

History and eradication of smallpox in Turkey



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Turkey has played a prominent role for the Western World in the prevention of disease from two different angles. The first is the İstanbul connection from where the variolation originated. The Ankara connection, on the other hand, provided the source for the modified *Vaccinia Virus Ankara* (MVA) as both the third generation smallpox vaccine and the recombinant vector for modern day vaccine development. In this article, the history of disease and eradication efforts both in the Ottoman Empire and in the Republic era of Turkey will be discussed with an emphasis on the worldwide significance of İstanbul and Ankara connections in the history of smallpox.

During the 600 years of Ottoman history smallpox was ever-present alongside other epidemics such as plague and cholera. The proximity of the Anatolian plateau to South-western Asia and major trade routes where it is believed to have originated from was probably the reason for its presence in Asia Minor since ancient times. Written records before the 15th Century are scarce and details of the disease in the Empire remain under-documented. Even after the 15th Century, record-keeping was inadequate due to a lack of understanding of infectious disease control and its importance in public health. The Ottoman Empire was represented at the *First International Sanitary Conference* in Paris (1851), which ended without any successful resolution to disease control. At the 13th International Sanitary Conference (1926), smallpox and typhus were recognised as diseases to be controlled with quarantine measures¹. Most documents related to the disease in the empire date back to 19th Century. While disease prevention and Jenner type vaccination started during the collapse of the empire, full eradication occurred only after the foundation of the Republic of Turkey.

Causative agent and short history

The causative agent of smallpox is the variola virus (*Orthopoxvirus*) within the family *Poxviridae*. Genomic studies indicate the

presence of two or three different clades of the virus². The date of origin of the virus is unknown. Although disease-indicating scars were detected on Egyptian mummies, the virus itself has never been identified³. So far the only molecular evidence for the existence of the virus was detected in 300-year-old Siberian mummies. Further analysis indicated the roots of the virus date back to 928 AD⁴; however, some historians take the origin back to 10,000 BC, speculating on its possible relationship with the cowpox virus⁵. On the other hand, Gubser and Smith⁶, following their studies on the DNA analysis of the virus, revealed a relationship between the virus and the camelpox virus: possibly these two viruses originated from the same ancestor. Babkin and Babkina⁷ suggested that the taterapox, camelpox and variola viruses originated from the same ancestor around the Horn of Africa and spread to East Africa through camel movements dating back 3500 years.

Manifesting itself with fever and flaky skin, the disease has four different clinical types: ordinary; (vaccine) modified; flat; and hemorrhagic smallpox². Strains resulting in varying degrees of manifestation have been identified as (i) the variola major resulting in 10–30% in death and (ii) the variola minor that results in <1% in death. Historical records show diseases similar to smallpox were transmitted by ancient Egyptians to Hittites (1350 BC), from there to Iran (430 BC), to Sicily (395 AD) and to China (48–49 AD), from Mesopotamia to Rome (165 AD) and from China to Korea (583 AD) and finally from Korea to Japan in 585 AD⁸. However, difficulties encountered in those days in distinguishing between diseases showing similar symptoms render the records vague in relation to smallpox. The first clinically valid record for distinguishing between smallpox and measles was achieved by the Iranian physician El-Razi (910 AD)⁹ (Box 1), who considered smallpox as a form of coagulation in children's blood.

Smallpox repeatedly arrived in Anatolia through the crusades (1096–1291) and spread through trade routes crossing the great Sahara and reaching East and West African ports¹⁰. In the early 16th Century, it became widespread in most European cities and with the first explorers it spread to Americas, Australia and Africa. With the Spanish conquistadors it was transmitted to the native population of Cuba and Hispaniola (today's Dominican Republic) resulting in the extermination of the Aztecs and Incas. These epidemics also resulted in the loss of work-force and subsequent introduction of African slaves in Americas¹¹. The Spanish and Portuguese, respectively, introduced the disease to Chile in 1554 and to Brazil in 1555. It

