

From inoculation to vaccination: the fight against smallpox in Siena in the 18th and 19th centuries

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SUMMARY

Smallpox is a contagious viral disease. In the fight against smallpox, stimulation of the immune system by means of inoculation of human smallpox and subsequent vaccination constituted a very important step forward in the history of medicine. First reported in ancient Greece and in the Egypt of the Pharaohs, smallpox reappeared in the middle of the 16th century, becoming the leading endemic disease in the following century and periodically causing hundreds of thousands of deaths. In the 18th and 19th centuries, Europe was afflicted by

numerous epidemics. While their consequences in large urban centres are well known, we know little about the diffusion, morbidity and mortality of the disease in rural areas. To shed light on this issue, we scrutinised the main initial experiences of the use of inoculation in Siena and the scientific, healthcare, social and political consequences that stemmed from them.

Keywords: Smallpox inoculation, history of vaccination, Grand Duke Ferdinand III of Lorraine, Siena.

INTRODUCTION

Smallpox ("*variola*" in late Latin, derived from *varius*, meaning "varied, variable, mottled") is an acute, infectious, contagious and epidemic viral disease characterised by a typical vesiculo-pustular rash. Reported since ancient times, smallpox constantly reappeared after the middle of the 16th century, becoming the leading endemic disease in the following century [1].

It had a severe effect on society, striking younger age-groups in particular and impacting negatively on the reproduction of the population.

In the 18th and 19th centuries, smallpox was rife throughout Europe, being responsible for nu-

merous epidemics. While the consequences of these outbreaks in the large urban centres are well known, we know little or nothing about the diffusion, morbidity and mortality of the disease in rural areas. In the largest and most populous cities, where the risk of contagion was greatest, smallpox burst out in generalised epidemics at intervals of 5-10 years, as soon as a sufficiently large population of non-immunised residents was reconstituted.

Nevertheless, in comparison with the recurrent, devastating epidemics of plague that scourged the European continent, smallpox was often deemed to be of secondary importance.

During the 18th century, news came from England of a method of inoculating material from forms of human smallpox that were not particularly aggressive, and which conferred immunity to this serious disease [2]. This prompted the scientific community to discuss the possibility of a proph-

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ylaxis that might reduce contagion and even lead to eradication of the disease.

In 1713, Emanuel Timoni (1670-1718), a Greek doctor educated at Oxford, who served at the British Embassy in Constantinople, sent to the Royal Society in London a description of the method of variolation used in the East by the Circassians and Georgians, and by a few African populations: professionally trained individuals extracted pus from mature pustules on the body of a smallpox patient and inoculated it into a healthy subject through an incision in the arm or leg. Timoni's description was published in the Royal Society's Philosophical "Transactions" in 1714 [3].

Two years later, the Royal Society published *Nova et tuta variolas excitandi per transplantationem methodus, nuper inventa & in usum tracta*, a very detailed analysis of the eastern preventive practices written by Giacomo Pylarini (1659-1718), an Italian doctor and Consul for the Republic of Venice in Ismir.

In reality, however, the first known scientific account of these practices of immunisation date from 1675, when Thomas Bartholin (1616-1680), a pathologist at the University of Copenhagen and, subsequently, physician to the King of Denmark and Norway, Christian V, provided a scientific description of the technique of variolation, which had long been used in Asia, and published an article on variolation in Danish rural areas [3].

A fundamental role, however, was played by Mary Wortley Montagu, the wife of the English ambassador in Constantinople. She herself was left disfigured after contracting smallpox.

During her stay in the Ottoman Empire, she bore witness to the practice of inoculation against smallpox, or variolation, which she called "grafting" and which she described in many of her letters. Her personal experience, together with the diffusion of the writings by Timoni and Pylarini, led to her being invited by the College of Physicians in London to attend an experimental test in 1722. During this demonstration, Richard Mad, the King's physician, inoculated some inmates of Newgate prison who had been condemned to death; having survived this treatment, the prisoners had their lives spared. In addition, Lady Montagu had her second son vaccinated in the presence of the Royal Court, thereby eliciting the trust of the Royal family, some of whose members subsequently underwent variolation. After suffering a mild attack of smallpox, they all recovered.

