

OVERVIEW

The Spanish Influenza Pandemic: a lesson from history 100 years after 1918

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Keywords

History of Pandemic • Flu • Public Health • Mortality rate

Summary

In Europe in 1918, influenza spread through Spain, France, Great Britain and Italy, causing havoc with military operations during the First World War. The influenza pandemic of 1918 killed more than 50 million people worldwide. In addition, its socioeconomic consequences were huge.

“Spanish flu”, as the infection was dubbed, hit different age-groups, displaying a so-called “W-trend”, typically with two spikes in children and the elderly. However, healthy young adults were also affected.

In order to avoid alarming the public, several local health authorities refused to reveal the numbers of people affected and deaths. Consequently, it was very difficult to assess the impact of the disease at the time.

Although official communications issued by health authorities worldwide expressed certainty about the etiology of the infection, in laboratories it was not always possible to isolate the famous

Pfeiffer’s bacillus, which was, at that time, deemed to be the cause of influenza.

The first official preventive actions were implemented in August 1918; these included the obligatory notification of suspected cases and the surveillance of communities such as day-schools, boarding schools and barracks.

Identifying suspected cases through surveillance, and voluntary and/or mandatory quarantine or isolation, enabled the spread of Spanish flu to be curbed. At that time, these public health measures were the only effective weapons against the disease, as no vaccines or antivirals were available.

Virological and bacteriological analysis of preserved samples from infected soldiers and other young people who died during the pandemic period is a major step toward a better understanding of this pandemic and of how to prepare for future pandemics.

War and disease: the spread of the global influenza pandemic

On March 4, 1918, Albert Gitchel, a cook at Camp Fuston in Kansas, was afflicted by coughing, fever and headaches. His was one of the first established cases in the history of the so-called Spanish flu. Within three weeks, 1100 soldiers had been hospitalized, and thousands more were affected [1].

In Europe, the disease spread through France, Great Britain, Italy and Spain, causing havoc with First World War military operations. Three quarters of French troops and more than half of British troops fell ill in the spring of 1918. In May, the flu hit North Africa, and then Bombay in India; in June, the first cases were recorded in China, and in July in Australia.

This first wave is not universally regarded as influenza; the symptoms were similar to those of flu, but the illness was too mild and short-lasting, and mortality rates were similar to those seen in seasonal outbreaks of influenza [2].

In August, a deadly second wave of the Spanish pandemic ensued. This was probably caused by a mutated strain of the virus, which was carried from the port city of Plymouth in south-western England by ships bound

for Freetown in Sierra Leone and Boston in the United States. From Boston and Freetown, and from Brest in France, it followed the movements of the armies.

This second wave lasted almost six weeks, spreading from North America to Central and South America, from Freetown to West Africa and South Africa in September, and reaching the Horn of Africa in November. By the end of September, the flu had spread to almost all Europe, including Poland and Russia. From Russia the epidemic spread throughout northern Asia, arrived in India in September, and in October it flared up again in China. In New York, the epidemic was declared to be over on 5th November, while in Europe it persisted, owing to the food and fuel shortages caused by the war. Most cases of illness and death due to the pandemic occurred during the second wave [3].

Deadly clusters of symptoms were recorded, including nasal hemorrhage, pneumonia, encephalitis, temperatures of up to 40°C, nephritis-like blood-streaked urine, and coma [4]. While the new virus struck military personnel, influencing war strategies, it did not spare those who lived in privileged conditions, one of the most famous cases being that of the King of Spain, Alfonso XIII, who was certainly not afflicted by the privations of the war.

By December 1918, much of the world was once again flu-free, and in early 1919 Australia lifted its quarantine measures. However, in the austral summer of 1918-1919, more than 12,000 Australians were hit by the third wave of the disease. In the last week of January 1919, the third wave reached New York, and Paris was hit during the post-war peace negotiations. Overall, fewer people were affected by the disease during the final influenza wave. Nevertheless, mortality rates are believed to have been just as high as during the second wave [5]. In May 1919, this third pandemic was declared finished in the northern hemisphere. In Japan, however, the third epidemic broke out at the end of 1919 and ended in 1920.

