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The enigma of the 1889 Russian flu pandemic: A coronavirus?



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ABSTRACT

The “Russian flu”, which raged from 1889 to 1894, is considered as the first pandemic of the industrial era for which statistics have been collected. This planetary event started in Turkestan and hit the Russian Empire, before reaching all European countries, the United States of America, and the whole world. Contemporaries were surprised by its high contagiousness as evidenced by attack rates averaging 60% in urban populations, its rapid spread in successive waves circling the globe in a few months by rail and sea, and the tendency of the disease to relapse. Despite its low case-fatality rate (0.10%-0.28%), it is estimated to have caused one million deaths worldwide. On serological grounds, it is generally accepted that the causative agent of Russian influenza was *Myxovirus influenzae*, the virus identified for all influenza pandemics since the “Spanish flu” of 1918. In light of the Covid-19 pandemic, which has underscored the extraordinary epidemic potential of coronaviruses, this assumption has recently been questioned. Coronaviruses come from wild reservoirs (bats, rodents, birds, . . .). They induce respiratory symptoms mimicking influenza, possibly leading to respiratory distress with pneumonia. In addition to the Covid-19 pandemic, recent deadly and limited epidemics, such as SARS in 2002 and MERS in 2012, have occurred. Russian influenza presented as an influenza-like syndrome with clinical peculiarities (multivisceral and neurological involvement, skin rash, early iterative relapses), evoking some particularities of Covid-19. Four other coronaviruses circulating in the human population for decades (HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1) have been found to be responsible for 15 to 30% of seasonal colds. All of these viruses are of animal origin. Recently, phylogenetic studies have revealed the genetic proximity between a bovine coronavirus BCoV and the human virus HCoV-OC43, indicating that the latter emerged around 1890, at the time of the Russian flu, when an epizootic was raging among cattle throughout Europe. Could the current human virus be the attenuated remnant that appeared after the Russian flu in 1894? Was there a coronavirus pandemic before Covid-19?

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1. Introduction

Since the Renaissance, the world has faced multiple influenza pandemics, punctuated by lulls lasting a few decades. “Influenza” has been defined by the sudden onset of respiratory signs with fever and high contagiousness in the population. In the 19th century, several pandemics originating in the East were reported, including 1831–1833, 1847–1848 and, finally, from 1889 to 1894, the so-called “Russian flu”, which spread throughout Europe and then the world. This episode was well-documented in many countries in several official reports, medical sources, and numerous press articles that covered the pandemic on a daily basis [1–9].

2. The Russian influenza pandemic

The first cases were reported in May 1889 in the city of Bukhara in Turkestan; curiously, a few cases were also reported in the city of

Athabasca in Western Canada and in Greenland. In mid-October 1889, influenza reached the Russian Empire. It was reported in Tomsk in western Siberia, Ufa (100 km from the Ural Mountains), Kazan on the Volga River in western Russia (700 km east of Moscow), Jekaterynoslav on the Dnieper River in Ukraine, and Novgorod near St. Petersburg. Kiev was stricken, as was the entire region of Lake Baikal, and then Siberia up to the island of Sakhalin. The capital of the Empire was severely hit in November 1889, with 20,000 cases. The flu afflicted all levels of society, including Tsar Alexander III himself. By the beginning of December, one third of hospital beds were occupied by flu patients. Economic activity ground to a halt, factories were closed, as were barracks and schools; 25–50% of soldiers and children had fallen ill. The peak of the epidemic occurred on December 1, 1889 in St. Petersburg. The first wave lasted five weeks with a total of 180,000 victims in a city of one million inhabitants [1,3]. From St. Petersburg, the Baltic ports were contaminated, notably Stockholm and the rest of Sweden, where the flu infected 60% of the population for eight weeks, and then Copenhagen and Oslo. The German Empire was affected in December, particularly in Poznań, Warsaw and Lodz. The epidemic resulted in 150,000 cases in Berlin for a population of

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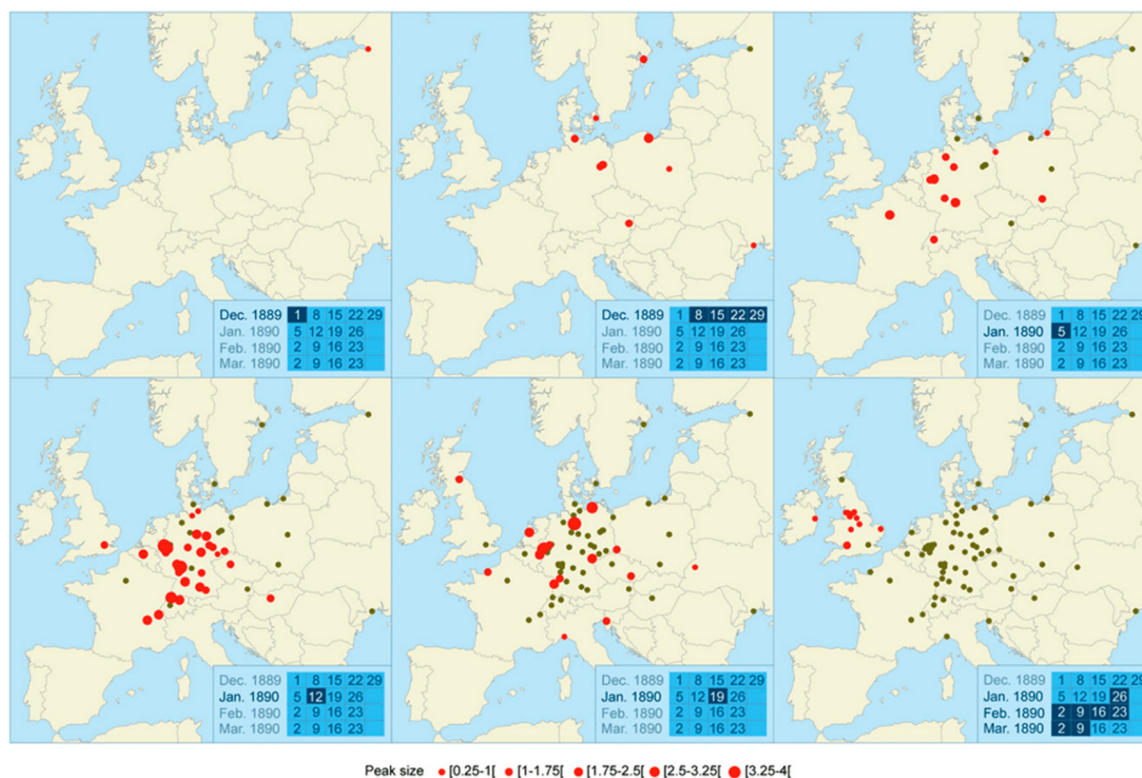


