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Covid-19, an unfinished story

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ABSTRACT

The Covid-19 pandemic appeared in China in December 2019 as a cluster of transmissible pneumonia caused by a new betacoronavirus. On March 11, 2020, the World Health Organization (WHO) declared it a pandemic. Covid-19 is a mild infection in 80% of cases, serious in 15% and critical in 5%. Symptomatic forms include a first phase of flu-like viral invasion, and at times a second phase, dysimmune and inflammatory, with acute respiratory distress syndrome, multiorgan failure and thromboembolic complications. Degree of severity is related to age and comorbidities.

SARS-CoV-2 is the third highly pathogenic Betacoronavirus to cross the species barrier. Its genome, an RNA of 29,903 nucleotides, shows strong homogeneity with bat coronaviruses from southern China, but the conditions for its passage in humans have yet to be elucidated. Mutations can give rise to variants of concern (VOC) that are more transmissible and able to evade the host's immune response. Several VOCs have succeeded and replaced one another: Alpha in October 2020, Beta and Gamma in December 2020, Delta in spring 2021 and Omicron in November 2021. The Covid-19 pandemic has evolved in five waves of unequal amplitude and severity, with geographical disparities. Worldwide, it has caused 395,000,000 confirmed cases including 5,700,000 deaths.

Epidemiological surveillance applies several indicators (incidence rate, test positivity rate, effective R and occupancy rate of intensive care beds) supplemented by genomic monitoring to detect variants by sequencing.

Non-pharmacological measures, particularly face mask wearing, have been effective in preventing the transmission of SARS-CoV-2. Few currently available drugs have proven useful, with the exception of dexamethazone for patients requiring oxygen therapy. Development of SARS-CoV-2 vaccines began early on many platforms. Innovation was brought about by the Pfizer-BioNTech and Moderna messenger RNA vaccines, which claim protective efficacy of 95% and 94.1% respectively, far higher than the 70% minimum set by the WHO.

Governments have hesitated between two strategies, mitigation and suppression. The second has been favored in critical periods such as April 2020, when 2.5 billion people throughout the world were confined. Vaccination campaigns got underway at the end of December 2020 and progressed without reaching sufficient herd immunity, leading some nations to consider compulsory vaccination or to require a vaccine or health pass, in order for persons to access different activities.

Will the pandemic stop with Omicron and become endemic? This part of the Covid-19 story remains to be told.

1. Introduction

Telling the story of Covid-19 may seem premature as long as the SARS-CoV-2 pandemic remains active on all continents. It's like leaving your seat before the end of the performance or depriving yourself of the relief of putting the full stop at the bottom of the last page. But will the completion of this exceptional episode be as interesting to relate as its appearance and will it bring together as many fascinating and unexpected elements as the successive and unpredictable epidemic waves that have struck all of humanity?

2. Genesis of a pandemic

It all started in China, in the city of Wuhan in the province of Hubei. On December 16, 2019, a woman was hospitalized with pneumonia. The samples sent to the laboratory made it possible to identify a virus of the SARS family. On December 21, an outbreak of viral pneumonia appeared in the same city and several similar cases were hospitalized in the following days. The majority of the patients had

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frequented the Huanan seafood market, where a saleswoman, who fell ill on December 10, is believed to have been the first known case. [1]. In this type of wholesale market, different species of live wild animals were sold, a form of commerce developing at the time to compensate for the drop in the supply of pork meat following the African swine fever epizootic in 2018 [2].

On December 30, Li Wenliang, a 34-year-old ophthalmologist on duty at Wuhan Central Hospital, alerted his colleagues by internet messaging that a coronavirus had been identified in 7 patients. Li Wenliang was arrested on January 1 with his comrades for "spreading rumors" and "seriously disturbing the social order", and then released after signing a warning letter acknowledging that he had "disturbed the social order". Having contracted the infection in January, he was hospitalized in intensive care and died on February 7. On December 31, the Wuhan Municipal Health Commission officially reported the occurrence of 27 clustered cases of pneumonia of unknown etiology. All patients were placed in isolation and their contacts actively sought. On January 1, 2020, Huanan Market was closed to the public after disinfection [3]. On January 9, the first death was officially declared: a 61-year-old man.

On the same day, the Chinese CDC revealed that the causative agent of 15 of the cases of pneumonia had been isolated on human epithelial cell cultures and identified as a new betacoronavirus (2019-nCoV) of which the genome sequence, determined by researchers from the Fudan University in Shanghai and the University of Sydney, was filed during the following days in the international databases GenBank and Gisaid [4], allowing the development of RT-PCR detection tests.

On January 13, the first case outside China was recorded in Thailand in a traveler who had stayed in Wuhan. On January 22, a WHO mission to Wuhan found evidence of human-to-human transmission. In accordance with the International Health Regulations, an Emergency Committee was convened to assess whether the epidemic constituted a public health emergency of international concern, but its members considered that the phenomenon was still too limited and asked to be reconvened within 10 days to have more information [5]. On January 23, with a total of more than 1000 cases including 25 deaths, the Chinese authorities decided to place the 11 million inhabitants of Wuhan in strict quarantine and to lock down the entire province of Hubei, i.e. 60 million inhabitants. On January 30, after several dilatory exchanges with the Chinese CDC, the Director General of the WHO finally declared that it was a public health emergency of international concern.

On February 11, the International Committee on Taxonomy of Viruses (ICTV) announced that the name of this new virus would be SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) given its genetic proximity to the SARS-CoV responsible for the 2003 epidemic. On the same day, the WHO named this new disease “Covid-19” (coronavirus disease 2019) [6]. On March 11, with SARS-CoV-2 having spread outside China to Asia, Europe, the United States and Australia and having claimed more than 4000 people in 114 countries, the WHO finally considered that Covid- 19 could be called a pandemic.

