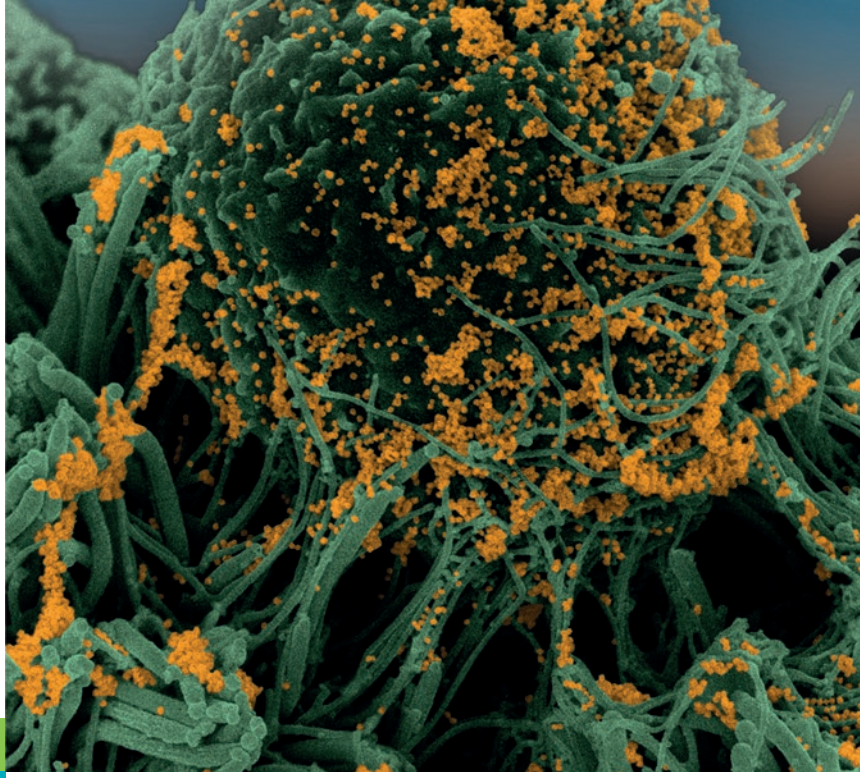


SARS-CoV-2, COVID-19 epidemic

The Institut Pasteur's response, scientific research and discoveries in 2020

INSTITUT PASTEUR

This document was first completed between November and December 2020 and subsequently finalized in January 2021 in the current unprecedented COVID-19 pandemic. Continuing and untiring efforts to fight SARS-CoV-2 result in a workload increase for many Institut Pasteur teams.
We wish to extend our heartfelt thanks to all contributors for their commitment in these challenging times and to the readers of this "COVID-19 special" for their understanding when reading these pages.

Editorial

On January 25, 2021, we were preparing to share our summary of the Institut Pasteur's response to COVID-19 in 2020. Our dedicated teams of scientists and administrative staff had been working since November on the document that you are reading. But on January 25, with deep sadness and an immense sense of responsibility, the Institut Pasteur had to take the decision to discontinue the program of one of its SARS-CoV-2 vaccine candidates. The intermediate results of the Phase I clinical trial were not as positive as had been hoped. In scientific terms it was the only decision left for us to take, and we had to do so with humility.

We began sharing our results in late January, but I wanted to add a personal message, a few days after the event, to remind you all that for any self-respecting scientist, modesty and perseverance are virtues. For more than 130 years now, they have also been values that have characterized the Institut Pasteur as it carries out its work for the benefit of human health.

So we are determinedly pursuing the development of other vaccine candidates which have reached preclinical phase, alongside our other efforts to tackle the COVID-19 epidemic. We are engaged in research in multiple fields – in diagnostics to identify positive cases, in modeling to monitor the outbreak, and in basic research to help understand the virus.

After such an eventful, turbulent year in 2020, it is important for us to remain united and committed. Like you, and like all the Institut Pasteur teams, I have been impressed by the incredible resilience shown by people in France and around the world in the face of such a brutal epidemic. I was moved by their solidarity and generosity as they went out of their way to make masks, support healthcare workers, help isolated neighbors and show their support for research and scientists.

Driven by this collective momentum, in sometimes difficult working conditions – as was the case for everyone –, the Institut Pasteur conducted extensive research on COVID-19 and the SARS-CoV-2 virus which causes the disease, with the support of its partners in hospitals, academia and industry. I would particularly like to express my thanks to the healthcare workers who worked with us on the many clinical trials launched in 2020. Thanks to their efforts, and yours, we were able to be quick off the mark and to launch a huge number of projects, many more than we thought.

Our response has been unprecedented, and our dedication will not waver!

Stewart Cole,
President of the Institut Pasteur, Paris

Report on the response and main achievements of the Institut Pasteur in 2020

On December 31, 2019, the China Country Office of the World Health Organization (WHO) was informed that clustered cases of pneumonia of unknown etiology had been detected in the city of Wuhan, in the Chinese province of Hubei. On January 9, 2020, the Chinese health authorities and WHO announced the discovery of a novel coronavirus, thought to have emerged in Wuhan in December 2019, that was responsible for the outbreak. The date of emergence of the virus in China was subsequently called into question. The coronavirus, named SARS-CoV-2 on February 11, was identified as the agent responsible for a new infectious respiratory disease subsequently named COVID-19 (coronavirus disease 2019). This officially marked the start of an epidemic that would rapidly spread across the globe and be classified as a pandemic by WHO on March 11, 2020.

Institut Pasteur at the heart of the national response in France

The Institut Pasteur found itself on the front line of the response in France from the very start of the epidemic, in January 2020. The Institut Pasteur hosts several National Reference Centers (CNRs), designated by the French General Directorate of Health and Santé publique France, which are responsible for monitoring various infectious diseases. These include the CNR for Respiratory Infection Viruses (including Influenza), which had the task of diagnosing, monitoring and analyzing cases of COVID-19 in mainland France as soon as the first cases were suspected. The Laboratory for Urgent Response to Biological Threats (CIBU), set up in 2001 by the Institut Pasteur with the support of the General Directorate of Health so that it could intervene 24/7 in the event of an outbreak, was immediately mobilized to support the work of