Box 1. Excerpts from Rhazes' *Smallpox and Measles Treatise*⁹

Now the Small-Pox arises when the blood putrefies and ferments, so that the superfluous vapours are thrown out of it, and it is changed from the blood of infants, which is like must, into the blood of young men, which is like wine perfectly ripened: and the Small-Pox itself may be compared to the fermentation and the hissing noise which take place in must at that time. And this is the reason why children, especially males, rarely escape being seized with this disease, because it is impossible to prevent the blood's changing from this state into its second state, just as it is impossible to prevent must (whose nature it is to make a hissing noise and to ferment,) from changing into the state which happens to it after its making a hissing noise and its fermentation. (p. 29)

You should know that the Measles which are of a deep red and violet colour are of a bad and fatal kind; and that the Small-Pox in which the pustules are yellow, hard, close together, confluent, numerous, and of a deep red or violet colour, and that kind which spreads like herpes, and gives the surface of the body the appearance of vibices, are all bad and mortal. (p. 94)

was introduced to North America by the British in 1617 with serious consequences to American Indian populations. The disease was reported in South Africa in 1713, in Australia in 1872, New Zealand and Pacific Islands from 1872 onwards, thus becoming a problem worldwide^{8,12,13}.

Following the 1953 proposal of Dr Brock Chisholm, General Secretary, WHO and the 1958 call by USSR delegation member Victor Zhdanov, WHO initiated a global eradication campaign in 1967. With the last case reported in October 1977 it was declared eradicated (reviewed in Fenner *et al.*⁸ and Henderson¹⁴) and the final report of the Global Commission, WHO for the Certification of Smallpox Eradication confirmed these results (1979). The final declaration was made by the World Health Assembly at the Geneva Meeting (1980) to the health ministers of all participant countries. Today limited amounts of variola strains are kept in two different WHO collaborative reference centres: (i) Centre for Diseases Control and Prevention (Atlanta, GA, USA); and (ii) The State Research Centre of Virology and Biotechnology (moved from Moscow to Novosibirsk, Russia after 1994)^{8,15}.

Smallpox prevention: variolation and vaccination

Variolation (or *inoculation*; during the 18th Century these two terms were used interchangeably) technique was based on the observation that the patients had gained immunity against a second infection. In ancient China, powdered variola crusts were used to infect healthy individuals via nasal inoculations or insufflations. In ancient India, intradermal inoculations of lesion material were practised. Although information prior to 1550 was reported to be speculative by Boylston¹⁶, in the Ottoman Empire similar practices to those in India were used (see below). Vaccination, on the other hand, was derived from the observation that human beings gained immunity against smallpox after exposure to cowpox. Materials taken from cowpox lesion were inoculated intradermally to healthy people. Similar administrations were carried out in England on a

popular level, which was later given a scientific basis by Edward Jenner in 1796 (reviewed in Boylston¹⁶ and Bazin¹⁷).

Smallpox and variolation in Ottoman times

The evidence of disease existence near Anatolia dates back to the Elephant War (570 AD). The arrival of the disease in Constantinople dates back to 12th Century and important evidence can be found in the poem of Theodore Prodromos:

The body is heated violently through with extraordinary torches from the fever. . . little by little [the pimples] gradually on the seventh day become murderous pustules. Have you ever seen a violent shower of rain coming down on a lake, how the entire surface of the lake swells up on account of the closely packed bubbles? (cited in Hopkins¹⁸, p. 27)

Evidence of the application of inoculation technique in Ottoman Empire can be found in the letters of two Greek Physicians. These two letters written by Emanuel Timonis (born in Chios, Greece of Italian parents; family physician to the British Ambassador to the Porte, Sir Robert Sutton, and to his successor, Lord Edward Wortley Montagu); and Jacob Pylarini (a native of Cephalonia and a graduate of Padua in both law and medicine, previously, physician to Tsar Peter the Great in Russia, practised in İstanbul and served as Venetian Consul at Smyrna) were presented to the British Royal Society¹⁹. Both physicians witnessed the application of inoculation technique, and also administered it themselves during the smallpox outbreak in Constantinople in 1701. Also, Timonis later sent a communication to the Royal Society for the meeting in May 1714, describing in detail how to collect variola crust, when to sample, how to preserve and apply²⁰ (Box 2).