3. Covid-19, a new disease

The first clinical descriptions of Covid-19 were given by Chinese doctors from a series of 1099 confirmed cases admitted to 552 hospitals up until January 29, 2020. The incubation period averaged 5 days (range: 2 to 12). The most common symptoms on admission were fever (43.8%) and cough (67.8%), with chest CT scans showing bilateral ground-glass images of pneumonia (56.4%) [7]. Another Chinese series of 44,672 patients distinguished 81% mild forms, 14% serious forms and 5% critical forms. Among hospitalized patients, 74−86% were at least 50 years old, 60−90% had comorbidities such as hypertension (48−57%), diabetes (17−34%), cardiovascular disease (21-28%), chronic lung disease (4-10%), chronic kidney disease (3-13%) and malignant tumors (6-8%) [8]. The main symptoms were fever (up to 90%), dry cough (60 to 86%), shortness of breath (53 to 80%), fatigue (38%), nausea/vomiting or diarrhea (15 to 39%) and myalgia (15 to 44%). Anosmia or ageusia were reported in 64 to 80% of patients, sometimes as the only revealing symptoms (3% of patients).

In some patients, the viral invasion phase was followed by inadequate immune response, usually 8 to 10 days after the first symptoms. This second phase, dysimmune, is also called cytokine storm. It is marked by worsening pulmonary symptoms with acute respiratory distress syndrome, multivisceral inflammatory syndrome that can affect the heart, brain, liver, kidneys, and coagulopathy with venous and arterial thromboembolic complications [9].

From a series of 72,314 cases followed by the Chinese CDC, the overall case fatality rate was estimated at 2.3%. Depending on age, case fatality rates (CFR) were zero before 10 years, 8% between 70 and 79 years, and 14.8% after 80 years. CFRs were high in patients with comorbidities: cardiovascular diseases (10.5%), diabetes (7.3%), chronic respiratory diseases (6.3%), hypertension (6%) and cancer (5.6%), and reached 49% in the event of hospitalization in critical care [10].

In most cases, the symptoms disappear within 2 to 6 weeks, but they may persist or reappear for weeks or months after initial recovery, even after a mild form. Long Covid has been reported in more than 20% of patients after 5 weeks and in more than 10% of patients after 3 months. It brings together polymorphic signs such as chronic fatigue, respiratory or digestive disorders, loss of taste or smell, headaches and neurological damage with confusion [11].

In children, Covid-19 cases are milder and rarely result in hospitalization, with only a small percentage (<7%) of hospitalized cases requiring mechanical ventilation. Pediatric inflammatory multisystem syndrome (PIMS) occurring 3 to 12 weeks after SARS-CoV-2 infection is similar to Kawasaki disease. An uncommon occurrence (2 cases out of 100,000 before the age of 21), it consists of a high fever with impairment of the general condition accompanied by digestive disorders, and which can be complicated by respiratory and cardiac disorders. It has been reported in Europe and North America [12].

4. SARS-CoV-2 and its variants

SARS-CoV-2 is not the first coronavirus to be isolated in humans. We were previously aware of 4 endemic coronaviruses responsible for usually mild respiratory infections, 2 belonging to the Alphacoronavirus genus (HCoV-229E and HCoV-NL63) and the other 2 to the Betacoronavirus genus (HCoV-OC43 and HCoV-HKU1). Two other Betacoronaviruses, responsible for severe acute respiratory syndrome in humans, have emerged over the past twenty years. SARS-CoV-1, which appeared in 2003, spread to 29 countries and caused 8096 cases and 774 deaths, but was brought under control within a few months. MERS-CoV, which first appeared in 2012, spread to 27 countries and caused more than 2494 cases with mortality approximating 35%; it remained weakly endemic in the Middle East. SARS-CoV-2 is the third highly pathogenic Betacoronavirus to have crossed the species barrier, but it is the first to have succeeded in becoming pandemic [13].

The virus (2019-nCoV) isolated from the bronchoalveolar lavage fluid of one of the first patients admitted to Wuhan Central Hospital had all the characteristics of coronaviruses: spherical in appearance, measuring 120 to 160 nm in diameter, with an envelope covered with petal-shaped spicules, the protein S (spike), giving the coronavirus a crown shape (Fig. 1). Its genome, fully sequenced, is an RNA of 29,903 nucleotides whose phylogenetic analysis has shown that it is closely related to coronaviruses of the genus Betacoronavirus, subgenus Sarbecovirus, known in China in bats [14]. These data were

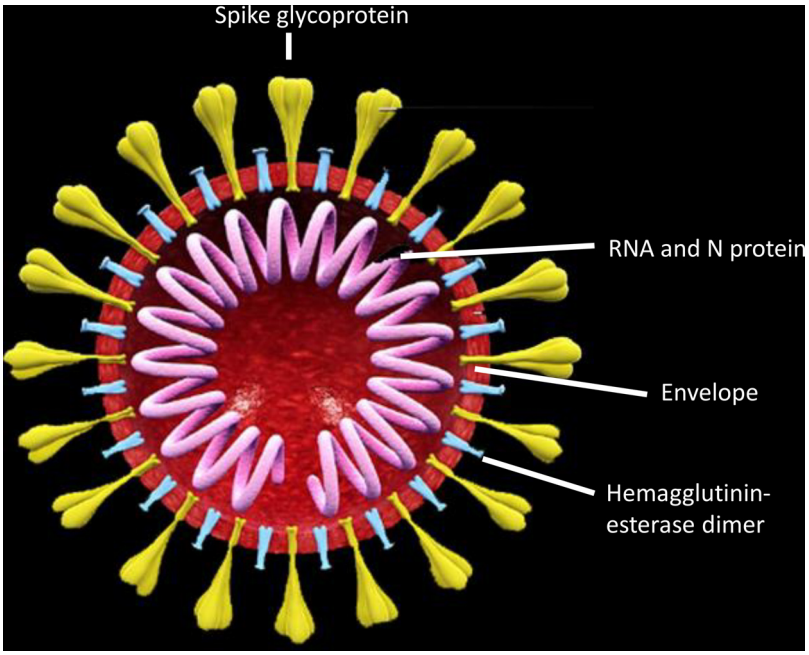

Fig. 1. Structure of SARS-CoV-2.