Fig. 1. Kinetics of the spread of Russian influenza in Europe in 1889–1890 (with the calendar). Red dots: cities hit by the pandemic (their size corresponds to the magnitude at the peak). Green dots: extinguished outbreaks (from AJ Valleron [17]).

1.5 million [5,6]. Within a few weeks from December 1889, all of Europe was ablaze. It was mainly an urban pandemic initially striking the capitals: Paris, London, Vienna, Madrid, Rome, Geneva [1,7,8]. At the beginning of 1890, the first wave spread around the Mediterranean, from Constantinople, where half of the population caught the flu, to Egypt [1,5,9]. The spread of flu to major European cities during the first wave is illustrated in Fig. 1 [1].

The pandemic hit Paris in November 1889, afflicting 670 of the 8000 employees of the *Grands Magasins du Louvre*. It was a mild influenza that subsided in about four days. However, it seems to have worsened during the last two weeks of December 1889. Cases of severe pneumonia were reported around December 25–28, with 200 deaths from pneumonia or lung congestion. Patients flocked to hospitals where barracks and emergency tents were set up in the gardens (Fig. 2). Virtually all the doctors of Hôtel-Dieu contracted the disease. The peak occurred on December 28. There were 180,000 symptomatic cases among the 2.5 million inhabitants of Paris. Mortality in the capital was estimated at 62/1000, a 30% increase compared to the previous winter [4,9]. The epidemic subsided in January 1890, only to return to Paris in late February, after which influenza spread throughout the country, initially affecting regional hubs such as Toulouse, Grenoble, Lyon, Toulon, Montpellier and Angers [9].

What to do? Almost everywhere the unprepared authorities recommended hygienic measures such as ventilation, disinfection of public places and patients' rooms, prohibition of public gatherings, isolation at home... Needless to say, there was no effective treatment at the time. Quinine was used to treat fever, but without success, as well as treatments such as strychnine, phenol inhalation, carbonic smoke ball that were dangerous... or fanciful (castor oil, electric current, brandy, oysters...). Commercial activity likewise collapsed, and schools, colleges, universities, public services, transportation and factories were shut down: a true disaster! Numerous eminent

personalities – the President of the Republic, ministers, deputies – were stricken.

From mid-December 1889, the same scenario played out in the United Kingdom. In January 1890, there were 2258 deaths in London, including 1070 from pneumonia, far exceeding the seasonal average. The disease spread to other cities, including Edinburgh, Glasgow, Birmingham (50,000 cases) and Dublin [10–13]. Mortality per million due to influenza in the United Kingdom from 1847 to 1905 is reported in Fig. 3. The Russian flu was probably prolonged by waves up until 1899–1900, when the so-called flu epidemic occurred [14,15].

The epidemic soon crossed the Atlantic, and the first cases in the United States were reported on 18 December 1889. The wave lasted five weeks, reaching a peak on 12 January 1890. The epidemic spread along the East Coast before reaching Chicago, Kansas City and San Francisco. Soon afterwards, from Mexico City to Buenos Aires, Latin America was likewise contaminated. In spring 1890, the pandemic spread widely in Africa and Asia. If Africans called it “the white man's disease”, it was because they had apparently never previously known influenza. The map of the Russian flu pandemic is shown in Fig. 4.

The Russian flu pandemic evolved in sequential waves, at least four of them occurring between 1889 and 1894, and rather mysteriously, they varied in severity. In the United Kingdom, the second and third waves were more deadly than the first; the mortality rate (n° deaths/population) was 157 per million in 1890, 574 in 1891 and 534 in 1892 [12]. Similar figures were reported in the United States [2,13]. For example, in Indiana (near the Great Lakes), the epidemic began in January 1890, resulting in 3200 deaths; the waves in that state illustrate the pattern of fatalities during the pandemic (Fig. 5). Case fatality rates (n° deaths/ n° symptomatic patients) were 1.56 per 1000 influenza cases in 1890, 1.64 in 1891 and 2.15 in 1892 [16]. Similar rates were recorded in France (1.6/1000) and Germany (1.3/1000) [7,9]. Mortality was highest among people over 50 years of age,