According to Pylarini, the inoculation technique was introduced to Constantinople by a Greek lady in 1660 that was welcomed by the Christian population, yet declined by the Moslem population of the city due to their belief²¹:

The Turks alone, so addicted are they to their predestinarian notions, and so riveted to ancient prejudices, neglect to reap any advantage from it.

Box 2. Excerpts from Emanuel Timonis' Communication read by John Woodward²⁰

The writer of this ingenious discourse observes, in the first place, that the Circassians, Georgians, and other Asiatics, have introduced this practice of procuring the smallpox by a sort of inoculation, for about the space of forty years, among the Turks and others at Constantinople.

That although at first the more prudent were very cautious in the use of this practice; yet the happy success it has found to have in thousands of subjects for these eight years past, has put it out of all suspicion and doubt; since the operation, having been performed on persons of all ages, sexes, and different temperaments and even in the worst constitution of the air, yet none have been found to die of the smallpox; when at the same time it was very mortal when it seized the patient the common way, of which half the affected dyed. This he attests upon his own observation.

Next he observes, they that have this inoculation practised upon them are subject to very slight symptoms, some being scarce sensible they are ill or sick; and what is valued by the fair, it never leaves any scars or pits in the face.

The method of the operation is thus. Choice being made a proper contagion, the matter of the pustules is to be communicated to the person proposed to take the infection; whence it has metaphorically, the name of incision or inoculation. For this purpose they make choice of some boy, or young lady, of a found healthy temperament, that is seized with the common smallpox (of the distinct, not flux fort) on the twelfth or thirteenth day from the beginning of his sickness; they with a needle prick the tubercles (chiefly those on the shins and hams) and press out the matter coming from them into some convenient vessel of glass, or the like, to receive it; it is convenient to wash and clean the vessel first with warm water: a convenient quantity of this matter being thus collected, is to be stopped close, and kept warm in the bosom of the person that carries it, and, as soon as may be, brought to the place of the expecting future patient.

The patient therefore being in a warm chamber, the operator is to make several little wounds with a needle, in one, two or more places of the skin, till some drops of blood follow, and immediately drop out some drops of the matter in the glass, and mix it well with the blood issuing out; one drop of the matter is sufficient for each place pricked. These punctures are made indifferently in any of the fleshy parts, but succeed best in the muscles of the arm or radius. . .

Box 3. Excerpts from Patrick Russel's communication²²

. . . About nine or ten years ago, while on a visit at a Turkish Harem, a lady happened to Express much anxiety for an only child, who had not yet had the Smallpox; the distemper at that time being frequent in the city. None of the ladies in the company had ever heard of inoculation; so that, having once mentioned it, I found myself obliged to enter into a detail of the operation, and of the peculiar advantages of it. Among the female servants in the chamber was an old Bedouin, who having heard me with great attention, assured the ladies, that my account was upon the whole a just one, only that I did not seem so well to understand the way of performing the operation, which she asserted should be done not with lancet, but with a needle; she herself had received the disease in that matter, when a child; had in her time inoculated many; adding moreover, that the practice was well known to the Arabs, and that they termed it buying the Smallpox.

For these several years past, very few slaves have been brought from Georgia. From what I could collect among those already here, who remember anything of their own country, inoculation was well known there: I have seen several old Georgian women, who had been inoculated, when children, in their father's houses.

In Armenia, the Turcoman tribes, as well as the Armenian Christians, have practised inoculation since the memory of man; but, like the Arabs, are able to give no account of its first introduction among them.

It has already been mentioned, that the Turks at Bagdad and Mousul make no scruple to inoculate their children. I have seen also some Turkish strangers here, who had been inoculated at Erzeroon. Hence it is probable that the Turks, in other parts of the Ottoman empire, do not merely, as fatalists, reject inoculation; but that other considerations, which have influence in countries where fatalists are ridiculed or anathematized, concur likewise in Turkey, to oppose the reception of a practice to beneficial to mankind.

