



Lady Mary Wortley Montagu with her son Edward, by Jean Baptiste Vanmour. Alamy photos

The birth of evidence-based medicine in the London smallpox epidemic of 1721-1722

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The deliberate infection of smallpox through the skin of a naïve patient to confer life-long immunity from the disease, first became widely practiced during the London smallpox epidemic of 1721-1722. It first began as a fad among the British aristocracy made fashionable by the charismatic Lady Mary Wortley Montagu (1689-1762) who had her son, Edward, inoculated in 1718 in Constantinople where her husband, Edward Wortley Montagu, served as ambassador. She had a public demonstration of the inoculation of her daughter, Mary Stuart, Countess of Bute, during the London outbreak of 1722, an event that led to a rush of inoculations among the children of London nobility, including the son and daughters of Caroline, Princess of Wales (1683-1737). Then two prominent deaths threatened an end to the practice of inoculation.¹

Inoculation as a legitimate intervention for smallpox was rescued by James Jurin (1684-1750), physician, mathematician, and secretary to the Royal Society under

the presidency of Isaac Newton.² From 1722-1724 he collected the early experience of inoculators in England to show mathematically that those receiving inoculation had a mortality rate of only 2.1 percent, where the prevailing rate was 12.8 percent for the actual disease.²

Jurin's use of hard numbers demonstrated, for the first time, the power of quantitative data in evaluating a medical intervention. The ratios he presented would not constitute statistical proof under present-day standards, but his diligence in collecting a wide sample from multiple practitioners was the first attempt to judge the results of medical treatment on the basis of numerical evidence rather than anecdotal experience. Three-quarters of a century later, numerical data again were used to support Edward Jenner's use of fluid from cowpox lesions (1796) as an alternative to that obtained from patients with active smallpox, an innovation that within a decade was adopted throughout the world.³

The current COVID-19 vaccination controversy echoes the turmoil engendered by smallpox inoculation three centuries ago. Jurin's dispassionate use of numbers allayed popular misconceptions of inoculation, something we look to in our medical and scientific leadership today.

Smallpox

At the onset of the 18th century, it was accepted that everyone eventually contracted smallpox and suffered through its predictable stages. First came high fever, headache, and myalgia, followed by intractable salivation, vomiting, and diarrhea. Unable to sustain decent hydration, the victim was tormented with a desperate thirst. Within days a diffuse rash appeared that swelled the face beyond recognition and obstructed the mouth and nasal passages so that swallowing and breathing were nearly impossible.

The rash coalesced into vesicles of first clear fluid, then sores that drained foul-smelling pus. Death was a constant threat. Those who survived were at risk for permanent blindness and delirium. Survivors were left with unsightly pits and scars on their faces as the lesions from the acute disease healed. The single blessing—if one survived—was lifelong immunity from ever contracting the disease again.

Smallpox had afflicted humans since antiquity, but epidemics became a feature of 17th century life as cities became increasingly crowded, and seafaring trade brought contagious disease with its cargo. The English scientific community, through its leading organization, the Royal Society, became intensely interested in the induction of a weak form of smallpox that would still confer the protection so desperately sought.⁴

In the *Journal Book* of the Royal Society of 1699-1700 there were two accounts of the Chinese practice of placing dried pus from active pockmarks up the nostrils of naïve recipients.⁴ In October 1713, the practice of inoculation in Turkey was brought up in discussion. Its official journal, the *Philosophical Transactions*, published separate letters from Emanuel Timoni and Jacob Pylarius in 1714 and 1716, respectively, that described inoculation as it was practiced in Constantinople.^{5,6} It was so simple that lay practitioners performed the procedure: First drawing blood from the skin with a needle, then as the scratch bled mixing pus from someone with active disease directly onto the wound.

Despite its simplicity the London medical establishment was wary of adopting it. They dismissed it as an exotic folk remedy practiced in the Orient, Gold Coast, Levant, and even in remote areas of Wales and Scotland.¹ To the scientific mind of the 18th century, deliberately infecting someone with smallpox made no sense.