confirmed by complete sequencing of 5 viruses isolated in Wuhan, which revealed 96% homogeneity with a coronavirus (BatCoV RaTG13) previously identified in a bat from Yunnan province, *Rhinolophus affinis*. The 2019-nCoV virus presents 79.6% sequence identity with SARS-CoV-1, with which it shares the same cell entry receptor, the human angiotensin-converting enzyme 2 (ACE2). [15]. Analysis of another animal-derived coronavirus, Pangolin-CoV, showed 91% sequence homogeneity with SARS-CoV-2 and 90.5% with BatCoV RaTG13, suggesting that the pangolin may be an intermediate host between bats and humans [16]. But analysis of 70 SARS-CoV-2 genomes from 13 countries ruled out this hypothesis by highlighting the absence of a single peptide sequence (PRRA) of the spike protein in the Pangolin-CoV genome [17].

Viruses very similar to SARS-CoV-2 (BANAL-103, BANAL-236, BANAL-52) have been isolated in northern Laos in different species of bats. These 3 coronaviruses recognize the human ACE2 receptor with the same affinity as SARS-CoV-2, which reinforces the hypothesis that SARS-CoV-2 could have originated from populations of bats living in caves in karst reliefs located northern Laos and Vietnam and in southern China [18].

Although the animal origin of SARS-CoV-2 is no longer in doubt, the conditions for its crossing the species barrier have yet to be elucidated. A joint WHO-China international team conducted an investigation in January and February 2021. Its conclusions consider four hypotheses: (1) direct zoonotic transmission to humans, deemed possible to probable, (2) passage through an intermediate host, deemed probable to very likely, (3) introduction through food products, considered possible, (4) a laboratory incident, considered extremely unlikely [19].

In addition, the Chinese origin of Covid-19 could be called into question by the *a posteriori* confirmation of SARS-CoV-2 infections having occurred in Europe before the first cases in Wuhan [20].

Like all coronaviruses, SARS-CoV-2 has great genetic diversity linked to the plasticity of its genome. Point mutations arise during replication (amino acid substitution or deletion, insertion, duplication), and they are not always corrected by viral exoribonuclease. Some of these mutations have evolutionary potential, particularly those concerning the gene encoding the S protein which is involved in attachment to the cell receptor ACE2. They can alter the properties of the virus, especially its ease of transmission and spread, the severity of the disease it causes, its susceptibility to the host's immune response, and they can invalidate diagnostic or treatment measures. So it is that variant viruses can emerge, classified by the WHO in three categories: variants of concern (VOC), variants of interest (VOI) and virus under monitoring (VUM). This surveillance and the nomenclature of new variants are carried out by the Technical Advisory Group on the evolution of the SARS-CoV-2 virus (TAG-VE for Technical Advisory Group on SARS-CoV-2 Virus Evolution) in liaison with the laboratory networks GISAID, Nextstrain and Pango.

The first major variation was detected at the beginning of April 2020 in connection with the D614G mutation in protein S: substitution of aspartic acid (D) by glycine (G) at residue 614. The G614 variant was characterized by greater infectivity and higher viral loads than the D614 virus of the first human cases from Wuhan [21]. Five variants of concern then successively emerged:

- the Alpha variant, called B.1.1.7 or "UK variant", appeared in the United Kingdom in October 2020 and quickly spread to Europe, and then to all continents [22]. Carrier of the N501Y substitution in the RBD (receptor-binding domain) and twice as contagious as the original Wuhan strain, it became predominant in March 2021 and circulated until July, causing 1,200,000 confirmed cases in 160 countries.
- the Beta variant, called B.1.351 or "South African variant", was detected in December 2020 in South Africa, and then in Europe before spreading to 131 countries, totaling 28,500 confirmed cases until August 2021. It carries N501Y, K417N, and E484K mutations in the RBD, expressing greater affinity for the cellular receptor ACE2 and through partial escape from acquired immunity after prior infection [23].
- the Gamma variant, called B.1.1.248 or P.1 variant, was detected for the first time in a Japanese tourist returning from a trip to Brazil. It emerged in December 2020 in Manaus, in the Brazilian state of Amazonas, striking a population that had previously been 70% infected with SARS-CoV-2 [24]. It has spread to 78 countries, totaling 52,000 confirmed cases as of August 2021. Although it associates the N501Y, K417T and E484K mutations, the latter of which can lead to immune escape, it is significantly less resistant to post- infectious or post-vaccination antibodies than the B.1.351 variant [25].

- the Delta variant, called B.1.617 or "Indian variant", appeared in October 2020 in central India in Maharashtra. There are in fact three lineages (B.1.617.1, B.1.617.2 and B.1.617.3) sharing the L452R mutation. The B.1.617.2 lineage has an advantageous transmissibility profile, linked to the T478K substitution, which renders it 40 to 60% more contagious than the other variants in circulation. It quickly spread to all continents and was reported in 148 countries by August 2021, becoming dominant everywhere in the last quarter of the year. In addition, it partially but significantly escapes neutralizing antibodies targeting N-terminal domain (NTD) and RBD epitopes developed after infection or vaccination. [26].
- the Omicron variant, belonging to the B.1.1.529 lineage, appeared in November 2021 in South Africa in the Gauteng region, and was immediately noticed by the speed of its spread in Europe and the rest of the world. It is the most divergent variant detected since the start of the pandemic: its genome has 62 mutations compared to the original Wuhan strain, of which 15 are located in the RBD-binding domain with 3 deletions and an insertion in protein S [27]. Its transmissibility, three times greater than that of the Delta variant, and its ability to infect previously infected or vaccinated people give it a major advantage and have enabled it to supplant the other variants throughout the world in a few weeks [28]. On the other hand, its virulence is less than that of the previous variants, the risk of hospitalization and management in intensive care being reduced by 50 to 60% [29].