A "great clamour" surrounding the issue of smallpox inoculation

A few decades later, in the middle of the 18th century, the debate over variolation spread to the states of the Italian peninsula, involving doctors and men of culture. This is mentioned by Pietro Verry in his article *Sull'innesto del vaiuolo*, published in 1766 on the pages of magazine "Il Caffè" [4]. Only a few months earlier, the poet Giuseppe Parini had written his ode *L'innesto del vaiuolo*, coming out in favour of variolation and the progress of science in general.

The members of the Academy of Sciences (also called *Accademia de' Fisiocritici*) in Siena were much involved in this debate.

The Academy was founded in 1691 by Pirro Maria Gabrielli, a teacher of theoretical Medicine and Botany at the University of Siena in order to "promote the Study of Natural Things with that noble and wise freedom of research and observation which is unable to desist until the truth is revealed". Indeed, the motto of the Academy was taken from a verse of Lucretius: "*Veris quod possit vincere falsa*", "(that which) by truth can confute the false" [5].

In 1761, the prestigious Academy devoted the first volume of its journal, which is still published today, precisely to the issue of variolation, and publicised the details of the reports on smallpox inoculation carried out in Siena between 1758 and 1760 [6]. It therefore became a "significant voice" in the debate between those in favour and those against the inoculation of Arabian smallpox.

Among the "Fisiocritici" themselves, however, dissenting voices were also raised, such as that of Ottavio Nerucci, a teacher of anatomy, who, at a July 1759 meeting of the Academy, presented his *Discorso sopra all'innesto vajolo*, in which he spoke against the practice of variolation, citing the high percentage of deaths among the persons treated and the high risk of recurrence [7].

To this were added several reservations of a theological nature; protecting people against the disease by means of inoculation was interpreted as an attempt to oppose divine Providence.

The volume published by the Fisiocritici was made up of a preface, which reported the first experiences of the method, and the descriptions provided by the physicians who had performed the procedure.

The first "experiment" was carried out in Siena in October 1755 and was prompted by the "zelo

dell' *Illustrissimo Signor Cav. Pannilini Girolamo, Vigilantissimo Rettore dello Spedale di S. Maria della Scala* [8, 9]. He summoned the physician Domenico Peverini of Città di Castello, who was "among the first to practice inoculation in Tuscany and the Papal State", to conduct an experiment on some «gittatelli», children placed in the care of the Hospital by their extremely poor parents.

The description provided is very detailed and testifies to the fact that variolation was frequently performed on orphans, illegitimate children and those cared for by charitable institutions.

We are told that the first subjects to undergo the procedure were three boys who, following the administration of a purgative and one day of rest, underwent inoculation by means of "three different needles smeared for this purpose with the rotten matter from a mild case of smallpox tending towards decline". "Soffrirono un Vajuolo assai benigno, il quale, dopo aver fatto il suo decorso felicemente a capo a diciassette giorni, prosciugate le bolle, lasciò loro solamente il contento d'aver pagato questo quasi indispensabile tributo, con tanto suo poco incomodo" [8].

This very favourable outcome prompted the Rector of the Hospital to proceed with a second inoculation on 19 August 1756; this time on 14 boys aged from 4 to 8 years and two girls, of 18 and 14 years of age, by the hand of the physician Leone Pagliai, some by means of incision, others by needle puncture. "Introdotta per via di tali operazioni il seminio del morbo, risvegliò in tutti il Vajuolo, il quale ebbe un corso felice, perciò che non fu accompagnato da sintomi cattivi nell'eruzione, né minacciò pericoli nella sua maturazione, né portò conseguenze di rimarco nel suo prosciugamento" [8]. In this case, too, the outcome of inoculation was favourable.

In the journal of the Academy, the description of these first two experiments, conducted at the Santa Maria della Scala Hospital, was followed by the reports of the "experimenting physicians", whom the Academy had asked to report on the various cases.

These so-called "detailed accounts" begin with the testimony of Dr. Francesco Caluri and refer to 20 procedures carried out by him in Siena from 1758 to 1760.