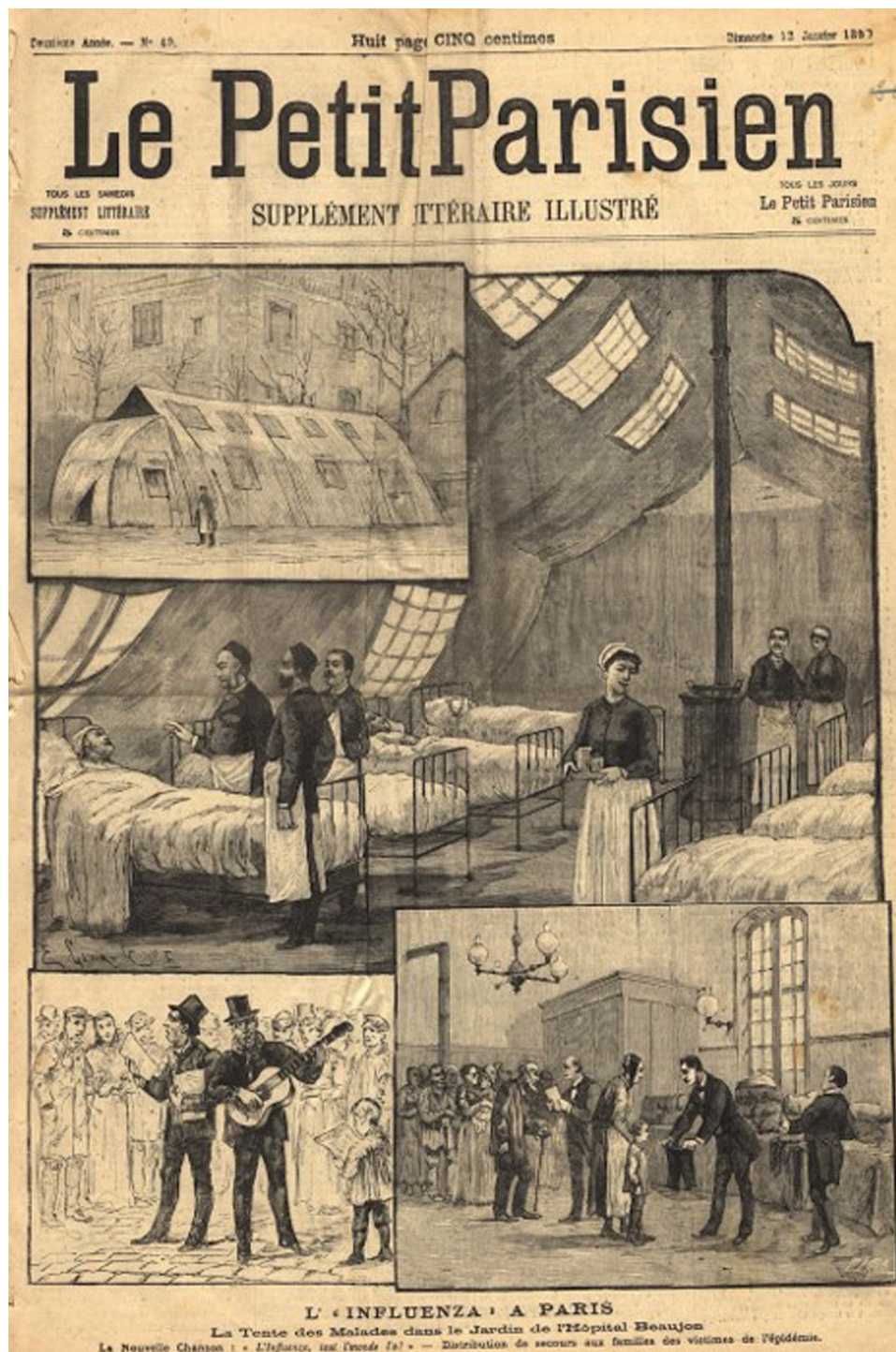


Fig. 2. "Influenza in Paris". The tent of the sick in the garden of the Beaujon Hospital. Le Petit Parisien (January 12, 1890)- The National Library of Medicine.

whereas usually influenza affects the oldest and the youngest. A highly detailed study estimated case fatality rates in Europe as ranging from of 0.10 to 0.28%, proportions similar to those of Asian influenza in 1957 and Hong Kong influenza in 1968 [17]. Russian influenza is therefore considered to be fairly mild. However, it resulted in 250,000 deaths in Europe, including 125,000 in England and Wales, 100,000 in the United States, and a total of about one million deaths worldwide, a toll nonetheless in no way comparable with the hecatomb of the Spanish flu of 1918, which killed at least 50 million people worldwide [18].

3. The singularities of the Russian flu

Compared to the previous pandemics of the 19th century, the rapid spread of influenza was surprising. How can it be explained? In 1890, at the outset of the Pastorian era, the proponents of contagion still clashed with those of the miasma theory, which explained the rapid spread by air. In reality, the first wave did not progress steadily from east to west. It first hit successively the major European cities and capitals, which were closely connected by railroads, before disseminating to regions; this explains its predominantly urban impact.

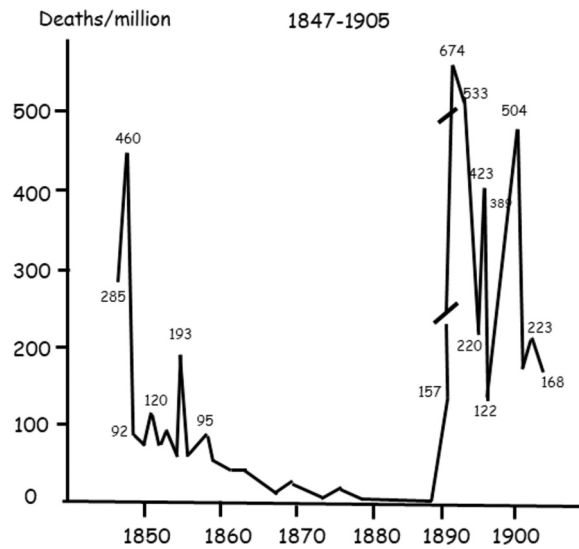


Fig. 3. Mortality of influenza from 1847 to 1905 in the United-Kingdom. Mortality reached 674/million in 1890, followed by several peaks up until the epidemic of 1900 (modified from [14,15]).

