



ISCIII AND COVID-19: OUR WORK OVER THE THREE YEARS OF THE PANDEMIC



GOBIERNO
DE ESPAÑA

MINISTERIO
DE CIENCIA, INNOVACIÓN
Y UNIVERSIDADES



Instituto de Salud Carlos III

Content

▶ INTRODUCTION	5
Raquel Yotti, Secretary-General for Research, Ministry of Science and Innovation	5
Cristóbal Belda, Director of the Carlos III Health Institute (ISCIII)	6
▶ INTRODUCTION	9
▶ THE ISCIII AS A FINANCING ORGANISATION	13
Introduction	13
COVID-19 Fund	13
<i>A first-hand account. Pilar Gayoso, Assistant Director of the ISCIII</i>	18
▶ SCIENTIFIC PRODUCTION AND RESEARCH RESULTS	19
Introduction	19
Summary of the main results	20
The ISCIII in the context of international scientific production on COVID-19	21
The ISCIII in the context of Spanish scientific production on COVID-19	24
ANNEX I: Top 25 COVID-19 publications in Spain with the highest number of citations received as of 31 January 2023	26
ANNEX II: Top 25 ISCIII COVID-19 publications with the highest number of citations received as of 31 January 2023	28
▶ RESEARCH AT THE ISCIII DURING THE PANDEMIC	31
COVID-19 projects: five examples	31
ENE-COVID	31
<i>A first-hand account: Marina Pollán, National Centre for Epidemiology</i>	36
ENE-COVID-Senior	37
COSMO-Spain	38
<i>A first-hand account: Maria João Forjaz, National Centre for Epidemiology</i>	43
COMBIVACS	44
<i>A first-hand account: Maria João Forjaz, National Centre for Epidemiology</i>	46
Long COVID	47
<i>A first-hand account: Vicky Serra, CIBER de Epidemiología y Salud Pública (CIBER-ISCIII)</i>	49
▶ PROVISION OF SCIENTIFIC AND TECHNICAL SERVICES	51
Introduction	51
Actions at the beginning of the pandemic: crisis microbiology	51
<i>A first-hand account: Jesús Oteo, National Centre of Microbiology</i>	53
Epidemiological data: information to ensure better action	54
<i>A first-hand account: Amparo Larrauri, National Centre of Epidemiology</i>	59
▶ PARTICIPATION AT THE EUROPEAN AND INTERNATIONAL LEVEL	61
<i>A first-hand account: Inmaculada Casas, National Centre of Microbiology</i>	63
▶ CONCLUSIONS	65

INTRODUCTION



Raquel Yotti

Secretary-General for Research
Ministry of Science and Innovation

On 5 May 2023, the World Health Organisation announced the end of the SARS-CoV-2 international health emergency. The best tribute the Ministry of Science and Innovation can pay to the men and women who have worked tirelessly for more than three years, contributing their scientific knowledge to help combat the pandemic, is to explain their work to Spanish society. Thousands of people working in research and science management in universities, health research institutes, hospitals, foundations and public research organisations have been working across the country and contributing their intelligence, experience and hard work. Most of them have done so silently, away from the spotlight and the media.

This document, in collaboration with the Spanish Foundation for Science and Technology (FECYT), takes stock of the huge amount of work carried out by one specific public research organisation: the Carlos III Health Institute (ISCIII). As many people know, the ISCIII played a key role in minimising the impact of the pandemic in Spain. True to its mission and founding purpose, and above all, thanks to the expertise of its staff and its well-established lines of research developed over decades, this organisation has used science to protect the health of the nation. It has used science to save lives.

There is no doubt that the wound inflicted on our society by the pandemic will take a long time to heal and that the scars from the loss of our loved ones will never fully disappear. However, as the years go by, we will also be able to see more clearly that the pandemic was an example of how to overcome adversity and learn together. It was an example of generosity and collaboration. The information that readers will find in this report helps to put these statements into context.

During the toughest months of the pandemic, I had the enormous responsibility of running the Carlos III Health Institute and, therefore, I am very familiar with the work it performed. Over that period, the extraordinary community of people working at the ISCIII managed to increase the microbiological diagnostic capabilities in Spain, generate epidemiological parameters to better understand the evolution of the pandemic and track daily excess mortality. They also managed to design the largest population-based study in the world to identify the prevalence and real impact of infection with SARS-CoV-2, promote and develop clinical trials to generate evidence about new vaccination guidelines, analyse public opinion on the pandemic and disseminate the knowledge generated in a simple but meticulous way. In addition, and above all, they constantly provided the different governmental organisations with scientific and technical advice to help them design the best public health measures. By taking the lead through being the main source of finance and coordination for biomedical research in Spain, the ISCIII was also instrumental in making possible the launch and development of research and innovation projects throughout the country aimed at combating COVID-19, which included, among other objectives, research on vaccines.

Editing, coordination and content development:
Instituto de Salud Carlos III (ISCIII).

Thanks to the Spanish Foundation for Science and Technology (FECYT) for its help in the preparation of this report.



This report is a tribute to the true dedication of the women and men who, from all the organisations attached to the ISCIII, built that wall of Science that kept us safe from the pandemic.

