Inserm's commitment to the fight against the Covid-19 pandemic

April 28, 2020

1. React rapidly to accelerate research and tackle the pandemic

Appearing in the central Chinese city of Wuhan in December 2019, the novel SARS-CoV-2 coronavirus has rapidly spread across the world, leading to the most serious pandemic in recent history. From the very outset of this global health crisis, Inserm has played a leading role in the French and international research spheres, rallying its many experts in subjects related to fundamental research, therapeutic research, and modelling. Participating also in France's solidarity effort, the Institute has taken action to distribute tens of thousands of masks, gloves, gowns, shoe covers and reagents to medical teams working in the nation's hospitals.

By April 13, 2020, Inserm had already participated in 44 scientific publications on COVID-19 (including preprints), reflecting the unfailing energy and proactiveness of its researchers. This research primarily concerns potential therapeutic approaches, the search for a vaccine, epidemiology, the deployment of telemedicine, predicting the spread of the virus in various countries, and its transmission. A large part of the research published has been financed by the REACTing consortium seed fund.

A key player in fighting the COVID-19 pandemic, REACTing – which stands for *REsearch and ACTion targeting emerging infectious diseases* – launched and coordinated by Inserm since 2013 under the egis of Aviesan, has been tasked with preparing and coordinating French research into emerging infectious diseases in order to prevent and fight epidemics.

The consortium has therefore been assigned coordination of French COVID-19 research by the Ministry of Solidarity and Health and the Ministry of Higher Education, Research and Innovation (MESRI). A number of task forces (New Therapeutic Approaches, COVID-19 Vaccines, Animal Models, Modelling, and Digital) have been created in order to reflect on the major research priorities and evaluate the projects submitted to the consortium by research teams across France and in other countries.

In addition, Inserm researchers are participating in various World Health Organization (WHO) working groups, the Scientific Advisory Board consulted by the government, and the Analysis, Research and Expertise Committee (CARE) set up by the Ministry of Solidarity and Health.

Never has Inserm's mission – Science for Health – been so important as it is right now. Although many questions remain unanswered concerning the evolution of the pandemic, Inserm will continue its efforts to inform public decision-making with research of excellence that combines rigor and ethics. The information contained in this press kit is likely to change as research progresses.

2. Treat patients

Within REACTing, the New Therapeutic Approaches Task Force meets weekly to evaluate the many projects submitted to it regarding research into treatment avenues. Experts in the various subjects addressed are invited in order to enrich discussions, as well as members of CARE, the Health Directorate, MESRI, and the REACTing COVID-19 Scientific Advisory Board.

The antivirals approach: focus on the Discovery trial

Of all the research projects concerning treatments, it is most certainly the Discovery trial coordinated by Inserm that is generating the most public interest and questions. Discovery is a European project, whose French component has started thanks to REACTing seed funding, paid jointly by MESRI and the Ministry of Solidarity and Health. It is also funded by the Program for Clinical Research in Hospitals (PHRC) and has been incorporated in the WHO international Solidarity trial.

The trial evaluates the efficacy of various antiviral treatments in limiting the viral multiplication observed in certain hospitalized patients whose immune response is too weak, and whose condition deteriorates often around the seventh day of the disease.

It intends to recruit 3,200 European patients with moderate to severe COVID-19, at least 800 of whom in France, admitted to a medical department or directly to intensive care.

- The treatments

The objective of Discovery is to evaluate the efficacy and safety of various experimental therapeutic strategies which, according to current scientific knowledge, have been identified as potential therapeutic candidates for COVID-19. As a recap, it involves testing and comparing the following five strategies:

- optimal standard of care;
- optimal standard of care plus remdesivir;
- optimal standard of care plus lopinavir and ritonavir;
- optimal standard of care plus lopinavir, ritonavir and interferon beta;
- optimal standard of care plus hydroxychloroquine.

Therefore, none of the patients enrolled in the trial is left without treatment and none of the patients is receiving placebo.

- Why an open-label randomized trial?

Discovery is a randomized trial, meaning that the treatment is not chosen by the doctor but assigned randomly. Each arm of the clinical trial is assigned an equal number of patients so that it is balanced, with sufficient data obtained for each treatment tested.

An open-label trial design was chosen in order to save valuable time during this pandemic. It must be remembered that the molecules tested are not all available in the same dosage forms. For a double-blind trial to be possible, it would take a long time to prepare placebos that resemble each of the treatments being tested, therefore delaying the start of the trial.

However, in order to limit bias, although the patients and doctors know which treatment is being administered, the researchers responsible for statistical analysis do not. This controlled, open-label trial design will therefore make it possible to obtain results as rapidly as possible whilst respecting rigorous and high-quality methodology.