Learned physicians of the time emphasized treatment, using concepts dominated by Thomas Sydenham (1624-1689), the English Hippocrates of the previous century. To Sydenham, the eruptions were the natural process

of ebullition, the elimination of “morbific matter” from the body.⁷ Interventions that heated the blood, such as cordials and covering the patient with heavy blankets, brought out the pustules. Sydenham’s innovation was cooling the patient when the pocks became confluent, an intervention that required judicious timing.⁷

Lady Mary Wortley Montagu

Isobel Grundy of the University of Alberta, a scholar of early feminist literature and one of the founders of the Orlando online database of British woman authors, wrote on Montagu and the pivotal roles of woman leaders of London society in popularizing inoculation.⁸

Montagu was an aristocratic beauty descended from William the Conqueror and the formidable Bess of Hardwick. Denied a formal education because of her sex, she was self-educated, teaching herself languages, writing, and poetry. Under the mentorship of men of letters, her poems and eclogues attracted a readership among the esthete that included Alexander Pope, John Gay, and Joseph Addison. Her writing and satires were intended only for her literary friends, but she also gained a popular following through widely circulated pirated manuscripts that she did nothing to suppress.⁸

Smallpox killed her brother in 1713. When Montagu suffered smallpox in December 1715, she survived with her face marred by the loss of her comely eyelashes. She soon resumed her writing and active social life, but she retained from the horrible experience a deep distrust of the motives and abilities of the physicians who attended her.⁸

When her husband was assigned ambassador to the Ottoman Empire in 1717, she and their children accompanied him to Constantinople. Her correspondence found its way to an audience eager for her fascinating accounts as a woman traveler in the Levant, especially the harems and baths of Turkish woman elites, exotic worlds inaccessible to men.⁸

Inoculations

“The bathhouse, as a site for multiple hygienic and aesthetic functions, was also a place where therapeutic practices were carried out,” wrote Srinivas Aravamudan, dean of humanities at Duke University, and past president of the American Society for Eighteenth-Century Studies. “It was common in that environment to find female herbalists, magicians, and medical practitioners.”⁹

Among the procedures the women performed in the bath houses were inoculations. Montagu wrote:

There is a set of old women who make it their business to perform the operation every autumn.... The old woman comes with a nutshell full of the matter of the best sort of small-pox and asks what vein you pleased to have opened. She immediately rips open [the vein] that you offer to her with a large needle (which gives you no more pain than a common scratch) and puts into the vein as much matter as can lye [sic] upon the head of her needle, and after that binds up the little wound with a hollow bit of shell.¹⁰

She resolved not only to inoculate her children but took on a messianic mission to bring the procedure to England. Her dim view of physicians surfaced when she wrote:

I am patriot enough to take pains to bring this useful invention into fashion in England; and I should not be able to write to some of our doctors very particularly about it, if I knew any of them that I thought had virtue enough to destroy such a considerable branch of the revenue for the good of mankind. But the distemper is too beneficial to them.... Perhaps, if I lived to return, I may, however, have cause to war with them.¹⁰



Caroline of Ansbach, Queen of the United Kingdom by Michael Dahl. Public domain

In March 1718, Montagu asked the embassy surgeon, Charles Maitland, to arrange to have her six-year-old son inoculated. He found a local woman to do the procedure, only to take over when he saw her needle was blunt and rusted and she was hurting the child.¹⁰

The inoculation took, a rash appearing on the boy's face on the third day, then a mild bout of fever as about 100 pocks erupted over the rest of his body. As mother and surgeon sat vigil and feared the worst, his fever broke. The pocks crusted and healed without scars. Within a week the boy was, in his mother's words, "singing and playing, [and] very impatient for supper."¹¹

The procedure was pronounced a success. Montagu decided against having her infant daughter inoculated because her nurse had not yet had the disease.¹⁰

The Montagus returned to London in time for the 1721 smallpox outbreak. In April, she asked Maitland, who had retired to the country after his service to the embassy, to inoculate her daughter, now three-years-old. Maitland hesitated, insisting that the procedure be done in "the presence of any two physicians—as safeguards and eyewitnesses."¹¹ Once more, a mild illness was induced, and the child recovered. One of the physician witnesses, James Keith, was so impressed he had his sole surviving son inoculated in May.¹¹