Design and layout:
a.f. diseño y comunicación • www.afgrafico.com

Follow us on

- @SaludISCIII
- [linkedin.com/company/instituto-de-salud-carlos-iii/](https://www.linkedin.com/company/instituto-de-salud-carlos-iii/)
- [youtube.com/c/InstitodeSaludCarlosIII](https://www.youtube.com/c/InstitodeSaludCarlosIII)



This licence allows others to remix, tweak and build upon your work for non-commercial purposes, and although your new creations must be credited to you and cannot be used commercially, they do not have to be licensed under the same terms.

This was a titanic task which we describe in this document through the first-hand accounts of some of the men and women who, together with their teams, made it all possible. Many others did even lower profile but equally vital work in management, administration and service positions. All the scientific activity and achievements would have been unthinkable without the conscientious but simultaneously extraordinarily diligent management of all the administrative processes, from the contracting procedures to the management of donations and the importing of scientific equipment.

I will always be deeply grateful to each and every person who made this possible. I hope that this report helps to spread this feeling of gratitude among the readers, and above all, emphasise the need to take care of the ISCIII and its professionals.

Cristóbal Belda

Director
Carlos III Health Institute (ISCIII)

It is more than three years since the pandemic caused by the SARS-CoV-2 virus appeared in our lives, changing the way we understand the world and revealing the unconscious interdependence that was seeping through the seams of our society. For some time now, we have been relieved to see a cautious return to a world without distancing and personal protective equipment, with a gradual resuming of normal life.

Science, both theoretical and applied, has played a leading role in allowing us to move on. The Carlos III Health Institute (ISCIII) and its related organisations, as a melting pot of science and health, has demonstrated to the general public that it is one of the strongest and most outstanding organisations in the national and international field of health research. Over these three long years, our organisation has financed and produced an enormous amount of science, making the Spanish scientific production on COVID-19 some of the best in the world, in terms of both quality and quantity.

All this has been possible thanks to the work of thousands of researchers and dozens of institutions that have focused their activity and talent on generating knowledge to combat the virus and its consequences. Here, we cannot forget that the ISCIII was set up more than 35 years ago to respond to exactly this type of situation. I can safely say, without the shadow of a doubt, that our organisation, working together with all our separate organisations, has shown that it is more than capable of responding to the scientific needs emerging during the pandemic.

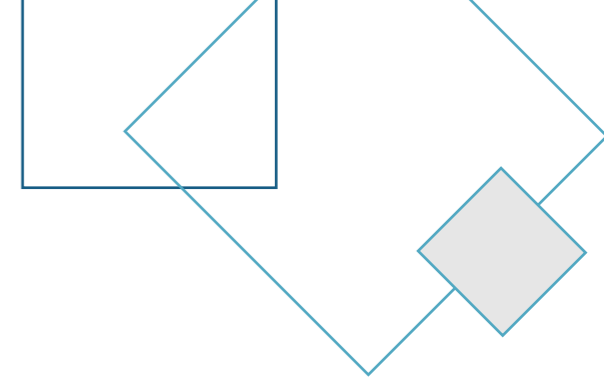
This document includes much of the evidence that supports this claim, compiled thanks to the brilliant work of our colleagues at the Spanish Foundation for Science and Technology (FECYT). I would like to highlight a few facts which are explained throughout the report. Firstly, the ISCIII is one of the top ten organisations in the world in terms of scientific production on COVID-19, and ranks fifth in terms of production quality: one out of every three articles produced by the Institute is among the ten most cited documents in the world. Beyond bibliometric indicators, the scientific production of the ISCIII has had an impact on people's health that is difficult to understand just through numbers.

Secondly, the work of the staff in the Institute's different centres, with a key role being played by the National Centre of Epidemiology (CNE) and the National Centre of Microbiology (CNM), has provided the best scientific foundation from which to

interpret the evolution of the pandemic, and their work has been an essential input to the decision-making process. Specifically, the seroprevalence study carried out in 2020 (ENE-COVID) revealed the spread of the virus and allowed policies to be designed based on this information. Nor can we forget the daily all-cause mortality monitoring system (MoMo), the weekly reports from the CNE, the Combivacs study on the use of heterologous vaccines and the creation of the CNM macro-laboratory at the start of the pandemic.

Finally, financing through the COVID19 Fund for urgent science in the Spanish National Health System (SNS for its Spanish initials) has been essential in organising the various initiatives launched by the different research groups. We thus gained information on different risk profiles, potential markers and we could even rule out some treatments as ineffective. Similarly, it was the ISCIII that brought together different vaccination platforms for the first time, resulting in a versatile and efficient vaccination system. Finally, among many other advances, it was the Institute that promoted studies to explore the duration of immunoprotection after the first dose in the at-risk population (ENE-COVID-Senior study), as well as public knowledge and opinion studies about the pandemic (COS-MO-Spain study).

All of this, and much more, is explained in this document, which aims to provide accountability in return for the trust placed in the ISCIII over its more than 35 years. The report is also a way to pay tribute to the thousands of women and men who have shone brightly during this time, doing what they do best: science to protect health. I hope that the readers will feel as proud as we do when we recall the impact the ISCIII had during the pandemic and the results of this.