The immunomodulation approach: focus on Corimuno-19

Some hospitalized patients present a specific profile in which the deterioration in their condition does not seem to be due to the multiplication of the virus but to their excessive immune response to the infection. One avenue currently being explored by Inserm researchers is to understand and evaluate the effect on COVID-19 patients of treatments that would modulate this response.

This is the challenge of the Corimuno-19 project, a cohort of open-label, randomized and controlled trials. The overall objective of this large-scale study is to test various treatments (especially immunomodulator treatments) and determine which present the most favorable risk/benefit ratio in adult patients hospitalized for COVID-19 pneumonia – diagnosed either at the moderate to severe stage and requiring no mechanical ventilation, or at the critical stage requiring mechanical ventilation.

The antibodies approach: focus on Coriplasm

Particularly mediatized is Coriplasm – one of the Corimuno-19 clinical trials, and which is sponsored by the Paris hospitals group (AP-HP). With the support of Inserm and REACTing, the French Blood Establishment (EFS) is deploying a process to enable the collection, qualification, preparation and provision to the clinical teams of plasma from convalescent patients. The idea is to evaluate whether their plasma is capable of immediately transferring this immunity to other patients, as had been the case when treating various infectious respiratory diseases such as SARS-CoV-1, MERS-CoV or H1N1 influenza. The objective is to determine whether this strategy reduces the frequency of severe forms of COVID-19 and their associated mortality.

Other treatment repurposing initiatives

Therapeutic repurposing consists of finding new therapeutic indications for treatments that are well-known, safe and already available. Within the context of the COVID-19 pandemic, a number of teams are testing molecules used for other diseases on SARS-CoV-2, in order to evaluate their effects. The team of Inserm researcher Manuel Rosa-Calatrava at the International Center for Research in Infectious Diseases (Inserm/Université Claude-Bernard Lyon 1/CNRS/ENS Lyon) is working on the development and validation of a strategy to repurpose drugs for new antiviral therapeutic indications. Having already repurposed *in vitro* two molecules available on the market for respiratory viruses, including MERS-CoV, the researchers are now testing them against SARS-CoV-2 on cell lines and on an *ex vivo* model using reconstituted human respiratory epithelium.

3. Find an effective vaccine

Although phase I clinical trials to test candidate vaccines have now been launched in the USA and China, many questions persist concerning immune response to the virus and a potential vaccine.

Throughout the world, over one hundred teams are working on the development of vaccines, including a number of French groups. Of the thirty or so teams working on the candidate vaccines in France, twelve are from Inserm. Although their development work remains in the early stages for the most part, it is still furthering knowledge of the virus and vaccine research as a whole.

In order to support them and identify research priorities, REACTing has set up a dedicated COVID-19 Vaccines Task Force. Its role is to collect information on the progress of the various candidate vaccines, catalogue the actions of the French teams, and discuss the most relevant measures to deploy in the national context.

It has defined criteria for assigning priority to the French teams' COVID-19 candidate vaccine development initiatives, which include the speed of the vaccine production cycle, minimization of the risk of disease exacerbation caused by immune mechanisms, the potential for producing the vaccine on a very large scale, and the availability of preclinical test results suggestive of the induction of disease protection.

The search for a new vaccine

REACTing Vaccination Task Force member Frédéric Tangy (Institut Pasteur) heads up a team that is working on a COVID-19 candidate vaccine at quite an advanced stage of development. It uses as a platform the attenuated measles vaccine that had already been used in the development of certain candidate vaccines, notably against Chikungunya. A phase I clinical trial is scheduled for September 2020.

The Vaccine Research Institute under the supervision of Inserm also has a role to play in vaccines research within the context of the COVID-19 pandemic. Its researchers are mobilized for the accelerated development of an SARS-CoV-2 coronavirus vaccine based on its expertise and the technology developed for other infectious diseases, such as HIV. The novel approach of the Institute is based on the targeting of dendritic cells, key cells in immune response.

Thanks to the involvement of this institute in French Covid-19 – the national cohort of patients infected with SARS-CoV-2, coordinated by REACTing in line with 56 hospitals in France (including Henri-Mondor Hospital in Créteil), the objective of the research conducted there is to characterize patient immune response. Understanding this aspect of the infection is an essential prerequisite for the development of any vaccine.

The BCG vaccine to protect medical staff?

Several studies suggest that some live vaccines, such as BCG or the oral polio vaccine, have non-specific beneficial effects on certain infections. Therefore it is possible that BCG could reduce the intensity of SARS-CoV-2 infection by stimulating the memory of innate immunity, the first line of immunity in the face of infection, and thereby inducing "trained innate immunity". Furthermore, what few contraindications there are to the use of this vaccine are well known, and its very low cost is an advantage.

