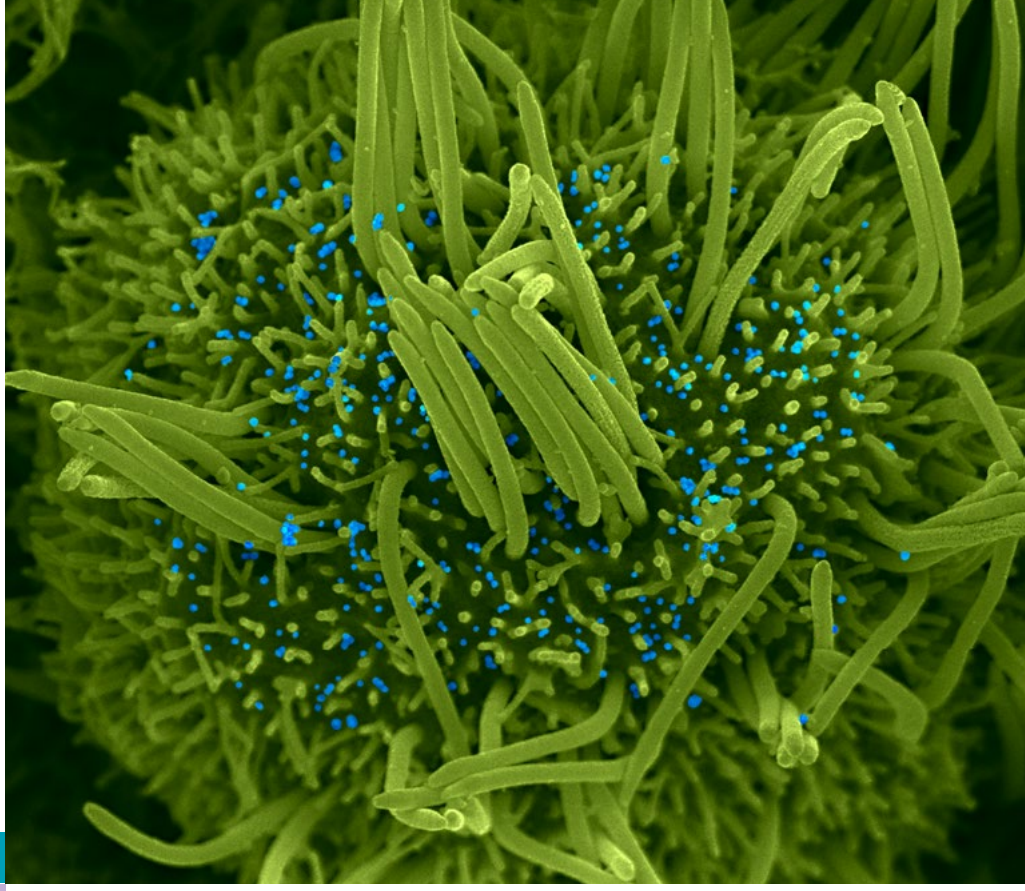

SARS-CoV-2, COVID-19 epidemic

The Institut Pasteur's response and impact in tackling the COVID-19 crisis

2020 & 2021

INSTITUT PASTEUR

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Editorial

The COVID-19 crisis is unfortunately not yet over. The Institut Pasteur has continued to strengthen its response for more than two years. The aim of our scientific efforts is firstly to protect the health of the population as a whole, via our expertise in epidemiology and modeling, and secondly to improve treatment options for individuals, with several projects to further our understanding of the SARS-CoV-2 virus and COVID-19, and to develop safe and efficient solutions.

I would like to commend the response and impact of the Institut Pasteur's scientists and physicians in tackling the COVID-19 crisis. Our research has made a significant contribution to the national and international response in this area. The National Reference Center (CNR) for Respiratory Infection Viruses has achieved a great deal, with the support of our sequencing platforms. The crisis has highlighted the importance of our public health mission.

Our scientific response has enabled us to achieve considerable breakthroughs in pathogenesis as well as in the development of diagnostic, vaccine and therapeutic strategies. I would particularly like to mention the scientists from the Humoral Immunology laboratory who identified and characterized a SARS-CoV-2-neutralizing monoclonal antibody that is also effective against all known variants and is currently in fast-track development. I also want to highlight our research efforts in long COVID which is a major challenge.

Finally, I would like to thank all our donors, our sponsors, our industrial and academic partners who support our scientific and medical teams, and our support staff, all of whom contribute to the Institut Pasteur's response and impact.

We are pursuing our mission to advance science and health for the benefit of us all.

Pr Sir Stewart COLE,
Directeur général de l'Institut Pasteur (Paris)

Interview with Christophe d'Enfert

Senior Executive Scientific Vice-President of the Institut Pasteur and Head of the Coronavirus Task Force launched 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 are implemented as effectively as possible.

What scientific lessons should be learned from two years of COVID-19 pandemic?

The Institut Pasteur achieved a great deal. Modeling enabled us to monitor and forecast the development of the outbreak in France. Through the ComCor study, we gained insights into the epidemiology of the virus. The emergence of the Delta and Omicron variants was effectively monitored (p. 20) thanks to the expertise of our CNRs, which play a key role in our organization and are crucial for detecting emerging diseases.

We produced monoclonal antibodies effective against all known variants through our startup SpikImm, and developed a nasal vaccine which is entering the clinical phase (p. 23).

Progress is being made in pinpointing the origin of the virus through work conducted by the Pasteur Network (Paris and Laos) on bats. Moreover, numerous articles were published on humoral immune response, ciliated cells, anosmia, etc. We can be proud of the work achieved.

What did the Institut Pasteur choose to invest in to further our understanding of the SARS-CoV-2 virus and the COVID-19 disease it causes?

A number of long-term "COVID" projects were launched (see inset below) to gain insights into SARS-CoV-2 and COVID-19 over a sufficient period to allow proper analysis. Equipment funded within this context will boost our capacity for future research alongside the numerous technologies in which we are currently investing (single cell analysis, imaging, therapeutic molecule screening, artificial intelligence, etc.).