INTRODUCTION

The COVID-19 pandemic has been a huge challenge worldwide and for all countries, with the entire population exposed to a real risk to their health. In this context, Spain activated all the structures that support the Spanish Science, Technology and Innovation System (SECTI) and the Spanish National Health System (SNS). Both systems have operated as immovable barricades, responding to this pandemic, which has caused a public health crisis unlike any in recent history, and keeping it contained. The scientific and health systems are responding to a massive challenge. The Carlos III Health Institute (ISCIII) has been playing, and continues to play, an important role in its management.

More than three years after the start of the pandemic, we now understand that public health crises not only affect people's health. The effects are not restricted to health issues, but instead, put all areas of a country at risk, including the economy, education and, of course, scientific research. As a result, the response to the SARS-CoV-2 virus and COVID-19 has involved all levels and areas of government, which have been strongly committed to overcoming this global crisis. All governmental organisations, within the scope of their powers, continue to actively manage the consequences and aftermath of the pandemic.

On 11 March 2020, the World Health Organisation (WHO) declared the COVID-19 crisis to be a global pandemic. Earlier, on 30 January of that year, the outbreak had been declared a public health emergency of international concern. Three years and three months later, on 5 May 2023, the WHO declared the end of this international emergency. From the moment COVID-19 appeared, the public science and research system in Spain set out to provide answers and some degree of certainty, at a time when uncertainty and a lack of knowledge was a feature of practically everything. The international scientific community was attempting to sequence and isolate the new SARS-CoV-2 coronavirus, and simultaneously trying to gather information in order to understand more about the virus, the disease it causes and its transmissibility.

In Spain, the ISCIII focused all its efforts on strengthening its research capacity and helping the SNS contain the pandemic. Its four main objectives - in-house research, training, the financing of science and the provision of scientific and technical services - have been directed, without forgetting about its other tasks, towards joining forces to better manage SARS-CoV-2 and the COVID-19 crisis. The Ministries of Science and Innovation and Health, to which the ISCIII reports, have always provided the necessary promotion of biomedical and health R&D and innovation activities. Our commitment is strong and unwavering.

Since its declaration as a global pandemic, the epidemic has experienced several waves in Spain over the last three years. The first was from January 2020 to June of that year. The second came after the summer, which saw the end of full lockdown in Spain. The third started in the middle of the Christmas period. The fourth and fifth waves followed in spring and summer 2021. The omicron variant of SARS-CoV-2 caused the sixth wave in November 2021, and the seventh wave, with a more limited impact, thanks in part to the vaccination programme, appeared in spring 2022.

Since 2022, thanks to the impact of the vaccines and the ever-greater control of the pandemic, the situation has been returning to some degree of normality, albeit cautiously and with certain preventive measures

The COVID-19 pandemic has been a real challenge, on a global scale and for all countries



continuing. It is important to highlight that the authorities were taking decisions to safeguard the right to life and physical safety and the right to protection of health in accordance with the instruments available in our legal system. The management of the health crisis caused by COVID-19 has further demonstrated the value of the principles that underpin the SNS.

In this context, this report arises from the need to describe the most important actions that the ISCI has carried out during the last three years, with the conviction of fighting COVID-19 through research, with the support of the scientific and health community, patients and civil society as a whole. It should be noted that one of the key events during this period, namely the publication of Spanish Royal Decree 463/2020 in the Official State Gazette of 14 March 2022, declaring a State of Alarm, made it possible to manage the exceptional circumstances and the risk to the Spanish public as a whole. In this scenario, ISCI's responsibilities and actions were a catalyst for generating R&D tools to face the challenges and difficulties caused by the pandemic.

Two years after the end of the pandemic, a first attempt at this work was made with a shorter [informative report](#). The aim of this updated and expanded report is, with the invaluable help of the Spanish Foundation for Science and Technology (FECYT), to take a deeper, more exhaustive and more detailed look at the work of the ISCI during the three years of the pandemic.

The aim of this document is to demonstrate its resilience during the most difficult moments of the pandemic, and the ability of its centres and units to work together. It also analyses and demonstrates to society as a whole the immense scientific production generated about COVID-19 and its capacity for leadership in this area. Its work has dominated scientific publications in all fields and reflects the international importance of its research.

Above all, the aim is to give a first-hand account of the research processes and their impact on improving the quality of life of the public, which is the ultimate goal of each of the projects implemented by the public research system during the COVID-19 epidemic. This report encapsulates an institutional, professional, scientific, social and human vision. One common factor can be seen throughout the document, which is recognition of all ISCI staff for their commitment and dedication in the search for solutions to the challenges that SARS-CoV-2 and COVID-19 have generated.

The Carlos III Health Institute

Over these years, the ISCI has strengthened its position as a leading public health and biomedical research institution, taking on a prominent role alongside other public organisations in the fight against COVID-19. This was the case both in the early stages of the pandemic, when it was necessary to deal with limited knowledge and misinformation about the virus, and in the last few years, when the ISCI's scientific output has made it possible for us to gain an in-depth understanding of the challenge we have been facing. In line with the Institute's values, the aim has always been to provide a public service that improves people's health through science.

During the course of the COVID-19 pandemic, the ISCI has played a triple role as a researcher, financier and service provider. This is in addition to its training, consultancy, information, communication and dissemination work.

Firstly, it has operated as a financing organisation through calls for proposals, such as the COVID-19 Fund, which led to the creation of nearly 130 projects, research lines and expressions of interest that allowed the research community in Spain to begin researching the best ways to mitigate the effects of the pandemic, promoting science and innovation in health sciences and biomedicine.