5. A multiphasic evolution

Pandemics generally evolve in several successive phases, compared with "waves" according to epidemiologists who have reported on the Spanish flu. Covid-19 followed this pattern by alternating more or less intense epidemic phases, each time involving a rapid rise in the number of new cases, a peak or a plateau, and then a decrease. By the end of January 2022, the Covid-19 pandemic was considered to have traversed five waves, but with significant geographical disparities [30] linked to infection control policies ("zero Covid" strategy in China) or to more complex factors (lower incidence in sub-Saharan Africa). Worldwide, it has caused 395,000,000 confirmed cases including 5,700,000 deaths; in Europe, 123,600,000 cases including 1,900,000 deaths; and in France, 18,400,000 cases including 130,000 deaths. The countries with the highest mortality are the United States (900,000 deaths), Brazil (630,000 deaths), India (500,000 deaths), Russia (350,000 deaths) and Mexico (310,000 deaths), these rapidly changing Fig.s being subject to significant variations depending on the data sources. Covid-19 has also caused profound socio-economic upheavals and a significant decline in global growth. In 2020, gross domestic product fell by 4.7% in advanced countries, 3.5% in the United States, 4.9% in Germany, 8.2% in France, 8.9% in Italy, 9.9% in the UK and 11% in Spain, but only 2.3% in China (data from the International Monetary Fund).

Despite time lags, the countries of Europe, the American continent and the Indian subcontinent suffered comparable episodes. The course of the epidemic in France can be taken as a representative example (Fig. 2):

- the first wave (February - May 2020) peaked between April 6 and April 10 before gradually descending from April 20 to the beginning of June.
- the second wave (September - November 2020) began at the end of August, with circulation of the virus reappearing mainly among young adults. After a drop in the number of new cases in the second half of September, a rapid rise was observed from October 1, following a general drop in temperatures, reaching a peak between November 12 and 19, 2020.
- the third wave (March - April 2021) appeared in mid-March 2021 with an average of 50,000 new cases a day. The peak was reached on April 12 with 495 new critical care admissions.
- the fourth wave (July – August 2021), mainly linked to the Delta variant, started at the beginning of July and presented two peaks, on July 29 and August 12. Affecting mainly young people (80% of confirmed cases are under 50 years) and limited by increased vaccination coverage, it resulted in fewer hospitalizations and deaths than previous waves.
- the fifth wave (November 2021 – February 2022?) appeared in October 2021. Initially linked to the Delta variant, it was considerably amplified by the eruption of the Omicron variant at the beginning of December, with a dramatic increase in the number of contaminations throughout the country, exceeding 400,000 new cases per day for more than a week in January and mainly affecting children under 15 and young adults between 30 and 44 years old. The epidemic peak, expected in mid-January, had not yet been reached at the end of the month. The reason for this may be the occurrence of an Omicron B.A2 subvariant which is spreading very quickly in India, Denmark and many other countries.

Can the rapid spread of the Omicron variant give hope for the establishment of generalized herd immunity and the end of the pandemic? Will the fifth wave be the last or will there be a sixth? No one can predict today: if the duration of acquired immunity after infection remains uncertain, the genetic variability of SARS-CoV-2 and the sudden eruption of the B.A2 sub-variant do not rule out the emergence of a new variant that would be even more transmissible and capable of immune evasion.

6. Epidemiological surveillance

Following the framework defined by the WHO [31], most countries have implemented a surveillance system to assess the epidemiological situation of Covid-19, the objectives being to adapt preventive measures, to limit the spread of the virus by breaking the chains of transmission, to identify risk factors and vulnerable populations and to share the data collected internationally.

The evolution of the epidemic is monitored by registering people in whom SARS-CoV-2 infection has been confirmed by diagnostic tests [32]. In France, the SI-Dep file (integrated screening and prevention service) was created in May 2020. This nominative database includes the results of serological tests and RT-PCR tests and was subsequently extended to antigenic tests and supervised self-tests. The epidemiological surveillance of Covid-19 is based on four main indicators, updated each week [33]: (1) the incidence rate, i.e. the number of people tested positive (RT-PCR or antigenic test) relative to the size of the reference population per 100,000 inhabitants; (2) the positivity rate of virological tests; (3) the virus reproduction rate (R effective) defined as the average number of people an infected person can infect; (4) the occupancy rate of intensive care beds by patients with Covid-19.

Epidemiological surveillance is complemented by genomic surveillance for the detection and monitoring of variant viruses. Some of the clinical samples found positive by the RT-PCR test are sent to a high-throughput sequencing platform. In France, sequencing capacities have been increased to deal with the pandemic, currently making it possible to process nearly 12,000 samples each week in the framework of the EMERGEN consortium and to deposit the sequences in the international Gisaid database.