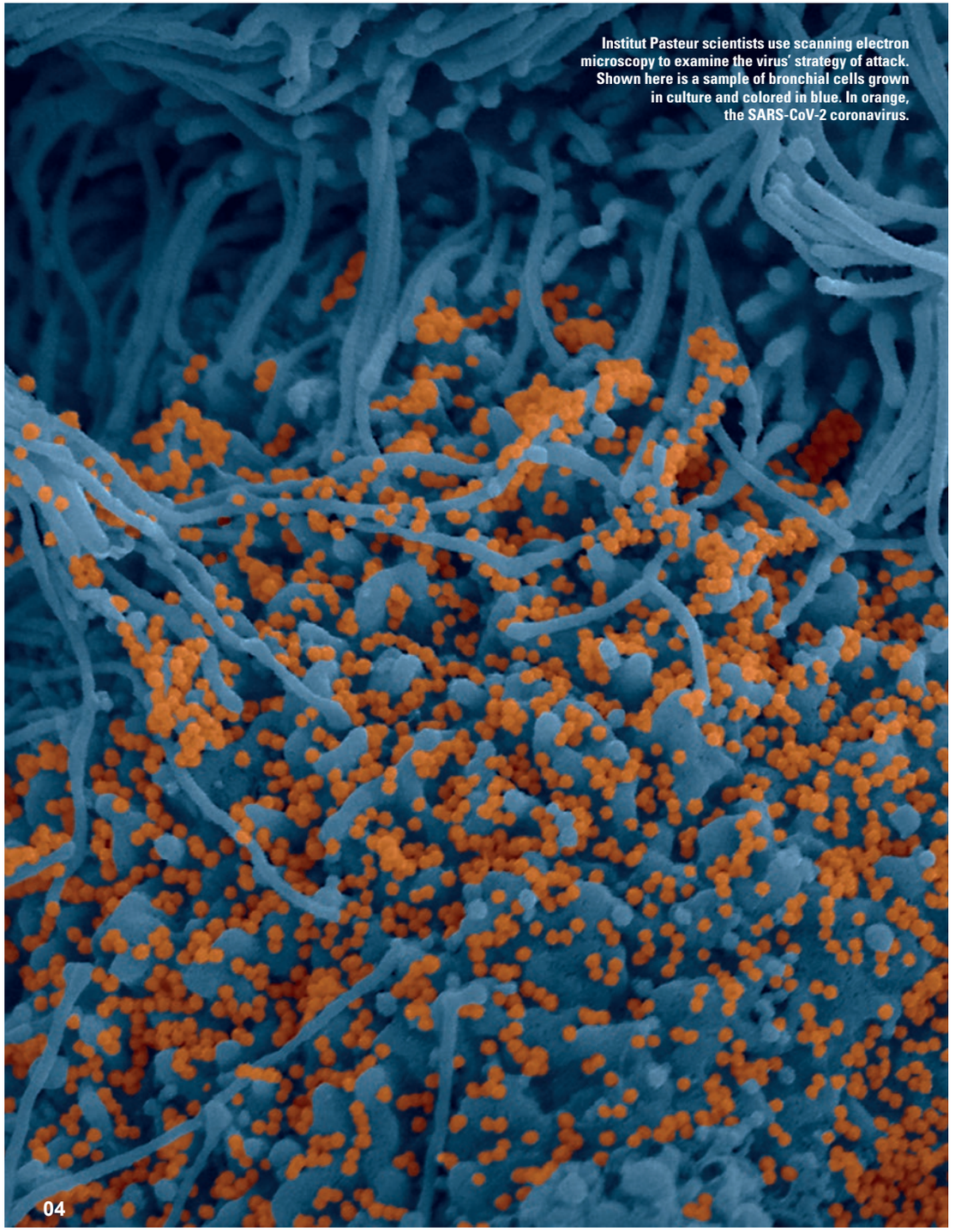
the CNR. The first suspected cases in France were identified on January 24, 2020 (source: French Ministry of Health). The samples taken from these patients were analysed by the CNR, which confirmed infection with the SARS-CoV-2 virus (by now sweeping through China), based on the sequence that Chinese scientists had shared with the international scientific community.

Task force rapidly set up

The Institut Pasteur is a leading global center for infectious disease research, one of the priority research areas identified in its 2019-2023 Strategic Plan. On January 27, 2020, as the 11 million inhabitants of the Chinese city of Wuhan, where COVID-19 had originated, found themselves in a strict lockdown, the Institut Pasteur set up a task force to provide an emergency response to the health crisis by studying the virus and the disease it causes. The task force continues to draw on the expertise of Institut Pasteur scientists in several research fields:

- **Knowledge of the virus and its pathogenesis;**
- **Development of new diagnostic and serological tools;**
- **Research into therapeutic strategies, including antibody-based approaches;**
- **Vaccine development;**
- **Epidemiology and modeling to develop outbreak control strategies.**

Around 20 research projects were launched in late January, and 89 projects in total over the whole of 2020.



Institut Pasteur scientists use scanning electron microscopy to examine the virus' strategy of attack. Shown here is a sample of bronchial cells grown in culture and colored in blue. In orange, the SARS-CoV-2 coronavirus.

The Institut Pasteur's response

More than 450
Institut Pasteur scientists
involved in COVID-19 research,
in 69 teams

79 "COVID" scientific papers
Source: Web of Science. January 18, 2021. This figure may change between now and March 2021.

19 patent-protected inventions
for diagnostics, vaccines or potential treatments for SARS-CoV-2
(as of December 2, 2020)

78 contracts
signed with industry
(as of December 2, 2020)

→ **Deep involvement of technological platforms** in COVID research, while maintaining essential activities

→ **Ongoing support from administrative departments** to ensure that research can progress as quickly as possible

→ **Tech transfer: 78 contracts covering collaboration agreements, licenses, service agreements** (diagnostics, vaccines, therapeutics) signed with industry
(as of December 2, 2020)

→ **Calls for proposals to launch new,** more ambitious interdisciplinary research projects involving several teams

Sources: Scientific Secretariat General, Scientific Information Resources Center, Technology Transfer and Industrial Partnership Department Institut Pasteur (Paris).

COVID-19: the major achievements of the Institut Pasteur in 2020

The first diagnostic test for patients

In the second half of January, the National Reference Center (CNR) for Respiratory Infection Viruses, tasked with monitoring infectious diseases, developed a direct detection test for the coronavirus using a molecular biology method known as RT-qPCR.

This test was used to diagnose the first patients in France and was then rolled out in hospitals, serving as a benchmark for the development of other PCR tests in France. In 2020, the Institut Pasteur also developed an RT-LAMP test for rapid diagnosis in 10 to 30 minutes.

Phylogenetic analyses and serological assays to describe and map the epidemic

Phylogenetic analyses, like the one performed by the Institut Pasteur in early 2020 on around a hundred patient genomes, help scientists to understand and describe how a virus is introduced in a geographic region (such as France), and how it first circulates.

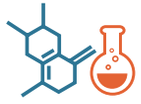
The Institut Pasteur also developed various serological assays, which detect SARS-CoV-2 antibodies in the blood and determine whether an individual has been infected by the virus in the preceding weeks. These serological assays are used to map the spread of the virus in the population, via seroprevalence studies in a given region (in Crépy-en-Valois, at national level, etc.) or cohort monitoring (e.g. among hospital/non-hospital staff from the Institut Curie and the Institut Pasteur in the Curie-O-SA study).

Modeling to visualize the evolution and progression of the epidemic

How can we best predict the evolution of the epidemic situation? How can we anticipate the admission of severely ill patients to hospital? Drawing on its expertise in the mathematical modeling of infectious diseases, the Institut Pasteur developed tools to analyze the spread of the epidemic in real time, week after week. The data are regularly updated to improve the accuracy of possible evolutionary scenarios.

Basic research to improve understanding of the coronavirus

Nearly a hundred research projects were launched over the year to shed light on the biology and structure of the SARS-CoV-2 virus, the organs it attacks, the inflammation and neurological signs it causes, the immune response triggered and any potential genetic susceptibility.



Antiviral strategies to treat COVID-19

The Institut Pasteur launched several studies – searching for molecules involved in the key stages of the viral cycle, identifying those that target essential cell functions, conducting clinical trials and demonstrating the antiviral action of drugs already on the market – and set up a group to assess antiviral strategies.

Vaccine candidates to protect the population and curb the spread of the epidemic

Two research programs for vaccine candidates entered preclinical development in 2020 and are continuing in 2021: one vaccine using a lentiviral vector and one DNA vaccine.

The Institut Pasteur has decided not to pursue the clinical development of its vaccine candidate based on the measles platform, despite the Phase I clinical trials carried out on the vaccine last August, as the immune responses induced were not strong enough.

The scientists involved in the program will analyze the results obtained in more detail to try to understand why.

They will make further research proposals, some of which may be based on the same platform *(see page 26 and the press release of January 25, 2021)*.

