



Thomas Nettleton and the dawn of quantitative assessments of the effects of medical interventions

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DECLARATIONS
None declared

Competing interests
None declared

Funding
None

Ethical approval
Not applicable

Guarantor
AB

Contributorship
AB is the sole contributor

Acknowledgements
Additional material for this article is available from the James Lind Library website (www.jameslindlibrary.org), where it was originally published

Thomas Nettleton (1683–1742) was one of the first, possibly the first, to use quantitative assessments of the effects of medical interventions. Prior to establishing a medical practice in Halifax, West Yorkshire, Nettleton had been educated at Bradford Grammar School, and had studied medicine at Edinburgh and Leyden, where he was awarded his Doctorate of Medicine. In December 1721, during an epidemic of smallpox in West Yorkshire and frustrated by the lack of any effective therapy for the disease, Nettleton began to use variolation, which at the time was known as inoculation. Variolation to immunize people against smallpox was introduced into Europe and North America in 1721.^{1–3} However, there was uncertainty and debate about whether it did more good than harm. To address this uncertainty, Nettleton collected statistics on the mortality associated with naturally-acquired smallpox and compared these with mortality following variolation. He communicated his findings in a series of letters and a pamphlet published in 1722 and 1723.^{4–7}

Early clinical trials of variolation in Britain

The practice of variolation in Europe begins with its importation from the Middle East by a Scottish surgeon, Charles Maitland, who accompanied Lady Mary Wortley Montague, her diplomat husband and their children to Constantinople.¹ Lady Mary discovered that variolation was widely practised in Turkey and that it was considered safe and effective in preventing fatal smallpox. She had her son inoculated by an ancient Greek practitioner, assisted by Maitland.

In April 1721, back in England, Maitland was asked by Lady Mary to inoculate her daughter. Maitland agreed, but insisted on observers, one of

whom, John Keith, a physician, immediately asked Maitland to inoculate his sole surviving son.

Impressed by the mild inoculated smallpox and complete recovery of the two children, a group of physicians approached King George I with a request to expand this initial experience by experimenting on condemned prisoners. After being promised a complete pardon for their crimes, six prisoners confined at Newgate agreed to be inoculated. In August 1721, observed by several members of the Royal Family, various apothecaries, surgeons, and Fellows of the Royal Society and College of Physicians, Maitland variolated the six prisoners. Five of them developed mild, distinct smallpox; one did not develop any pustules and subsequently admitted that he had had smallpox six months before. In February 1722, Maitland published his account of the Newgate experiment,⁸ and conducted two further trials on parish orphans.¹

Maitland's early trials of variolation in Britain were intended to demonstrate its relative safety and the mild resulting smallpox, and they led to a decision in April 1722 to inoculate two daughters of the Prince of Wales, the future George II. Although the princesses suffered no ill-effects, news of two deaths following variolation in Britain and others in Boston led to an intense debate about the safety and advisability of the procedure.

Recognition of the need to compare mortality following inoculated and 'natural' smallpox in large populations

Just before the princesses had been inoculated, a letter from Thomas Nettleton to William Whitaker – a friend in London – revealed that he had inoculated over 40 individuals in the parish of

Halifax, with no deaths and only a few cases of severe disease.⁴ Nettleton's letter was read to the Royal Society on 17 May 1722, and a correspondence ensued between Nettleton and James Jurin, the mathematically-inclined secretary of the Royal Society. Nettleton informed Jurin that he had encountered vigorous local opposition to inoculation, but that he believed that objections would melt away after inoculation had been 'set in its true Light'.⁴ Jurin invited him to submit his letter to Whitaker for publication in the *Philosophical Transactions*, and asked for any further experience of inoculation that Nettleton might have.

On 16 June 1722, Nettleton wrote to Jurin:

'Sir, I doubt not that when you have collected a sufficient Number of Observations for it, you will be able to demonstrate, That the Hazard of the Method is very inconsiderable in proportion to that in the ordinary way by accidental Contagion ... In order to satisfy myself, what Proportion the number of those who die of smallpox might bear to the whole number that is seized with the Distemper I have made some enquiry hereabouts.'