An Inserm team is preparing the implementation of a French double-blind trial to test the non-specific protective effects of the BCG vaccine, the idea being to evaluate whether it could offer medical staff a certain level of protection against COVID-19. Collaboration between this team and Spanish scientists who are also conducting research in the area would enable large-scale comparison of the benefits of BCG versus a placebo common to both countries. Should such a trial go ahead, the participants would need to be followed up for several months in order to obtain reliable data.

4. Model and monitor the epidemic

The Mathematical Modelling of Infectious Risks Task Force has been set up very quickly. The modelling concerns the general population, as well as specific populations such as medical staff.

Modelling the spread of the epidemic

Since January 2020, work by the team of Inserm researcher Vittoria Colizza has made it possible to model the spread of the epidemic from China to Europe and Africa, with the objective being to better orient prevention policies and improve surveillance of the epidemic.

Their first publication, in the journal *Eurosurveillance*, concerned the risk of importing the virus into Europe. This was based on the scenario of all Chinese provinces declaring more than ten cases at that time as well as on data from January 2019 on air travel flows from these regions to Europe,

produced by the OAG (a global leader in the collection of flight data). Another study published by the group mid-February in *The Lancet* evaluated the risk of importing the virus into Africa, with Egypt, Algeria and South Africa presented as the countries most at risk.

Another major research avenue explored by Colizza and her team in collaboration with telecommunications group Orange is the impact of confinement on population mobility, by studying aggregated and anonymized cell phone network data. The researchers are particularly interested in spontaneous changes in mobility occurring before and during confinement, and their impact on the evolution of the pandemic. The collected data will also be integrated into models of pandemic spread developed by the team. This is to improve predictions of how the virus will spread and identify regions at risk of becoming clusters and having their healthcare systems overwhelmed.

The team is also working on the modelling of potential deconfinement scenarios in order for quarantine to be lifted under the most favorable conditions. In a report published mid-April on the EPIcx laboratory website, the researchers stress the need to support all deconfinement strategies with measures involving mass testing, the identification of those having been in contact with confirmed cases, and the isolation of detected cases.

Surveillance of the epidemic intensified with Covidnet

Established in 2012 by the Sentinelles network (Inserm/Sorbonne Université) and the French Public Health Agency, the GrippeNet.fr study is a comprehensive information resource for epidemiologists wishing to monitor the evolution of seasonal influenza. Each year, the network collects epidemiological data on influenza directly from the population, online and in an anonymous manner. GrippeNet.fr began its ninth season at the end of November 2019 and has over 7,200 participants so far, who each week declare the symptoms that they had or had not experienced since they last logged on. For better monitoring of the current epidemic, the GrippeNet.fr study has become Covidnet.fr. Based on questionnaires sent to the volunteers of the GrippeNet.fr/Covidnet.fr cohort, it is currently the only health surveillance system in France that makes it possible to study the symptoms presented by patients having not sought assistance from the healthcare system.

Risk of hospital transmission

The research also includes studies that aim to model the risk of SARS-CoV-2 transmission in the hospital setting (nosocomial risk). One such study is being conducted by Didier Guillemot and Lulla Opatowski, researchers at the Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases laboratory (Inserm/Institut Pasteur/Université de Versailles Saint-Quentin-en-Yvelines).

5. Study confinement and its impacts

The Sapris study and the social challenges of confinement

Sapris, a vast survey based on five large, national, general-population cohorts (Constances, Étude familiale E3N-E4N, Elfe / Epipage 2, NutriNet Santé) conducted in close coordination with the leaders of those cohorts, looks at the epidemiological and social challenges posed by the exceptional prevention measures deployed against COVID-19. Coordinated by Nathalie Bajos, Inserm Research Director and sociologist-demographer, and Fabrice Carrat, Professor of Public Health at Sorbonne Université in collaboration with the Public Health Agency, the study involves a multidisciplinary group of researchers from Inserm, France's National Institute for Demographic Studies (Ined), National Center for Scientific Research (CNRS), Université Paris-Saclay, Sorbonne Université, Sorbonne Paris Nord and Université Paris Dauphine-PSL, National Health Insurance Fund (CNAM), Institut Gustave Roussy and the National Research Institute for Agriculture, Food and Environment (INRAe), covering fields as varied as epidemiology, sociology, demographics and economics.

By means of a questionnaire sent out at the start of April, which will be repeated several times during confinement and after it has ended, participants are asked about the specific challenges of the epidemic and the confinement measures. The main themes studied are the incidence of COVID-19 symptoms and other health problems, the use of treatment for other health conditions or failure to seek

treatment, the perception of risk to oneself and in general, the effects of the prevention measures on daily life, social relationships, work, and the education of children. In addition, once serological tests become available, the researchers would like to be able to establish the prevalence of COVID-19 based on self-sampling offered to the study participants, which will provide information on prevalence on a national scale.