The pandemic also moved upstream, along the rivers; in addition, numerous grouped family cases were reported, indicating that influenza spreads directly through human-to-human contact. There is little doubt that influenza was borne by the European railroads, which were constantly expanding, with 202,887 km of track, and by the ever more rapid steamboats plying the waterways and seas. From May 1889 onwards, influenza was transported from Central Asia to the Russian Empire by the Transcaspian line to Samarkand in August, and then to Tomsk, 3200 km away, in October. The spread towards the East was slower because the Trans-Siberian Railway did not yet exist. St. Petersburg was afflicted in November 1889 via the Volga River trade routes [1,3].

The high contagiousness of Russian influenza explains its rapid spread. The average attack rate of symptomatic patients was reported to be 60% of the infected urban population [17]: 50% in Berlin, and 25% in London. The average reproduction rate (R0) was estimated to be 2.15, based on the epidemiological data from 33 European cities collected weekly between November 1889 and February 1890 [17]. In some cities, such as St. Petersburg, Amsterdam, and Stuttgart, it was much higher. It bears mentioning that due to their benignity, many cases were not reported.

Russian influenza was more common in men and particularly severe in the elderly [24–26] or in patients with comorbidities, including phthisis, cardiopathies, cerebral diseases and nephritis...

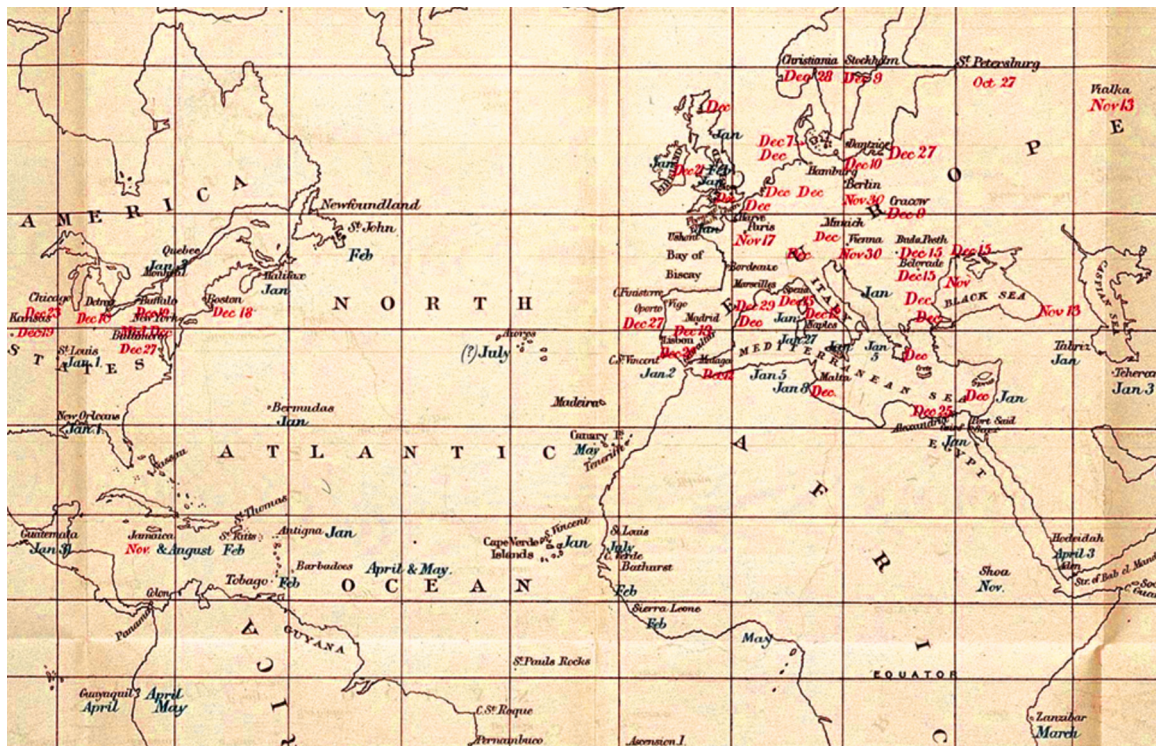


Fig. 4. Map of the distribution of the Russian influenza pandemic in Europe and the United States of America (from [1] p.65). Outbreaks are shown in red. Photo : Wellcome Collection Gallery, Creative Commons, London. Copyright: Copyrighted work available under Creative Commons Attribution only licence CC BY 4.0 <http://creativecommons.org/licenses/by/4.0/>.