But inoculation was slow to take hold. Raymond Stearns, professor at the University of Illinois and a noted historian of early Colonial America who wrote on the contemporaneous Boston smallpox epidemic of 1721-1722, described the adoption of inoculation in England as "a kind of social osmosis."¹

Caroline and inoculation of the aristocracy

Osmosis got a boost one year later when Caroline, Princess of Wales, had two of her five children inoculated in April 1722 (she would have seven survive infancy) and thus gave the procedure her royal imprimatur.^{12,13}

Anticipating the death of the childless Queen Anne, Parliament decided in 1704 that the throne would pass to the reliably Protestant descendants of James VI in northern Germany, bypassing the Stuarts and their problematic Catholic affinities. When Anne died in 1714, George Louis of Hanover, an elector in the Holy Roman Empire, ascended to the British throne as George I. The country fell into riots and rebellion as Jacobite partisans fought to reinstall the Stuart line.¹³

Caroline of Ansbach thus fell into politics when her father-in-law became King. As Princess of Wales, and later as Queen, she proved to be a formidable politician

working with her allies behind the scenes as her husband George Augustus, Prince of Wales, and later King George II, took her advice.¹²

Caroline contracted smallpox in 1707 while still in Hanover, before the throne was given to George Louis. In 1720, her 11-year-old daughter, Anne, became sick with the disease. Sir Hans Sloane, Anne's physician, wrote that she "[fell] so ill of the small-pox in such a dangerous way, that I very much feared for her life."¹⁴

In May 1721, with the London outbreak in full force, the royal nursery had an additional scare when another of Caroline's daughters fell ill with a febrile illness and rash until it became clear she instead had scarlet fever.¹⁰

Caroline knew that the Montagu children had been inoculated. Not satisfied with anecdotal experience, the Princess prevailed on the King to offer royal pardon to condemned inmates at Newgate Prison if they would undergo the procedure as an experiment. In August, under royal command, Maitland inoculated six prisoners, of which five duly contracted smallpox and survived. A sixth suffered the discomfort of having dried pus into her nostrils, which was without effect. In November, the Princess had inoculation tested on six orphan children in the parish of St. James's. All but one contracted the disease and survived. The sixth failed to fall ill and was later discovered as having had the disease before.¹⁴

Caroline asked Sloane for his opinion. He supported inoculation but was careful in revealing his true position before the royal family. Impatient with his circumspection, "the Princess then asked me if I would dissuade her from it," Sloane wrote. "To which I made answer, that I would not, in a manner so likely to be of such advantage."¹⁴

Caroline then ordered that Sloane speak with the King. Before the monarch Sloane was even more cautious noting, "there might happen dangerous accidents not foreseen."¹⁴ The King noted that complications were common after many medical interventions, including phlebotomy. He gave his assent for the inoculation of the royal grandchildren.

Claude Amyand, surgeon to the King, successfully inoculated Caroline's son, Frederick, and daughters, Amelia and Caroline, in April 1722, establishing the procedure as accepted practice in London.

London society followed the fashion: all six children and a 19-year-old servant of Lord Bathurst; the two-and-a-half-year-old son of the Earl of Sunderland; and the children of Lady Byng, who also was inoculated even though she was pregnant.

Lady Gower had refused to have her son inoculated, only to have the boy later die of the disease. Her father, the Duke of Kingston, then allowed to have his young daughter and another grandson undergo the procedure.¹¹

Opposition

In her article on the history of smallpox and inoculation, Genevieve Miller of the Dittrick Medical Museum at the Case Western Reserve University summarized the opposition to inoculation.¹⁵ William Wagstaffe, a physician and member of the Royal Society, in June 1722 published a tract that decried physicians giving in to "an Experiment practiced only by a few Ignorant Women, amongst an illiterate and unthinking People."¹¹

Isaac Massey, apothecary to Christ's Hospital, argued that more time was needed—at least 10 to 12 years—to ascertain the long-term effects of inoculation before it was applied widely among the boys at the public boarding school.¹¹

Publishers and writers took advantage of the controversy to sell their newsletters to a public in a frenzy over fear of the disease and the debate over the procedure. In February 1722, *Applebee's Journal* reported, "the New England epidemic was still raging unchecked and they have had but bad Luck [with their] Project of Inoculation,"¹⁵ referring to the procedure being widely performed in Boston, where a concurrent outbreak was taking place.