Another indicator of the circulation of the virus, still underused, is provided by analysis of wastewater to detect SARS-CoV-2 in wastewater treatment plants. The quantification of viral load in wastewater by RT-PCR is correlated with the level of circulation of the virus in the population served. In addition, the variations observed are predictive

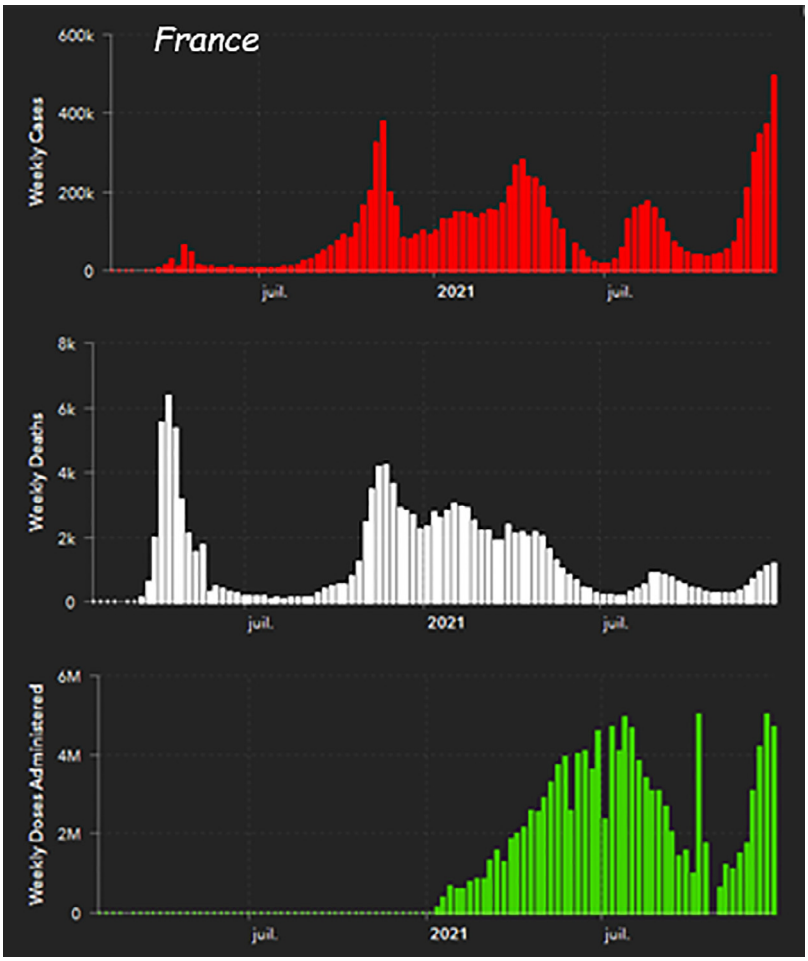

Fig. 2. The Covid-19 pandemic in France: 5 waves from March 2020 to November 2021 (red bars: weekly cases; white bars: weekly deaths; green bars: weekly doses of vaccine administered).

of the evolutionary trends of the Covid-19 epidemic and make it possible to detect the appearance of a variant virus at a very early stage [34]. In France, the wastewater epidemiological observatory (OBEPINE), created in April 2020, covers a representative sample of 200 wastewater treatment plants throughout the country. It is now part of the Covid-19 epidemiological surveillance system [35].

7. Measures against Covid-19

7.1. Non-pharmacological measures

Learning from the experience of outbreaks of respiratory-borne viral infections in the past, health authorities have implemented non-pharmacological interventions to prevent the contamination and spread of SARS-CoV-2; they include physical distancing, barrier measures, regular hand washing with water and soap and disinfection with hydroalcoholic gel. However, by making reference to influenza viruses or SARS-CoV-1, scientists have overlooked two original properties of this emerging virus: the first is the contagiousness of infected people, even when they are asymptomatic or presymptomatic [36]; the second is the transmissibility of the virus by aerosols, and not only by droplets [37]. The late consideration of these two characteristics essential for understanding the epidemiology of Covid-19 explains the hesitations of the WHO and governments before recommending the wearing of anti-projection masks in public space, especially in enclosed places and public transport. In France, this doctrine was advocated on April 2, 2020 by the *Académie nationale de médecine* [38], but it was not actually applied until six months later.

When scrupulously observed, these measures were the most effective public health interventions before safe and effective vaccines were available to protect those at risk of severe Covid-19. [39].

7.2. Drugs

From the first weeks of the pandemic, researchers around the world have drawn on the pharmaceutical arsenal already available to find effective drugs against Covid-19, either in the primary phase of viral replication or in the secondary immuno-inflammatory phase. The search for a molecule active on SARS-CoV-2 has been unsuccessfully directed towards known antivirals and towards antibiotics and antiparasitics with an antiviral action *in vitro*:

- Remdesivir is a nucleotide analogue prodrug that inhibits viral RNA-dependent RNA polymerase, originally developed for the treatment of Ebola virus, but it has not been proven effective in reducing Covid-19 mortality [40].
- Lopinavir-ritonavir is a viral protease inhibitor used for the treatment of HIV/AIDS infection, but it is not effective in patients hospitalized for Covid-19 [41].
- Hydroxychloroquine, a derivative of chloroquine, is prescribed in the treatment of systemic lupus erythematosus and rheumatoid arthritis due to its anti-inflammatory and immunomodulatory effects. Despite wide use worldwide for the treatment of Covid-19 and after lengthy international controversy, hydroxychloroquine

has not been found to reduce mortality in hospitalized patients, and in combination with azithromycin, it significantly increases mortality [42].
- Two other antiparasitic drugs have not confirmed in vivo their broad-spectrum antiviral efficacy observed in vitro: ivermectin [43] and nitazoxazide [44].

More recently, other antiviral molecules have been proposed for the treatment of Covid-19 in the early phase: molnupiravir is a prodrug metabolized into a broad-spectrum mutagenic ribonucleoside active on RNA viruses; in France, it has not been approved due to its efficacy having been deemed insufficient [45]. On the other hand, early access authorization was granted for the viral antiprotease combination nirmatrelvir/ritonavir (Paxlovid®), which can be prescribed in community medicine and administered orally [46]. Severe forms of the disease require careful monitoring of respiratory status and hemoglobin oxygen saturation, with acute respiratory distress syndrome likely to appear one week after the onset of symptoms. The Covid-19 experience has considerably advanced respiratory resuscitation and oxygenation strategies by clarifying the indications for endotracheal intubation by adapting the pressure and volumes of mechanical ventilation so as to protect the lungs, placing patients in deep sedation and prone positioning in the event of refractory hypoxemia and using extracorporeal membrane oxygenation if necessary [47].