Sharing information with the scientific community to advance knowledge more quickly

On January 29, the Institut Pasteur sequenced the whole genome of SARS-CoV-2. The following day, it deposited the complete sequences of the virus samples taken from two of the first French cases on the GISAID (Global Initiative on Sharing All Influenza Data) platform. This transfer of information between scientists helps the international community to understand more about the evolution and spread of viruses.

Since April 1, every day from noon to midnight, the Institut Pasteur has contributed to the task of processing the many SARS-CoV-2 genomes submitted to GISAID (from dozens to hundreds every day worldwide) to validate the quality and reliability of the sequences and their metadata.

Again reflecting its ongoing efforts to advance knowledge, Institut Pasteur scientists deposited several preprints (preliminary versions of publications prior to acceptance by the peer review board of a scientific journal) throughout the year, both on the Institut Pasteur open archive and on international open science sites like medRxiv.org and bioRxiv.org.

All these major achievements are a testament to the unprecedented response from the Institut Pasteur's teams.

> “For both SARS-CoV and MERS-CoV, cells known as Vero E6 cells were identified and can be used to culture the two coronaviruses. In January 2020, we brought them out of our collection, which is kept under strictly controlled conditions, so that we would be ready as soon as we detected a positive sample for the 2019-nCoV coronavirus.”

Sylvie van der Werf,
Director of the National Reference Center (CNR) for Respiratory Infection Viruses at the Institut Pasteur.

Cytopathic effect of SARS-CoV-2 coronavirus on Vero E6 cells. Cell layer with a visible cytopathic effect (CPE); the cells attacked by the virus have been destroyed.

COVID-19: major advances from January to December 2020

DECEMBER 31, 2019
The China Country Office of the World Health Organization (WHO) is informed that clustered cases of pneumonia of unknown etiology have been detected in the city of Wuhan, in the Chinese province of Hubei.

DECEMBER 31, 2019 TO JANUARY 3, 2020
44 patients with this pneumonia of unknown etiology are reported to WHO by the Chinese authorities. The pathogen causing this new disease has still not been identified *(source WHO)*.

JANUARY 7
Informal discussions on the subject between various members of the Institut Pasteur Senior Management Board at the first meeting of the new year in January.

JANUARY 9
Chinese authorities and WHO raise the alarm.
The CNR for Respiratory Infection Viruses begins to monitor the novel coronavirus in France. This coronavirus is different from two other viruses known to have caused recent respiratory disease outbreaks: SARS-CoV, responsible for the SARS outbreak in 2003 (in February 2020 this virus was renamed “SARS-CoV-1”), and MERS-CoV, responsible for an outbreak that has been under way since 2012 in the Middle East. The Institut Pasteur was actively involved in tackling these previous outbreaks, which yielded valuable lessons for the current situation.

JANUARY 12
China shares the genetic sequence of the novel coronavirus (known for the time being as 2019-nCoV, for “novel coronavirus that emerged in 2019”) so that countries can use it to develop specific diagnostic kits.

JANUARY 13
The Thai health authorities report the first laboratory-confirmed imported case of the novel coronavirus from China.

WEEK OF JANUARY 13
The outbreak gains more media coverage and experts from the Institut Pasteur start replying to requests from the media.

JANUARY 20
Health authorities in South Korea report the first case of novel coronavirus in the Republic of Korea. To date, 282 confirmed cases of 2019-nCoV have been reported to WHO by four countries: China (278 cases), Thailand (2 cases), Japan (1 case) and the Republic of Korea (1 case) *(source WHO)*. From January 20, WHO provides a daily report of all confirmed cases of infection with the novel coronavirus that are reported to it.

Find out more
See all the situation reports on the WHO website www.who.int. Home/Emergencies/Diseases/Coronavirus disease(COVID-19)/Situation reports.

JANUARY 21
A first Institut Pasteur COVID-19 fact sheet is made available online to inform the public. It is updated on a regular basis.

JANUARY 22
A first scientific consultation and leadership meeting is held in connection with the first priority research area of the Institut Pasteur's Strategic Plan, "emerging infectious diseases."

Find out more
Institut Pasteur 2019-2023 Strategic Plan www.pasteur.fr/en/our-missions/strategic-plan-2019-2023

JANUARY 24
The first samples (from the first imported French cases) arrive at the Institut Pasteur from Bichat Teaching Hospital. An RT-qPCR diagnostic test that had been under development by the CNR for Respiratory Infection Viruses, with information shared with the international community, is ready for use. Detection of the virus is confirmed by the CNR that same evening.

JANUARY 25
Work to isolate the strains and sequence the viral genome begins at the Institut Pasteur.

JANUARY 27
Morning: the virus is isolated by the Institut Pasteur.

JANUARY 28

An unprecedented response to the COVID-19 epidemic

INTERVIEW

Three questions for CHRISTOPHE D'ENFERT, Scientific Director of the Institut Pasteur, who leads the Coronavirus Task Force that was set up on January 23, 2020. The Task Force is composed of scientific experts from several disciplines and support staff from the Institut Pasteur's technical departments to ensure that scientific projects can be carried out as effectively as possible.

What have been the Institut Pasteur's strengths in dealing with the COVID-19 epidemic?

Above all, its ability to respond quickly, which is facilitated by its economic model – its status as a foundation greatly simplifies the launch of new projects. Many of the projects initiated this year were also made possible by the successful public fundraising appeal. It provided the funds needed to embark on major research in diagnostics, vaccine development, epidemiology and therapeutics back in mid-February, alongside the projects already started in January (see Interview with Arnaud Fontanet, page 24). Without this outpouring of generous support, we would not have been able to launch as many projects. It was quite remarkable. The other strength is of course the expertise of our teams, which were immediately able to apply their knowledge to the novel coronavirus.

Can you give us some examples?

A thorough knowledge of viruses was crucial; we have carried out significant research in recent years on other coronaviruses, like SARS-CoV-1, which emerged in the early 2000s, then MERS-CoV. We also have technological expertise, such as vaccine strategies, which we were able to apply to the novel coronavirus. Another example is the expertise of one of our teams in identifying antibodies with therapeutic potential, which led to the rapid identification of drug candidates to treat COVID-19. We have specialists in a wide range of fields and a depth of basic knowledge that paved the way for relatively rapid progress. Scientists on campus with no links to virology also stepped up. For example, teams from the Department of Neuroscience started working on COVID-19 because of its association with neurological disorders such as loss of taste and smell.

How are things looking at the end of 2020?

Thanks partly to the generosity of the general public, we have funded dozens of projects and galvanised the efforts of nearly 400 people for multidisciplinary research on COVID-19 and SARS-CoV-2. Although we responded on a large scale in recent years to outbreaks of chikungunya, Ebola and Zika, our response to the COVID-19 pandemic has been quite unprecedented.