Looking for the Spanish flu bacillus

Although official communications issued by health authorities worldwide expressed certainty about the etiology of the infection, in laboratories it was not always possible to isolate the famous Pfeiffer's bacillus, the *Haemophilus influenzae* bacterium first identified by the renowned German biologist in the nasal mucus of a patient in 1889, which, at the time, was considered to be the causal agent of influenza [6]. In October 1918, Nicolle and Lebaillly, scientists at the Pasteur institute, first advanced the hypothesis that the pathogen responsible for the flu was an infectious agent of infinitesimal dimensions: a virus. Its immuno-pathological effects transiently increased susceptibility to ultimately lethal secondary bacterial pneumonia and other co-infections, such as measles and malaria, or co-morbidities such as malnutrition or obesity [7, 8].

The Spanish flu hit different age-groups, displaying a so-called "W-trend", with infections typically peaking in children and the elderly, with an intermediate spike in healthy young adults. In these last cases, lack of pre-existing virus-specific and/or cross-reactive antibodies and cellular immunity probably contributed to the high attack rate and rapid spread of the 1918 H1N1 virus, and to that "cytokine storm" which ultimately destroyed the lungs. Only in 1930 was the flu pandemic rightly attributed to a virus, and in 1933 the first human influenza virus was isolated [9].

Public health measures to control the disease

There was no cure for the disease; it could only be fought with symptomatic treatments and improvised remedies. Moreover, the return of soldiers from the war fronts, the migration of refugees and the mobility of women engaged in extra-domestic activities had favored the rapid spread of the virus since the onset of the first pandemic wave. Preventive public health measures were therefore essential, in order to try to stem the spread of the disease [10].

The first official preventive measures were implemented in August 1918; these included the obligatory notifica-

tion of suspected cases, and the surveillance of communities such as day-schools, boarding schools and barracks. In October 1918, local authorities in several European countries strengthened these general provisions by adding further measures, for instance the closure of public meeting places, such as theaters, and the suspension of public meetings. In addition, long church sermons were prohibited and Sunday instruction was to last no more than five minutes.

Street cleaning and the disinfection of public spaces, such as churches, cinemas, theaters and workshops, were considered to be cornerstones in controlling the spread of Spanish flu, in addition to banning crowds outside shops and limiting the number of passengers on public transport. However, they did not prove very effective.

Among public health interventions, local health departments distributed free soap and provided clean water for the less wealthy; services for the removal of human waste, the regulation of toilets, and the inspection of milk and other food products were organized; spitting in the street was forbidden, which determined the spread of pocket spittoons, and announcements in newspapers and leaflets advertised the therapeutic virtues of water.

To simplify mortuary police services, many administrations in the worst affected centers in Italy set up collection points for corpses and abolished all the rituals that accompanied death.

In addition, identifying cases of illness through surveillance, and voluntary and/or mandatory quarantine or isolation, also helped to curb the spread of Spanish flu, in a period in which no effective vaccines or antivirals were available.

The silence of the press: the censored Spanish flu

As Spain was neutral in the First World War, newspapers there were free to report the devastating effects that the 1918 pandemic virus was having in that country. Thus, it was generally perceived that the pandemic had originated in Spain, and the infection was incorrectly dubbed "Spanish flu" [2]. During the fall of 1918, the front pages of Spanish newspapers were filled with the names of those who had died of the pandemic in the country [2, 3]. In other European countries, however, the press refrained from reporting news of the spreading infection, in order to avoid alarming the general population, which was already suffering the privations caused by the First World War. On 22nd August 1918, the Italian Interior Minister denied the alarming reports of the spread of the flu pandemic, and in the following months, both national and international newspapers followed suit. Nor was censorship restricted to news of the spread of the fearsome infection; it also extended to information and comments that contrasted with the official versions of the nature of the disease.