Research has also been directed towards drugs with anti-inflammatory or immunomodulatory properties. Colchicine, a classic treatment for gout attacks, has aroused therapeutic interest in Covid-19, but a meta-analysis has shown that it provides no benefit in patients with Covid-19 [48]. On the other hand, dexamethazone has shown some efficacy; on September 18, 2020, after reviewing the interim results of the RECOVERY study, the European Medicines Agency (EMA), approved its use in patients with COVID-19 and placed on oxygen therapy or mechanical ventilation [49]. Similarly, better understanding of the mechanisms upstream from coagulopathy and immunothrombosis in Covid-19 has made it possible to optimize anticoagulant treatments in hospitalized patients at different stages of severity [50].

Passive immunotherapy with convalescent plasma yields variable results depending on antibody content [51], in the absence of obvious benefit, it is not recommended by the WHO [52]. Tocilizumab is a humanized anti-IL-6 monoclonal antibody used for the treatment of rheumatoid arthritis. In patients hospitalized with severe COVID-19, it reduces the need for invasive mechanical ventilation and mortality [53]. Another interleukin inhibitor, anakinra (anti-IL-1), may reduce mortality risk in patients admitted to hospital with moderate to severe COVID-19 pneumonia [54]. Other monoclonal antibodies (MABs) have been developed to bind to the spike protein of SARS-CoV-2 and prevent the virus from invading human cells. Used alone or in combination, they may provide benefit in patients at high risk, aged over 65, immunocompromised, with comorbidities or having contraindications to vaccination. The neutralizing activity of MABs, directed towards the S protein of SARS-CoV-2, can disappear in case of variant viruses. Among all the formulations currently on the market, only one remains effective against the Omicron variant, namely sotrovimab (Xevudy®, GSK) [55].

7.3. Vaccines

The development of vaccines against highly pathogenic coronaviruses for humans, was suspended after the disappearance of SARS-CoV-1 in 2003, had not pronouncedly advanced with MERS-CoV. However, there remained a knowledge base that proved useful to researchers. To be sterilizing, humoral immunity requires neutralizing antibodies that bind to the RBD to prevent virus entry into target cells. The importance of cellular immunity had also been demonstrated in patients cured of SARS: after 8 years, while the neutralizing antibodies and the memory B lymphocytes responsible for their synthesis had completely disappeared, specific anamnestic responses of the T lymphocytes persisted [56].

Research to obtain vaccines against SARS-CoV-2 began in January 2020, as soon as the genetic sequence of the virus became available. They then progressed at an unprecedented speed. By August, more than 180 vaccines, based on different platforms, had reached different stages of development [57]. On December 10, the WHO identified 52 candidate vaccines in clinical evaluation, either developed from traditional platforms (inactivated or attenuated virus vaccines), or having already resulted in approved vaccines (recombinant protein vaccines and viral vector vaccines), or totally innovative (DNA or RNA vaccines) [58]. While the different development phases of a new vaccine usually require more than ten years, the health emergency context has mobilized scientific teams around the world and considerable financial resources from the European Union (more than 250 million euros) and the United States (several billion dollars).

The most extraordinary scientific advance, opening a new page in the history of vaccinology, is undoubtedly the advent of the first messenger RNA vaccines. This technology, however, was not new. It was designed by the biochemist Katalin Karikó in the 1990s and perfected from 2005 to 2012 at the University of Pennsylvania in collaboration with the immunologist Drew Weissman. Since then, many teams have worked on mRNA vaccines in oncology and infectious diseases before the Covid-19 pandemic provided them with an opportunity to put them into practice [59]. In 2008, two German doctors of Turkish origin, Ugur Sahin and Özlem Türeci, bio-oncology researchers, founded BioNTech, a biotechnology company specializing in immunotherapy. In January 2020, they developed the first messenger RNA vaccine against Covid-19 and on March 17, they signed a partnership with the American pharmaceutical company Pfizer for the development and production of two candidate vaccines "BNT162b1" and "BNT162b2". For its part, the American company Moderna (for "Modified RNA"), engaged for ten years in research on messenger RNA in therapy, joined forces with the National Institute of Allergy and Infectious Diseases (NIAID) to develop a vaccine against SARS-CoV-2, thereby benefiting from significant government aid, in particular from the Biomedical Advanced Research and Development Authority (BARDA).

The context of the international health emergency has motivated unprecedented efforts to accelerate the development of vaccines and shorten the stages of development, with phase III clinical trials starting as soon as analysis of the intermediate results of phases I/II [60]. In December 2020, the performance of the first two candidate messenger RNA vaccines was revealed. On December 20, a randomized clinical trial of the candidate vaccine BNT162b2 (BioNTech / Pfizer) carried out on 43,548 people aged 16 or over showed 95% protective efficacy against Covid-19 and satisfactory safety [61]. On December 30, another phase III, randomized and controlled trial of the mRNA-1273 vaccine (Moderna) conducted on 30,420 volunteers showed efficacy of 94.1% [62]. More than merely encouraging, these first results greatly exceeded the objectives set by the WHO according to which clinical trials had to attest to protective activity of at least 70%.