Caluri is remembered as "the first to have promoted and performed such an experiment for the private Houses of this city, and perhaps in greater number than any other physician, being himself

a firm and zealous advocate of the same". Caluri ends his case with the description of the "metodo che tiene per fare l'innesto del Vajuolo. Egli raccoglie primieramente la materia per l'innesto dalle bolle di Vajuolo d'ottima qualità, trapassate da parte a parte con un ago infilato con un filo di bambagia, il quale facilmente si inzuppa della marcia contenuta dentro le bolle nelle gambe ovvero nelle braccia del vaiolante. E lo conserva in un vaso d'argento di dentro dorato, per servirsene in appresso quando a lui bisogna fare gl'Innesti, e vi si pone un biglietto, nel quale è notato il tempo in cui questa materia è stata presa, da qual soggetto, e se è materia di Vajuolo innestato, ovvero naturale. Per fare l'innesto egli usa un leggerissimo taglio, che non passi la lunghezza di tre linee di Pollice parigino, da cui esca appena una gocciola di sangue. Questo taglio lo fa lungo il braccio nella parte esterna, sopra la piegatura del gomito. In ciascuno di questi tagli applica e adatta un filo d'eguale lunghezza della predetta preparata bambagia. E gli medica ponendovi sopra una foglia d'Edera Arborea di Gasparo Bauhino spalmata di lardo lavato, ovvero d'unguento rosato» [8].

There follow two stories of inoculations performed by Annibale Bastiani, a physician in San Casciano de' Bagni in 1759 during a raging epidemic of smallpox. Against the population's hostility towards the practice of inoculation, in order to demonstrate the efficacy of the method, he carried out variolation on his niece who had just turned three years old.

The description of an inoculation carried out in Siena by Buonaventura Perotti, a "worthy physician and Professor of Logic and Geometry at our University", is followed by an important report by Dr. Salvatore Galletti Castellucci on the inoculation of smallpox in 17 boys and 8 girls at the Regio Spedale di Santa Maria della Scala in Siena in 1760. On the morning of 2 June 1760, they were vaccinated in public by the "graft surgeon" Angelo Mancini. The technique adopted was that already described in the other cases. However, it is interesting that "the grafts are protected not only by the usual bandage, but also by glass cups shaped like walnut shells". The vaccines were then hospitalised in two public infirmaries, where "barometers and thermometers had been set up, as they might serve to regulate the environmental air", and the subjects were scrupulously supervised according to precise orders.

There is also an interesting account of the results of the "Analisi delle orine de' vajuolanti", analyses

conducted by Galletti Castellucci on urine from vaccinated subjects; the urine samples were mixed with various substances, such as tartaric oil, tincture of violet and spirit of vitriol.

It is noteworthy that, as public infirmaries were involved, "it was permissible for anyone whatever to see and observe the symptoms, course and outcome of the inoculated persons [...] so that all might satisfy their curiosity". Indeed, it was intended that the event should resonate far and wide and acquire propaganda value.

The tome ends with an appendix: a transcription of the speech made at the Academy's assembly of 25 June 1761 by the anatomist Pietro Tabarrani, who was famous for his studies of normal and pathological human anatomy, which he collected in his *Observationes anatomicae*, and who was Paolo Mascagni's mentor. Tabarrani reported the arguments and the doctrinal bases underpinning variolation, a practice that he regarded as the only means of protecting the population against the severe forms of the disease, which were almost always deadly; it was therefore "*una delle più utili scoperte che sieno mai fatte in prò della Umanità*" ("one of the most useful discoveries ever made in favour of Humanity") [8].

However, the experience of collective variolation in Siena did not end with the above-mentioned experiments.

In 1777, the physician Biagio Bartalini, who taught physics, chemistry and, later, natural history at the University of Siena, inoculated 11 children, aged from 2 to 10 years; once again, these subjects were chosen from among the foundlings from *Santa Maria della Scala*.

In his report, he wrote that inoculation was carried out by means of "needles that had been soaked in smallpox pus 12 days earlier; and the region selected was the space between the thumb and index finger of both hands. One of the 11 children did not present any manifestation; 10 contracted benign smallpox, which started around the 4th-5th day and resolved around the 18th-20th day; two died of sepsis on the 24th and 25th days" [10].