Other publications ridiculed the Newgate experiments as just an opportunity for criminals to be freed. Reports of deaths after inoculation in both Boston and England hardened further resistance against the procedure.

No one—lay populace, medical profession, nor scientific community—understood the rationale behind inoculation. Many saw it as a heathen practice from faraway countries. Robert Halsband, a professor at Hunter College and Montagu biographer, summarized the Calvinist argument put forth by the Reverend Edmund Massey, "Inoculation opposed the will of God, who sends disease (including the smallpox) either to try our faith or to punish us for our sins."¹¹

Montagu responded in September with a counterattack of her own in an anonymous letter signed, "a Turkey merchant," where she again railed against physicians who opposed inoculation. She suspected they opposed inoculation because they would lose income if patients became immune to the disease. She wrote:

Out of compassion to the numbers abused and deluded by the knavery and ignorance of physicians, I am deter-

mined to give a true account of the manner of inoculating the small pox as it is practiced at Constantinople with constant success, and without any consequence whatever. I shall sell no drugs, nor take no fees, could I persuade people of the safety and reasonableness of this easy operation.¹¹

Halsband recognized Montagu as the author of the letter. “[She was] too much an aristocrat to enter the controversy openly,” he wrote, “[but] too aggressive a thinker to sit by passively when she believed in [inoculation] so firmly.”¹¹

The popularity of inoculation was also shaken when Sunderland’s son and the young man under Bathurst died



Portrait of James Jurin (1679-1750), by James Worsdale. Royal Society

after their inoculations. By summer, its two most noted practitioners, Maitland and Amyand, stopped doing the procedure. Enthusiasm for the procedure, among the upper levels of London society was waning even before Princess Caroline inoculated her newest child, two-year-old William August, in the spring of 1723.¹

James Jurin

Innoculation was resurrected when James Jurin aggregated the results of dozens of practitioners to

demonstrate that the mortality rate among inoculated patients was a fraction of that in naturally acquired disease. Jurin’s biographer and curator of his correspondence, Andrea Rusnock of the University of Rhode Island, wrote, “[It was] arguably the first use of numerical evidence to evaluate a medical practice. ... It was to play a decisive role not only in the debates over inoculation but also in subsequent evaluations of medical knowledge and practice.”¹⁶

Jurin “epitomized the enlightened ideas of English culture.”¹⁷ Educated at the Royal Mathematical School at Christ’s Hospital, he earned a full scholarship at Trinity College, Cambridge, where he was immersed in Newtonian natural philosophy, mathematics, and experimental physiology. He received his baccalaureate in 1705 and became a fellow in 1707. After a term as schoolmaster at Newcastle-on-Tyne, he returned to Cambridge to earn a degree in medicine in 1716. As a scholarly Cantabrigian and Newton acolyte, Jurin’s ascent in the Royal Society was assured, with his first meeting in 1716, being elected a fellow in 1717, then secretary to the Society under Newton’s presidency in 1721.

Through its debates and publications, the Society became the authoritative forum for inoculation. Unscrupulous pamphleteers opposing the procedure announced the deaths of inoculated children when they were very much alive. Frustrated parents appealed to the Society to correct the falsehoods. Jurin, as secretary of the organization, made certain that the true conditions of their children were reported.¹⁸

In April 1722, a letter was read before the Royal Society from Thomas Nettleton, a physician in Halifax, who took up inoculations on his own initiative after reading the accounts from Constantinople in the *Transactions*. Independent from Maitland and Amyand’s experience, Nettleton had done 40 procedures: 38 contracted smallpox without a death; two did not come down with the disease.¹⁹

Impressed that the disease induced was far milder than the naturally acquired variety, and none of his patients had died, Nettleton wrote to Jurin in June and proposed that the relative death rates from inoculated and natural smallpox be compared directly. He had already done a pilot study, surveying three towns in his vicinity and finding an average mortality from smallpox of 22 in 100. Nettleton wrote:

Sir, I doubt not but when you have collected a sufficient Number of Observations for it, you will be able

to demonstrate, That the Hazard in this Method is very inconsiderable, and proportion to that in the ordinary way by accidental Contagion, so small, that are not deter any Body from making use of it.²⁰

The inoculations in New England, conducted by Boston physician Zabdiel Boylston and encouraged by the Puritan preacher Cotton Mather, provided an opportunity to test Nettleton's hypothesis. Mather reported Boylston's experience in a letter to Jurin in May, and in the *Transactions* in December.²¹

The numbers from America were approximations: five or six deaths of "near 300 inoculated," a ratio of one in 60.²¹ (The actual figures were six of 282.) It was less than the average mortality rate of one in 14 deaths from smallpox that occurred in London annually from 1701-1722. This was based on data Jurin took from the yearly bills of mortality that documented all causes of death in London since the Great Plague of 1665-1666, and the Great Fire of 1666.²¹

The data favored inoculation, but Jurin recognized the problem of comparing death rates in London with those from inoculations across the Atlantic. He proposed that those performing inoculations do what Nettleton did—go from house to house asking who among the household had smallpox during the previous year, and whether they died of it.²¹

Through correspondence and advertisements placed in the *Transactions* Jurin attracted correspondents eager to participate in his project. By far most of the respondents were medical practitioners: apothecaries, surgeons, and physicians. He also heard from the gentry, local clerics, and one weaver-turned-inoculator.

Jurin laboriously extracted usable data, one chatty letter by chatty letter. As his respondents gradually learned what he was after, the information became more direct and somewhat easier to get.¹⁶

To verify the information, Jurin relied on names and ages of the patients who were inoculated. Some of the practitioners balked, insisting that their patients retain their anonymity. Jurin reassured them that such information would not be divulged, as individual results would be congregated in the aggregated data.¹⁶

With so many respondents doing inoculations, Jurin ran into a problem that confounds clinical trials to the present day: patients that did not follow protocol. In many cases the inoculated form of the disease did not look anything like the naturally occurring disease, raising questions whether the procedure was done correctly.

In other cases, it was doubtful whether the inoculator did the procedure at all. Jurin used the term, "imperfect smallpox by inoculation" for these tricky cases.¹⁶

With the instincts of a modern investigator, Jurin distilled his research to two straightforward questions and two concrete outcome measures. His first question was, "whether the Distemper given by inoculation be an effectual Security to the Patient, against his having the Small Pox afterwards in the natural Way?" The second was, "whether the Hazard of Inoculation be considerably less than that of the natural Small Pox?" "If these two points were effectually settled," Jurin wrote, "there would, I suppose, be an End of the Dispute, at least among Physicians."²²

Jurin's two endpoints were death and failure of inoculation to protect against a subsequent bout of smallpox. The former was easy, but the latter was more difficult to assess because the length of follow-up was not sufficient.

He published his first report in 1724.²² His data showed a 16.1 percent mortality from smallpox (2,351 of 14,559) compared with 1.9 percent among inoculees (nine of 474). Under the modern standards of statistics and clinical trial design, Jurin's results were simplistic and inadequate to answer his questions. Edward Huth, who as longtime editor of the *Annals of Internal Medicine* was an early advocate of rigor in reporting scientific data, noted that Jurin's analyses were little more than "eyeballing the data."²³

The deficits in his analysis should not detract from his achievement, Rusnock argues. "The eventual overwhelming success of numerical arguments, should not obscure the very long and difficult process of establishing what is too easily taken for granted," she explains.¹⁶

Yet Jurin's data was convincing. His contemporaries immediately recognized the power of numbers to determine, without bias, the effectiveness of a medical treatment. The stark difference in mortality rates, conducted under the authority of the Royal Society, converted many doubters to inoculation supporters. One of Jurin's correspondents wrote, "I think the Method you pursue of convincing the World by matter of fact is fair & just & prejudices in reference to Inoculation can I think, be removed by no other means."¹⁶

Another wrote, "The less you appear to favour the side of Inoculation & the more weight your impartial Representation of it will have with the generality of Mankind who are very much prejudiced against it."¹⁶ Yet another physician who had been against inoculation wrote that he had decided to inoculate his only daughter based on Jurin's report.