In order to avoid public alarm, several local hygiene authorities refused to reveal the numbers of people affected and deaths [11]. Moreover, it was announced that

the average duration of the epidemic did not exceed two months. By the middle of October 1918, however, it had become impossible to verify this claim.

Some scientists believed that one of the causes of the epidemic was the poor quality of food, which was rationed at the time of the epidemic crisis. The extent to which the gravity of the pandemic was accentuated by malnutrition among war-tired populations is unclear. However, the fact that the disease, even in serious forms, spread through countries that were neutral or completely uninvolved in the war, such as Spain, seems to suggest that malnutrition was not a key factor.

Another thesis was that the disease had been triggered by a bacteriological war waged by the Austro-German enemy. On the one hand, newspapers were essential to publicizing emergency measures to contain the epidemic, such as closing cinemas and theaters or prohibiting other types of gathering, including funerals. On the other, any mention of the horror that was unfolding was to be avoided. Even sounding death bells was sometimes forbidden, to prevent their continual dismal tolling from revealing the extent of the tragedy that was to be hidden. The unseen enemy mainly attacked young people, causing major social upheaval; if Spanish flu did not take the lives of children, it made them orphans.

A tragic legacy: mortality worldwide

The influenza pandemic of 1918 killed more than 50 million people and caused more than 500 million infections worldwide. In the military camps and trenches during the First World War, the influenza pandemic struck millions of soldiers all over the world, causing the deaths of 100,000 troops. However, it is not clear whether it had an impact on the course of the war [12]. The highest morbidity rate was among the Americans in France, during the Meuse-Argonne offensive on the Western Front from September 15 to November 15, 1918, when over one million men of the US Army fell sick [12].

General understanding of the healthcare burden imposed by influenza infections was unclear. Several factors were suspected of increasing the risk of severe flu: length of service in the army, ethnicity, dirty dishes, flies, dust, overcrowding and the weather. In overcrowded camps, the risk of flu, and its principal complication, pneumonia, increased 10-fold [13]. Bacterial pneumonia secondary to influenza was the overwhelming cause of death, owing to increased susceptibility due to transient immuno-pathological effects and dysregulated, pathological cellular immune responses to infections [14, 15]. It is difficult to ascertain the mortality rate of the pandemic, as data on deaths were transmitted in incomplete form to the Central Statistical Office. In Italy, the “Albo d’oro” collected documentation on the number and demographic characteristics of the soldiers who died during the conflict, which enabled more accurate data to be obtained on deaths due to influenza among military personnel [16].

Military nurses and medical officers were intensively and repeatedly exposed to the influenza A (H1N1) pandemic strain in many areas. However, during the lethal second wave, nurses and medical officers of the Australian Army, and other groups of healthcare workers, displayed influenza-related illness rates similar to those of other occupational groups, and mortality rates that were actually lower. These findings suggest that the occupational group most intensively exposed to the pandemic strain had relatively low influenza-related pneumonia mortality rates [17, 18]. The dynamic relationship between the host and the influenza virus during infection, the unusual epidemiological features and the host-specific properties that contributed to the severity of the disease in the pandemic period still remain unknown [19, 20].

Conclusions

The 1918 pandemic influenza was a global health catastrophe, determining one of the highest mortality rates due to an infectious disease in history.

Virological analysis of preserved samples from infected soldiers and others who died during the pandemic period is a major step toward a better understanding of this pandemic. Such knowledge may contribute to the discovery of new drugs and the development of preventive strategies, including insights into the appropriate timing of the administration of antivirals and/or antibiotics, thereby providing indications on how to prepare for future pandemics.

The 1918-1919 pandemic led to enormous improvements in public health. Indeed, several strategies, such as health education, isolation, sanitation and surveillance, improved our knowledge of the transmission of influenza, and are still implemented today to stem the spread of a disease that has a heavy burden.