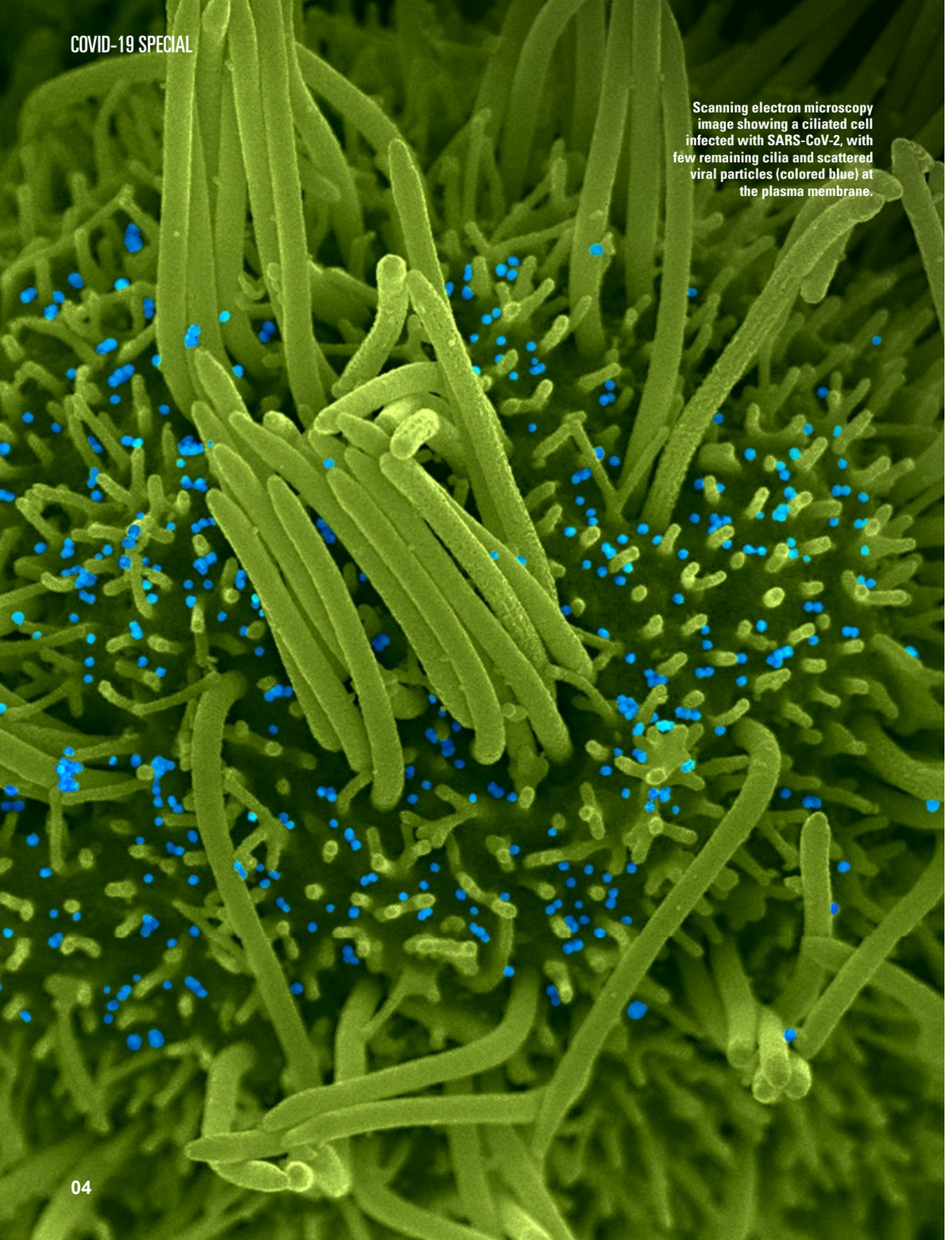
We also made the decision to build a vector-borne diseases center with an ad hoc working environment which is due to open by 2026. These projects will prepare us for the future and increase our capacity to respond to future emerging diseases.

Long-term collaborative projects

Seven long-term projects were launched in 2021 to improve understanding of the biology of the SARS-CoV-2 virus and COVID-19, the disease it causes. The topics addressed were:

- **Elucidating the biology of the virus through genetic engineering**
- **Understanding the phenomenon of prolonged post-COVID-19 symptoms, or long COVID**
- **Examining virus interaction with target cells using structural imaging technology**
- **Examining SARS-CoV-2 infection through animal imaging**
- **Examining virus interaction with host cells**
- **Developing therapeutic strategies**
- **Examining immune response to infection and vaccination**

What is long COVID?
Learn more on pasteur.fr



Scanning electron microscopy image showing a ciliated cell infected with SARS-CoV-2, with few remaining cilia and scattered viral particles (colored blue) at the plasma membrane.

The Institut Pasteur's response

500 + Institut Pasteur scientists
involved in COVID-19 research **in nearly 80 teams.**

380 + scientific publications on COVID-19.

Source: Web of Science (articles, e arly access articles, reviews and letters excluding preprints), at July 11, 2022.

25 patent-protected inventions
for diagnostics, vaccines or potential treatments for SARS-CoV-2.

1 startup launched (SpikImm).

112 technology transfer agreements:
ccollaboration agreements, licenses and service agreements (diagnostics, vaccines and treatments) with manufacturers (figure at August 30, 2022).

7 long-term collaborative research projects
launched in 2021 to improve understanding of the biology of the SARS-CoV-2 virus and COVID-19, the disease it causes.

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

The Institut Pasteur's impact in tackling the COVID-19 crisis

Since January 2020, the Institut Pasteur has made several major scientific discoveries, leading to a number of applications that are now commercially available. The Institut Pasteur also initiated a proactive international response via the Pasteur Network and has engaged in significant efforts to inform and raise awareness among the public.

Key advances in research and innovation

Isolation of the virus on January 24, 2020 and first sequencing in Europe;

Development of the first serological diagnostic assays (RT-PCR) used in hospitals in France;

Large-scale genomic surveillance of SARS-CoV-2 in conjunction with Santé publique France and the ANRS (French Agency for Research on AIDS and Viral Hepatitis, which in 2021 became "ANRS | Emerging Infectious Diseases");

Modeling the dynamics of the epidemic and the impact of control measures;

Identification of places and practices associated with SARS-CoV-2 transmission in France and evaluation of vaccine efficacy in the population;

Study of the immune response after natural infection and vaccination, including recent research on how the Omicron variant evades vaccination and monoclonal antibodies;

Several vaccine candidate programs (one reached clinical phase but did not prove effective enough in humans) **and candidate treatments** (including a promising monoclonal antibody, SPK001) launched in the early weeks of 2020;

Therapeutic molecule discovery platform to assess the antiviral potential of 500 molecules from academic and industry partners;

More than 380 scientific publications associated with SARS-CoV-2 and COVID-19 (as of July 11, 2022), with a high number of citations and views per publication;

Launch of a French startup (SpikImm) and 112 technology transfer agreements signed with industry partners.

The Institut Pasteur President, Prof. Sir Stewart Cole, at the international conference "COVID-19: Advances and Remaining Challenges," from September 29 to October 1, 2021, Institut Pasteur (via video conference and onsite).

International response via the Pasteur Network

Unprecedented response from the 33 Pasteur Network members in 25 countries. A total of 33 research projects selected by the COVID-19 task force and funded by the Institut Pasteur in Paris.

Introduction of emergency funding systems via core programs in the field of One Health. Examples: ECOMORE II in South-East Asia (funded by the French Development Agency) and MediLabSecure, which is being rolled out in 22 countries from the Sahel region to the Black Sea (funded by the European Union).

Public information and advice to public authorities

An important role providing information and engaging in scientific outreach in a context dominated by the rapid and large-scale spread of fake news, which we are actively tackling. Provision of useful resources online: a COVID-19 fact sheet, epidemiological modeling and a "Fake News" section.

Impact in 2020: 8.7 million users on the pasteur.fr website (79% more than in 2019).

Participation in several bodies established to offer advice on managing the COVID-19 crisis to the French government (Scientific Council, CARE, Vaccine Strategy Council) and to international organizations (the European Commission, the World Health Organization).

COVID-19: major progress

2020

► JANUARY 9, 2020
The Chinese authorities and World Health Organization (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.