But certainly, the most interesting part of this report refers to the "strict measures of isolation to which both the little patients and the serving staff were subjected, unlike what was done in the case of the collective demonstration in 1760. The inoculations were performed in a farmhouse owned by the Hospital, situated in the country just outside

the city. The 13 children and two serving wenches had to undergo a veritable period of reclusion throughout the course of the disease, under the supervision of the doctors of the Hospital" [10].

Thus, in terms of the number of inoculations performed, and the organisation and method utilised, the Siena experience set a record in the battle against smallpox in the era prior to Jenner. This was made possible by the reformist policy implemented by those of the House of Lorraine who governed the Grand Duchy of Tuscany, and particularly by the progressist ideas of the Grand Duke Peter Leopold.

The preserving virtue of the vaccine

Forty years after the descriptions of smallpox inoculation published in the Acts of the Fisiocritici, Edward Anthony Jenner published *The Origin of the Vaccine Inoculation* [11].

Having observed that individuals who had recovered from cowpox ("bovine smallpox") did not contract "human smallpox", Jenner deduced that the former could confer protection against the latter. He therefore formulated the hypothesis - which he subsequently demonstrated successfully - that artificially infecting a healthy individual with matter from a pustule on the body of a patient with cowpox would immunise the individual against smallpox. As was later demonstrated, this immunising effect was due to the resemblance of the antigens of the two viruses; indeed, the antibodies elicited against the cowpox virus were also active against the smallpox virus. Thus, Jenner founded the principles of vaccination (from the Latin *vaccinus*, derived from *vacca*, meaning cow), a preventive therapy against smallpox that was more effective than inoculation.

Naturally, the practice advocated by Jenner also had its supporters and opponents, and a heated scientific and cultural debate ensued. "Inevitably, there were those who opposed a discovery that seemed to promise such a great, and indeed almost incredible, benefit. Among the objections raised was the specious contention that the discovery was too fresh to be able to assert that the vaccine might be the overwhelming antidote that could destroy smallpox, and that many other experiments would be needed before its preservative virtue could be established" [12].

The above statement is taken from the text of an *Esercizio Accademico di Lettere e Armi* (Academic

Exercise of Letters and Arms) recited in August 1804 on the occasion of the visit to Siena of Maria Luisa di Borbone, Infanta of Spain by birth, Queen of Etruria and reigning Duchess of Lucca, following her marriage to Louis I of Borbon-Parma. Given the importance of this illustrious visitor to Siena, the topic chosen for the Academic Exercise was “*una delle più strepitose scoperte moderne, quale si è la Vaccinazione*” (“one of the most clamorous modern discoveries: vaccination”) [12].

The event in honour of the august visitor opened with praise for the discovery of vaccination and for the work and the person of Jenner. “Before Jenner, whole countries had experienced vaccination and had enjoyed by chance a benefit that preserved them from smallpox. But only Jenner was struck by this effect and foresaw the destruction of one of humanity’s greatest scourges”. They continued with an amoebae song in which the differences between vaccination and the inoculation of human smallpox were compared, “concluding that the former far surpassed the latter” [12].

The diffusion in Siena of Jenner vaccination according to the method of Jenner

In the scientific environment of the Grand Duchy of Tuscany, a state that was enlightened and progressive, the new technique introduced by Edward Jenner met with great approval, though the procedure was limited by practical issues; indeed, in the early years, until the Milanese physician Luigi Sacco managed to identify some cases of cowpox in Lombardy, the material for vaccination had to be brought from England [13].

In Siena, Jenner’s ideas were promptly endorsed by Giacomo Barzellotti, a pupil of the anatomist Paolo Mascagni and a teacher of surgical institutions at the University of Siena and, after 1810, of legal medicine in Pisa. Being particularly interested in infectious diseases, he applied the new technique of cowpox vaccination in Siena from 1802 onwards [14].

The first successful inoculation of the cowpox vaccine in Siena was performed by Prof. Niccolò Semenzi in April 1804 on two children of the nobleman Domenico Placidi, using good quality pus brought from Florence. Having scarified the skin of the left arm of the older child, aged three years, Semenzi applied the purulent material. Subsequently, he took some of the pus from the pustule that had formed on the child’s arm and

used it to vaccinate the younger child, aged little more than two months. In the same period, vaccination according to Jenner’s method was tested on abandoned children in the hospitals, as well as on the children of noble families.