Acknowledgments

Funding sources: this research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Conflict of interest statement

None declared.

Authors' contributions

MM and IB conceived the study, MM and IB drafted the manuscript, VG and NB revised the manuscript. IB, MM, VG and NB performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

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■ Received on January 15, 2019. Accepted February 22, 2019.

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OVERVIEW

Anti-rabies vaccination between the 18th and 19th centuries and its pioneer Eusebio Giacinto Valli (1755-1816)

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Keywords

Physician E.G. Valli • History of vaccinology • History of rabies vaccination and fever vaccination

Summary

An eclectic, versatile Tuscan doctor, Eusebio Giacinto Valli (1755-1816) was a scholar of several branches of medicine, particularly public health, preventive medicine and epidemiology. His brilliant and wide-ranging education, and his intense passion for physics and chemistry, as applied to the human body, enabled him to conduct numerous studies in the field of vaccinology.

He travelled to the Middle East in order to study the epidemiology of the plague and carried out experiments aimed at discovering a cure and a prophylaxis for rabies, succeeding in attenuating the

rabies virus by inoculating a mixture of saliva from rabid dogs and gastric juice from frogs.

Having travelled to Spain and then to Cuba, where he undertook the study of yellow fever, he died in Havana in September 1816, after injecting attenuated germs of the disease into his own body.

He was buried in the great Monumental Cemetery “Cristobal Colon”, where his tomb bears the epigraph: “victima de su amor à la humanidad (“a victim of his love for humanity”).

The life of Eusebio Giacinto Valli

Born in Casciana Alta di Lari (Pisa) on 16 December 1755, Eusebio Giacinto Valli was the son of a local doctor, Giuseppe Valli (from the family once known as Valle, Valla, della Valle, and today Valli) and Anna Maria Iacononi, both of whom originally came from Ponsacco. He was a multifaceted, eclectic physician, whose interests included pathophysiology, internal medicine, public health and preventive medicine, epidemiology and vaccinology, though his greatest passions were physics and chemistry, especially as applied to the human body. In September 1816, he died in Havana, Cuba, where he is buried in the great Monumental Cemetery “Cristobal Colon”, a “*victima de su amor à la humanidad*” [1].

After completing his high-school studies in Florence, where he studied classical languages and a few modern languages (English and French), and also dabbled in poetry, Valli took a degree in philosophy and medicine, after his elder brother, Jacopo, had graduated in canon and civil law.

In 1776, when Valli was in the second year of his degree course, his father died. The following year, his mother also died. Despite his restricted financial circumstances (he lodged at the house of one Domenico Cola in via Santa Maria, in the historical centre of Pisa), he managed to win a place at the Collegio della Sapienza di Pisa (which later became today’s Scuola Normale di Pisa); his uncle Michelangelo Valli acted as his guarantor.

Having graduated in philosophy and medicine, he moved to Turkey (Izmir, Constantinople), and then to Greece and the Aegean islands (1783-1785). Here, he became friends with the Greek physician, scientist and theologian, Angelo Kalogerà (1699-1768), author of a “Collection of Scientific and Philological Pamphlets” [2, 3]. During his stay on the islands, Valli visited “*in 1784, the beautiful, picturesque, rocky Island of Chios, Homer’s native land*”, which was at that time in the grip of the plague. He probably wrote a brief tract on the epidemic that afflicted the Island of Chios, but this has, unfortunately, been lost to us.

He subsequently travelled to Paris (1785-1786), where he served as a doctor in the Cablys’ regiment, then to Hindustan (today Pakistan, in 1786-1788), and finally to Egypt, to study the epidemiology of the plague, of small-pox, and of certain “malignant putrid fevers” (probably outbreaks of malaria).

Eusebio Valli’s scientific discoveries

In 1781, he discovered the anti-fermentation action of the red precipitate in wine preparation.