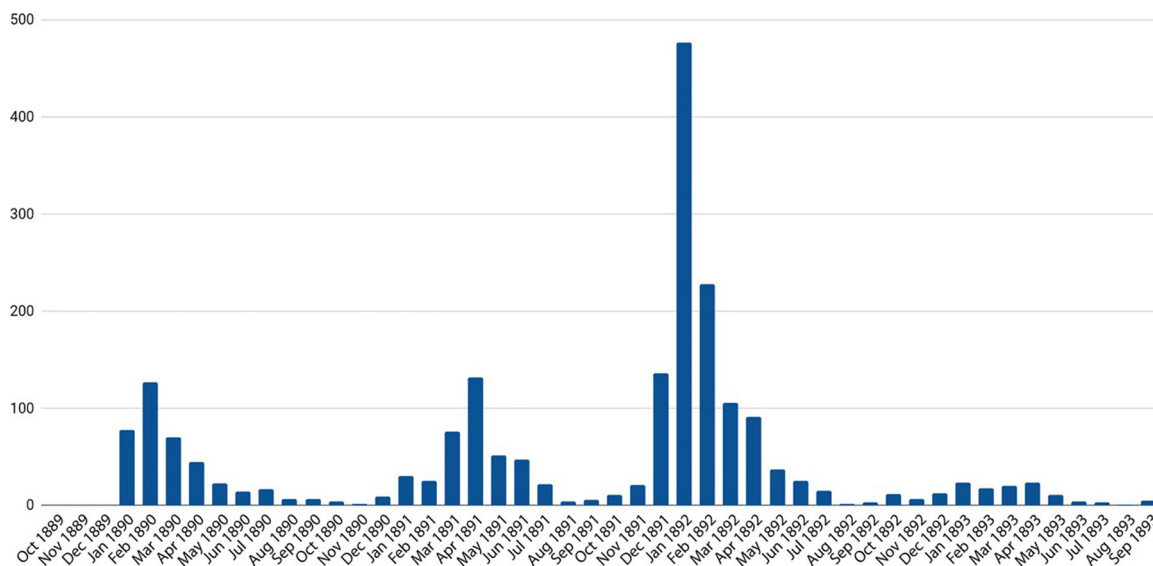


Fig. 5. Mortality statistics during the Russian influenza in 1890 in Indiana (USA), showing a third wave associated with higher mortality (modified from [16]).

In the United Kingdom [1] and in Switzerland [25], children were attacked much less frequently than adults, in contrast to flu epidemics, which affect the oldest and the very youngest (Fig. 6). That said, young adults were not spared from rare fatal forms; in London, due to pneumonia caused by influenza, the Duke of Clarence died at the age of 28, even though he had no previous medical history.

Physicians of the time distinguished four clinical forms of Russian influenza [19]: a simple, uncomplicated febrile form with mild respiratory symptoms and fever that increased in 48 h and disappeared in three or four days; a gastrointestinal form with moderate gastric symptoms, fever, and prostration; an uncommon catarrhal form; and a “nervous” form with intense paroxysmal neuralgic pain. Many people were surprised by the relative rarity of catarrh, which is

habitually associated with influenza [1]. For example, around 1780, William Cullen referred to influenza as “catarrhal fever” (*catarrhus a contagio*) [20], leading to further textbook definition of contagious influenza [21].

At first glance, Russian influenza resembled pandemic episodes having occurred in previous centuries. It begins suddenly with an intense headache, high fever, chills, sweating, sneezing, watery eyes, and dry cough. Some patients suffer from painful bone and muscle, in the back, and in the entire body “up to the hairline”. They become prostrate, without appetite, sometimes with slight delirium. Occasionally a loss of smell and photophobia are reported. The illness generally lasts three to five days [1,9]. Rashes of the face and body and unusual swelling of the hands are quite frequent [1,9], possibly

% death by influenza

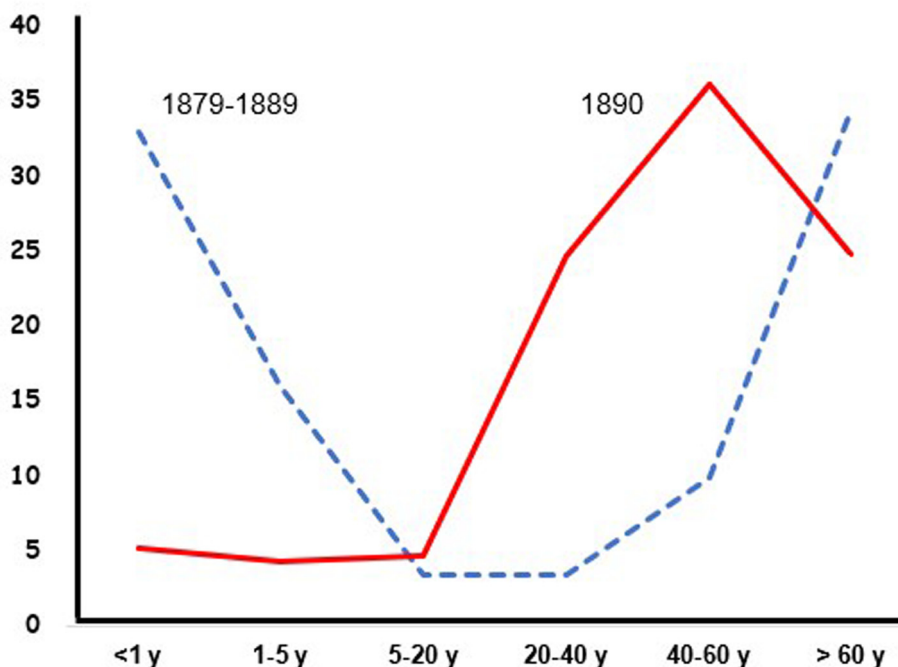


Fig. 6. Proportion at several ages to 100 deaths from influenza, comparing the period 1847–1889 to 1890 mortality (modified from [1]).