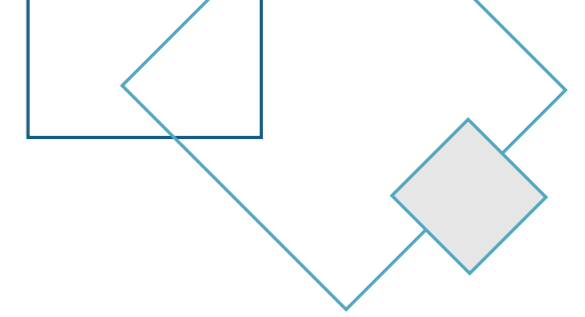
In addition, the ISCI has also led research in our country, becoming the Public Research Body (PRB) with the highest scientific output. Some of the key projects implemented by the ISCI include the ENE-COVID study, which allowed us to identify the real rate of the virus among the population through a clinical seroprevalence study. We should also mention the COSMO-Spain study, promoted by the World Health Organisation and coordinated in Spain by the ISCI, which identified public opinion about the pandemic through surveys conducted throughout the course of the epidemic. In addition, the CombiVacs trial confirmed the option of using heterologous vaccination schedules at a time when the SARS-CoV-2 vaccine was causing the greatest problems among the population, the ENE-COVID Senior trial looked at immunity to infection by analysing the effect of vaccines and the study on long COVID aimed to provide answers and facilitate consensus among the scientific community.

Finally, these research and financing efforts have been combined with all the initiatives linked to the provision of services so that the scientific and health systems could benefit from the Institute's work and expertise. Our key units, our laboratories, the ad hoc work groups created and, in short, our staff, have been making data, resources, spaces, statistics, advice, reports, infrastructures, documents and people available to the biomedical community for more than three years.

In the following pages of this scientific and informative report, the aim is to reflect the role of the Institute in all its facets over the three years of the pandemic. The intention is to highlight the immense work carried out by all the Institute's staff during the most complicated moments of the pandemic, reinforcing the SNS when necessary and advancing our knowledge of COVID-19. It is this work that has enabled the ISCI to play a prominent role in biomedical research in our country and become an international leader, with publications of great importance that are extensively cited by the scientific community.

To this end, this report consists of chapters that refer to the Institute's role as a financing organisation and promoter of health initiatives and projects, to the scientific production generated by the Institute over recent years and, lastly, to the ISCI's actions throughout the course of the COVID-19 pandemic, from its contributions in the early stages, to the coordination of major studies of huge international importance.

Alongside the information, ISCI researchers have told their stories, with the objective being to provide a first-hand account of the role of the institute and its staff during the darkest moments of the pandemic. The aim is to offer a human and very personal look at the research, going beyond the results and showing what happens behind the scenes of COVID-19 research in the leading Spanish biomedical research institution.



THE ISCIII AS A FINANCING ORGANISATION

Introduction

One of the main responsibilities of the ISCIII, as a Public Research Body (PRB), is to finance research. The ISCIII is coordinator and manager for Health Strategic Action (Acción Estratégica en Salud), the main public sector tool for financing biomedical and health science in Spain. As such, it has gone beyond its annual work of awarding grants, contracts and projects to promote health-related R&D. In response to the emergency and thanks to the support of the Government, it launched a tool that allowed the rapid completion of studies to improve the management of the pandemic. As a result, in March 2020, the COVID-19 Fund was set up.

COVID-19 Fund

During the early stages of the pandemic, ignorance and uncertainty dominated our society. Against this backdrop, science set its wheels in motion to contribute its solutions and knowledge to the big questions that were emerging about SARS-CoV-2. Given this, and the real need to lead the start of research in our country, in March 2020 the ISCIII launched the COVID-19 Fund. This was an extraordinary call for proposals offering a total of more than €24 million to finance projects and research on the biology of the virus, epidemiology, vaccine development, identification of at-risk groups, search for antiviral medicines, and improvements in the diagnosis and treatment of the disease, among others.

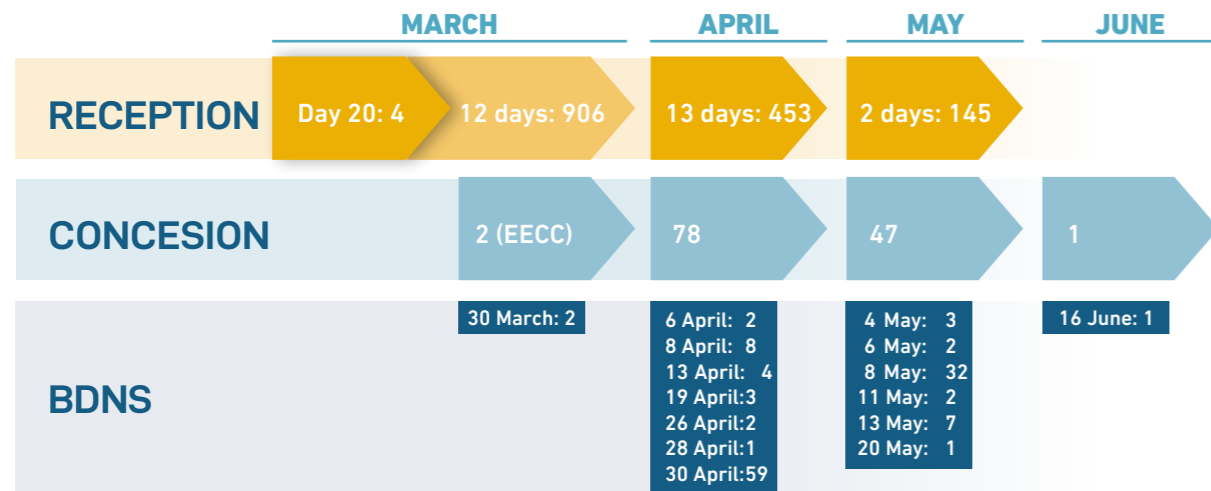
On 19 March 2020, the ISCIII published the Institute Management Resolution approving the Call for expressions of interest in funding research projects on SARS-CoV-2 and the COVID-19 disease under the COVID-19 Fund. This was all within the framework of Spanish Royal Decree-Law 8/2020, of 17 March, on extraordinary urgent measures to address the economic and social impact of COVID-19.