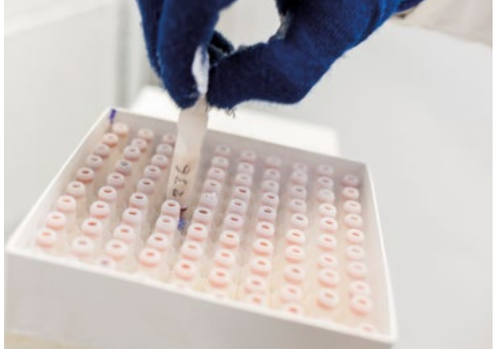
► JANUARY 21, 2020
A first "Institut Pasteur" COVID-19 fact sheet is made available online to inform the public. It is updated on a regular basis.

► JANUARY 22, 2020
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."

Further information
Institut Pasteur 2019-2023 Strategic Plan

"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



► JANUARY 24, 2020
The first samples (from the first imported French cases) arrive at the Institut Pasteur from Bichat Teaching Hospital. An RT-qPCR diagnostic test is developed by the National Reference Center (CNR) for Respiratory Infection Viruses and information is shared with the international community.
Detection of the virus is confirmed by the CNR the same evening.

► JANUARY 25, 2020
The strain isolation work and the virus genome sequencing begin at the Institut Pasteur.

► JANUARY 27, 2020
The virus is isolated by the Institut Pasteur.

► JANUARY 30, 2020
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. This assay, enabling highly sensitive, specific detection of the virus through nasopharyngeal swab specimens, is sent to hospitals and provided to the World Health Organization (WHO) to be shared among the global network and with the scientific community.

"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

► FEBRUARY 11, 2020
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.

► FROM MARCH 9 ONWARDS 2020
A “COVID-19” internal scientific meeting is held at the Institut Pasteur every Monday. At the height of the pandemic, scientists will often be more than a hundred. In 2022, this meeting is held once a month.

► MARCH 11, 2020
WHO announces that the outbreak is now a pandemic.

FAKE NEWS

► MARCH 17, 2020
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.

► 17-20 MARCH, 2020
Given the viral nature of the initial erroneous information in social and mainstream media, a large-scale fact-checking campaign is launched and extensively shared via a wide variety of platforms (threads, video, series, etc.) and by several institutions and official outlets.

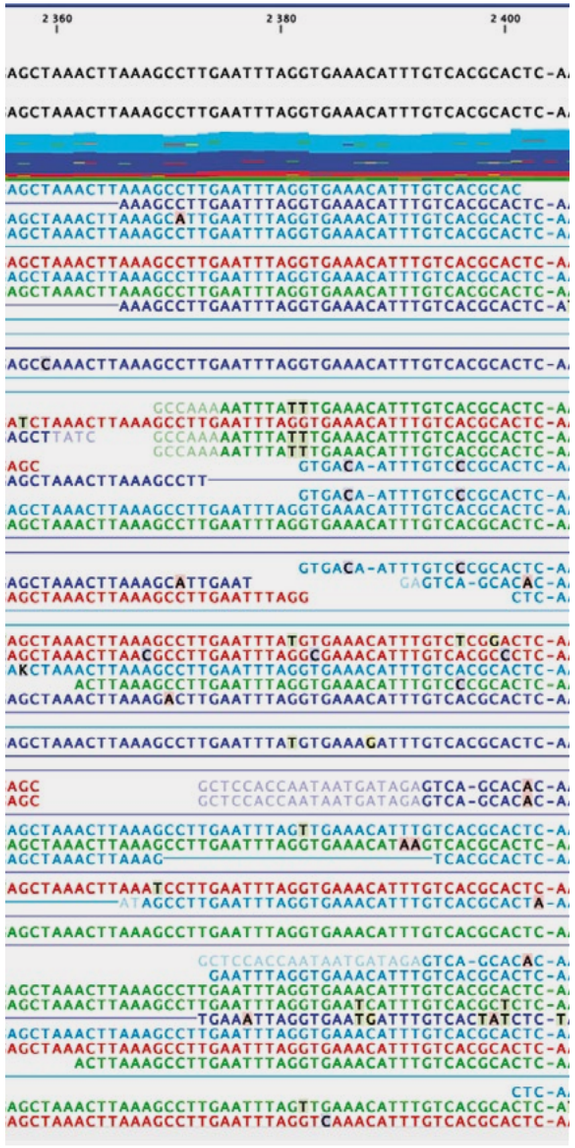
Learn more
See the special fake news page at www.pasteur.fr

INNOVATION

With 25 international patent applications filed between January and March 2020,* the Institut Pasteur (like the CNRS) was among the top 20 applicants worldwide. The 25 invention disclosures were in four fields:

DIAGNOSTICS	**55%**
VACCINES	**24%**
THERAPEUTICS	**19%**
TECHNOLOGIES	**2%**

Source: The European Patent Office.



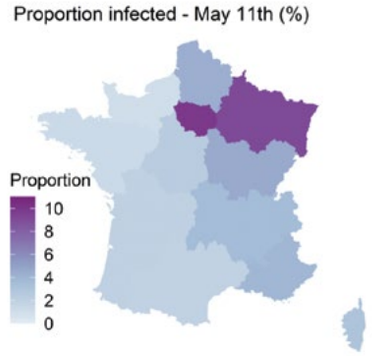
Close-up of the whole SARS-CoV-2 coronavirus sequence in one of the first French cases, determined at the Institut Pasteur. The viral RNA bases can be seen.

► LATE MARCH 2020
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.

FAKE NEWS

► MARCH 26, 2020
Given the impact of the video and the threats it caused, the Institut Pasteur had 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 policy of this prosecutor.

► APRIL 21, 2020
Modeling carried out by the Institut Pasteur indicates that between 3% and 7% of French people have been infected.

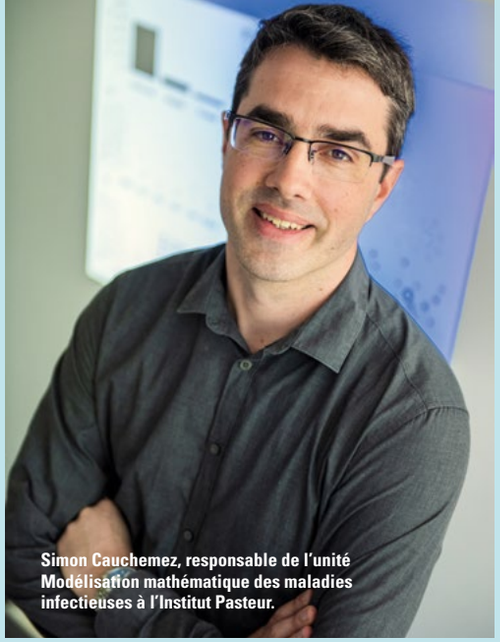


Estimation du pourcentage, par région en France, de personnes infectées par le SARS-CoV-2 d'ici au 11 mai 2020.

► APRIL 23, 2020
Following the epidemiological survey carried out in Crépy-en-Valois (Oise) 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.

ZOOM

Predicting and anticipating with models


Simon Cauchemez, responsable de l'unité Modélisation mathématique des maladies infectieuses à l'Institut Pasteur.