He had collected the outcomes of 1245 patients with natural smallpox and found that 270 had died, 'nearly 22 out of every hundred'. At the time Nettleton had inoculated 55 individuals with no deaths.⁵

However, news of the deaths following inoculation in Britain and Boston led to controversy. William Wagstaffe MD, FRS, physician to St Bartholomew's Hospital, attacked the practice on several, sometimes contradictory, grounds.⁹ On the one hand, he argued that the disease that appeared in inoculated patients was not true smallpox, while on the other hand he said that inoculation was dangerous because it would spread the disease; and while arguing that inoculation should be banned, he also insisted that more experience was needed before it could be evaluated. Nevertheless, one of his charges was significant: he complained that inoculation had not been given a fair trial because he claimed that almost all those who had been inoculated were children and that their mortality from natural smallpox was only 1%. He also complained that different inoculators used different techniques and, therefore, their results could not be compared.

On 25 September 1722, John Arbuthnot¹⁰ published a booklet in which he pointed out the many

contradictions in Wagstaffe's article. While citing Nettleton's initial findings,⁵ Arbuthnot also used the Bills of Mortality of London and figures for the Polish city of Breslaw to arrive at an estimate that about one in 10 of all people over the age of 1 year died of smallpox. However, his calculations were based on assumptions about the lack of mortality from smallpox among the very young and also on the number of cases of smallpox that there were in London each year.

On 16 December 1722, Nettleton sent Jurin another letter, and this seems to have triggered the latter's subsequent attempts to quantitate the effects of inoculation:⁶

'... Inoculation which is so vehemently opposed by many and countenanced by very few. It is to me perfectly indifferent as to any private interest of my own whether the Thing is received or exploded but I must own that I am strongly possess of an Opinion that it will in time prove to be of very great Service to Mankind & as it is Experience principally that must determine whether it will be so or not. You will excuse my freedom in communicating to you some observations I have had the Opportunity to make regarding the Matter.'

*There are two propositions advanced by the Favourers of the Practice concerning which the Publick seems to require more full Satisfaction. That the Distemper raised by Inoculation is really the Small Pox & That it is more mild and favourable & far less mortal than the Natural Sort.'*⁶

Nettleton dealt with the first proposition by giving a number of reasons why he believed that the disease transmitted by inoculation was identical to the mild form of natural smallpox that every doctor had observed. As far as the second proposition was concerned – that is, that inoculated smallpox was 'less mortal' than naturally acquired smallpox, he wrote:

'The truth of this I suppose can only be found by making a Comparison in so far as our Experience will extend.'

He then gave figures for the mortality of natural smallpox in several towns and parishes across the north of England revealing that 636 of 3405 patients (19%) had died. None of the 60 patients that he had inoculated had succumbed. He continued:

*'I am very sensible You will require a great Number of Observations before you can draw any certain Conclusions.'*⁶

Nettleton's letter was read to the Royal Society on 21 December 1722, and Jurin wrote acknowledging Nettleton's valuable observations.⁷ He revealed that he had been thinking along similar lines but, like Arbuthnot, he had attempted to calculate the mortality of natural smallpox from the Bills of Mortality collected from London parishes. Jurin acknowledged that these figures were difficult to interpret, in part because they took no account of early childhood deaths. Nettleton's direct approach was clearly superior.

On 17 January 1723,¹¹ Jurin read his own paper, citing Nettleton and information from a few other inoculators.^{1,12} His paper was mostly well received, but it was criticized by Isaac Massey,¹³ apothecary to Christ's Hospital, and the uncle of Edmund Massey who had preached a famous anti-inoculation sermon in 1722. Massey's point was that the comparison between inoculated and natural smallpox was unfair because many patients with natural smallpox might have survived if they had been given the same medical support as those who were inoculated. Also many patients with natural smallpox who had died were unwell from other diseases whereas inoculated individuals were usually in good health. Massey suggested that:

*'... not above One in Forty that have the Small Pox, would die of that Distemper, if treated with equal Care with those that are inoculated: but to form a just Comparison, and calculate right in this Case, the Circumstances of the Patients, must and ought to be as near as may be on a Par.'*¹³

However, the generally enthusiastic response to Jurin's paper led him to appeal for information through an advertisement placed in the *Philosophical Transactions*.¹ Over 120 letters were received by the Royal Society, where the originals are available in the archives (Royal Society Archives CP XXIII. Inoculation Papers). The replies to this appeal formed the basis for the quantitative assessment of the benefits of inoculation subsequently published by Jurin.³

Nettleton replied with a direct statement of the value of quantification:⁷

'Whenever any shall happen to miscarry under this Operation, that will indeed be very unfortunate & ill, but in this Case you will have recourse to the Merchant's Logick state the Accounts of Profit and Loss to find on which side the Balance Lyes ... and form a Judgement accordingly.'