reflecting vasculitis. During SARS-CoV-2, skin lesions, peripheral vascular disease, persistent and painful sudden-onset redness and urticarial lesions with transient vesicles, at times resembling frostbite, have been reported [22]. In severe forms of Russian influenza, patients have difficulty breathing and may experience respiratory distress due to pneumonia, resulting in death [19]. Severe forms with renal, digestive or neurological involvement have also been reported. Dr James Goodhart (1845–1916), who treated numerous patients at Guy's Hospital in London, emphasized the diversity of symptoms and wrote: "There would appear to be no organ or tissue that has become the subject of attack" [23]. Astonishingly diverse nervous symptoms were observed: various types of algia, peripheral nerve neuritis with paresis, facial neuralgia, pneumogastric nerve neuritis with alternating tachycardia and bradycardia, occasional loss of smell (anosmia). Frequent psychic manifestations are also known to occur, including a state of prostration in contrast with the apparent benignity of the disease, profound and lasting asthenia, post-influenza depression or melancholy with suicidal tendencies, lethargic, cataleptic, or even psychotic states.

Another peculiarity compared to classical influenza is a tendency to induce short-term recurrences, encountered in about 15% of patients (including the tsar), the first relapse being the most serious [1]. Due to sequelae, influenza reportedly left thousands of convalescents weakened, depressed, in debt, and unable to work [11]. In London, laborers suffered months of numbness in their limbs, progressing to spinal paralysis after a second bout of influenza in April 1891. Cases of respiratory muscle atrophy, heart failure and tongue paralysis were likewise noteworthy [11]. This atypical symptomatology of Russian influenza combined with splenomegaly, which is generally absent in the course of usual influenza, led the eminent professor of the Paris Faculty of Medicine, Pierre Potain (1825–1901), to affirm that it was something other than usual influenza [9].

4. The Russian flu virus

Which agent was responsible for the pandemic? Needless to say, during the Pastorian revolution search for the germ of Russian flu became a priority, but the search began with a 50-year mistake. In the 1890s, viruses were still unknown. In November 1891, the German Richard Pfeiffer isolated a previously undescribed bacillus, which grew only on blood agar, from patients' nasopharyngeal samples. Terming it *Bacillus influenzae* (now *Haemophilus influenzae*), on January 4, 1892 he announced that he had discovered the agent responsible for influenza [27]. Unfortunately, he was unable to reproduce the disease experimentally in animals and did not fulfill the Koch's postulates, which might have established a causal link. He hypothesized that the agent was a very specific human pathogen, comparable to those of leprosy or cholera. As the bacillus was repeatedly isolated during cases of flu, Pfeiffer's observations seemed to be corroborated. In the years following the discovery, however, the bacillus was also found independently of any epidemic in otitis, mastoiditis, meningitis and pneumopathy. This is in contradiction with the existence of a specific germ at the origin of influenza. During the Spanish flu of 1918, this bacterium was once again incriminated, and many unsuccessful attempts were made to vaccinate against *H. influenzae*. At present, we know that it is a superinfection germ often present in nasopharyngeal samples.

At the end of the First world war, there were serious doubts about the etiology of the Spanish flu. The first major step was taken by Richard Shope, a young physician at the Rockefeller Institute for Medical Research in Princeton. In 1931, he discovered an ultrafiltrable virus that caused swine flu [28], a disease similar to human flu that was sometimes transmitted to humans. The viral trail led to the discovery in London in 1933 by Wilson Smith, Patrick Laidlaw and Christopher Andrews of the human influenza virus (*Myxovirus influenzae*) [29]. It was later shown that influenza viruses originate from birds

and pass through an intermediate host, the pig, before infecting humans. Recently, it has become possible to sequence the entire genome of the Spanish flu virus from human remains dating back to 1918 [30], and to show by nucleotide sequence analysis that the H1N1 virus is indeed the agent of the Spanish flu and the ancestor of all subsequent flu pandemics [31,32]. The 1918 virus is believed to be of avian origin and adapted to humans. The H1N1 virus later acquired three new genes by reassortment in pigs, resulting in the H2N2 virus responsible for the Asian influenza of 1957. A new recombination event substituted two new genes, yielding the H3N2 virus of the 1968 influenza pandemic [32]. The same was true for the 2009 swine flu [33]. In 2005, the H1N1 virus of the Spanish flu was resurrected by synthesis and proved to be highly virulent for primates [34].

After the discovery in 1933 of the influenza virus, it seemed logical to hold it responsible for all the pandemics recorded since the Renaissance, including the 1889 Russian flu. But how can this be proven? There exists a "sero-archeological" approach, which consists in titrating antibodies to strains carrying the H1, H2 or H3 hemagglutinins in the serum of patients born before or after the 1889 pandemic [35]. During the 1957 Asian H2N2 influenza, Dutch researchers found higher levels of anti-H2 antibodies in persons aged 71 to 94 years born between 1863 and 1886 in the two weeks preceding the epidemic wave in the Netherlands. Could the Russian flu virus be the H2N2 virus? However, the same antibodies were also detected in younger people born after 1910 [36,37]. Moreover, the sera were collected just before the pandemic. Other serological studies suggest the H3 virus. During the 1968 H3N2 pandemic, there was less mortality in the elderly, with a higher peak of anti-H3 antibodies, in contrast with a much lower rate of anti-H2 seroprevalence (15–29%), which seems to rule out H2 virus as the cause of Russian influenza. It consequently appears likely that the H1N1 virus may have circulated as seasonal influenza from 1919 to 1957, when it disappeared during the Asian influenza, before reappearing in 1977, probably due to a laboratory accident [38]. The H3N2 virus eliminated the H2N2 from the Asiatic flu and has persisted up until now along with the H1N1 virus. It has been suggested that the agent of the Russian flu and the "mild pandemic" of 1898–1900 was the H3N8 virus [39], which caused epizootics in horses. During the 1889 pandemic in the United Kingdom, Parsons reported the concomitant occurrence of epidemics of "pink-eye" [1], a form of equine influenza due to endemic H3N8 in horses, birds and dogs. However, the H3 virus hypothesis is based only on sero-epidemiological studies, which provide indirect evidence, and are not free of artifacts related to cross-reactions or serum inhibitors, for example.