The Institut Pasteur's Mathematical Modeling of Infectious Diseases Unit uses models to predict how outbreaks will develop and analyze the outbreak risk of emerging viruses. *"We work closely with Santé publique France to try to answer very specific questions and help the health authorities with their decision-making in the event of a crisis,"* explains unit head Simon Cauchemez. *"During the Zika outbreak in Martinique in 2016, for example, the challenge was to predict how many people would develop neurological complications such as Guillain-Barré syndrome (GBS). Although these cases were rare, the patients required ventilation in intensive care units. Since there were only eight ventilators on the island, the authorities wanted to know whether this would be enough. Using mathematical modeling, and basing our work on a previous outbreak in French Polynesia, we determined various possible scenarios. After a period of uncertainty, the arrival of new data on the outbreak demonstrated that transmissibility was lower than in French Polynesia, and our predictions on the number of GBS cases proved to be relatively accurate."* The team's work also involves preparing for potential future outbreaks. In 2019, it contributed to a study* on the Nipah virus. This virus, transmitted by bats and found throughout South and South-East Asia, is fatal in 70% of cases, and there is no treatment or vaccine. WHO believes that it could evolve to become more transmissible, triggering severe outbreaks in the near future. An analysis of epidemiological data over the past 14 years in Bangladesh, the most affected country, showed that adults with respiratory symptoms were more contagious and that contacts of these patients (such as spouses), especially those exposed to respiratory secretions, had a higher likelihood of infection. *"We have identified which patients particularly need to be placed in isolation. This could help control virus spread if an outbreak were to occur,"* concludes Simon Cauchemez.

** Conducted by scientists from the Institut Pasteur, the CNRS and the Johns Hopkins Bloomberg School of Public Health, in collaboration with the International Center for Diarrheal Disease Research, Bangladesh (icddr,b), the Institute of Epidemiology, Disease Control and Research (IEDCR), and the American Centers for Disease Control and Prevention (CDC).*

2019 study about Nipah virus.
Learn more on pasteur.fr

► APRIL 30, 2020
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.
(Nature)

Learn more
See the press release "Revealing how SARS-CoV-2 hijacks human cells; points to drugs with potential to fight COVID-19" at www.pasteur.fr

► MAY 14, 2020
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.
(Allergy, European Journal of Allergy and Clinical Immunology)

Learn more
See the article "LuLISA project: bioluminescence as a tool for human diagnostics" at www.pasteur.fr

► MID-MAY 2020
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 29, 2020
An epidemiological study led by several Institut Pasteur teams in primary schools in Crépy-en-Valois since April, involving 1,340 people, does not reveal significant transmission between children or from children to teachers, and confirms that children are more often infected by adults at home.
(Eurosurveillance)

Learn more
See the press release "COVID-19 in primary schools: no significant transmission among children or from students to teachers" at www.pasteur.fr

ZOOM

COVID-Oise: a large-scale study in Crépy-en-Valois offers a representative image of viral circulation in the general population

After the virus was revealed to be circulating in Crépy-en-Valois in the Oise department in late February 2020, the French Ministry of Health commissioned an investigation of the town's high school from the Institut Pasteur. The scientists documented the dynamics of the epidemic in the high school, then the spread of the virus in families, at a time when the population was unaware that this was COVID-19 and therefore took no protective measures.
The initial investigation developed into the COVID-Oise cohort study, which analyzed changing immune responses during the various waves and over the course of the vaccination campaign. Until April 2022, the Institut Pasteur teams came back every six months to take nasopharyngeal swabs and saliva and blood samples from more than 600 people. As of mid-2022, there is still a huge amount to analyze in these samples. The analyses should provide information about the nature and durability of the immune response to infection and vaccines, and also the immunological aspects of long COVID, a syndrome experienced by 5 to 10% of the infected population who continue to have chronic symptoms after acute infection.

▸ JULY 15, 2020
Thanks to the discovery of an association between a type 1 interferon deficiency in the blood and severe COVID-19 forms, early detection and a potential therapeutic approach can be offered to at-risk patients.
(Science)

Learn more
See the press release "Type 1 Interferon deficiency: a blood based signature" at www.pasteur.fr

▸ JULY 24, 2020
An intranasal lentiviral vaccine in development provides significant protection in animals.
(Cell Host & Microbe)

Learn more
See the press release "A lentiviral vaccine candidate for intranasal administration" at www.pasteur.fr

▸ AUGUST 2020
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.

▸ OCTOBER 6, 2020
Lung-on-a-chip research shows the effect of SARS-CoV-2 on ciliated cells.
(Source biorxiv.org)

FAKE NEWS

▸ OCTOBER 7, 2020
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 13, 2020
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.
(The EMBO Journal)

Learn more
see the press release "Innate immunity and fusion of cells infected with SARS-CoV-2" at www.pasteur.fr.

▸ OCTOBER 15, 2020
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.
(Science)

Learn more
See the press release "Common vulnerabilities across SARS-CoV-2, SARS-CoV-1 and MERS coronaviruses" at www.pasteur.fr

FAKE NEWS

▸ NOVEMBER 2, 2020
Senlis Criminal Court finds the author of the video guilty of defamation against the Institut Pasteur.

Learn more
See the article "COVID-19: Senlis Criminal Court convicts the author of a fake news video for defamation" at www.pasteur.fr

▸ NOVEMBER 3, 2020
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.
(Nature)

Learn more
See the press release on the "number of COVID-19 deaths in under-65s" at www.pasteur.fr

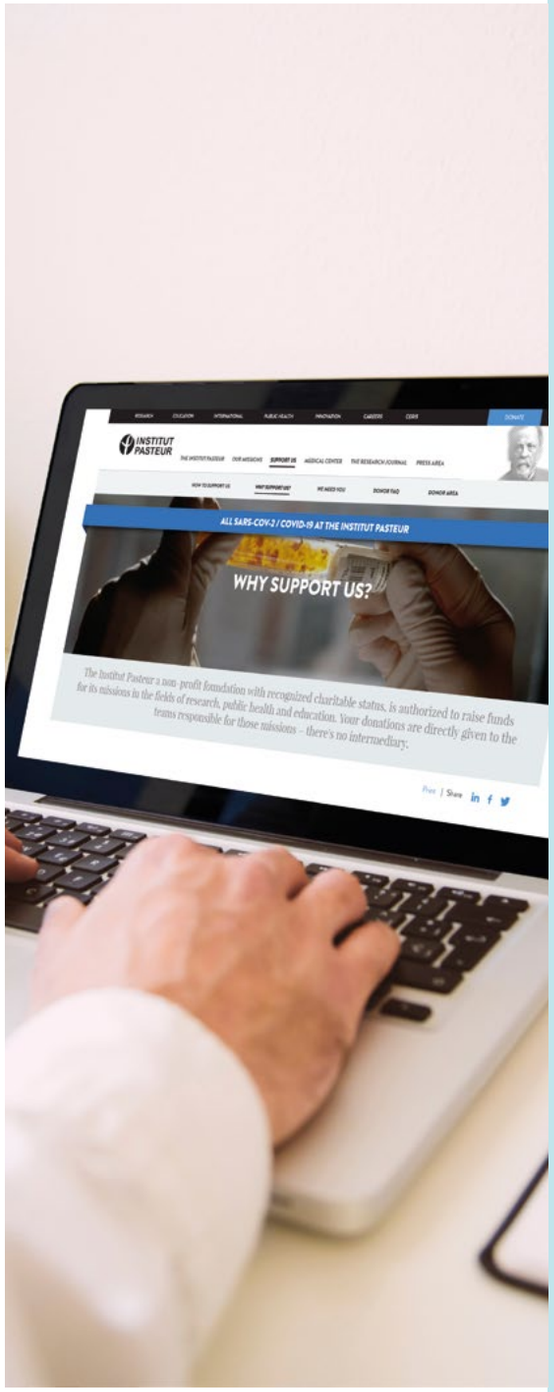
▸ NOVEMBER 18, 2020
The first results are published concerning the link between SARS-CoV-2 and the nervous system; COVID-19-associated olfactory dysfunction reveals SARS-CoV-2 neuroinvasion and persistence in the olfactory system.
(Source biorxiv.org)

▸ NOVEMBER 23, 2020
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).