This resolution, with all the technical information on the submission of projects and the details of the process, was immediately made available to the scientific community. The period for the submission of proposals started on 19 March and ended on 13 April. It was then reopened for two days, 21 and 22 May, for the submission of proposals in the area of "Environmental and social factors affecting transmission", with a special focus on veterinary research on the SARS-CoV-2 situation in animal reservoirs.

In addition, the Resolution of 19 March established the creation of the Scientific-Technical Committee for the Evaluation of Expressions of Interest for Research Projects on COVID19 and SARS-COV-2 (CTE-COVID19), an organisation designed to support ISCIII's management in coordinating research project funding.

Given the urgency of the pandemic and the volume of expressions of interest received, intensive workflows were established in order to optimise, as far as possible, the procedures for the submission, evaluation and awarding of proposals.. Meeting such tight deadlines was only possible with the support of all the profes-

sionals involved in scientific management and evaluation, both from the ISCIII and from other Spanish and European centres and institutions. The principles of transparency, methodological rigour and independent evaluation were maintained throughout.

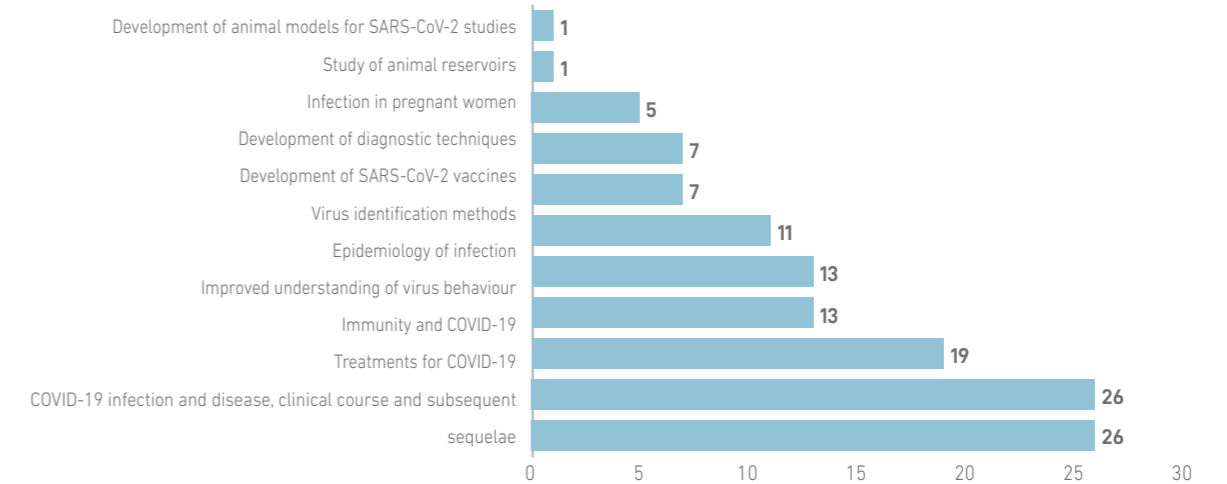


Timeline of the call with the phases for the submission of proposals, awarding and publication of the call in the Spanish National Grants Database (BDNS).

In total, the ISCIII received 1,504 applications, of which [129 projects received funding](#) to start their research in the different expressions of interest; 27% were led by a female scientist. This means that 8% of the applications were accepted for funding. This funding was distributed across the different subject areas:

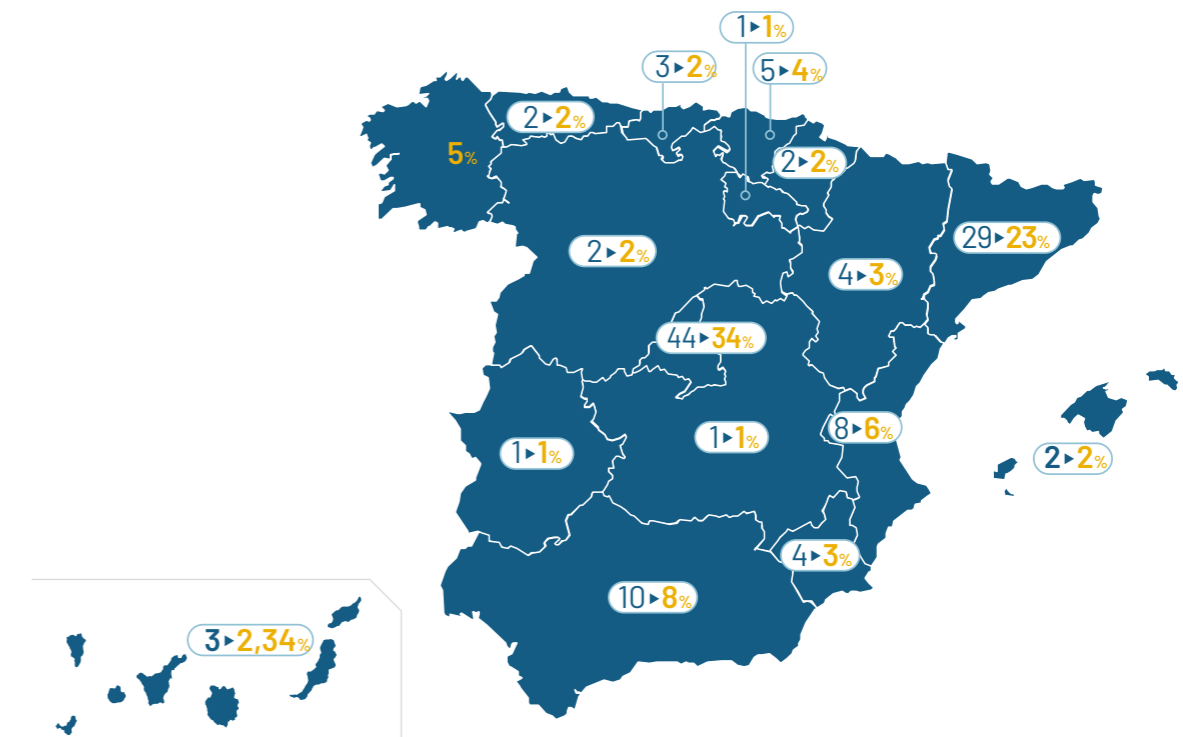
- COVID-19 infection and disease, clinical course and sequelae (26 studies).
- Treatments for COVID-19 (26 studies).
- Immunity and COVID-19 (19 studies).
- Improved understanding of the behaviour of the virus (13 studies).
- Epidemiology of the infection (13 studies).
- Virus identification methods (11 studies).
- Development of diagnostic test (7 studies).
- Development of SARS-CoV-2 vaccines (7 studies).
- Infection in pregnant women (5 studies).
- Animal reservoir study (1 study).
- Development of animal models for SARS-CoV-2 studies (1 study).

STUDIES BY SUBJECT IN THE ISCIII COVID-19 FUND



One of the key aspects was the cooperation of the scientific community. More than 60% of the studies financed are multi-centre studies, carried out by research groups from health centres and research and public health institutions throughout Spain. We can mention epidemiological studies such as CIBERESU-CISCOVID, which studied COVID patients admitted to Spanish intensive care units, and clinical trials such as SOLIDARITY, launched on 18 March 2020 at the initiative of the WHO and in which Spain has participated from the beginning. We should also highlight the collaboration between the autonomous communities in the development and coordination of the different studies. All the autonomous communities have led at least one research project.

DISTRIBUTION OF THE PROJECTS FUNDED BY AUTONOMOUS COMMUNITY



The COVID-19 Fund made it possible to launch different research projects and [open up new lines of research that have been extended over time](#) and developed through access to other calls for proposals and financing lines. For example, during the early months of the pandemic, hospitals across Spain worked on different treatment methods for the disease. The ISCIII encouraged the scientific evaluation of these methods by financing clinical studies in phase 3.

The running of clinical trials, especially in the early stages of the pandemic, was crucial in providing scientific evidence to support treatment decisions about this previously unknown infection. The ISCIII promoted the scientific evaluation of different treatment regimes, always based on the principle of applicability, for both the treatment and chemoprophylaxis against COVID-19. The results allowed us to establish their safety and efficacy and to demonstrate the absence of any benefit from some medicines that, due to the severity of the situation, were being used worldwide without sufficient scientific evidence.

On the other hand, given the need for diagnostic tests for screening and the optimisation of diagnostic tests to confirm the presence of the disease, the COVID-19 Fund financed studies on different approaches to virus identifying that allowed the development of reliable and efficient diagnostic tests for use in clinical and public health settings.

Effective management of the infection, once it has occurred, requires a thorough understanding of its biology and the mechanisms of interaction with humans. This required the deployment of different disease models to study the aforementioned interaction in controlled preclinical scenarios, both in silico and with animal and organoid models. With a focus on genetic determinants, extensive genomic studies of viral susceptibility have been financed, from the perspective of both human and SARS-CoV-2 genetic variability. This identification work continues to generate valuable knowledge about the virus-host relationship.

A large number of epidemiological studies financed by the COVID-19 Fund were conducted on the behaviour patterns of the infection in different situations. Specific studies were carried out on children and people over 65 years of age, pregnant women, healthcare workers and residents in nursing and retirement homes, and people with chronic diseases or with immunosuppression disorders. Their results provided answers to many questions about the management of infection. In addition, they generated knowledge to characterise the course of the infection and the COVID-19 disease, establishing the factors associated with the severity of the disease and its prognosis. The tracking of these cohorts has made it possible to study post COVID-19 symptomatology and its impact, including perceived level of health and quality of life.