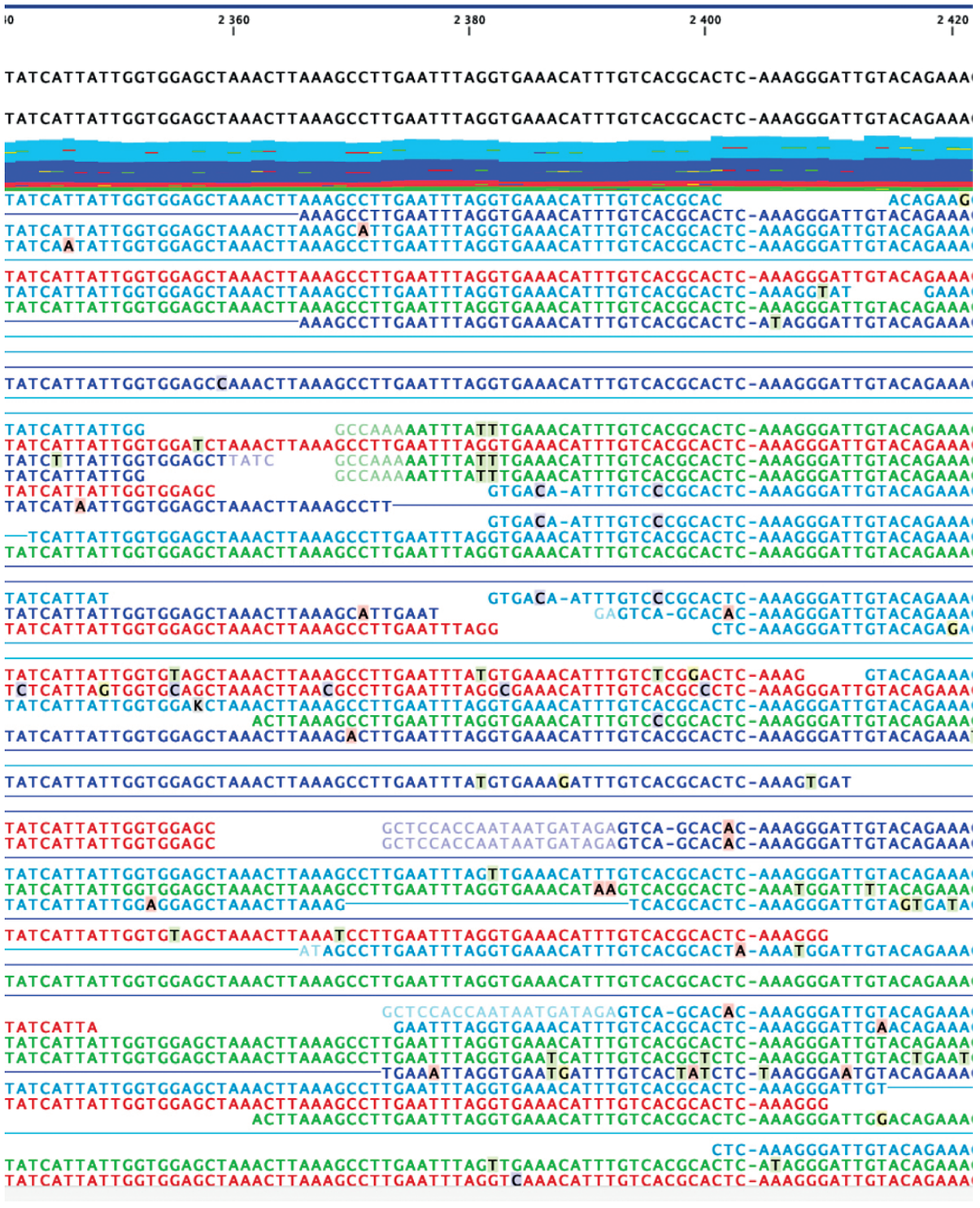
> "The Institut Pasteur has specialists in a wide range of fields and a depth of basic knowledge that paved the way for rapid progress in 2020."

JANUARY 28
First meeting of the Task Force on the novel coronavirus involving leading scientists from the Institut Pasteur in each of the key disciplines and some support departments. From this point on, the Task Force meets every week and sets up thematic groups. The Task Force initiates the first scientific research programs launched by the Institut Pasteur from mid-February 2020.

JANUARY 30
The Institut Pasteur is the first in Europe to sequence the whole genome of the novel coronavirus. The sequence is shared with the international scientific community via the GISAID website.

In parallel, an RT-qPCR diagnostic test is developed by the CNR for Respiratory Infection Viruses. The RT-qPCR technique developed by the CNR for Respiratory Infection Viruses, enabling highly sensitive, specific detection of the virus through nasopharyngeal swab specimens, was transferred to hospitals and made known to WHO so that it could be shared among the global network and with the scientific community as effectively as possible.

JANUARY 31
The Institut Pasteur holds a first press conference to announce the isolation and sequencing of coronavirus strains identified in France. During this press conference, a targeted fundraising campaign, “Coronavirus Emergency”, is launched to support the Institut Pasteur’s research.



> “Whole-genome sequencing of the novel coronavirus is crucial to be able to develop specific diagnostic tests and identify potential treatment ‘options’.”

Vincent Enouf, Deputy Director of the National Reference Center (CNR) for Respiratory Infection Viruses at the Institut Pasteur.

Close-up of the whole SARS-CoV-2 coronavirus sequence in one of the first French cases, determined at the Institut Pasteur. The viral RNA bases can be seen.

Progress in diagnostics and epidemiological genomics

Here are some examples of the headway made, taken from the wide-ranging research carried out by the Institut Pasteur:

- **Development of an RT-qPCR diagnostic** test by the CNR for Respiratory Infection Viruses *(see "Operation and reliability of RT-PCR tests in the detection of SARS-CoV-2" www.pasteur.fr).*

- **Rollout of the CNR's RT-qPCR test in French teaching hospitals.** Various industry players and medical test laboratories also contacted the Institut Pasteur to benefit from its development of an RT-qPCR test that complies with the criteria of the French National Authority for Health, at a time when there was a vital need for testing to slow down the spread of the virus. The Institut Pasteur enabled the manufacture of three products based on its RT-qPCR development.

- **Development of a diagnostic test by the Hong Kong University-Pasteur Research Pole and rollout in the International Network.**

- **Development of the RT-LAMP rapid diagnostic test.** The Institut Pasteur's Laboratory for Urgent Response to Biological Threats (CIBU), which specializes in outbreak management, contributed its expertise together with key reagents to obtain a test that was as sensitive and specific as the RT-qPCR test – but with a result in under 30 minutes. LAMP technology can be used outside medical test laboratories, for example in care homes, on ships or even in car parks. A consortium of industry partners was set up for the development of this test.

- **Provision of serological tests to assess** whether an individual has developed antibodies against SARS-CoV-2 proteins and therefore previously contracted the virus. These seroconversion tests can be used by epidemiologists to map the spread of the virus over a given area. They can also be used in conjunction with RT-qPCR tests in diagnosing patients. They are CE marked and approved by the US Food and Drug Administration.

- **Phylogenomic studies showing the different introductions of the virus in France** *(see "Introductions and early spread of SARS-CoV-2 in France" – www.pasteur.fr).*

- **Rollout of assays using novel seroneutralization techniques** to determine whether patients have developed neutralizing antibodies. These assays can also be used for diagnostic purposes, or to verify and confirm the performance of vaccines in development (via serum samples taken from vaccinated individuals). Another potential use is to ensure that specific populations, especially elderly people, have developed neutralizing antibodies following vaccination.

- **Collaboration with diagnostic startups to develop innovative lateral flow antigen tests:** rapid results in 10 to 30 minutes, and higher sensitivity, reducing the need for RT-qPCR confirmation for those receiving a negative result (as is the case with current antigen tests).

- **Bioinformatics Hub involved in curating genomes sequenced worldwide** (GISAID) *(see the article "The Bioinformatics and Biostatistics Hub on the front line" at www.pasteur.fr).*

Find out more
https://www.pasteur.fr/en/all-sars-cov-2-covid-19-institut-pasteur

FEBRUARY 2
The first death outside China is officially announced, in the Philippines *(source WHO).*

FEBRUARY 11
Forget the terms “Chinese flu” or “Wuhan coronavirus” – WHO announces that the disease responsible for the current epidemic is now called COVID-19 (for “coronavirus disease 2019”). The virus that causes the disease belongs to the family of SARS viruses and is now known as SARS-CoV-2 (an acronym derived from “severe acute respiratory syndrome coronavirus 2”). Why “2”? Because a first coronavirus (SARS-CoV-1) was already identified as the cause of a first epidemic that emerged in Hong Kong in 2002-2003.