Learn more
See the article "Use of the maladiecoronavirus.fr web application" at www.pasteur.fr

▸ DECEMBER 14, 2020
In 2020, an initial publication demonstrated the efficacy of an intranasal lentiviral COVID-19 vaccine. It drastically reduces viral loads and prevents pathogenic pulmonary inflammation in animals.
(Cell Host & Microbe)

Learn more
See the press release of December 2020 about this lentiviral vaccine candidate. A second publication goes on to confirm its efficacy *(see October 2021 – page 26)* at www.pasteur.fr



ZOOM

Public information and advice to public authorities

The Institut Pasteur has been working since January 2020 to inform the public and engage in scientific outreach in its areas of expertise – a particularly important task in a context dominated by the rapid and large-scale spread of fake news, which the Institut Pasteur is actively tackling.

On pasteur.fr, the dedicated space "All SARS-CoV-2 and COVID-19" contains the COVID-19 fact sheet (viewed nearly 3 million times between January and June 2021), the epidemiological modeling carried out by Simon Cauchemez's unit, and a "Fake News" section. Nearly 8.7 million users viewed the pasteur.fr website in 2020 (79% more than in 2019).

As well as the online response, more than 50 scientific experts stepped up to respond to thousands of media requests, 76 press articles were published, several press conferences were held and a huge range of educational material (videos, books, etc.) was produced. To raise awareness among the public, more than 100,000 interviews, quotations and mentions of the Institut Pasteur were published/broadcast in the media in 2020 (compared with 13,000 in a normal year). The Institut Pasteur came under the media spotlight at a time of heightened political and social debate related to the COVID-19 crisis, and the institute and its scientists became the target of attacks as questions were raised over the origins of the virus and the effectiveness of vaccination and the health pass.

Finally, the Institut Pasteur was involved in informing and advising public authorities about the management of the COVID-19 crisis, through the participation of scientists in several advisory bodies at national level (Scientific Council, CARE, Vaccine Strategy Council) and international level (European Commission, World Health Organization).

In 2020,
8.7 million
users on pasteur.fr

In 2020,
more than
100,000
interviews, quotations and mentions in the media

2021

▸ JANUARY 2021

The Institut Pasteur sets up a dedicated space for viewing the research of the Mathematical Modeling of Infectious Diseases Unit, led by Simon Cauchemez. The space contains data about the dynamics of the epidemic and the impact of control measures.

Learn more
See the Institut Pasteur website (in French) on COVID-19 modeling at www.pasteur.fr

▸ MARS 7, 2021

A study conducted on hospital staff who contracted a mild form of COVID-19 seems to suggest that immunity lasts longer in women than in men.
(The Journal of Infectious Diseases)

Learn more
See the article "COVID-19: neutralizing immune response lasts longer in women than in men" at www.pasteur.fr

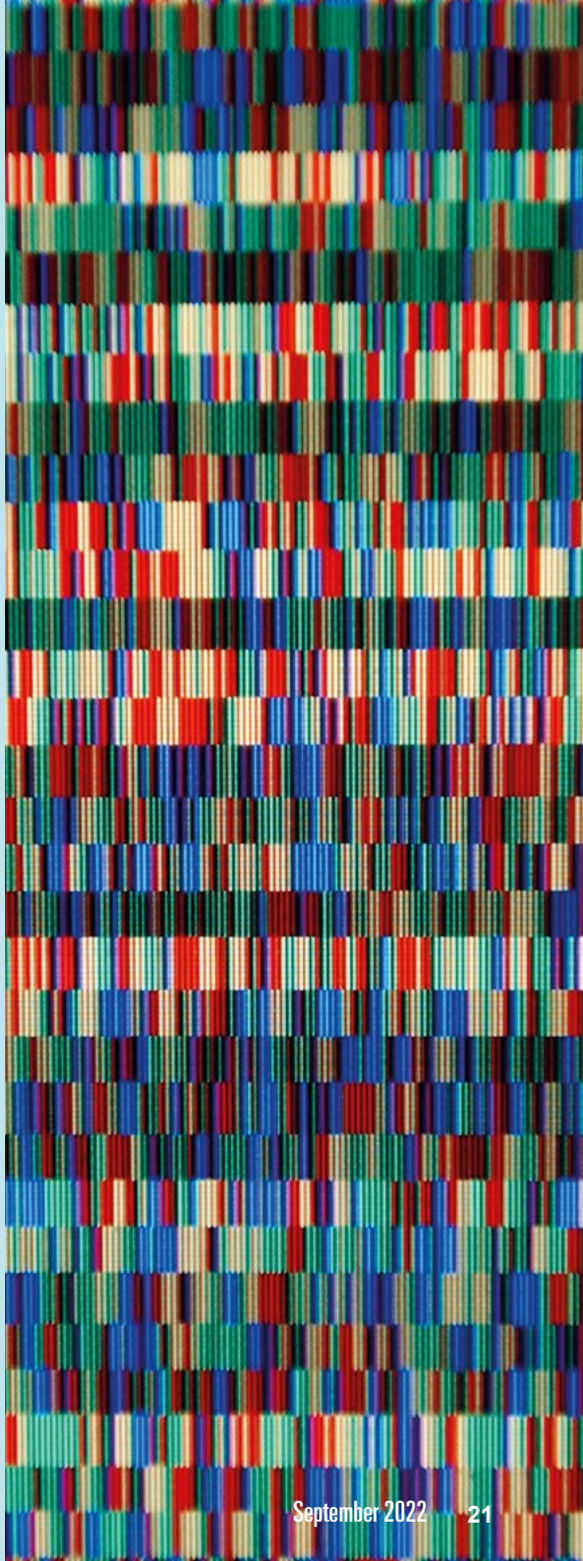
ZOOM

EMERGEN: sequencing of SARS-CoV-2 variants

To closely monitor the development of the SARS-CoV-2 outbreak and the emergence of new variants, the French health authorities set up EMERGEN (a consortium monitoring and researching infections by EMERging pathogens through microbial GENomics) in January 2021, with a view to rolling out a SARS-CoV-2 genome surveillance system throughout France for public health and research purposes. Whole genome sequencing of the virus is the only technique capable of characterizing new emerging variants and identifying their specific mutations and recombinations. Analysis of new variants combined with patients' clinical data at the time of sampling is used to determine variants' functional impact in terms of virulence, infectiousness, and ability to affect vaccinated individuals, etc.