Nevertheless, the so-called experimental phase ended only when the French took over the government of Tuscany. In 1805, in the Principality of Lucca, Elisa Bonaparte had her own children vaccinated, thereby demonstrating that she complied with the obligation to vaccinate all babies within a few months of their birth.

In 1808, the Central Committee for Vaccination in the Department of Ombrone was instituted. This area, of which Siena was the main city, encompassed the southern part of Tuscany and was administered by Giacomo Barzellotti himself, who set the objective of “spreading the healthy practice of vaccination”. The Committee was made up of doctors, representatives of civil society and cultural institutions, and also of churchmen, in order to reassure the most timorous citizens that the Church approved of this practice.

In order to implement his programme of mass vaccination, which became obligatory in 1809, Barzellotti involved some 26 physicians from the Department, including some professors from the Medical School of Siena, such as Giuseppe Lodoli, Giovanni Niccolò Semenzi, Benedetto Sabatini, Girolamo Angeloni and Anastasio Gambini [15]. The Hospital of Santa Maria della Scala in Siena provided a dedicated facility where vaccination was carried out free of charge and infected material was kept. Subsequently, thanks to the large number of foundlings vaccinated, the hospital became the main provider of material for vaccination.

In the same year, the volume *La vaccina trionfante di tutti i suoi nemici e imposta alle nazioni dalla natura, dalla religione, dalla politica e dalle leggi civili* was published in Florence. This hailed the successful results yielded up to that time by vaccination according to the Jenner method, and explicitly rejected the previous practice of smallpox inoculation: “now that Providence has decreed that a man devoted to the public good should have the fortune to discover a very easy and safe means of ridding us totally of this scourge, human smallpox must on no account be inoculated” [16].

Between 1809 and 1811, the Committee coordinated by Barzellotti vaccinated about one seventh of

the inhabitants of the Department, and in particular an ever-growing number of children (3,083 in 1810, 5,140 in 1811, 5,872 in 1812), without, however, managing to reach all newborn babies. This great achievement enabled the spread of smallpox to be curbed, albeit without eradicating the disease. Indeed, a document published in 1812 contained a table that reported the monthly data on vaccinations carried out and their outcome: in 1810, 296 cases of smallpox and three deaths were recorded; the following year, 80 cases and two deaths occurred, but in 1812 the figures rose again, to 118 cases and six deaths [17]. In the following years, smallpox reappeared several times, causing numerous victims, particularly between 1818 and 1822 and in 1832 [18, 19].

“On the method of inoculating the Jenner vaccine”

In order to promote the “Jenner method” of vaccination and to “spread the healthy practice of inoculating the vaccine safely and successfully”, the Central Committee for Vaccination printed 300 copies of the booklet *Istruzione sul metodo d’inoculare il vajolo vaccino (Instructions on how to inoculate cowpox)*, which contained seven watercolour illustrations showing the development of the small lesion on a shoulder following inoculation of the vaccine [20].

Section I of the booklet dealt with the “*Character and Quality of Cowpox or Bovine Smallpox*” and provided a detailed description of the pustules caused by cowpox and a warning to doctors of the need to distinguish between “Bovine Smallpox” and “Spurious Smallpox”; indeed, unlike the former, this latter, if inoculated, did not safeguard the recipient against contracting the disease. “The pustule caused by true bovine smallpox is circular, somewhat flat and indented at the centre. That caused by spurious smallpox is neither flat nor indented in the middle; rather, it is pointed, like a pimple” [20]. In addition to these features, information was provided on the eruption and course of the pustules and on their content.

Section II, *Conditions required of subjects to be inoculated*, indicated the best periods for vaccination, the preference for vaccination during childhood, the possibility to carry out vaccination “without any predisposing or preparatory treatment” and the need to postpone vaccination if the subject manifested any febrile illness [20].

Section III was devoted to the *Method of inoculating Cowpox*. This emphasised the need to prepare the material for vaccination correctly and explained the method of inoculation: “once the virus has been drawn off by means of a grooved needle, as described above, the needle is inserted horizontally between the epidermis and the dermis of the subject to be vaccinated, as far as is needed to deposit it there” [20]. For this purpose, more than 100 needles “fluted for the inoculation of [bovine] smallpox” were produced in Siena; these needles were endowed with a special groove, so that the serum drawn from the udders of cows infected by cowpox could easily be inoculated into the patient’s shoulder.

