



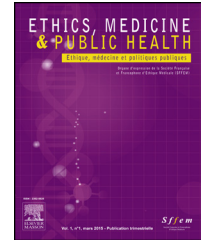
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## LETTER TO THE EDITOR

### Bayesian versus frequentist clinical research now and then: Lessons from the Greco-Roman medical scholarship



**Keywords** Statistics; Bayesian; Frequentist; Public health; History of medicine

Dear Editor,

It is evident nowadays that the Covid-19 pandemic has challenged the conventional patient randomization in treatment and control groups since all Covid-19 patients required efficacious treatment, and all the available treatments were constantly re-evaluated. Randomized Embedded Multifactorial Adaptive Platform (REMAP) Trials emerged as a solution to this, enabling simultaneous evaluation and comparison of multiple treatment domains [1]. Delving deeper into the matter, this practice might mark a gradual transition from frequentist to Bayesian statistics.

In principle, the Bayesian approach assigns a probability to each tested hypothesis and compares the pre- and post-test probability, while frequentist hypotheses are tested without being assigned a probability [2]. As a matter of fact, the debate about frequentist or Bayesian clinical research is older than Covid-19 and can be traced back to the Greco-Roman antiquity and the discourse between Rationalists and Empiricists. A critical overview of the discourse of these ancient schools of medical thought on the matter can provide additional lessons for the Covid-19 era and beyond.

To begin with, probability and subsequent uncertainty have been acknowledged as principal features of the art of Medicine in a famous epistemological aphorism of Hippocrates (460 BC - 375 BC) [3]. Within the art of medicine, whose length overcomes the short duration of the physician's life, the fact that in the face of the "fleeting crisis", "*experience [is] perilous and decision [is] difficult*" implies that the accuracy of clinical decisions and outcomes is subject to probability. In the treatise "On Ancient Medicine", Hippocrates and his accolades note that predicting the response of a patient to a specific treatment lacks precision [4]. Subsequently, Hippocratic case reports usually conclude with a standard phrase, which can be transcribed as "It is probable that (...) the cure/the demise of the patient can be attributed to" [5]. Despite the lack of mathematical infrastructure, the efforts of ancient Greek and Roman physicians to address probability in their practice, has been reflected in their writings.

On these grounds, Aristotle (384 BC - 322 BC) acknowledged that medicine necessitates a specific type of

reasoning, where a conclusion is valid in case the probability of obtaining the same effect only by chance is very low. This has been regarded as a predecessor of statistical significance. The notion of quantification- or enhancing a conclusion by means of a sufficient number of examined cases - first appeared in the Sorites paradox. This consisted of a philosophical example in which the inquiry for the exact amount of sand that forms a heap indicates that decisions can be taken only on the grounds of sufficient cases [6].

The philosophical quest for quantified evidence reflected on the division of medical practitioners of the time in two major schools of thought, the empirical and the rationalistic one. Each of these groups attempted to tackle the issue of probability. Rationalistic physicians examined each patient as a unique case. They diagnosed and treated patients on the basis of the assumed etiology of their condition. On the contrary, empirical physicians would decide on the treatment of a condition based on the previous experience they had with a large number of patients with similar symptoms and course of disease. Essentially, rationalists attempted to minimize probability by building a concrete pathogenetic rationale, while empiricists "seized the day" and availed probability as a guide to the most likely diagnosis [6]. Therefore, in modern terms, the rationalistic school of thought is closer to the frequentist statistics, where pathogenetic mechanisms are impartially allowed to define the outcomes of the patients and the control group. Simultaneously, empiricist physicians are closer to a Bayesian approach, where diagnostic or working hypotheses are accompanied by a pre-test probability ranking.

Galen (130–210 CE), probably the most prominent Greco-Roman physician after Hippocrates, sought common ground by inquiring about the number of cases that would make a probabilistic diagnosis safe enough to be accepted by rationalistic physicians [7]. However, Galen's question would remain unanswered for centuries. His teaching did not cease to guide physicians until the Renaissance, while tools for biostatistical analysis were not widely employed until the 18th century. Since then, frequentist statistics dominated the growing body of clinical research and clinical research ethics, because of the "first do not harm" principle [8]. In the field of clinical research, risking a treatment on the basis of a pre-test probability is considered less safe than the frequentist approach. In this context, the frequentist practices of randomization and blinding assign similar risk and benefit to each participant and a mainstay treatment can change only when sufficient evidence has already been collected.

Nonetheless, in daily clinical practice, decision-making is considered rather Bayesian. For instance, if both an obese 55 years old man and a 32 years old female athlete present

with heartburn, the average clinician tends to assign to the former a working diagnosis of myocardial infarction and to the latter a working diagnosis of gastroesophageal reflux [9]. Although further testing is deemed necessary in both cases, experience suggests that clinicians tend to adopt this rationale, which would be unacceptable in the formal design of a frequentist clinical trial.

Overall, the Covid-19 pandemic accelerated innovation in the design of clinical trials and paved the way for the integration of Bayesian approaches. However, harnessing probability in terms of conducting clinical research whilst providing the most efficacious treatment available is also a lesson from the Greco-Roman antiquity and particularly from the feud between rationalist and empiricist physicians. Digging deeper into ancient debates on evidence, probability and uncertainty might help address dilemmas in research and related ethics. Thus, the need to integrate medical humanities in contemporary research-related dialogues should be considered as an additional aftermath of the pandemic.

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The authors declare that the work described has not involved experimentation on humans or animals.

#### Informed consent and patient details

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