioned most political choices. But how could one arrive at a wise decision through a 'democratic process' when there were various loyalties and interests at play? Bernoulli suggested that the way out of this maze was a calculus of probabilities to estimate the errors in human judgment with a high degree of accuracy.[3] The calculus would be the basis of a science of decision-making.[4]

One of Jacob's nephews, Daniel Bernoulli, yet another member of the famous Basel family of mathematicians, physicists and physicians, attempted this by calculating the advantages provided by the inoculation of smallpox. He sent a *Mémoire* to the *Académie Royale des Sciences* in Paris, and an academic debate ensued.

An academic debate in 18th-century Paris

Various historians have written about these deliberations. Their work allows me to summarise the story. Daniel, this younger Bernoulli (b.1700), had extended Jurin's work on 'chance' (i.e. probability). Applying a calculus of probabilities to the life tables elaborated by Edmund Halley, his elder British contemporary, he had calculated a life expectancy at birth of 26 years and 7 months (Hald, 1998, pp. 131–141). This would be increased by three years if a population were inoculated systematically (taking account of the then current estimate of lethality of the procedure of 1 in 200). This result, he wrote, '*appeals to all reasonable (raisonnable) men*'. Furthermore, it was in the interest of the State (Marks, 2005). It illustrated how the calculus of probabilities was able to provide 'certainty' (i.e. high probability) to medical practice by estimating its proximate risk. This practical example of his uncle's programme of applied probability in practice illustrates an early example of consciously used, formal probabilistic reasoning.

This sophisticated paper was read at a meeting of the *Académie* on 13 April 1760. It provoked a violent reaction from Jean Le Rond d'Alembert (b.1717), a younger yet already internationally known French mathematician. He was also the co-editor, with Denis Diderot (b.1713), of the monumental Enlightenment work, the *Encyclopédie*.

D'Alembert, a longstanding anti-probabilist, reacted to Bernoulli's memoir in a lecture to the *Académie* on 12 November 1760. He pointed out that estimating an additional two years of life, on average, at an undetermined time in the future, would not tempt an individual to risk immediate death from inoculated smallpox. He stressed particularly that neither mothers nor the crowds would accept such a risk, for he considered both as irrational when he said: '*We know how heavily the proximity of feared danger, or of a hoped-for advantage weighs in influencing the crowds*' (quoted by Rusnock[2], p. 86).

Contrary to Bernoulli's concern with the interests of the state, d'Alembert thus advanced that this did not at all persuade an individual who must risk death (Miller, 1957, p. 228). Finally, he held that the calculus of probabilities did not permit the assessment of chance (i.e. probability), since there existed no way of estimating future chance (Huber, 1959). Indeed, he deemed the calculation of the probability of a probability an impossible task!

Thus, the debate turned about two fundamental kinds of issues, which we shall come across several times in this study: (i) risk assessment using comparisons of groups; and (ii) the controversial applicability to individuals of results derived from groups, the 'group-versus-single patient/case problem'.

When Bernoulli's memoir was eventually published by the *Académie* five years later, he defended his arguments by correspondence. He thought that rational actions, as defined by calculation, and actions chosen by individual citizens were synonymous, and that contrary opinions, as held by d'Alembert, were ridiculous and partly attributable to the latter's jealousy because he had not made the discovery himself (de la Harpe and Gabriel, 2010).

Nevertheless, d'Alembert's critique drew attention to problems of psychological experience in the interpretation of data which do not seem to have been resolved mathematically even today (Daston,[3] pp. 84–91; Marks, 2005). By contrast, the data and their applicability were precisely Bernoulli's concern.

This debate was an intellectual highlight, now considered 'a classic' in the history of probabilistic thinking.[5]

The mathematical path and the clinical path

From the middle of the 18th century onwards, French mathematicians continued their efforts and established a tradition of formal mathematical treatment of probabilities. In 1840, this led Jules Gavarret – a young French physician and mathematician – to apply the calculus of probabilities to clinical practice. Meanwhile some clinicians had independently become involved in probabilistic thinking by informal quantification (Tröhler, 2006).

Initially this consisted of nothing more than what had been known since Jurin's times: the systematic collection, counting and tabulation of observations; assembling them in groups, ideally for fair comparisons (avoiding bias); calculating averages (means); and then drawing inferences from them. Such calculations – actuarial *medical arithmetic* – implied probabilistic thinking, albeit unconsciously at first. It was also used in Geneva, a Swiss city with particular scientific links to Britain (Bibliotheca Britannica, 1824; Ruffieux, 2020; Tröhler, 2010).[6]

By the late 18th century, a methodological toolbox was thus available for unconscious probabilistic approaches to the evaluation of clinical practice and therapeutic innovations. And they were used, mainly in British medicine and surgery (Chalmers et al., 2017). It amounted to 'Evidence-Based-Medicine *avant la lettre*'. These approaches were later also used in post-Napoleonic France. As many foreign students went to Paris at that time, they brought these ideas back to their home countries, particularly to Germany and the United States. All this entailed a new type of medical knowledge and was therefore disputable, prompting discussions about the new way of thinking (LaBerge, 2005).