Despite these early communications, European interest in the inoculation technique in Ottoman Empire was achieved after the efforts of Lady Montagu, Dr Charles Maitland and Sir Hans Sloane in Britain (see below). On the other hand, the technique was used to apply partly in the Empire by the Moslem population²² (Box 3). The Ottoman Court also endured the disease including the sultans

themselves as did their children and wives. Sultans Ahmet I (1604), Ahmet III (1708) and Abdülmecid (before 1839) all had the disease²³. Daughters of Murad III (1599) and Abdülhamid I (1782) and the sons of Mustafa III (1771) and Mahmut (1825) both died of the disease although the sons of Abdülhamid I and Mahmut both survived the infection (including the crown prince Mehmet

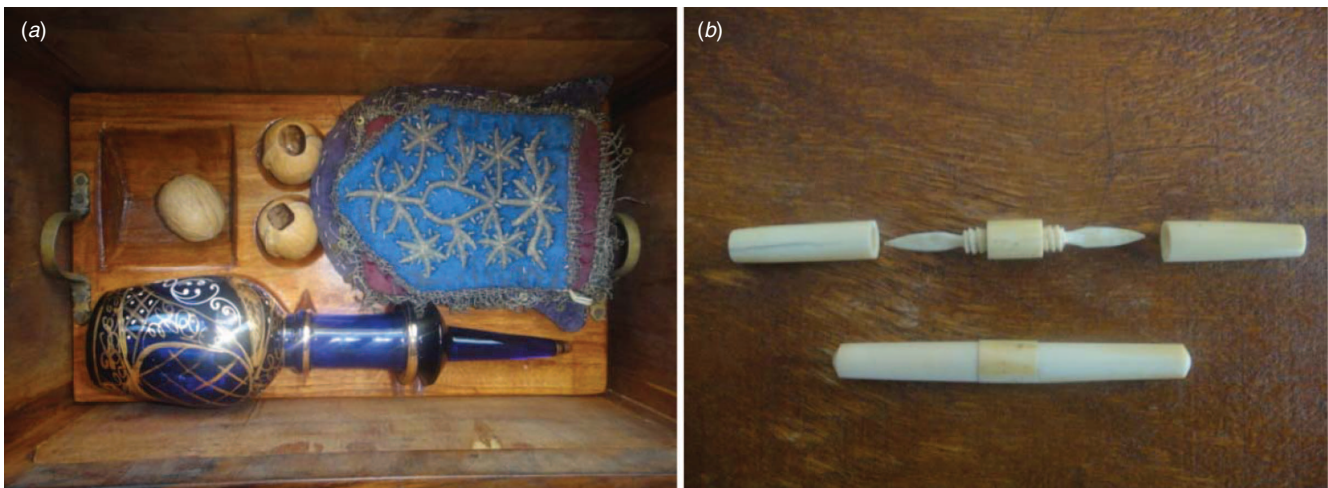


Figure 1. (a) Vaccinator's bag of collection for vaccine material, rosewater bottle and walnut shells used to hydrate dried vaccine material, (b) ivory vaccination needle, or *vaccine pen* (19th Century) (Courtesy of Prof. Dr İler Uzel).

Nusret)^{18,23,24}. Such information indicates the lack of any inoculation practice in the Ottoman Court although it was practised in other parts of the Empire.

Smallpox was experienced in İstanbul as an epidemic in 1701, 1706, 1825 (extension of the European pandemic between 1824–1829), 1845, 1871 and 1877–1878 as well as small outbreaks of 1881, 1887, 1890, 1891, 1894, 1908, 1809 and 1923. İstanbul had always been the most crowded city of the Empire and most epidemics hit this city first, although outbreaks occurred haphazardly in provincial towns from time to time (e.g. 1847–1887)²⁵. The first records of inoculation practice in the Ottoman Court derives from the palace physician İsmail Pasha's lithographic book *Menafîül'etfal* (Benefits for Children)^{23,25}. In this book, an Anatolian man arrives in İstanbul in 1679 and applies the inoculation technique to children.

The inoculation technique spread with the Seljuks (1055) from the Caucasus region to Asia Minor and subsequently passed on to Ottomans²³. The technique was mostly applied by house women who dried samples of variola crusts inside walnut shells, which were applied to healthy individuals inter-dermally after re-suspension using rose water in May (Figure 1). Inoculation needles and implements have also been through series of changes, used also for vaccination, and the current design bifurcated needle was introduced in 1965 (reviewed in Baxby²⁶).