At the same time, several vaccines have been constructed with non-replicating adenoviral vectors, a technique already used to vaccinate against the Ebola virus. Different adenoviruses genetically modified to express protein S have been used. The University of Oxford and the Anglo-Swedish firm AstraZeneca have developed the ChAdOx1 nCoV-19 vaccine from a chimpanzee adenovirus. Interim analysis of early clinical trials showed average vaccine efficacy of 70.4% against symptomatic COVID-19 [63]. In Russia, the Sputnik V vaccine was developed by the Gamaleya Research Institute with two different human adenoviruses, HAdV26 (first dose) and HAdV 5 (second dose) to prevent anti-vector immunity from developing after the first

injection and limiting the effectiveness of the second; in a phase III trial on a cohort of 21,977 adults, its efficacy was evaluated at 91.6% [64], but it has not been approved by the WHO. The American company Johnson & Johnson (Janssen) chose the adenovirus HAdV26 for a single dose immunization, given the results of phase I/II clinical trials comparing one or two doses [65].

A very rare but serious adverse event has been reported in people vaccinated with the AstraZeneca ChAdOx1 nCoV-19 vaccine or the Janssen Ad26.COV2.S vaccine, namely thrombosis with thrombocytopenia syndrome (TTS), similar to heparin-induced thrombocytopenia (HIT). It has been shown that these vector adenoviruses can bind to platelet factor 4, which is involved in HIT pathogenesis [66]. For this reason, in France, the Haute Autorité de Santé (HAS) reserved the prescription of these two vaccines to people over the age of 50, who are much less at risk of TTS [67].

Alongside vaccines targeting protein S only, traditional whole-virus, inactivated or attenuated vaccines have been developed. Produced in Vero cell cultures, the viruses are inactivated by heat or ß-propiolactone to preserve the three-dimensional structure of protein S. Unlike vaccines that only target protein S, these vaccines elicit an immune response against all viral proteins preserved upon inactivation. Two inactivated formulations have been developed in China, the anti-Covid-19 vaccine of the Sinopharm firm, and the Covid-19 vaccine CoronaVac (or Sinovac) of the Sinovac Biotech firm, and approved by the WHO for emergency use. The Sinopharm vaccine claimed 79% efficacy against symptomatic infection and the Sinovac vaccine 51% efficacy. These two vaccines account for almost half of the 7.3 billion doses of COVID-19 vaccine delivered worldwide, particularly in less wealthy countries: about 2.4 billion doses have been administered in China and nearly one billion doses distributed in 110 other countries (Indonesia, Brazil, Pakistan, Turkey, Iran, Philippines, Morocco, Thailand, etc.). Numerous studies have shown that immunity after two doses of these vaccines wanes rapidly, that levels of neutralizing antibodies are lower than those elicited by messenger RNA vaccines, and that older people are less well-protected against severe and fatal disease [68]. Neither vaccine has been approved by the EMA.

8. Strategies for disease control

All of the pandemic crisis plans updated by WHO [69], as well as national epidemic prevention and control strategies [70], were developed to deal with a new influenza pandemic. The emergence of a highly pathogenic coronavirus, against which no one was immune and against which there was no vaccine or antiviral drug, was not foreseen, despite the heralding episodes of SARS in 2003 and MERS in 2012.

To manage such a crisis situation in a context of urgency and uncertainty, governments had to choose between two strategies: mitigation and repression. The mitigation strategy, initially considered by the Netherlands, Sweden and the United Kingdom, was to let the virus spread in the population so that they were immune, but it did not protect populations at risk from serious forms, and it exposed them to the risk of numerous hospitalizations and deaths, in addition to overburdened health systems. The suppression strategy was to prevent the spread of the virus through comprehensive social distancing measures that could go as far as total containment of the population. It was effective in containing the infection if applied very early, but at a very heavy social and economic cost. This was the strategy applied very quickly by the Chinese government in the province of Hubei and, later, in many European countries. As of April 2020, 42 countries or territories had implemented generalized confinement of their population, i.e. 2.5 billion people worldwide. Depending on the phases of the pandemic and the occupancy rate of intensive care services, the health authorities of each country alternately combined the two strategies.

At the geopolitical level, a difference has emerged between countries with democratic regimes, in which the constraints imposed on populations have been limited by protests of attacks on freedoms, and countries with authoritarian regimes, which have quickly succeeded in containing the circulation of the virus, at the cost of strict containment measures and border closures. However, the "zero Covid" strategy has been implemented not only by dictatorial states, but has shown excellent results in democratic countries such as Iceland, Australia, New Zealand and Japan, with a positive impact on mortality and less disruption of the economy [71], before being abandoned due to the emergence of the Delta variant.

In France, the government set up two expert committees to inform public decision-making on the management of the health situation, a Scientific Council created on March 11 and an Analysis, Research and Expertise Committee (CARE) installed on March 24, 2020. According to the 2011 nationwide “influenza pandemic” prevention and control plan [70], the strategy was divided into four stages. France entered phase 1 on January 24, 2020 with notification of the first case, then phase 2 on February 29 (100 cases, 2 deaths) and phase 3 on March 14 (4,500 cases, 91 deaths). As the virus was then circulating throughout the territory, the objective was no longer, as in stage 2, to slow the spread of the virus, but rather to mitigate its effects. On March 16, the Government decided to confine the population for a period of at least 15 days [72]. After two extensions, the lockdown was lifted on May 11. An emergency law, passed on March 23, 2020, added to the public health code the option of establishing a state of health emergency [73]. Once the second wave had arrived, the state of health emergency was re-established throughout the territory, on October 14, 2020. Partial confinement was introduced in 54 departments in the form of a curfew maintained until mid-December. During the following waves, the measures restricting movement and activities were modulated according to territorial situations and the risks of hospital congestion.