FEBRUARY 12
The first SARS-CoV-2 call for scientific proposals is launched for Institut Pasteur staff with submissions accepted on an ongoing basis until May 15, 2020.

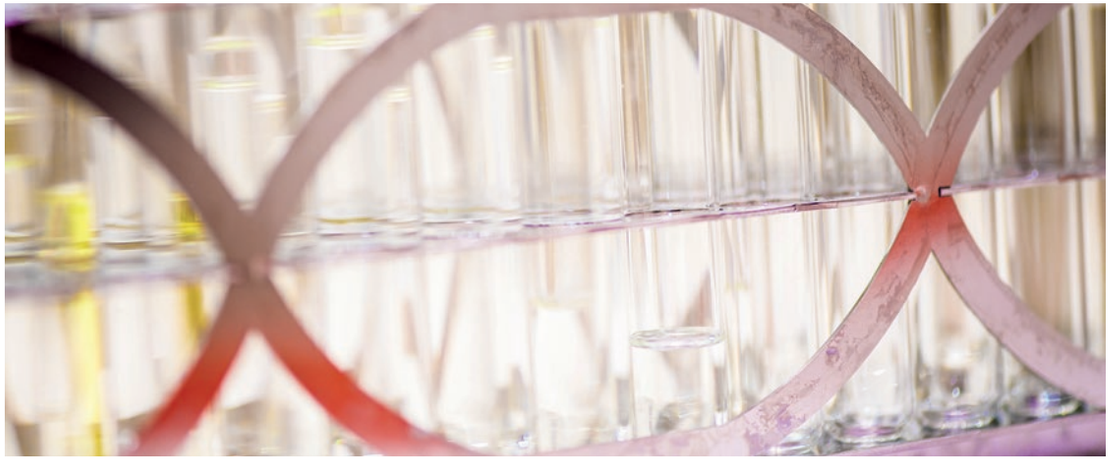
FEBRUARY 14
First death caused by an indigenous case in France, related to the cluster in Crépy-en-Valois.
Also on February 14, Stewart Cole, President of the Institut Pasteur, plays host to His Excellency Mr. Lu Shaye, Chinese Ambassador to France, on a visit to the Institut Pasteur to express his support, both personally and on behalf of his country, for the Institut Pasteur’s efforts in response to the novel coronavirus outbreak.

Find out more
See the article “The Chinese Ambassador to France visits the Institut Pasteur” at www.pasteur.fr

FEBRUARY 20
The epidemic spreads to Italy, where it progresses relatively quickly.
On February 22, WHO reports 9 confirmed cases *(source WHO).*
On February 23: 76 confirmed cases *(source WHO).*
On February 28: 65 confirmed cases *(source WHO).*
On March 1: 1,128 confirmed cases *(source WHO).*

FEBRUARY 22-23
After the epidemic outbreak in China in January and February, the epidemic situation has developed at global level, with the escalation of outbreaks in South Korea, Japan and Singapore and the emergence of new outbreaks in Iran and Italy. These countries are witnessing community spread, with no identified link with cases imported from China.

FEBRUARY 28
WHO raises its assessment of the risk of spread and impact of COVID-19 from “high” to “very high” at the global level *(source WHO).*



MARCH 4
WHO notes that “Disruptions to the global supply of personal protective equipment (PPE) are leaving healthcare workers ill-equipped to care for patients” *(source WHO).*

MARCH 6
100,000 cases recorded worldwide
In France, the Prime Minister prepares the public for the country’s potential transition to phase 3 of the epidemic. If this happens, it will indicate that the coronavirus is circulating throughout the country and that the priority is to mitigate its impact, while treating the most severely affected patients.

MARCH 7
Launch of the first SARS-CoV-2 call for proposals for research projects to be implemented within the Institut Pasteur International Network (21 projects proposed by the International Network are selected by the Task Force out of a total of 36 proposals).

FROM MARCH 9
A “COVID-19” internal scientific meeting is held at the Institut Pasteur every Monday. Twenty experts from the Institut Pasteur attend this first meeting; now the number attending the meetings is often more than a hundred.

MARCH 10
All the countries in the European Union now have cases of COVID-19.

The Institut Pasteur senior management team informs its staff that it is preparing for the COVID-19 epidemic to potentially enter phase 3 (gradual transition to a reduced mode of operation, restriction of travel to at-risk countries, protection of sensitive populations, working from home, restriction of in-person meetings). A team responsible for the Business Continuity Plan (BCP) is set up.

MARCH 11
WHO announces that the outbreak is now a pandemic.

MARCH 12
In France, the President announces extraordinary measures for the entire country, to come into force on Monday March 16, including closing all schools and universities and asking companies to move to remote working.

MARCH 13
The Institut Pasteur moves to a reduced operating schedule based on statements by the French President and the spread of the pandemic. The decision is implemented gradually from the beginning of the following week.

MARCH 14
The French Prime Minister confirms that the epidemic has reached phase 3. The SARS-CoV-2 coronavirus is now circulating actively throughout France. The country is moving from a strategy of containment to mitigation.

MARCH 16
Start of the (first) lockdown in France.

MARCH 17
Nearly 400 scientists (out of a total of 2,780 staff members) are authorized to come onto the Institut Pasteur campus to continue research on SARS-CoV-2 and COVID-19. The Institut Pasteur is forced to impose remote working for most of its staff members who are able to work from home.

COMBATING FAKE NEWS

MARCH 17
A misleading, defamatory video is posted online. Based on a misinterpretation of a patent filed in 2004, the video claims that the Institut Pasteur invented COVID-19 for commercial gain.

Maintaining "non-COVID" research activities

TESTIMONIAL

ANNA-BELLA FAILLOUX leads the Arboviruses and Insect Vectors Unit at the Institut Pasteur in Paris, and with her team she manages an insectarium to breed mosquitoes that may be viral vectors (they may transmit viruses to humans). Large quantities of mosquitoes are bred in this vast facility in controlled conditions. The aim is to be in a position to respond to future challenges caused by emerging vector-borne diseases.

On Monday March 16, 2020, we were told that we were going to have to close the laboratory. There are normally twelve of us in the team. On March 17, just four of us came in to look after the mosquitoes, to change them, feed them and carry out the necessary maintenance. Most of the species housed in the insectarium need daily maintenance. If we hadn't been able to work as a smaller team, we would have lost all thirty mosquito populations, many of which come from our work in collaboration with the Institut Pasteur International Network.
The atmosphere was rather strange on campus as it was empty, but there was a real feeling of solidarity among Institut Pasteur staff. We were well looked after, we felt like we were valued. It was quite difficult, of course, but we managed to keep things going, because it is so important for the Institut Pasteur to maintain its "non-COVID" activities. It is one of the rare places in Europe with such a large number of research teams working in such varied fields, with international reach. There are so many pathogens that we need to continue investigating so that we can get to know them better and be in a better position to tackle them if and when they emerge.

Extract from the Pasteurdon conference on October 8, 2020.

Anna-Bella Failloux,
Head of the Arboviruses and Insect Vectors Unit and the insectarium at the Institut Pasteur in Paris.

"We did all we could not to lose the benefit of several years of work."

COMBATING FAKE NEWS

MARCH 17-20
Given the viral nature of the initial false information in social and mainstream media, a large-scale fact-checking campaign is launched and extensively shared via a wide variety of platforms (threads, videos, series, etc.) and by several institutions and official outlets.