Jurin explained his undertaking in a first account of the information he had received following his appeal for data:¹²

'This Controversy, though drawn out in many Particulars, seems principally to turn upon the two following Points:

- (1) *Whether the Distemper given by Inoculation be effectual Security for the Patient, against his having the Small Pox afterwards in the natural Way.*
- (2) *Whether the Hazard of Inoculation be considerably less than that of Natural Small Pox.*

If these two points were effectually settled there would, I suppose, be an end of the Dispute, at least among Physicians. For if either of them be fairly determin'd in the Negative the Practice of Inoculation must on all Hands be given up. And on the other Hand, if the Test of Experience should plainly declare for the affirmative Side of both these Questions, I doubt not that every Gentleman, who has the Honour to serve his Country in the Capacity of a Physician will have Integrity and Humanity enough to declare himself honestly and openly in Favour of the Practice. At least he will consider whether it will be for his Reputation when his Friend and Patient shall put his Life or the Lives of his Children into his Hands, to amuse himself with Theological Disputes and Scruples, whether it be lawful to save them. For if the Practice of Inoculation be really found to be a Means of preserving Life, it will not be easy to make the World believe that it is criminal to use it.'

Jurin showed that 2351 patients out of 14,559 with natural smallpox had died (16%), while only nine of 440 individuals successfully inoculated had succumbed (2%). In his analysis of the information, Jurin sensibly decided to count all deaths following inoculation as due to inoculation, regardless of the opinions of observers of individual cases about the cause of death. This dealt with possible observer bias in deciding whether a death was really due to inoculated smallpox. Jurin also avoided

another potential pitfall by counting only deaths, thereby avoiding subjective debates about the degree of severity of individual cases. Finally, Jurin acknowledged that, before it would be possible to know for certain that inoculation always conferred immunity to smallpox, it would:

'require a considerable time and a much greater Number of Experiments than have yet been made.'

Thus it was that the correspondence between Thomas Nettleton and James Jurin during the winter of 1722–1723 led to judgements about the effects of variolation being based not on impressions from a few cases or indirect arguments from past figures, but rather on comparisons of unambiguous outcomes (deaths) among large numbers of inoculated people, and among others who had contracted smallpox naturally.

The dates of the various letters between Nettleton and Jurin indicate that the idea of collecting mortality data was Nettleton's alone. He began his study before June 1722. Nettleton's analyses are the earliest examples so far identified of the use of numerical methods to assess the effects of any medical intervention.

Nettleton continued to correspond with Jurin until the secretary resigned his post at the Royal Society in 1727. They discussed individual cases, helped refute reports that some of Nettleton's inoculated patients had died, and collated further data from Yorkshire. Nettleton also sent Jurin various reports of meteorological phenomena which were of particular interest to the Royal Society.

What may have led Nettleton to use quantitative methods to assess the effects of medical treatment?

Nettleton may have been motivated to begin his studies by an interest in mathematics. He is reported to have taught mathematics to 'blind Professor Saunderson who soon outstripped his tutor'.¹⁴ Saunderson was an almost exact contemporary of Nettleton's and had lost both his sight and his eyes to smallpox during infancy (Oxford Dictionary of National Biography online edition) He later became the fourth Lucasian Professor of Mathematics at Cambridge. Perhaps Nettleton, like Jurin, was one of the physicians who became

interested in applying mathematics to medicine in the wake of Isaac Newton's book *Philosophiæ Naturalis Principia Mathematica* (The Mathematical Principles of Natural Philosophy).

In 1729 Nettleton published a book entitled *Some Thoughts Concerning Virtue and Happiness*,¹⁵ which was subsequently retitled *A Treatise on Virtue and Happiness*. The book ran through at least seven editions, the last of which appeared in 1766, 24 years after Nettleton's death.

On 9 January 1742, Thomas Nettleton died in Dewsbury (where he had been born in 1683), and he was buried in the churchyard there three days later. His grave and memorial stone have been lost; but his pioneering contribution to the dawning of quantitative evaluation of the effects of medical treatments deserves to be remembered.

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