During his stays in the Middle East and Asia Minor, Valli worked out a theory according to which the etiopathogenetic development of the plague required the so-called “principle of affinity”, that is to say, a sort of predisposition to the disease. “*The forces that it deploys in the*

various subjects depend more on the constitution of each individual than on the character of the miasma".

In France, he took part in the debate between the humoral theory and solidism, embracing the latter; solidism was expounded in the principal work, "*Elementa medicinae*", of the Scottish physician John Brown (1735-1788), which was published in 1780 and translated into Italian by the clinician Pietro Moscati (1739-1824) [4].

In his "*Discorso sopra il sangue considerato in stato di sanità e di malattia*" (*Discourse on blood in the state of health and of disease*), Valli claimed that alterations in haematological parameters were due to the influence not of humoral agents, but of solid agents, or bodily organs. "*The blood is never altered by the germ of any disease whatever, nor by the forces of diseases themselves; on the contrary, it is the most resistant fluid, even to the action of poisons*" [5].

In the spring of 1789, at the outbreak of the French Revolution, he returned to Italy and settled in Pavia, where he met Francesco Volta. Despite the friendship and the excellent relations between the two, Valli took the side of Luigi Aloisio Galvani (1737-1798) in the dispute over the origin of animal electricity or bio-electricity, calling Volta's electricity of metals "*imaginary*" [6-8].

Valli repeated Volta's experiments meticulously, in an attempt to reproduce the results. In 1797, the German scientist and naturalist Alexander von Humboldt (1769-1859) would also try to reproduce these experiments [9]. Valli subsequently became the head of a hospital department in Mantua, and in 1802 returned to Turkey to experiment with the inoculation of smallpox vaccine to protect against the plague [10].

Indeed, over the years, Valli had elaborated the theory that infection by smallpox excluded infection by the plague, and vice versa. "*Those who have had smallpox either do not contract the plague or, if they do, they do not risk death. The plague becomes a benign disease, or fades out as soon as a smallpox epidemic arises*".

Thus, he held, there were two "poisonous pura", one produced by the plague and the other by smallpox, and contamination between the two would give rise to a "good pus", which was potentially curative. Valli's experimentation, which was dubbed "*hazardous but fascinating*" by Pietro Moscati, a doctor and minister of the Cisalpine Republic, received a sort of scientific endorsement from this latter. Indeed, on 31 May 1792, Valli became a corresponding member of the Academy of Sciences in Turin. In 1799, in Livorno, Valli partly reproduced experiments conducted by the French abbot, mathematician and physician Robert Rimbaud Deidier (1670-1746). Since 1772, he had succeeded in immunising "*several animals by inoculating saliva taken from a hydrophobic dog. None of the animals inoculated with the saliva, to which gastric juice from frogs had been added, contracted rabies*". With this preparation, Valli succeeded in treating a certain Pisan lady named Rosermini and her maidservant, achieving a very good result [11].

In 1802 and in 1818-1819, these experiments would be repeated by the French military doctor René-Nicolas Dufriche Desgenettes (1762-1837) and by the Spanish

doctor Serafin Sola in Tangier (Marocco), as reported by the Swedish consul Jacob Graf Graberg Hemsö [12]. Valli subsequently travelled to Dalmatia as a military doctor with the Franco-Italian army. There, he treated an officer's wife, who had been bitten by a rabid dog; she did not contract rabies.

In June 1809, he went to Spain to serve on a military medical commission [13].

Following his return to Italy, he was appointed in 1811 by the Italian government to examine the thermal waters of Monte Ortone, south-west of Padua, in the Euganei hills. In 1815, he briefly stayed in Milan, but then returned to Mantua, a city he loved and regarded as his "*second home*".

Finally, he travelled to Cuba, arriving there from New York in September 1816. Accompanied by Dr. Antonio Mendoza, he visited San Juan de Dios Hospital, where he studied the epidemiology of yellow fever.