35,714
SARS-CoV-2 variants sequenced by the Institut Pasteur's technological platform "P2M" in 2021 for the CNR for Respiratory Infection Viruses alone through the EMERGEN project.

17,200
samples sequenced in 2019 by P2M, for comparison, for the 14 CNRs under Institut Pasteur supervision, of which approximately 4% were conducted for the CNR for Respiratory Infection Viruses.



DNA sequencing at the Institut Pasteur.

► MARCH 21, 2021
An analysis of the outcomes of hospitalized patients during the early months of the COVID-19 pandemic in France is conducted. A retrospective study of national surveillance data is used to develop a probabilistic model for analyzing detailed patient trajectories based on 198,846 hospitalizations in France during the first nine months of the pandemic.
(Lancet Regional Health Europe)

Learn more
See the press release (in French) on the retrospective analysis of national surveillance data at www.pasteur.fr

► MARCH 23, 2021
A study on sensitivity to neutralizing antibodies demonstrates that the UK (Alpha) variant is neutralized to almost exactly the same degree as the reference virus, whereas the South African (Beta) variant is six-fold less sensitive.
(Nature Medicine)

Learn more
See the press release on the analysis of the sensitivity of the variants to neutralizing antibodies at www.pasteur.fr

► MAY 5, 2021
Discovery of the mechanisms of short- and long-term anosmia. SARS-CoV-2 infects sensory neurons and causes persistent epithelial and olfactory nervous system inflammation, resulting in loss of smell. The olfactory epithelium could be a gateway to the brain and explain some of the neurological manifestations of long COVID.
(Science Translational Medicine)

Learn more
See the press release on the discovery of the mechanisms of short- and long-term anosmia at www.pasteur.fr

► MAY 6, 2021
COVID-19: SpikImm startup launched to develop monoclonal antibodies
The Institut Pasteur signs an exclusive worldwide license agreement with the biotech startup SpikImm SAS, founded by Truffle Capital, to develop anti-SARS-CoV-2 (COVID-19) monoclonal antibodies for therapeutic and diagnostic use.

Learn more
See the article on the launch of the startup SpikImm at www.pasteur.fr

ZOOM

Launch of the startup SpikImm

Monoclonal antibody therapy is one of the most novel approaches for treating COVID-19 patients and preventing progression to severe forms of the disease.
SpikImm, established by the Institut Pasteur and Truffle Capital in 2021, develops antibodies using an innovative process invented by the Institut Pasteur's Humoral Immunology laboratory (Inserm joint unit) led by Hugo Mouquet, enabling screening and selection of SARS-CoV-2-specific human neutralizing antibodies. The Institut Pasteur filed an international patent application and signed an exclusive global license agreement with SpikImm, under which clinical trials are due to begin in mid-2022.

One of SpikImm's monoclonal antibodies, SPK001, powerfully and effectively neutralizes the original SARS-CoV-2 strain as well as all variants of concern. SPK001 is a high-affinity monoclonal antibody targeting the RBD (receptor-binding domain) of the viral spike protein.

"The project led by the startup SpikImm on anti-SARS-CoV-2 monoclonal antibodies is a concrete example of the success that is possible with the Institut Pasteur's innovation development model. We were quickly able to transfer the technology to a leading industry partner, Truffle Capital."

Isabelle BUCKLE
Vice-President Technology Transfer and Industrial Partnership (DARRI)

► 21 MAI 2021
Based on its analysis of samples from over 11,000 individuals, the CNR for Respiratory Infection Viruses estimated 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.
(Nature Communications)

Learn more
See the article (in French) “Prevalence of SARS-CoV-2 antibodies in France” at www.pasteur.fr

► JULY 8, 2021
A study shows that the Delta variant is less sensitive to neutralizing antibodies than the Alpha variant, and antibody concentrations need to be four times higher to neutralize it. Three of the four therapeutic monoclonal antibodies tested are effective against this variant.
(Nature)

Learn more
See the press release on the analysis of the sensitivity of the Delta variant at www.pasteur.fr

► JULY 16, 2021
A publication describes how SARS-CoV-2 replicates in the respiratory tract. It destroys the cilia of the ciliated cells in the epithelium, inhibiting mucociliary clearance, a mechanism that expels inhaled particles and protects the respiratory tract from pathogens.
(Nature Communications)

Learn more
See the press release “SARS-CoV-2 damages ciliated cells and inhibits mucociliary clearance in the airways” at www.pasteur.fr

► SEPTEMBER 6, 2021
Modeling of COVID-19 epidemiology is conducted in a vaccinated population to assess a potential resurgence in autumn. Further modeling studies assess the high transmission and hospitalization rates among unvaccinated individuals. The studies also show that vaccination is less effective against Delta but continues to offer protection against severe forms, and forecast a third of total infections in children and teenagers.
(HAL Pasteur)

Learn more
See the Institut Pasteur website (in French) on COVID-19 modeling at www.pasteur.fr

► SEPTEMBER 21, 2021
Research shows that individuals vaccinated with a messenger RNA vaccine develop defenses against the Beta and Delta variants. Their immune system produces memory cells capable of recognizing and neutralizing variants of concern.
(Immunity)

Learn more
See the press release “Immune memory after mRNA vaccination to recognize variants” at www.pasteur.fr

► OCTOBER 15, 2021
After a first publication in December 2020, a second one shows the efficacy of an intranasal lentiviral COVID-19 vaccine. In animals, it not only reduces the viral load, but protects the brain and lungs.
(EMBO Molecular Medicine).

Learn more
See the press release “The intranasal lentiviral vaccine candidate protects brain and lungs” at www.pasteur.fr

Kamala Harris, Vice President of the United States, salutes the Institut Pasteur’s response in tackling the pandemic.

► NOVEMBER 9, 2021
US Vice President Kamala Harris meets several of the Institut Pasteur’s scientists and salutes the Institut Pasteur community’s response in tackling the COVID-19 epidemic.

Learn more
See the article on the official visit by Kamala Harris at www.pasteur.fr

► NOVEMBER 26, 2021
One component of the ComCor study gives results on places of infection and the effectiveness of RNA vaccines. The study identifies sociodemographic factors, places of SARS-CoV-2 infection and behavior linked to risk of infection, and assesses the effectiveness of RNA vaccines against the Delta variant.
(The Lancet Regional Health Europe).

Learn more
See the press release “ComCor study: new results” at www.pasteur.fr

► 23 DECEMBRE 2021
Omicron is resistant to most monoclonal antibodies but neutralized by a booster dose. This is the key finding of a study published in Nature: Omicron is much less sensitive to the antibodies currently used in clinical practice or obtained after two vaccine doses, but administering a booster dose increases antibody levels sufficiently to neutralize it.
(Nature)

Learn more
See the press release “Omicron: resistant to most monoclonal antibodies but neutralized by a booster dose” at www.pasteur.fr

ZOOM

Epidemiology: a highly useful discipline for guiding the decisions of health authorities

Interview with Professor Arnaud Fontanet, head of the Institut Pasteur's Epidemiology of Emerging Diseases Unit and a member of the COVID-19 Scientific Council.

What contribution did epidemiology make to controlling the COVID-19 pandemic?