Clinics and mathematics merge

After 1840, the work of Jules Gavarret (b.1809)[7] influenced a group of young German clinicians who promoted discussions of the new methods, using arguments, requests and cautions about formal probabilistic reasoning in clinical medicine. They then started a process of mathematisation, which, by the end of the 19th century, led to the insight that evaluation should become a science in its own right. By contrast, contemporaneous British and French clinical thinking hardly evolved in these ways at that time.

In parallel, medical developments, especially in hygiene and surgery, led to calls for evaluation (Tröhler, 2014), and these led to a resumption of discussions about methodological, evidence-based, probabilistic approaches, the *raison d'être* of such an evaluation science. Even so, the purpose of an evaluation science emerged only towards the end of the 20th century in the form of our contemporary, mathematised, probabilistic, evidence-based medicine.

Lately, debates were resumed about the problems of the evidence-based medicine approach. For example, modern genetics seemed to promise the reality of so-called 'personalised healthcare', apparently implying less relevance of mathematically sophisticated, probabilistic evaluation. This development reflects the eternal contrast between the empirical and the rationalist approaches for acquiring reliable medical knowledge. Evidence-based medicine is closer to empiricism than rationalism. Will the balance become more equalised (Howick, 2016)?[8]

The scope of my research

Since evidence-based medicine was thus 're-launched' in the 1990s, a variety of perspectives on it have emerged, including some from basic scientists, clinicians and historians. For example, Rosser Matthews considered the rise of the randomised clinical trial in the light of the debates about numerical thinking in the Parisian Academies in the 1830s,[9] and Laura Bothwell et al.[10] studied *Lessons from the history of randomized clinical trials (RCT)* after World War II. Other related research has studied the history and sociology of quantification in medicine and health from various standpoints – philosophical, mathematical, epidemiological, clinical, social and political (Gigerenzer, 2002; Gillies, 2000; Hacking, 1975; Jorland et al., 2005; Magnello and Hardy, 2002; Porter 1986, 1995, 2005; Schlich and Tröhler, 2006; Sheynin, 1976, 1978, 1982; Stigler, 1986; Warner, 1997).[1,2,5] Some of these studies have but marginally touched on the emerging use of probabilities in the clinical context.

As outlined in the Commentary by Chalmers and Abbasi introducing this series of nine articles covering the evolution of probabilistic thinking and the evaluation of therapies between 1700 and 1900, I have endeavoured to address this gap in the eight reports of my research which follow this introductory overview.

Note

a. The ten references listed below are chosen as essential to the reading of the article. However the full list of primary and secondary references is available online both on the Journal's website as supplementary material, and with the original publication at https://www.jameslindlibrary.org/articles/probabilistic-thinking-and-the-evaluation-of-therapies-1700-1900/.

References

1. Huth EJ. Quantitative evidence for judgments on the efficacy of inoculation for the prevention of smallpox: England and New England in the 1700s. *JLL Bulletin: Commentaries on the History of Treatment Evaluation.* See http://www.jameslindlibrary.org/articles/quantitative-evidence-for-judgments-on-the-efficacy-of-inoculation-for-the-prevention-of-smallpox-england-and-new-england-in-the-1700s/ (last checked 9 June 2020).

2. Rusnock A. *Vital Accounts: Quantifying Health and Population in Eighteenth-Century England and France.* Cambridge: Cambridge University Press, 2002.

3. Daston L. *Classical Probability in the Enlightenment.* Princeton NJ: Princeton University Press, 1995.

4. Matthews RAJ. The origins of the treatment of uncertainty in clinical medicine. Part 1: ancient roots, familiar disputes. *JLL Bulletin: Commentaries on the History of Treatment Evaluation.* See https://www.jameslindlibrary.org/articles/the-origins-of-the-treatment-of-uncertainty-in-clinical-medicine-part-1-ancient-roots-familiar-disputes/ (last checked 9 June 2020).

5. Gigerenzer G, Swijtink Z, Porter T, Daston L, Beatty J and Krüger L. *The Empire of Chance: How Probability Changed Science and Everyday Life.* Cambridge: Cambridge University Press, 1989.

6. Tröhler U. *'To improve the Evidence of Medicine': The 18th Century British Origins of a Critical Approach.* Edinburgh: Royal College of Physicians, 2000. (This book is freely available here https://en.wikipedia.org/wiki/URL).

7. Huth EJ. Jules Gavarret's Principes Généraux de Statistique Médicale: a pioneering text on the statistical analysis of the results of treatments. *JLL Bulletin: Commentaries on the History of Treatment Evaluation.* 2006. See http://www.jameslindlibrary.org/articles/jules-gavarrets-principes-generaux-de-statistique-medicale-a-pioneering-text-on-the-statistical-analysis-of-the-results-of-treatments/ (last checked 9 June 2020).

8. Howick J. Aulus Cornelius Celsus and 'empirical' and 'dogmatic' medicine *JLL Bulletin: Commentaries on the History of Treatment Evaluation.* See https://www.jameslindlibrary.org/articles/aulus-cornelius-celsus-and-empirical-and-dogmatic-medicine/.

9. Matthews JR. *Quantification and the quest for Medical Certainty.* Princeton NY: Princeton University Press, 1995.

10. Bothwell LE, Greene JA, Podolsky SH and Jones DS. Assessing the gold standard – lessons from the history of RCTs. *New Engl J Med* 2016; 374: 2175–2181.