Find out more
See the special fake news page at www.pasteur.fr

MARCH 19
CEPI (the Coalition for Epidemic Preparedness Innovations) funds the development of a SARS-CoV-2 vaccine based on a project led by a consortium composed of the Institut Pasteur, Themis and the University of Pittsburgh.

MARCH 20
Launch of the website maladiecoronavirus.fr *(see the press release "Lancement du site internet maladiecoronavirus.fr" [in French] at www.pasteur.fr).*

LATE MARCH
Scientists at the Institut Pasteur, with the support of the Hauts-de-France Regional Health Agency and the Amiens Education Authority and the backing of the French Blood Service (EFS), carry out an epidemiological survey on 661 people linked to a high school in Crépy-en-Valois, in the Oise department.

COMBATING FAKE NEWS

MARCH 26
Given the impact of the video and the threats it caused, the Institut Pasteur has no other choice but to lodge a complaint for defamation (for the first time since its inception in 1887), without prejudice to the right to freedom of expression, which the Institut Pasteur recognizes and defends. At the same time, given the serious breach of public order caused by the video, the Senlis Public Prosecutor decides to initiate legal proceedings for defamation against the author of the video, an unusual step given the this Prosecutor's policy.

APRIL 10
Launch of the second SARS-CoV-2 call for proposals within the International Network (for institutes in low- and middle-income countries).

APRIL 21
Modeling by the Institut Pasteur indicates that between 3% and 7% of French people have been infected *(published as a preprint on the Institut Pasteur's online archive site).*

APRIL 23
Following the epidemiological survey carried out in Crépy-en-Valois and the use of virus detection tests together with three serological tests developed by the Institut Pasteur, a study reveals that 26% of the surveyed population have been infected by SARS-CoV-2 and developed antibodies against the virus. The population continues to be monitored and other studies are successively published.

APRIL 30
The Institut Pasteur informs its staff about preparations for the implementation of the Progressive Business Resumption Plan (PBRP) on campus from May 11, after the French government announces the start date for the gradual easing of lockdown measures.

An international initiative comprising scientists from the University of California, San Francisco (UCSF), the Gladstone Institutes, the Icahn School of Medicine at Mount Sinai and the Institut Pasteur reveals the identification of promising compounds for clinical trials with the aim of tackling COVID-19. *(see the press release "Revealing how SARS-CoV-2 hijacks human cells; points to drugs with potential to fight COVID-19 and a drug that aids its infectious growth" at www.pasteur.fr).*

Photoshoot at the CNR for Respiratory Infection Viruses at the Institut Pasteur (Paris).

Avenues for therapeutic approaches

Here are some examples of the headway made, taken from the wide-ranging research carried out by the Institut Pasteur:

- **Creation of a group to evaluate antiviral strategies proposed by teams from the Institut Pasteur and also from academia and industry.**
  The idea was to respond to the many requests from private and academic groups in France and abroad wanting to find out whether certain small molecules or biological molecules (e.g. proteins or antibodies) were capable of blocking SARS-CoV-2 in a variety of cellular models. A working group evaluated the relevance of the 56 requests received and accepted 32 of them (15 from industry and 17 from academia).
  The aim of these analyses was to draw on the Institut Pasteur's expertise for the identification of novel therapies by the rapid development of models suited to specific viruses during pandemics, in this case the COVID-19 pandemic.
  The work enabled several private and public laboratories to confirm or refute scientific theories as part of their efforts to find therapeutic solutions to treat the virus.
  At the end of the process, a small number of molecules were found to have an effect, sometimes a powerful one, on this type of cellular model. The findings will have to be confirmed with subsequent analyses on more advanced models, some of which will involve research partnerships with the Institut Pasteur.
- **Identifying molecules and antibodies that target key stages in the viral cycle:** *fusion, replication and maturation (see "Innate immunity and fusion of cells infected with SARS-CoV-2" – www.pasteur.fr).*
- **International cooperation to identify molecules targeting cellular functions with an essential role in the viral cycle** (UCSF and Mount Sinai) *– (see "Revealing how SARS-CoV-2 hijacks human cells; points to drugs with potential to fight COVID-19 and a drug that aids its infectious growth" – www.pasteur.fr).*
- **Clinical studies:** evaluation of chemoprophylactic approaches for healthcare workers.
- **Demonstrating the antiviral action of drugs that already have market approval** (niclosamide) and launch of clinical trials by the Institut Pasteur Korea.

Find out more
www.pasteur.fr/en/all-sars-cov-2-covid-19-institut-pasteur

EARLY MAY
More than 120 scientists are registered for the internal COVID-19 scientific meetings at the Institut Pasteur. Meetings are held via video conference. Scientific work on COVID-19 at the Institut Pasteur is now divided among twelve working groups.
Specific shared tools are developed to optimize discussions and boost cooperation.

MAY 7
Following its first internal call for scientific proposals, 38 research projects led by the Institut Pasteur in Paris are selected by the Task Force out of a total of 55 proposals submitted.

MAY 11
Gradual easing of lockdown measures begins in France.

Progress in epidemiology and modeling

Here are some examples of the headway made, taken from the wide-ranging research carried out by the Institut Pasteur:

- **Modeling the epidemic and the consequences of lockdown on its progression** *(see "COVID-19: mathematical model indicates that between 3% and 7% of French people have been infected").*
- **Development of serological assays and tests to detect neutralizing antibodies** *(see "Development and evaluation of four serological assays to detect SARS-CoV-2 antibodies and two assays to detect neutralizing antibodies").*
- **Epidemiological studies** *(see the interview with Arnaud Fontanet page 24).*
- **Characteristics of community transmission (Crépy-en-Valois).**
- **Establishment and persistence of the immune response in symptomatic case** (Curie-O-SA, Crépy-en-Valois).
- **Nosocomial transmission** *(see* Clinical Infectious Diseases *"A Conceptual Discussion About the Basic Reproduction Number of Severe Acute Respiratory Syndrome Coronavirus 2 in Healthcare Settings").*
- **Telemedicine and new technologies** *(see Use of the maladiecoronavirus.fr web application at www.pasteur.fr).*

Find out more
https://www.pasteur.fr/en/all-sars-cov-2-covid-19-institut-pasteur

MAY 14
A serological assay using bioluminescence (known as LuLISA), developed by the Institut Pasteur, increases the sensitivity of detection of specific immunoglobulins and is shown to be effective in allergy assessment. The LuLISA assay is adapted to detect antibodies (immunoglobulins IgG, IgM, IgA and IgE) directed against proteins of the SARS-CoV-2 coronavirus, which causes COVID-19. The Institut Pasteur files a patent application for LuLISA *(see the article "LuLISA project, bioluminescence as a tool for human diagnostics, from allergy to COVID19" at www.pasteur.fr).*

MID-MAY
A seroprevalence study in the French population, led by Santé publique France, reveals that the frequency of seropositives is 5% and the frequency of neutralizing antibodies is 3.5%. The serological assays developed by the Institut Pasteur teams (LuLISA N, LuLISA S and pseudoneutralization) are used in this study (use of the LuLISA assay, see "May 14").

JUNE
The Curie-O-SA study, led by the Institut Curie in collaboration with the Institut Pasteur, will examine the long-term dynamics of humoral, cellular and mucosal immune responses in staff from the Institut Curie and the Institut Pasteur who have been infected by SARS-CoV-2. This epidemiological study makes use of the serological assays developed by the Institut Pasteur's teams.