The İstanbul Connection

British interest in the inoculation technique dates back to the appointment of Lord Edward Wortley Montagu as the Extraordinary Ambassador to Constantinople in 1716. His wife Lady Montagu was already a victim and carried scars on her face (1715): she had also lost his brother to the disease (1713). A keen observer and a writer, Lady

Montagu first mentioned the inoculation technique to her friend Sarah Chiswell (who later died of the disease in 1726), in her letter posted from Adrianople on the way to Constantinople (1717)^{18,27} (Box 4). Following her observations in Constantinople, she got her 5-year-old son inoculated with the support of the Embassy doctor Maitland (1718)²⁸. On her return to England, she also got her 3-year-old daughter inoculated during the 1721 epidemic in England. This application was the first example of the inoculation technique in Britain, generating interest widely among aristocrats. To test the safety of the inoculation technique before it was given to the daughter of Prince of Wales, Princess Caroline, six prisoners from Newgate were inoculated with the virus and the success of the application led to the release of these prisoners^{28–30}.

Upon these trials, and several others in private families, the late queen, then princess of Wales... sent for me to ask my opinion of the inoculation of the princesses. I told her Royal highness, that by what appeared in the several assays, it seemed to be a method to secure people from the great dangers attending that distemper in the natural way. (Sloane and Birch³¹)

Princess Caroline, following her successful inoculation, also had her 11- (Amelia) and 9- (Caroline) year-old daughters inoculated.

Smallpox and vaccination in Ottoman and Republic era of Turkey

Due to lack of interest in the inoculation technique at the Ottoman Court applications were conducted regionally. Jenner's definition of vaccination (*An Inquiry into the Causes and Effects of the Variolae Vaccinae, or Cow-pox*, 1798³²) was generated in the western medical environment of inoculation^{17,33}. His book titled *Inquiry* was printed in England in multiple copies from 1798 and new copies were also produced in Geneva, Hannover and Wien. Reprints of the

Box 4. Excerpts from Lady Montagu's letters²⁷

To Sarah Chiswell,

Adrianople, 1 April 1717

Apropos of distempers I am going to tell you a thing that I am sure will make you wish yourself here. The smallpox, so fatal and so general amongst us, is here entirely harmless by the invention to engrafting, which is the term they give it. There is a set of old women who make it their business to perform the operation. Every autumn in the month of September when the great heat is abated, people send one another to know if any of their family has a mind to have the smallpox. They make parties for this purpose and when they are met (commonly fifteen or sixteen together) the old woman comes with a nutshell full of the matter of the best sort of smallpox, and asks what veins you please to have opened. She immediately rips open 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 venom as can lie upon the head of her needle, and after binds up the little wound with a hollow bit of shell, and in this manner opens for or five veins. The Grecians have commonly the superstition of opening one in the middle of the forehead, in each arm and on the breast to mark the sign of the cross, but this has a very ill effect, all this wounds leaving little scars, and is not done by those that are not superstitious, who choose to have them in the legs or that part of the arm that is concealed. The children or young patients play together all the rest of the day, and are in perfect health until the eighth. Then the fever begins to seize them and they keep their beds two days, very seldom three. They have very rarely above twenty or thirty in their faces, which never mark, and in eight days' time they are as well as before their illness. Where they are wounded there remains running sores during the distemper which I don't doubt is a great relief to it. Every year thousands undergo this operation, and the French Ambassador says pleasantly that they take the smallpox here by way of diversion, as they take the waters in other countries. There is no example of any one that has died in it, and you may believe I am well satisfied of the safety of the experiment, since I intend to try it on my dear little son. I am patriot enough to take pains to bring this useful invention into fashion in England and I should not fail to write to some of our doctors very particularly about it if I knew anyone of them that I thought had virtue enough to destroy such a considerable branch of their revenue for the good of mankind. But that distemper is too beneficial to them not to expose to all their resentment the hardy weight that should undertake to put an end to it. Perhaps, if I live to return, I may, however, have courage to war with them. Upon this occasion admire the heroism in the heart of your friend, etc.