The most visible contribution is probably the use of mathematical modeling. Based on freely available data from Santé publique France, scientists like those in the unit led by Simon Cauchemez at the Institut Pasteur *(see inset "Predicting and anticipating with models" – page 13)* made predictions about the possible trajectories of the epidemic in different scenarios. This approach was very useful in helping health authorities take appropriate decisions, for example identifying critical moments and preventing hospitals from reaching saturation point. Epidemiology was also used to identify determinants of infection. That was the aim of my team with the ComCor case-control study that began in October 2020 – we wanted to identify places of transmission and activities associated with a risk of SARS-CoV-2 infection.

How was the ComCor study carried out?

The principle was simple: a link to the study website was sent to the "cases" – people who had been recorded by the French National Health Insurance Fund because they had tested positive for COVID-19. The Ipsos survey company then sent the same link to the "controls" – people of the same age, sex and place of residence as the cases, but who had not been infected. We asked the two groups the same questions about their sociodemographic characteristics, family and work environment, vaccine history and comorbidities, and also places they had visited, leisure activities and social gatherings. Using our statistical models, we then analyzed all these data to identify high-risk places and behaviors. The tool is still operational and continues to provide us with information about the variants. To date, more than 500,000 positive cases and 30,000 controls have been recruited.

Professor Arnaud Fontanet, head of the Institut Pasteur's Epidemiology of Emerging Diseases Unit

What results have you obtained, and what have they been useful for?

This study identified private gatherings, bars and restaurants, and indoor sports activities as SARS-CoV-2 infection risk factors. It also showed an increased risk of infection associated with the presence of children in the household: firstly teenagers, then primary school children once the teenagers had been vaccinated. Conversely, it demonstrated the protective role of working from home. These data resulted in several publications in *The Lancet Regional Health Europe.*

> "The Institut Pasteur was mobilized in Crépy-en-Valois, with Inserm*, for two Epidemiological studies led by Santé publique France**."

** Inserm: French National Institute of Health and Medical Research.*
*** Santé publique France: French Public Health Agency.*

500,000
positive cases and
30,000
controls have been recruited.

INNOVATION

Inventions related to SARS-CoV-2

By July 2022, 25 inventions related to SARS-CoV-2 had been developed, validated and protected by the Institut Pasteur, including:

Vaccine candidates

➜ MV-SRAS2 attenuated measles vector
➜ DNA/RNA vaccine against SARS-CoV-2 using the spike protein RBD
➜ Intranasal vaccine on the DNAFLAP platform

PCR assays

➜ A specific, sensitive PCR assay, recommended by WHO, available from February 2020 onwards
➜ An ultra-sensitive droplet PCR assay developed to predict infection progression and response to treatments
➜ A rapid PCR assay that can be used on different media

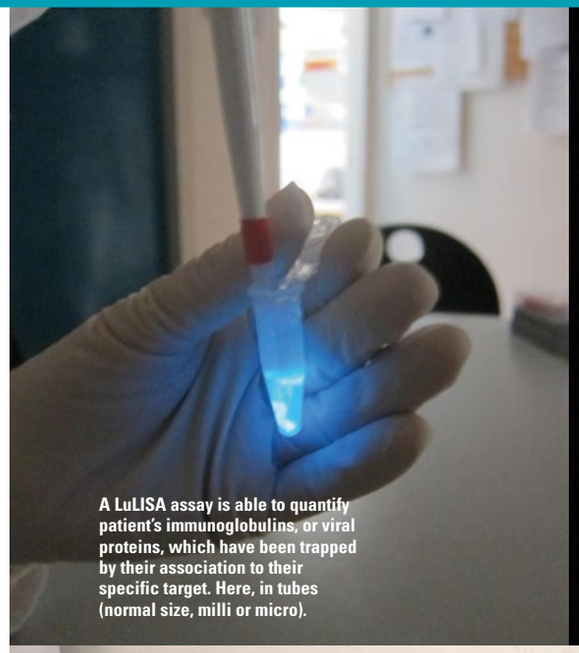
Seroneutralization assays

to examine and monitor vaccine efficacy

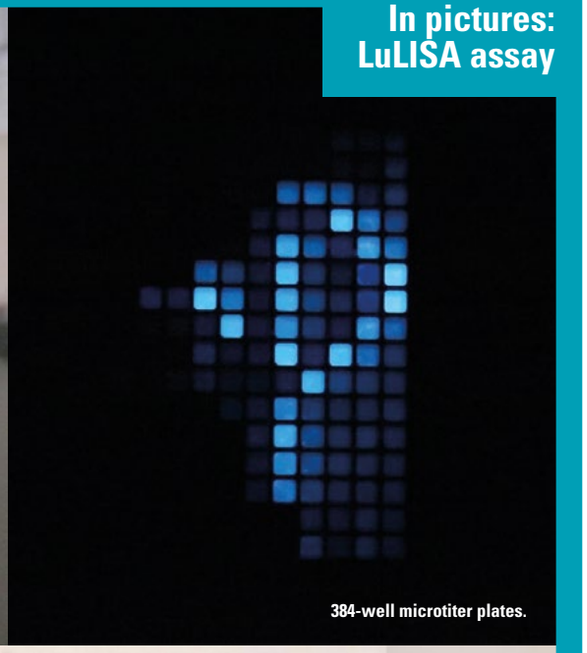
Serological antibody assays

➜ Best-in-class SARS-CoV-2 ELISA total antibody assay, available from April 2020
➜ Multi-antigen ELISA assay on beads to examine viral phases and detect infection as early as possible
➜ LuLISA assay to treat hundreds of samples at the same time
➜ Rapid assay with llama antibodies – anti-N and anti-S nanobodies