JUNE 29
An epidemiological study led by several Institut Pasteur teams was conducted in primary schools in Crépy-en-Valois. Launched in April, it involved 1,340 people. The study did not find significant transmission between children or from children to teachers, and confirms that children are more often infected by adults at home *(see the press release "In primary schools: no significant transmission among children or from students to teachers" at www.pasteur.fr).*

BEFORE SUMMER 2020 (northern hemisphere)
Circulation of the virus has fallen considerably in countries that have brought their first wave under control, but this is mainly because of the stringent measures taken to control the virus.

JULY
The Institut Pasteur Task Force launches a further call for proposals, aimed at all the teams in the Institut Pasteur International Network, for ambitious, multidisciplinary research projects carried out over several years that will involve recruiting contract researchers. The proposals will be assessed in autumn and will begin in early 2021.

JULY 15
Thanks to the discovery of an association between a type 1 interferon deficiency in the blood and severe forms of COVID-19, early detection and a potential therapeutic approach can be offered to at-risk patients *(see the press release "Type 1 Interferon deficiency: a blood based signature" at www.pasteur.fr).*

JUNE 23

Two questions for…

ARNAUD FONTANET, Director of the Department of Global Health and Head of the Epidemiology of Emerging Diseases Unit at the Institut Pasteur.

The Institut Pasteur carried out large-scale studies on the COVID-19 cluster that emerged in Crépy-en-Valois in February 2020. Which ones?

Yes, we got involved when the cluster emerged in Crépy-en-Valois. Working with Santé publique France, we carried out a study on March 5-6 which revealed that the virus was circulating actively in Oise and which also allowed us to take samples that we could use to develop serological assays. These samples were complemented by the samples from the national cohort led by Inserm, meaning that several teams on campus were able to develop serological assays based on various technologies, which we reported on in a scientific publication. As well as developing different types of tests, my team carried out two epidemiological studies in Crépy that enabled us to document an outbreak that had occurred in a high school in the town in the first fortnight of February and to confirm the fact that the virus was circulating in primary schools but without any major outbreaks.

What were the results of these studies in the high school and primary schools?

For the high school, we demonstrated that the virus was circulating actively: 41% of people who had been in contact with the high school, whether students, teachers or other adults, had been infected. We then tried to find out whether the outbreak had also occurred in primary schools in Crépy-en-Valois. The first finding of our study was that children aged between 6 and 11 had had mild forms of the disease, and that 44% of them had been asymptomatic. The virus had spread more in families, from parents and siblings to children rather than the other way round. In the period that we studied, there were three introductions of the virus in primary schools from symptomatic students, followed by silent transmission of the virus among students as revealed by the serological survey.

> "The Institut Pasteur was actively involved in Crépy-en-Valois, with Inserm, in two epidemiological studies carried out by Santé publique France."

JULY 24
An intranasal lentiviral vaccine in development provides significant protection in animals *(see the press release "A lentiviral vaccine candidate for intranasal administration" at www.pasteur.fr).*

AUGUST
The Phase I clinical trial to assess the safety and immunogenicity of vaccine candidate TMV-083 (also known as V591, previously MV-SARS-CoV-2) begins in France. This is the first time the vaccine candidate, developed by Institut Pasteur scientists in partnership with the companies Themis and MSD with the support of CEPI, has been administered to humans.

SUMMER 2020
A slowdown in the circulation of the virus is observed in the northern hemisphere, probably because the virus is being transmitted less between people who are spending time outside in summer. The virus continues circulating at a low level.

SEPTEMBER
An electron microscope photo of the coronavirus, taken by the Institut Pasteur, is published (see page 4).

SEPTEMBER 17
30 million cases and 930,000 deaths have been recorded worldwide.

Vaccine strategies

Since the beginning of 2020, the Institut Pasteur has been working on several vaccines for the SARS-CoV-2 virus, which causes COVID-19. Some examples:

- Seven vaccine strategies were under assessment in autumn 2020 at the Institut Pasteur, five for the induction of humoral responses (antibodies, spike protein) and two for the induction of cytotoxic responses.
- Collaboration with industry stakeholders at the national and international level has been vital to speed up the development of six of these vaccine candidates.
- Significant progress was made on three research programs in particular in 2020; one of these unfortunately had to be discontinued in January 2021 but work on the other two is continuing *(see below)*.
- Development of animal models.

Two vaccine candidates at the end of preclinical stage

The aim of the Institut Pasteur's vaccine candidates is to induce a specific immune response to SARS-CoV-2, especially the production of antibodies directed against a SARS-CoV-2 surface protein.

A vaccine using a lentiviral vector

This vaccine, designed for nasal administration, demonstrated good efficacy and extremely high production of antibodies in preclinical trials. The vaccine, developed with the biotech company Theravectys, is composed of a lentiviral vector. Lentiviruses are "slow" viruses (from the Latin *lentus,* meaning slow), characterized by a long incubation period before they become pathogenic. The virus is genetically modified to make it harmless for humans and to enable it to produce the spike protein.

- With Theravectys.

Find out more
See "A vaccine candidate using a lentiviral vector" in the "COVID-19/research projects" space" at www.pasteur.fr

A DNA vaccine

Of the various SARS-CoV-2 vaccines developed at the Institut Pasteur, the DNA vaccine is undoubtedly the one that uses the most cutting-edge technology. The principle is to inject a DNA molecule into human cells. These cells recognize the DNA molecule and transcribe it into an RNA molecule capable of producing the SARS-CoV-2 spike protein. This protein, which forms spikes all around the virus, is the entry key allowing the virus into the cell.

- With In-Cell-Art.

Find out more
See "A DNA vaccine" in the "COVID-19/research projects" space" at www.pasteur.fr

A vaccine using the measles vector

Following the intermediate results of the Phase I clinical trial, the Institut Pasteur stopped development of this vaccine candidate on January 25, 2021. The vaccine candidate was an attenuated live virus vaccine using the measles vaccine as a vector (or vehicle) and expressing a spike protein antigen from the SARS-CoV-2 virus (the protein that serves as the entry key allowing the virus into cells).

- Phase I in August 2020 (France and Belgium).
- Trial stopped in January 2021 due to unsatisfactory intermediate results.
- CEPI funding: fair access.
- Themis – MSD/Merck partnership.

The decision to stop the clinical trial has no adverse impact on the continuation of research to tackle the SARS CoV-2 virus, including that based on this platform using the measles vaccine virus as a vaccine vector, or the continuation of other vaccine research projects being conducted in partnership with Themis/Merck-MSD, with this same platform, and aimed at other infectious diseases (Lassa fever and chikungunya). A vaccine candidate for chikungunya is currently in Phase III clinical trials *(the results of the Phase I and II trials were published in* The Lancet*)*.

Find out more
See "Vaccine using the measles vector" in the "COVID-19/research projects space" at www.pasteur.fr

SEPTEMBER 29
A study based on the Institut Pasteur's modeling work shows how the lockdown has affected the COVID-19 epidemic in regions of mainland France. The lockdown appears to have succeeded in reducing the burden on intensive care units in the most severely affected regions, and in preventing epidemic outbreaks in other regions *(source* The Lancet*)*.

OCTOBER 6
Lung-on-a-chip research shows the effect of SARS-CoV-2 on ciliated cells *(source biorxiv)*.

COMBATING FAKE NEWS

OCTOBER 7
A hearing is held at Senlis Criminal Court for the author of the misleading video posted on March 17 following the complaint by the Institut Pasteur for defamation.

OCTOBER 7
The 14th edition of Pasteurdon is held against the backdrop of the COVID-19 epidemic *(see the press release "Une quatorzième édition du Pasteurdon" (in French) at www.pasteur.fr)*.