To Wortley,

Constantinople, 23 March 1718

... The boy was engrafted last Tuesday, and is at this time singing and playing and very impatient for his supper.

... I cannot engraft the girl; her nurse has not had the smallpox.

To Wortley,

Constantinople, 1 April 1718

Your son is as well as can be expected, and I hope past all manner of danger.

original article were in free circulation as well translations in various languages allowing the method to be introduced in many countries¹⁷. The Ottomans first read *Inquiry* in 1801, as Giuseppe Marchal's Italian text was translated into Turkish by Mustafa Behçet Efendi with the title *Risale-i Telkib-i Bakari*^{25,34}. Subsequently, in 1811, Şanizade Ataulhâh Efendi conducted a series of tests on his farm animals at Ayasağâ and made a number of recommendations to Sultan Mahmut II such as a new vaccination centre and mass vaccinations while dedicating a chapter of his book to this practice²³. Vaccination might have been known to the Ottomans since 1810, however, Sultan Abdülmeçid (born 1823, died 1861) had caught smallpox in infancy and this was probably the reason why caution was exercised in his administration. According to Walsh³⁵, the first instance of vaccination was at the time of Sultan Mahmut II, who allowed it to be administered to his children (by a French physician) after the death of his the eldest son in 1825, hence its acceptance by the rest of his subjects. Initially, imported vaccines were used throughout the empire however small amounts from Europe were insufficient to meet the demand and vaccination teams preserved quality lesion material after successful vaccinations of upper class

children²⁵. In fact, the first vaccination took place at the British Embassy in İstanbul, as a Swiss man, Jean de Carro, had secured a small amount of Italian vaccination material, which was taken to İstanbul by some friends of the British Ambassador (Thomas Bruce; Lord Elgin) and administered to the children at the Embassy in December 1800²⁸. Vaccination material supplied by de Carro reached as far as Bombay via Greece and Bagdad¹⁷.

The first imperial decree regarding smallpox vaccine was issued on 20 May 1840²³. Religious concerns expressed in Europe earlier^{36,37} were also voiced in İstanbul at this time and only after a fatwa by the Şeyhülislam declaring vaccination permissible according to the Islamic law, large-scale vaccination campaigns started at no cost to the public²³. Regardless, vaccine production did not start until 1872, and imported vaccine material was administered only on critical population segments such as military cadets or in cases of emergency, by vaccination teams from İstanbul²⁵. Vaccination professionals were trained at the School for Vaccinators within the vaccine production centre from 17 May 1898, which graduated 319 professional vaccinators until 1903²³. By 1910 village school teachers and

midwives were also admitted to this school and its name was later changed to Minor Health Officers School as minor surgery operations also became part of the school's curriculum. Despite interruptions to the program, the school stayed in existence until 1950s and trained countless vaccinators²³.

The Ottoman Empire made it an obligatory vaccine for children of school age and the *Regulation on Smallpox Vaccination* of 8 July 1885 denied school registration to those unable to produce any proof of vaccination. The second *Regulation on Smallpox Vaccination* of 21 July 1894 also dictated that newborns be vaccinated within six months of birth²³. Updates to the regulation were incorporated in 1904 and 1915 increasing the number of vaccinations for an individual to 3 by age 19. The common practice of human to human vaccination (variolation) also became strictly prohibited²³. Despite regulatory effort, the administration of smallpox vaccine hardly reached all corners of the empire, and a report titled *Reconstruction in Turkey* by the American Committee of Armenian and Syrian Relief in 1918 confirms the lack of systematic campaigns: 'Vaccination is practised in larger towns and cities and in the army. Only in the army is it systematically carried out.'³⁵ (cited in Özdemir³⁸, p. 224). After the foundation of the Republic, the Public Health Bill came into force (24 April 1930) and made smallpox vaccination obligatory for all citizens²³.