5. The coronavirus hypothesis

While the Covid-19 pandemic resembles the other influenza pandemics, the SARS-CoV-2 coronavirus was identified by sequencing a few weeks after its onset. There are seven coronaviruses pathogenic to humans [1]: three are highly pathogenic and epidemic: SARS-CoV-1 (9% mortality), MERS-CoV (30% mortality) and the current pandemic virus, SARS-CoV-2 (0.6%–2% mortality) [2]; four are the cause of 15–30% of common colds and have been circulating in populations for decades: HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1. These benign viruses are of animal origin (bats or rodents) [40] and evolve in small seasonal epidemics every three to four years during the autumn and the winter, conferring short-term immunity [41,42].

In 2005, Belgian researchers sequenced the entire genome of a laboratory strain of HCoV-OC43 (which had undergone multiple passages in culture), demonstrating its phylogenetic proximity to another beta-coronavirus of bovine origin, BCoV, which originated from rodents and yields acute diarrhea in calves [43]. The nucleotide sequence of HCoV-OC43 is almost identical to BCoV, from which it was derived in about 1890 (Fig. 7). These investigators confirmed their discovery by comparing different sequences of wild-type HCoV-

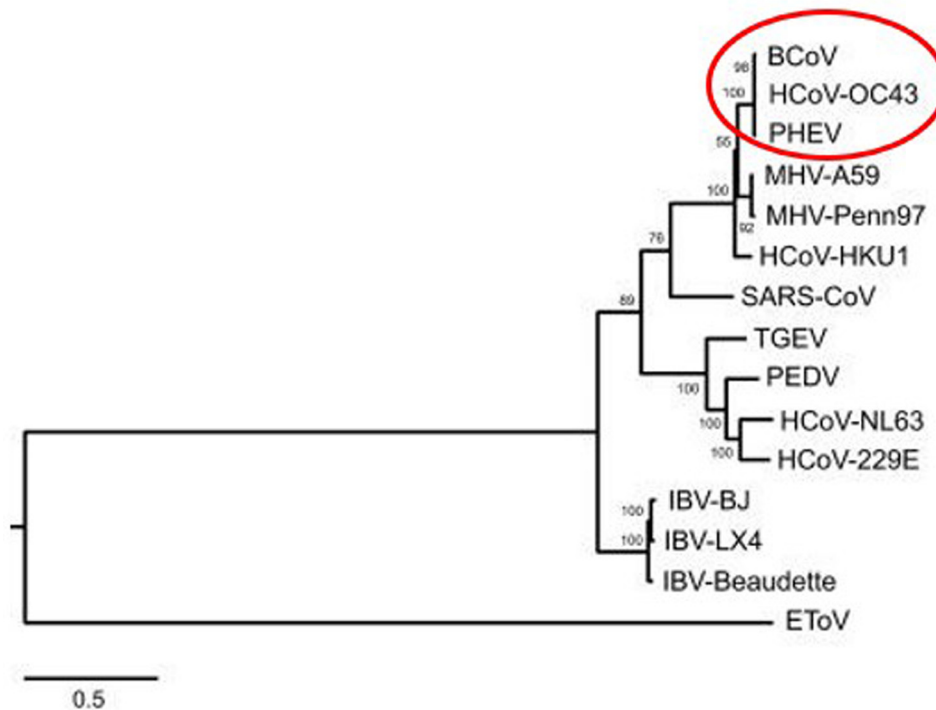


Fig. 7. The phylogenetic tree of amino acid sequences of HCoV (OC43, NL63, 229E, HKU1) compared to the animal coronavirus (bovine BCoV, porcine PHEV, PEDV, TGEV, murine MHV, avian IBV). The divergence between HCoV-OC43 occurred around 1890 (modified from [44]).

OC43 strains isolated from patients with acute rhinitis [44]. They also found these viruses to be close to PHEV, a coronavirus causing porcine hemagglutinating encephalomyelitis [45]. In light of the Covid-19 pandemic, these phylogenetic observations raise the question of the role of a coronavirus in Russian influenza and make HCoV-OC43 an unexpectedly plausible candidate.

Can epidemiological arguments support this hypothesis? It is known that the second half of the 19th century was marked by concerted expansion of the live cattle trade, which was greatly facilitated by railways. Between 1870 and 1890, the world's cattle herd was decimated by a panzootic of contagious peripneumonia attributed to *Mycoplasma mycoides*, a wall-less bacterium. This epidemic necessitated the slaughter of hundreds of thousands of cattle as a means of controlling the disease worldwide. It has been speculated that the operatives performing the stamping out were exposed to bovine respiratory viruses, including BCoV. Such a scenario occurred during the SARS epidemic in 2002, related to the slaughter of civets for human consumption. In 1889, it was noted that cows showed the same symptoms as humans [1]. This led to the hypothesis that an HCoV-OC43 mutant had emerged from a bovine virus, following contamination by people in contact with cattle. Direct transmission of BCoV to humans has been observed in the past, particularly in a six-year-old child with acute diarrhea [46]. Finally, by comparing the waves of flu pandemics (Fig. 8), the evolution of the Russian pandemic was not similar to the seasonality of the flu pandemics of 1918, 1957 and 1968 [47]. Recently, an attempt was made to predict the uncertain evolution of the Covid-19 pandemic using modeling based on the epidemiology of seasonal coronaviruses HCoV-OC43 and HCoV-HKU1. While the R_0 transmission rate was shown to be 2.2 during winter and 1.3 during summer [48], the emergence of highly contagious mutants of SARS-CoV-2 call these data into question. The hypothesis of a coronavirus at the origin of the Russian influenza is also corroborated by singular clinical features, for example the protean character of its clinical symptomatology, which resembles Covid-19, with multivisceral (pulmonary, digestive, renal, neurological) attacks, as well as prostration and psychiatric disorders

[49–51]. The early relapses and sequelae are likewise reminiscent of Covid-19 complications.