Jurin continued his annual compilations of inoculation data until he was voted out as secretary to the Royal Society in 1727. "Jurin was widely acclaimed for his disinterested advocacy of smallpox inoculation," Rusnock wrote.¹⁵ Huth wrote that it represented, "what was probably one of the first major attempts in any country to judge the validity of a medical treatment from quantitative data."²⁴

Jurin's project marked the beginning of the transition from anecdotal practice to evidence-based medicine.

Vaccination

Just as numeric data helped establish inoculation as accepted practice, they also demonstrated that using fluid from cowpox sores for the procedure offered the same protection against smallpox without the risk of inducing a fatal disease. The story of the transition from inoculation with smallpox to vaccination with cowpox was written by Stefan Riedel, a pathologist at Beth Israel Deaconess Medical Center with an interest in infectious agents and bioterrorism,³ and Abbas Behbehani, a clinical virologist at the University of Kansas in Kansas City, who marked his interest in smallpox from the time he saw persons with active disease during his boyhood in Persia.²⁵

Edward Jenner (1749-1823) trained in London under John Hunter, who pioneered the concept of testing new surgical procedures through experimentation. Practicing in his native parish of Berkeley, a town in the Gloucestershire countryside, he became familiar with the local knowledge that women and men who milked and tended cows were resistant to smallpox because they had already contracted cutaneous cowpox from their animals.³

Jenner hypothesized that inoculation with cowpox would confer immunity to smallpox. In May 1796, he took fluid from an open cowpox sore from Sarah Helms and used it to vaccinate nine-year-old James Phipps. Within days the boy got sick with cowpox. In July, Jenner tried to inoculate his young patient with smallpox. No pocks erupted, and the boy remained unaffected by the procedure.²⁶

Jenner concluded that the boy had the same resistance to the dread disease that the Gloucestershire dairy workers enjoyed. In 1797, he read his results before the Royal Society, which decided against publishing it because of insufficient data.²⁵ At his own expense he summarized his observations on the resistance of 13 of his cowpox patients to smallpox infection and his vaccination experiment on young Phipps.²⁶ In a later edition published in 1801 he had vaccinated seven patients with cowpox and challenged four with inoculation with smallpox.

None became infected.²⁵

Jenner's numbers were still too small to be taken seriously by the medical mainstream in London. He had attracted a sizeable opposition who considered vaccination with cowpox as "unnatural and dangerous."²⁵ Cartoons lampooned the procedure depicting human patients with cows erupting from their arms and legs and horns growing from their foreheads. His critics said he was not the first to try the procedure; in 1805, Benjamin Jesty claimed he had vaccinated his wife and two sons in 1774, nearly a quarter century before Jenner's achievement.²⁵

Jenner tirelessly campaigned for the adoption of his procedure. In 1798, Henry Cline, another of Hunter's students, attempted to treat a boy with an infected hip by inoculating a sample of Jenner's vaccine. While the hip remained infected, Cline unintentionally made the child immune to inoculated smallpox.

Cline's accidental success was noted by two of Jenner's erstwhile opponents, George Pearson and William Woodville. The latter ran a smallpox hospital near the parish of St. Pancras just outside London. They began to vaccinate patients using cowpox from infected udders of cows in a nearby dairy.²⁵

In 1800, Woodville reported an experience of "about 2,000 persons."²⁶ None of his inoculated patients developed a disease that resembled smallpox. He tried to inoculate "upwards of 400 of the patients" for smallpox. More than 100 had a disease "so very slightly that it neither produced any perceptible indisposition nor pustules."²⁷

Others in England had taken up the procedure. According to Behbehani, by 1801, 100,000 persons had been vaccinated in Britain.²⁵

Within 10 years of its inception, the practice had spread throughout most of the world. Japan was the last major country to receive vaccinations, in 1849, because of its rigid policy of strict isolation from foreign commerce.²⁸

In 1800, a supply of the vaccine reached Constantinople, where the British ambassador to the Sublime Porte had his children vaccinated. Vaccination with cowpox thus returned to where it began nearly a century before as inoculation, a folk remedy practiced by a woman healer in a Turkish harem.

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