The Ottoman production of smallpox vaccine started with the reopening of The Imperial Vaccine Production Centre (*Telkibane*) in 1892 in 1892 and domestic production was distributed all over the country bringing an end to imported vaccines²⁵. An inspectorate was established in 1890–1891 and Colonel Hüseyin Rahmi Bey became the first vaccine inspector (Figure 2). Later in 1894, the vaccine production centre was allocated a proper building during senior Inspector Remzi Bey's time (1895–97). After his death in 1896, the production centre directors were Dr Hasan Zühtü Nazif Bey (1896–1897) and Dr Rifat Hüsametdin Pasha (1897–1913) respectively²⁴.

After the Young Turk Revolution of 1908, it became the 'Ottoman Vaccination Centre'²³. In the years following, the centre directors were Dr Kemal Muhtar Bey (1913–1920), Dr Rifat Hüsametdin Pasha again (1920–1922), Dr Kemal Muhtar Bey again (February 1922 to September 1922), Dr Şerafettin Mustafa (in the Republican era Dr Şerafettin Mustafa Kam) (1923–1934). Between 1892 and 1913 a total of 7,260,784 tubes; and between 1914 and 1919 a total number of 27,688,449 tubes of vaccine were produced at this centre. During the War of Independence, The Red Crescent transported vaccines from this production centre to Anatolia; 566,000 in 1920, 1,770,000 in 1921 and 1,283,000 tubes in 1922 respectively. Between 1892 and 1923 inoculation viruses for



Figure 2. Cover page of the *Servet-i Fünun* magazine published on 17 November 1892. Hüseyin Remzi Bey (in the middle) and *Telkibane* staff are seen together with the calf used at the centre for vaccine production (courtesy of Volkan Gülçek).

vaccines were imported from Paris³⁹ even though information regarding the doses contained is unavailable. Vaccine standardisation until the 1960s was unknown; and in this period, 10-dose-tubes or 250 (5 mL) and 500 (10 mL) dose bottles were in circulation³⁹.

The Vaccine Production Centre moved to Ankara in 1934 and the production continued under supervisions of Dr Şerafettin Mustafa Kam (1934–1936), Dr Niyazi Erzin (1936–1942), Dr Nusret Fişek (1942–1947), Prof. Dr Zühdi Berke (1947–1962), Dr Elhan Özlüarda (1962–1977) and virologist Çiğdem Artuk until the production ended in 1981 (Mustafa Hacıömeroğlu, personal communication, 2004)²⁴. Vaccine production occurred also elsewhere in the empire such as Mecca, Basra, Sana'a, Bagdad and Damascus, and in Sivas, a production centre for rabies and smallpox vaccine was also established²⁴. However, these centres were short-lived and the main centre for production remained İstanbul. After the foundation of the Republic in 1923, records regarding smallpox improved considerably: the official number of infected cases and resulting deaths are provided in Table 1.

Table 1. The number of infected cases and resulting deaths during Republican Era.

Years	Infected	Deaths
1925	483	69
1926	429	117
1927	99	6
1928	47	8
1929	1746	870
1930	830	160
1931–1939	2524	727
1940	958	130
1942	1871	174
1943	12395	1380
1944	6093	678
1951	152	3
1957 ^A	128	7

^AThe last smallpox outbreak.

As a result, between 1925–1957 a total of 27,755 infected cases and 4039 deaths were reported^{38,40,41}. No smallpox infection was seen in Turkey after 1957 and the vaccine production came to an end in 1981 (Çiğdem Artuk, personal communication, 2004).

The Ankara Connection

As mentioned above, following the eradication of smallpox, only two collaborative reference centres recognised by WHO are officially entitled to hold live variola strains, however it is not known whether unauthorised laboratories have any holdings. Since the 1980s, smallpox vaccination has come to a stop but the majority of the world population is not immune to smallpox, nor to cross-infection with animal orthopoxviruses and concerted efforts to specifically develop vaccines against smallpox and all poxviruses have intensified⁴². Limitations of space do not allow further details here but the *Modified Vaccinia Virus Ankara* (MVA), which led to the development of (Imvamune[®]), a third generation vaccine will be explained. The origin of MVA dates back to the CVA dermovaccinia strain⁴³, which was the cross strain of those obtained from donkeys and calves. Dr Şerafettin Mustafa (Kam) claimed to have produced these specific strains (maintained between donkeys and calves) first at İstanbul Vaccine Production Centre in 1932⁴⁴. For the maintenance of the vaccine strain donkeys and calves were used and during the eradication campaigns seed cultures were obtained from WHO