One of the most critical aspects during the pandemic was linked to social contact as a way to control transmission. The impact of this restriction on social contact, including the lockdown during the first wave of the pandemic, was examined in studies financed by the COVID-19 Fund, which analysed, among others, the effects on mental health.

There are as many examples of the importance of this initiative as there are studies financed. One of

these clinical trials was the PANCOVID project, which studied patients with COVID-19 requiring inpatient care. It involved more than 27 healthcare centres and 205 patients and compared different antiviral schedules in the search for antivirals that were effective against the disease.

The ISCIII also promoted a study on the use of plasma from patients who had survived the disease as a treatment for COVID-19. This trial was conducted in collaboration with the ISCIII Platform for Clinical Trial Support and the National Centre of Microbiology (CNM), which demonstrated the ability of the ISCIII's platforms and their research centres to develop and implement such proposals.

In the interest of modelling the disease, the Spanish National Cancer Research Centre (CNIO) led a project to develop animal models for COVID-19 research. This was its key contribution during the early stage

of the pandemic, when costs and access to these models by researchers led to greater complexity.

The Centre for Biomedical Research Network (CIBER) Consortium also led a research project for the study and follow-up of critically ill patients admitted to an Intensive Care Unit (ICU), through the CIBERES-ICU-COVID project financed by the COVID-19 Fund. The study included more than 5,700 patients and analysed around 1,068 blood samples.

This project led to the creation of an ICU network that included more than 60 centres across the country. Among other results, CIBERES-ICU-COVID identified that in 80% of critically ill patients, the genomic material of the virus was present in their plasma, that the viral load of the plasma was closely linked to severity of the disease and that critically ill patients who were going to die had lower levels of antibodies than those who were going to survive.

Furthermore, the project was the starting point for the development of the *In Vitro Method For Predicting Mortality In Covid-19 Patients* patent, the results of which have been described in 18 scientific publications and in presentations at congresses and conferences, in addition to having received extensive national media coverage.

The development of the COVID-19 Fund has led to the creation of the COVID Register, in collaboration with the institutions and researchers carrying out

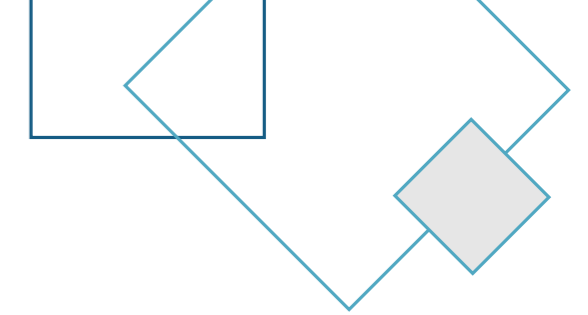
the studies being financed. This is also supported by the Telemedicine and Digital Health Research Unit (UITeS-ISCIII). This scientific partnership initiative has made it possible to integrate all the information collected in each of the studies with the aim of creating large databases for the scientific community that allow for studies with more representative populations.

In the same way, the CIBER also conducted research on the genetic determinants and genomic biomarkers of risk in COVID-19. A genome-wide association study (GWAS) was developed to find the genes involved in the development of the disease.

Among many other key projects, we should also mention the research carried out by the LACTO-COVID project, which provided more information about the transmissibility of the virus and its routes of infection, ruling out breastfeeding as a possible route of infection.

All of this is evidence of the dual role played by the ISCIII during the pandemic. On the one hand, it has acted as a financing organisation. On the other, it has been a key player in applied research. The National Centre of Epidemiology (CNE), the CNM, and the other groups that make up the ISCIII, have been a source of data and scientific information for many of the research groups throughout Spain that were financed through the COVID-19 Fund.

A large number of epidemiological studies financed by the COVID-19 Fund were carried out



SCIENTIFIC PRODUCTION AND RESEARCH RESULTS



A first-hand account

Pilar Gayoso

Assistant Director of the ISCIII

Silence. That is the first thing that comes to mind when I think about the start of the COVID pandemic. A resounding silence, unheard of in a bustling city like Madrid. Empty streets with only birds to be seen. Silence also in the face of a situation for which I had no point of reference and which forced me to reassess my certainties and priorities and face my fears. Handling the uncertainty while also worrying about the health of my family and loved ones were my dominant feelings during that first wave of the pandemic.

In that silence, however, the power of cooperation shone through. It was selfless, spontaneous and exceeded all expectations. At the ISCIII, it was clear to us that we had to keep going in order to provide a service to both research and researchers. In addition to establishing the necessary measures to support the assistance activities of the researchers and continue with its ordinary activities, the SGEFI implemented the call for projects under the COVID-19 Fund. This forced us to establish an unprecedented work system, with fully online management aimed at guaranteeing diligence in our evaluation and speed in our decision-making, in order to rapidly support transferable research on the health emergency.

I remember endless days, with meetings lasting until the early hours of the morning, but with nobody complaining about being tired or looking bored. There were constant email exchanges and lively debates between the sub-directorate's staff, who demonstrated dedication and commitment far beyond what was required. This commitment, together with the COVID-19 Fund, made it possible for the 2020 Strategic Action in Health calls to be completed without delay or incident, in addition to the IMPaCT call. These were months of collaborating and having long conversations with researchers from all over Spain. They were spent organising large studies, which in many cases could be conducted simultaneously with patient care, to identify the most effective treatment schedules, the best performing and most accessible diagnostic tests and the most effective and applicable prevention measures in different settings. The cooperation and generosity displayed has led me to think of this period as being like a wave that united us, producing a feeling of enormous respect for and trust in other people.