While HCoV-OC43 is mostly benign, it appears to have retained some neurotropism (as does HCoV-229E). In 2000, Canadian researchers found traces of HCoV-OC43 RNA (23% of samples) and HCoV-229E RNA (44%) in postmortem brain samples from 90 patients having died of various neurological diseases or due to non-neurological causes. HCoV-OC43 RNA was significantly more frequently found in patients with multiple sclerosis (39% versus 14% in controls) [52]. Respiratory infections are known to trigger relapses of multiple sclerosis. Another Canadian team described a 2003 epidemic of respiratory infections due to HCoV-OC43 in institutionalized residents (95 infected/142) and caregivers (53 infected/160). There were eight deaths among residents [53]. HCoV-OC43 coronavirus is thought by some to be an attenuated mutant of a pandemic virus that triggered Russian influenza.

6. Conclusion

The emergence of the SARS-CoV-2 pandemic prompts a revisiting of the cause of past influenza pandemics. It should be remembered that there exist many wild reservoirs of coronaviruses, including bats, rodents, and birds, in whom the viruses are not (or only weakly) pathogenic [54]. As many as 5000 types of coronaviruses have been identified, including 500 in bats, which may be the cause of many animal infections and epizootics. Could the loss of virulence be due to the natural evolution of pandemic viruses, an avatar of Darwinian selection of variants well-adapted to the species and persisting in the form of benign diseases or asymptomatic carriage, as in wild reservoirs? Chiropterans that appeared 50 million years ago [55], most of them asymptomatic carriers of many viruses, may have survived iterative lethal epidemics since the dawn of time. A balance was conceivably found between host-adapted viruses and hosts that developed specific and original defense systems conferring “natural” resistance to viruses [56].

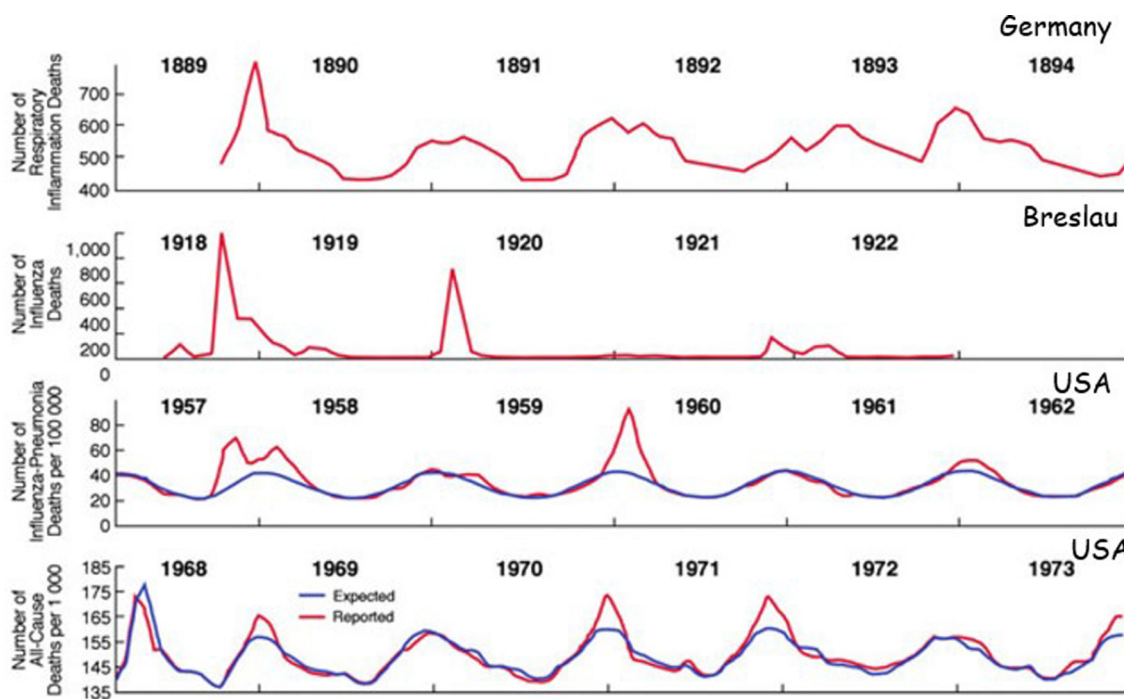


Fig. 8. Comparison of the waves of the flu pandemics since 1889 (modified from [47]).

Clinical, epidemiological and phylogenetic clues point to a coronavirus that caused the Russian influenza pandemic, as occurred in Covid-19, with its flu-like symptoms. Could there exist a historical precedent of a pandemic due to a coronavirus? Could the benign coronaviruses encountered in human populations be the relics of ancient epidemics yielding mild viruses that are perpetuated in the human species? This alternative hypothesis deserves further investigation.

Conflict of interest

None.

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