(Elhan Özlüarda, personal communication, 2005). Fenner *et al.*⁸ indicates the use of the Paris strain for vaccine production in Turkey between 1968 to 1971. German researchers took the CVA dermovaccinia strain to Germany and started its passage in 1958 using chicken embryo fibroblast cultures^{43,45}. After 300 passages changes in the plaque morphology of the strain were observed and at its 516th passage it was named MVA to differentiate it from other attenuated vaccine strains. The strain MVA was created as result of 574 dilution passage of the attenuated strain^{43,45}.

Complete genomic sequence analysis of the strain has been carried out revealing circa 15% gene loss compared to the original genome^{46,47}. MVA fails to replicate in human cells, which sets it apart from vaccinia virus. Thus, it poses no risk of spreading in or among the carriers, and gains importance in vaccine research as well as a vector delivery system^{48,49}. In the 1970s, MVA was used in clinical trials and regardless of minor local or general reactions, the resulting standard vaccinia virus reduced the diameter of skin lesions proving to be safe for human use⁵⁰. However, it should be stressed that this vaccine has not been tested against a major outbreak of smallpox so far. According to some writers^{51–53} MVA vaccine was tested on over 100,000 individuals in Germany and in Turkey without any complications, yet information about its use in Turkey is awaiting confirmation (Elhan Özlüarda, personal communication, 2005)^{54,55}. In Bayern, Germany, Gerner *et al.*⁵⁶ also mention the administration of this vaccine to around 140,000 children in the mid-1970s but there is no confirmation that this vaccine, produced by the Bavarian Vaccine Institute, reached Turkey.

Conclusions

In her review of the Ottoman Physicians and Medical Sciences, Historian of Medicine, San mentions the lack of data on the capabilities of the Ottomans in generating theory and their interest in the generation of new knowledge via research⁵⁷. Most medical reports produced in the Ottoman era were based on medical practice rather than the philosophical background or clinical observations, which was also the case in dealing with smallpox throughout the empire. Ottoman medical circles had no interest, even at the level of intellectual curiosity, in inoculation that was applied widely among the Sultan's subjects. Necessity led them to resort to vaccination as a novel technique in the 19th Century. Finally, due to the global quest for a better understanding of the nature of what causes the disease, they distanced themselves from Islamic traditions (Divine Wisdom) and Galenic understanding of diseases and for the first time in 1885 the vaccine was only applied to children²³ whereas it was compulsory in many other countries long before it was applied in the Ottoman Empire (Bavaria, 1807; Denmark, 1810;

Norway, 1811; Russia 1812)¹⁸. Although it is still unclear how German scientists obtained the strain that resulted in the development of the MVA, the Republican era of Turkey used contemporary scientific principles for disease prevention and eradication.

Acknowledgements

The author thanks Prof. Dr Zayre Erturan (İstanbul University, İstanbul Medical Faculty, Department of Medical Microbiology) for translations from German to Turkish.

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Biography

Prof. Osman Şadi Yenen (MD) is a graduate of İstanbul University, Medical Faculty (1974). Until 1997 he served as medical personnel in the Turkish Naval Forces, at Gülhane Military Medical Academy (GMMA), Ankara and at GMMA Teaching Hospital in İstanbul respectively as an expert of Infectious diseases and clinical microbiology. He was appointed as a full professor at the İstanbul University, Medical Faculty in 1997 and currently serves as a teaching academic at the Department of Microbiology, Virology and Immunology of the same faculty. He has over 100 peer-reviewed publications both in Turkish and English. He served as the secretary and the president of the Turkish Society for Clinical Microbiology and Infectious Diseases (KLİMİK) and was the co-convenor of the 11th European Congress on Clinical Microbiology and Infectious Diseases held in İstanbul (ECMID 1–4 April 2001) as well as being part of the organisation of many international conferences took place in Turkey including the IUMS in 2008.

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