"*At that time, Havana had a sad appearance: the streets were mostly narrow, winding and unpaved, which, together with the lack of gutters, contributing to maintaining the dirt, and also the unwholesomeness, which was exacerbated by the nearby swamps; consequently, diseases were common, and yellow fever raged more vigorously than in other parts of America. In the months of August and September, mortality was very high, and during that time the death rate was 25 per day on a population of about 130,000 inhabitants*". While attempting to find a remedy for yellow fever, Valli died, struck down by the germs of the terrible disease, which he had inoculated into himself, a "*voluntary martyr to an overarching boldness in his art*" [14].

Eusebio Valli and his scientific legacy

Valli was criticised by several academics. For example, Professor Giovanni Pietro Frank (1745-1821) said of him: "How could this young man have been able to write about chronic diseases, when I myself would perhaps be scarcely able to do so after practising medicine for more than 40 years?".

Instead Prof. Ulrico di Aichelburg, who taught microbiology at the University of Turin, described some of Dr Valli's important professional characteristics, including his particular interest and competence in the field of vaccinology:

"And it must be remembered... that Eusebio Valli strove to prevent disease by inoculating an attenuated form of its infectious principle (which, please note, was unknown in those days: this was in the 18th century) [...]. By mixing gastric juice with pus from plague and smallpox lesions, and with saliva from rabid dogs, and injecting these relatively innocuous mixtures into healthy persons, Valli claimed to have elicited immunity to the plague, smallpox and rabies [...].

We may doubt the results of Valli's claims, but we cannot doubt that he had inferred that scientific principle which Pasteur would later apply successfully: the principle of vaccination" [15].

Valli's studies and his various manuscripts, including the original copy of his death certificate, written by the Holy Guardian of the Church of the Angel in Havana, are now conserved in a room of the Istituto di Storia della Medicina (Institute of the History of Medicine) in Rome.

In the year in which a relative, the lawyer Giuseppe Valli, authorised the biography of Eusebio, Louis Pasteur devoted himself to developing an anti-rabies vaccine. On 6 July 1885, after four years of study, Pasteur succeeded in treating Joseph Meister (1876-1940), who survived [16, 17].

In both Casciana and Ponsacco, streets and plaques have been dedicated to Valli.

Conclusions

Eusebio Valli was a great physician and a pioneer of modern vaccinology: a personage who deserves to stand alongside Edward Jenner, whose work Valli greatly contributed to publicising. He blended observation and experimentation, being well aware that, without these, even the most fascinating hypotheses and theories “*are worth nothing*”. He possessed both courage and ambition: “*the man who is gnawed by the ambition of glory can overcome any obstacle*”. Moreover, he had to fight against “*the charlatans... the physicians who are ignorant or in bad faith, who... have discredited the greatest discovery of the century, shamelessly preaching the heresy that vaccination does not prevent and cannot protect against smallpox*” and, in doing so, he did not hesitate to boldly try his own remedies on himself.

Valli can be regarded as one of the first physicians, or perhaps the very first, to take up and publicise Edward Jenner's discovery of an anti-smallpox vaccination. Indeed, he formulated the principle according to which immunity to a contagious disease could be elicited by injecting the same, appropriately attenuated, “material” responsible for the infection. In this way, a mild form of the disease would be caused, which would be memorised by the immune system, thereby eliciting protection against more severe forms.

Moreover, Valli was the first vaccinator to operate in several countries in the world. In a sense, therefore, alone and as far as was possible at that time, he anticipated the activity, and to some extent also the philosophy, of *Médecins sans Frontières* [10].

Acknowledgements

Funding sources: this research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

■ Received on January 6, 2019. Accepted February 6, 2019.

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Conflict of interest statement

None declared.

Authors' contributions

MM and NB conceived the study, MM, NB drafted the manuscript, MM and BC revised the manuscript. NB, MM and BC performed a search of the literature. MM and BC revised critically the manuscript. All authors read and approved the last version of the manuscript.

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