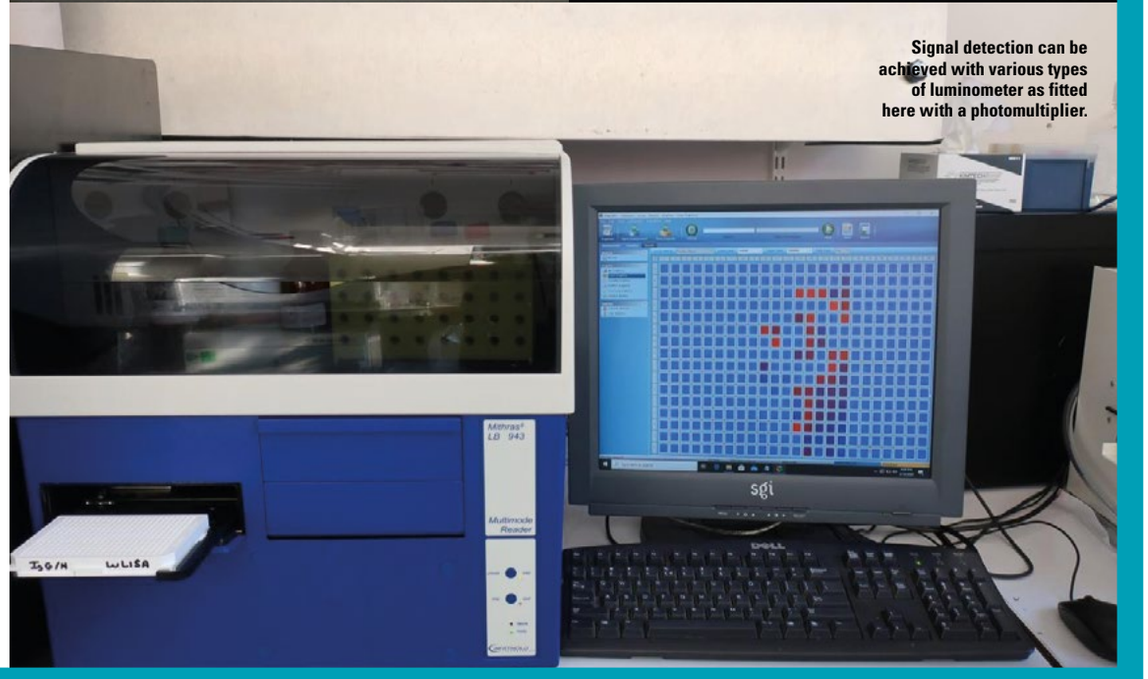
In pictures: LuLISA assay



A LuLISA assay is able to quantify patient's immunoglobulins, or viral proteins, which have been trapped by their association to their specific target. Here, in tubes (normal size, milli or micro).



384-well microtiter plates.



Signal detection can be achieved with various types of luminometer as fitted here with a photomultiplier.

Check out our report on pasteur.fr

A historic fight against emerging infectious diseases

(excerpt from our special report) - Introduction

Emergence, an inevitable and unpredictable fact of life

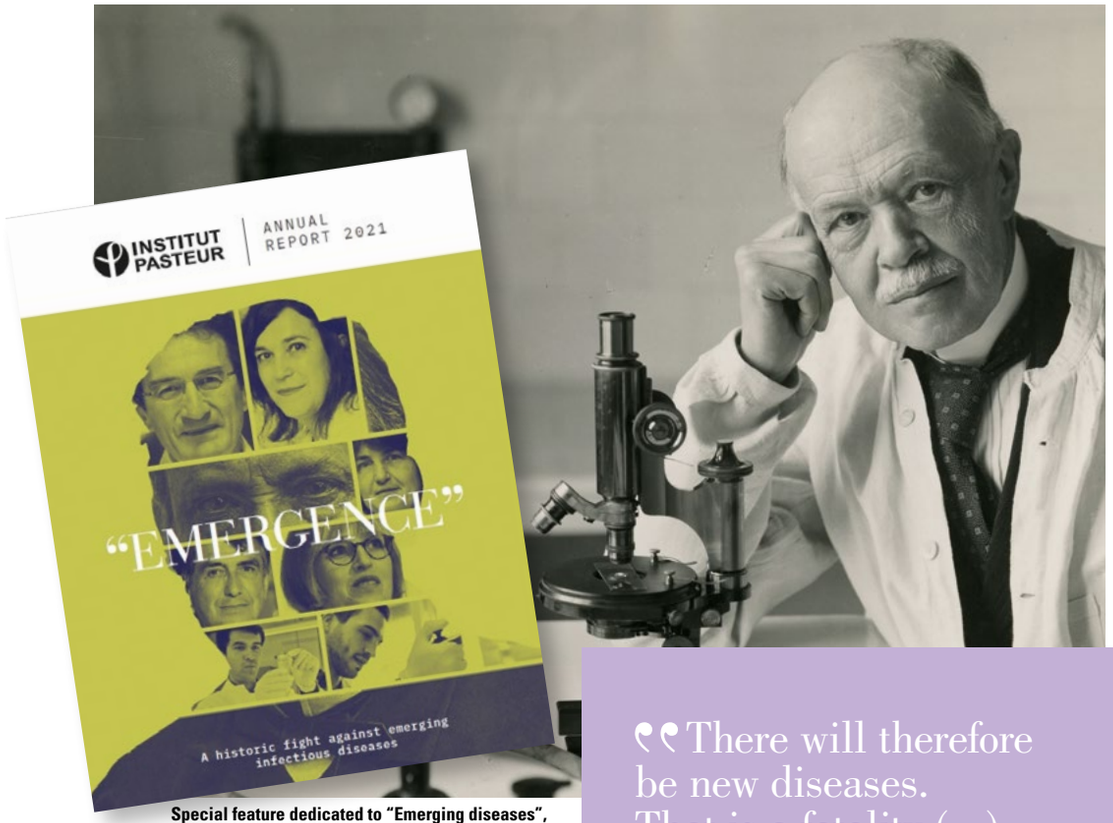
With Jean-Claude Manuguerra, head of the Environment and Infectious Risks Unit, the Laboratory for Urgent Response to Biological Threats and the Hantaviruses CNR, and co-head of the Emerging Animal Pathogens in Humans OIECC (World Organization for Animal Health Collaborating Center).

Between 1918 and 1919, in just a few months one third of the world's population was infected with Spanish flu. While Spain was the first country to report the disease, the outbreak probably started in Asia and subsequently spread to the United States before reaching Europe in a more virulent and lethal form with American soldiers. The risk of pandemics is higher now than in 1918 due to the speed of travel. Viruses can travel the world in a day, compared to a year in the 19th century. While research and public health responses are sometimes slowed down by regulations, alert systems have improved and the knowledge of the biology of viruses has progressed. Moreover, laboratory testing capacity has increased following the introduction of the International Health Regulations in 2005.

We also know that the introductory phase (or spillover – see report online on pasteur.fr, click on the QR code below) is the key one for tackling outbreaks. In 2003, rapid identification of the severe acute respiratory syndrome (SARS) virus led to effective containment measures as patients were not infectious prior to symptom onset, and it was thus possible to eradicate the virus. In contrast, COVID-19 spread quickly in 2020 following its introductory phase. WHO thus declared a pandemic, triggering an immediate response from the scientific community. A combination of vaccinations and lockdown measures then helped limit disease severity and spread.

Why are we still faced with such a risk today? An analysis of key factors in viral emergence since 1940 suggests that changes in land use play a dominant role in 1 in every 4 cases. While climate appears to have less of an impact, except in relation to arboviruses, this situation may well change with global warming.

What are the main causes? By definition, emerging viruses are unpredictable. However, often respiratory and easily transmissible RNA viruses such as influenza and coronaviruses present the greatest risk. In contrast, AIDS was caused by a retrovirus that emerged in the 1980s. The key takeaway is that emergences are an "inevitable fact" in the words of scientist Charles Nicolle. However, let's not be fatalistic as scientific progress is a constant source of hope.



Special feature dedicated to "Emerging diseases", from the 2021 annual report, available on pasteur.fr

> "There will therefore be new diseases. That is a fatality (…)."

"(…) Another fact, equally fatal, is that we will never be able to track them down from their origin. When we become aware of these diseases, they will already be completely formed, adult, one could say. How will we recognize these new diseases, how will we be able to suspect their existence before they manifest themselves as symptoms? Knowledge of infectious diseases teaches humans that they are brothers and united. We are brothers because the same danger threatens us, united because contagion comes to us most often from our fellow men."

Charles NICOLLE,
Le Destin des Maladies Infectieuses
[Fate of Infectious Diseases] (1933).

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25-28, rue du Docteur Roux

75724 Paris Cedex 15 – France

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