On March 16, 2020, Tedros Adhanom Ghebreyesus, the WHO's Director General, outlined a strategy to break the chains of transmission by testing all suspected cases: “*You cannot fight a fire blindfolded. And we cannot stop this pandemic if we don't know who is infected. We have a simple message for all countries: test, test, test*”. In France, this recommendation inspired the “*tester-tracer-isoler*” strategy applied from May 11, 2020 following termination of the lockdown. The RT-PCR test was recommended for suspected patients and for contacts of confirmed cases, the objective being to quickly identify and isolate people infected with SARS-CoV-2, whether symptomatic or not. But screening capacities were still low (35,000 RT-PCR tests per week compared to 500,000 in Germany). After the weekly number of tests had reached and exceeded 1 million, the July 24 decree allowing anyone to access the RT-PCR test, with or without a prescription, with full reimbursement by health insurance [74] led to a huge considerable influx of people wishing to be tested without valid reason. This strategy proved to be inefficient due to the congestion of screening chains and delays in reporting results. Promulgated on October 14, the modified « *tester-alerter-protéger* » strategy encountered the same obstacles and was unable to prevent increased contamination and a second wave of the epidemic.

The first vaccines against Covid-19 became available less than a year after the start of the pandemic. Without waiting for official approval, the most developed countries entered into competition to order large quantities of doses from the various platforms. So it was that the European Community had reserved 300 million doses of candidate vaccine at Sanofi-GSK (vaccine still pending), 400 million doses at AstraZeneca, 225 million doses at CureVac, 200 million doses at Johnson & Johnson and 80 million doses at Moderna, before reaching an agreement on November 11, 2020 for the delivery of 200 million doses of the Pfizer-BioNTech vaccine, with an option for an additional 100 million doses. All in all, these six agreements promised the delivery of 1.5 billion doses of vaccines to the European Union

countries. In France, as elsewhere, an order of priority of people to be vaccinated was established for the first phases of supply, placing in front of the line the elderly and vulnerable people housed in institutions [75].

Approved on December 21, 2020 by the EMA and recommended in France on December 24 by the HAS, the Pfizer-BioNTech vaccine (Comirnaty®), was the first to be used. The first injection was made on December 27 in a 78-year-old woman. Then came the Moderna vaccine (Spikevax®), which was approved on January 6, 2021 by the EMA. Given the fragility of RNA molecules, the preservation of these two vaccines required strict storage conditions in super-freezers, not exceeding 6 months, between -90°C and -60°C for Comirnaty®, and -25 °C and -15 °C for Spikevax®. After that, two adenoviral vector vaccines were released, the AstraZeneca vaccine (Vaxzevria®) on January 29 and the Johnson & Johnson vaccine (Janssen COVID-19 Vaccine) on March 11.

The national vaccination campaign started very slowly in France, with fewer than 100 people being vaccinated during the first three days. The health authorities envisaged vaccination by proximity rather than mass vaccination, which was nonetheless necessary in order to achieve the objective set by the government: 10 million first injections in mid-April and 20 million the following month. The creation of ephemeral vaccination centers, known as "*vaccinodromes*", was finally implemented in April 2021. However, hope of herd immunity was proving increasingly unattainable, what with a leveling off in the vaccination curve in adults and the surge of the Delta variant. Modeling by the Pasteur Institute showed that it would be possible to relax the control measures if, with 90% of those over 65 being vaccinated, 89 to 100% vaccination coverage was obtained among 18-64 year-olds, or 60 to 69% among 0-64 year-olds [76].

Around the world, several countries have imposed compulsory Covid-19vaccination: Ecuador, Indonesia, Micronesia, Tajikistan, Turkmenistan as well as New Caledonia. In Europe, certain countries have adjusted the vaccination obligation according to age group or profession (Austria, Italy, Greece, Poland, Hungary and Germany).

In France, Covid-19 vaccination was made compulsory on August 5, 2021 for professionals working in the health and medico-social sectors [77]. To increase vaccination coverage in the general population, two decisions were implemented. The first was the establishment on June 9, 2021 of a health pass attesting to vaccination status, or a negative test or recent infection with SARS-CoV-2 (recovery certificate), which was required to enter places open to the public. The second was the June 15, 2021 expansion of the population eligible for vaccination to minors aged 12 to 17. These measures came into force too late to contain the fourth wave of the epidemic, which appeared in July, and too partial to avoid the fifth wave, which appeared in November. They were supplemented on December 22 by the extension of vaccination to all children aged 5 to 11, and then on January 24, 2022 by the transformation of the health pass into a vaccination pass [78].

9. Lessons to be learned

The story of Covid-19 is not over. Well-adapted to its human host, SARS-CoV-2 will not disappear like SARS-CoV-1 in 2003. With the Omicron variant, it has become a virus in transition which will probably continue to circulate in an endemic mode, with seasonal epidemics mainly affecting non-immune children, as do coronaviruses causing winter colds [79].

However, we can draw the first lessons from this global health crisis.

Covid-19 is the most serious pandemic since the Spanish flu of 1918-19. It took the entire world population by surprise; since the 2009 A/H1N1 pandemic, which had proved to be relatively mild, the flu had ceased to be feared. Subsequently, the pandemic potential of the highly pathogenic Betacoronavirus agents of SARS and MERS were not taken seriously enough; confident in its warning systems and crisis plans, the world was not sufficiently prepared for Covid-19. Some states have been slow to share epidemiological and genomic data useful for a real-time response, thereby providing the virus with time to spread [80]. On the other hand, unbridled communication of dubiously accurate and misleading information has sowed doubt and distrust in people's minds, leading the Director General of the WHO to declare "*We're not just fighting a pandemic; we're fighting an infodemic*", justifying a resolution to combat misinformation throughout the world [81].

Nobody knows when the next great pandemic will happen, but on the day it does, it would be criminal to let it destroy millions of additional lives and devastate the world as Covid-19 did.

Declaration of Competing Interest

The author declare that he has no competing interest

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