Evaluating the contacts of French people during confinement

A population survey to collect and analyze data concerning the contacts between French people during confinement has been launched by Institut Pasteur in collaboration with Inserm and several universities. Called SocialCov, this study is based on online questionnaires concerning people's contacts before and during confinement, with the aim of gaining deeper insight into the impact of confinement on our social and professional lives. More specifically, the survey will make it possible to identify the number of contacts we have each day, their frequency, and distribute these results by age group.

Supporting mental health during confinement

The measures of social distancing, and particularly the confinement of the French population, will doubtlessly have an impact on mental health and wellbeing. Several studies have already examined this issue with, for example, a meta-analysis published in *The Lancet* suggesting that confinement is associated with a harmful psychological impact, characterized by mood disorders, confusion, and in the most extreme cases by the manifestation of post-traumatic stress disorder.

For a deeper insight into these effects, Anne Giersch, Inserm researcher and head of the Cognitive Neuropsychology and Pathophysiology of Schizophrenia laboratory in Strasbourg, is conducting a study in healthy volunteers. Its objective is to explore the positive and negative effects of confinement, particularly on mental health. The participants are asked to answer anonymous questionnaires on their general health, concern about infection risk, conditions of confinement, social network before and during confinement, and also on their mood, emotions and stress levels.

In order to help the general population deal with anxiety related to the pandemic, Inserm researchers have developed a COVID-19 extension of the StopBlues initiative. This initiative, based on a free website and application, was developed in 2018 by the Eceve-Inserm research team led by Karine Chevreul. Its users are assisted in order to identify the signs of their malaise, look for the possible causes and find concrete solutions for confronting it. Within the context of the pandemic, the COVID-19 extension of Stop-Blues includes the publication of short videos describing the emotions that can be felt in the face of fear of the disease, confinement difficulties, social isolation and family conflicts.

6. Test the population and protect and support medical staff

Inserm provides use of its laboratories

Inserm is participating in the population testing effort. A Decree and an Order published on April 5 authorize French prefects to requisition public research laboratories for COVID-19 testing using RT-PCR – a technique based on genetic material. For the laboratories under their supervision, the CNRS and Inserm have prepared for this by making inventories of the equipment available and the number of such tests that could be performed each day under the conditions set by the government. Some fifty structures with the capacity to perform over 100,000 tests per day could be involved under the coordination of Inserm.

Inserm launches a project to recycle masks

In close collaboration with Tours Regional University Hospital, Inserm Research Directors Nathalie Heuzé-Vourc'h and Mustapha Si-Tahar are leading a proof-of-concept study on an effective decontamination process for surgical and FFP2 masks, to enable their reuse. In the current context in which masks are in short supply, various decontamination processes are being compared. The team has already shown that when 70°C moist heat is applied for a period of one hour, there is no deterioration in the structure of the masks. The decontamination appears to be effective, destroying several viruses and bacteria tested in the proof-of-concept study. Also, the properties of the masks are similar to the untreated masks. These findings must now be consolidated by testing the process on masks contaminated with SARS-CoV-2.

Aphro-Cov, a project to strengthen the diagnosis and management of COVID-19 patients in five Sub-Saharan African countries

As part of the support given by France in response to the Coronavirus crisis, Rémy Rioux, Chief Executive of the French Development Agency (AFD) and Gilles Bloch, Chairman and Chief Executive Officer of Inserm announced in March the launch of a joint initiative to improve the health surveillance and management of suspected cases of COVID-19 in five African countries (Burkina Faso, Gabon, Ivory Coast, Mali, Senegal). Called Aphro-Cov, this program steered by REACTing is focused on the laboratories, early warning system, clinical departments, and – by means of raised awareness and reinforced communication – the population as a whole.

Because research is needed more than ever to protect the health of everyone and to address the challenges posed by this new pandemic, Inserm has set up a platform for donations and is calling on public generosity. The funds collected will be used to sustain and complete these different research projects.

To make a donation and support the work of our researchers:**https://don.inserm.fr/donner**

Inserm in the fight against fake news

Fighting false information and publishing clear and high-quality scientific information are key concerns for Inserm. This is particularly the case with the COVID-19 pandemic, given the various rumors and scientifically unfounded information circulating on social media and other platforms. To counteract this and give the public the most accurate information, Inserm has, since January 2020:

- Posted an episode on its *Canal détox* channel discussing the false information most often encountered.
- Published information bulletins with the most important news on the Institute and international research, and which also take a look at false information spotted online.
- Each week, the REACTing consortium prepares a thorough review of the scientific literature concerning SARS-CoV-2 and COVID-19. The group provides the public with a summary of high-quality scientific publications for those wishing to follow the scientific research more closely.