Improving understanding of the biology of SARS-CoV-2 and COVID-19

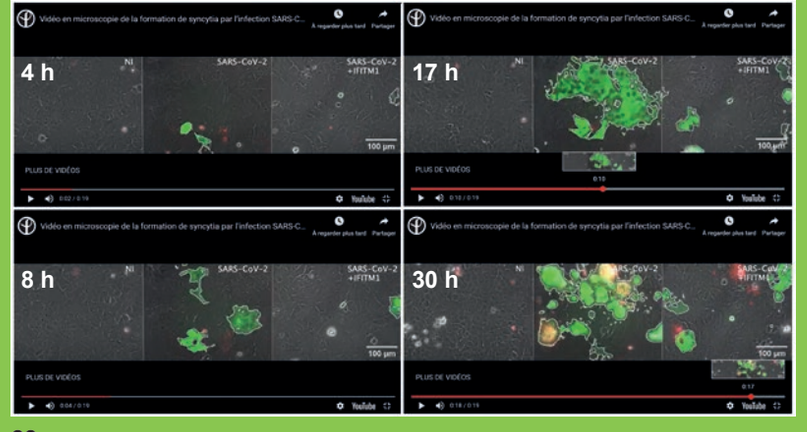
Here are some examples of the headway made, taken from the wide-ranging research carried out by the Institut Pasteur:

- **Biology of SARS-CoV-2** *(see the press release "Innate immunity and fusion of cells infected with SARS-CoV-2" at www.pasteur.fr).*

Video microscopy showing syncytium formation following SARS-CoV-2 infection https://youtu.be/CE69DI02-mU

- **Structural biology:** study of the viral cycle *in cellula* using cryo-electron microscopy, interactions between the S protein, receptors and antibodies.
- **Tropism:** lungs, digestive tract, neurons (organs-on-chips).
- **Cell biology:** intercellular traffic, interference with host functions (miRNA).
- **COVID-19 and host responses**
  – Humoral and cellular responses
  – Transition between viral and inflammatory disease *(see "In severe and critical patients, a severely impaired response of interferon (IFN) type I is associated with a persistent blood viral load and an excessive inflammatory response").*
- **COVID-19 and neurological signs** (in partnership with the Brain and Spine Institute).
- **COVID-19 and genetic susceptibility.**

Find out more
www.pasteur.fr/en/all-sars-cov-2-covid-19-institut-pasteur



Video microscopy showing syncytium formation following SARS-CoV-2 infection, at different stages of infection, after 4, 8, 17 or 30 hours. Each of the four images is divided into three panels.
Left panel: Non-infected cells.
Center panel: Cells infected with SARS-CoV-2.
Right panel: Inhibition of SARS-CoV-2 infection and syncytium formation by the antiviral protein IFITM1.
Green: fluorescent marker of cell fusion.
Red: fluorescent marker of cell death.

AUTUMN 2020
A new wave of the epidemic, feared by experts, is observed in the northern hemisphere, especially in Europe and the United States.

OCTOBER 13
Scientists from the Institut Pasteur and the CNRS set out to investigate the consequences of SARS-CoV-2 infection for cell function and the antiviral role of innate immunity. Using real-time video microscopy, they show that infected cells in culture can fuse with neighboring cells and then die. But interferon counters this phenomenon by inducing cellular proteins that prevent the fusion of infected cells *(see the press release "Innate immunity and fusion of cells infected with SARS-CoV-2" at www.pasteur.fr).*

OCTOBER 15
An international team of scientists (including members of the Institut Pasteur) identifies common vulnerabilities in the SARS-CoV-2, SARS-CoV-1 and MERS-CoV coronaviruses *(see the press release "Common vulnerabilities across SARS-CoV-2, SARS-CoV-1 and MERS coronaviruses" at www.pasteur.fr).*

OCTOBER 21
Based on its analysis of specimens from more than 11,000 individuals, the CNR for Respiratory Infection Viruses provides an estimate of the seroprevalence of SARS-CoV-2 antibodies in France (national serological surveillance conducted with Santé publique France): approximately 5% of French people had antibodies in mid-May, but only 70% of individuals testing positive for SARS-CoV-2 had detectable neutralizing antibodies *(source medrxiv).*

OCTOBER 28
The French President announces a second lockdown in France.

OCTOBER 29
The Institut Pasteur introduces new measures to reduce the presence of staff on campus, giving priority to scientists whose wet-lab research activities require laboratory access and extending remote working to all staff able to do so.

COMBATING FAKE NEWS

NOVEMBER 2
Senlis Criminal Court finds the author of the video guilty of defamation against the Institut Pasteur *(see the article "Senlis Criminal Court convicts the author of a fake news video for defamation" at www.pasteur.fr).*

NOVEMBER 3
The number of deaths from COVID-19 in under-65s is a more reliable indicator for evaluating infection rates in populations, according to the findings of an Institut Pasteur study demonstrating that a simple comparison of the total number of deaths between countries could offer a misleading picture of the actual level of SARS-CoV-2 transmission.

NOVEMBER 15
A study conducted on hospital staff who contracted a mild form of the disease caused by SARS-CoV-2 seems to suggest that immunity lasts longer in women than in men *(source medrxiv.org).*

NOVEMBER 18
Initial results are published concerning the link between SARS-CoV-2 and the nervous system; COVID-19-associated olfactory dysfunction reveals SARS-CoV-2 neuroinvasion and persistence in the olfactory system *(source biorxiv.org).*

NOVEMBER 22
The efficacy of ivermectin (a drug used to treat parasitic conditions such as scabies) on certain COVID-19 symptoms is proven in golden hamsters *(source biorxiv.org).*

NOVEMBER 23
An analysis of data obtained from the website maladiecoronavirus.fr and the application COVIDOM shows that these self-assessment tools can reduce the load for call centers and predict peaks in hospital admissions. A study demonstrates that use of the web application maladiecoronavirus.fr, a tool developed in partnership with the Institut Pasteur, led to an eightfold reduction in the number of unnecessary calls to the French medical emergency number (15) *(see the article "Use of the maladiecoronavirus.fr web application" at www.pasteur.fr).*

DECEMBER 1
First results of a serological survey (Curie-O-SA) conducted in May on 1,850 volunteers from the staff of the Institut Curie, in collaboration with the Institut Pasteur *(use of the LuLISA assay, see "May 14").* The results from this representative sample of the working population in the Greater Paris region reveal a high prevalence of immunization and a relatively short-lived immune response *(see the press release "Premiers résultats d'une étude d'envergure menée grâce aux collaborateurs de l'Institut Curie sur la réponse immunitaire contre le SARS-CoV-2" [in French] at www.pasteur.fr).*

DECEMBER 8
The results of a study reveal the importance of tailoring surveillance strategies to facilities' testing capacities *(see the press release "Optimizing surveillance in long-term care facilities" at www.pasteur.fr).*

DECEMBER 17
The Institut Pasteur, in partnership with the French National Health Insurance Fund (CNAM), Santé publique France and the Ipsos Social Research Institute, present the results of the ComCor epidemiological study on circumstances and places of infection with the SARS-CoV-2 virus *(see the press release "ComCor: where are French people catching the virus?" at www.pasteur.fr).*

Photo credits: Photothèque Pasteur - Institut Pasteur, Virus and Immunity Unit; Dominique Tardy; François Gardy; Institut Pasteur/Institut Pasteur CNR for Respiratory Infection Viruses; Institut Pasteur/Virus and Immunity Unit/colorization Jean-Marc Panaud; Raphael Olivier/The Pulses; Thomas LANG; Valérie Zeitoun; William Beaucardet.

Design and production: WAT- wearetogether.fr – 2012_01724.
ISBN: 978-2-901320-39-5

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