The booklet also explained how to prepare the thread soaked in the virus-laden serum and how to conserve the virus “for several days, always active and good for inoculation”, and “the thread, needles and any other serum-soaked substance in order to perform further inoculations”: “in airtight glass tubes, away from light, humidity and excessive heat” [20].

Section IV, *Course and Phenomena of the Cowpox Inoculated*, described the formation of the pustule for the fourth - sometimes fifth or sixth - day after inoculation, with whitish edges and a dark patch in the centre, as could be seen in the illustrations accompanying the booklet. Over the next few days, the pustule resolved, leaving a crust which “normally drops off on about the 16th day of the course of the pustule, a simple scar remaining on the skin” [20]. Formation of the pustule was accompanied by few symptoms: specifically, a fever, which appeared about a week after inoculation and persisted for a couple of days.

This section of the booklet went on to describe the characteristics of the *Course and Phenomena of Spurious Smallpox*, which did not guarantee immunisation. The main difference that the physician could observe was that, in this case, “on the second day after inoculation, and sometimes even on the first day, inflammation is manifested at the point of inoculation, where the skin is raised in a pointed pustule, and never indented at the centre [...]. The eruption caused by spurious Smallpox is not usually limited to the site of inoculation; rather, similar pustules develop [...] over the whole body [...]. The symptoms accompanying spurious smallpox were: “a much higher fever, sometimes accompanied by vomiting, usually appear-

ing soon after the development of the pustule, severe headache, anxiety and, not infrequently, convulsive movements" [20].

The author then provided a useful table comparing the "True Bovine Smallpox" with the "Spurious form", and cited particular cases, such as that of a subject affected by "Human Smallpox Fever" shortly after the inoculation of Cowpox serum; Cowpox developed, but this did not stop the development of the more serious human smallpox. Finally, indications were provided on the *Treatment of Cowpox*, the course of which did not normally present severe symptoms, but only mild alterations.

The booklet ended with the following consideration: "Given its weighty and sure advantages, who could possibly impede or delay the adoption of this system of vaccinating all newborns? No one, of course, as no man could look with indifference and without remorse upon the reign of this woeful and terrible disease, namely Human Smallpox, when there is a safe and easy means of ridding us of it for ever" [20].

■ CONCLUSIONS

When the presence of the French in Tuscany came to an end and the throne of the Grand Duchy of Tuscany was restored to the House of Lorraine, the practice of vaccination suffered a slowdown, though without the conservative excesses of the Papal State, where it was actually prohibited. After May 1814, Barzellotti promptly petitioned the Grand Duke Ferdinand III of Lorraine to allow the Committee to continue the work it had begun under the brief French domination. His response was affirmative.

Thus, Siena and Tuscany as a whole had the great merit of being among the first to adopt the practice of inoculation and, subsequently, smallpox vaccination according to the Jenner method. Moreover, they participated in the scientific debate surrounding these practices and contributed to spreading the knowledge that underlies the principle of immunisation through vaccination. From the standpoint of public health, vaccination against smallpox certainly yielded important results. Nevertheless, despite the commitment of the *Prefecture of Ombrone*, the efforts of the *Central Committee for Vaccination*, and the support of the Grand Dukes of Lorraine after their restoration to

the throne of Tuscany, only one person out of seven was immunised against smallpox in the first half of the 19th century. This was clearly not sufficient to vanquish the disease, not least because the efficacy of the vaccine inoculated was limited in time.

Only after the unification of Italy, with the 1888 healthcare reform, did smallpox vaccination become obligatory for all children. Significant results then began to be achieved, and the way was paved to the eradication of a disease that had been the scourge of entire populations for centuries.

Conflict of interest

None to declare.

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- [20] Istruzione sul metodo d'inoculare il vajuolo vaccino, pubblicata dal Comitato Centrale di Vaccina del Dipartimento dell'Ombrone. Siena, Dai Torchi di Onorato Porri, 1809; 1-40.