Introduction

The efforts made by the ISCIII in researching SARS-CoV-2 and COVID-19 have of course resulted in scientific publications recognised for their quality. Spain can be proud of its scientific output during the pandemic, ranking eighth in the world in terms of number of publications over the three-year period 2020-2022. However, it is not just about quantity. Quality is equally important. The ISCIII, which with its own centres and associated organisations ranks tenth globally among the world's leading institutions for the number of publications on COVID-19¹, and first among Spain's scientific institutions, has now risen to fifth position worldwide in terms of quality, as shown by its presence in the top 10% most cited publications. The global visibility of the ISCIII demonstrates the excellent performance of Spanish science in the face of the pandemic, measured in terms of scientific articles.

The COVID-19 pandemic has highlighted the vital role of science in our lives. The urgent need to find a rapid solution to the crisis prompted researchers, groups, centres and institutes from around the world to multiply their efforts and increase their collaborative work in order to develop rapid and reliable diagnostic methods, treatments and effective vaccines as quickly as possible. Technology and innovation have been key tools in overcoming this health crisis.

In times of crisis, the rapid dissemination of key scientific knowledge is of vital importance. Medical journals have significantly accelerated their publication process for coronavirus-related articles since the outbreak of the pandemic: the period between submission and publication has been reduced on average by 49%. The global scientific community put all its effort into the fight against the coronavirus pandemic, as demonstrated by the increase in the number of publications on COVID-19. In the 2020-2022 period, 624,135 papers dealing with COVID-19 were published worldwide, accounting for 6% of total global scientific output in that period, i.e. 6 out of every 100 scientific papers published worldwide in the three-year period 2020-2022 were related to COVID-19.

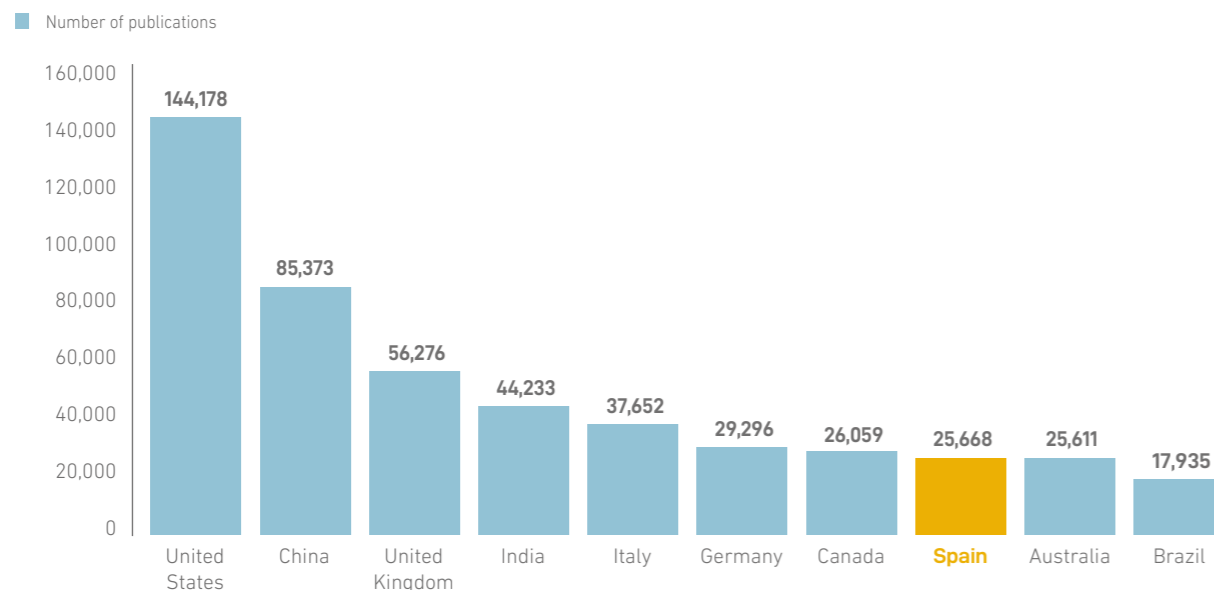
The United States leads the world's scientific output on COVID-19, accounting for 23% of publications between 2020 and 2022. Spain ranks eighth, with 25,668 documents published on this disease. This represents 4% of the world's scientific production on COVID-19 and 8% of Spain's total scientific production in this period (8 out of every 100 articles published in Spain between 2020 and 2022 were related to COVID-19).

¹ The following search terms were included in the search: ("COVID-19" OR coronavirus OR "Corona virus" OR "2019-nCoV" OR "SARS-CoV" OR "MERS-CoV" OR "Severe Acute Respiratory Syndrome" OR "Middle East Respiratory Syndrome")

Summary of the main results

- Spain ranks eighth in the world in scientific production on COVID-19. Eight out of every one hundred papers published in Spain in the three-year period 2020-2022 studied the causes, symptoms or consequences of COVID-19.
- Institutions publishing articles on COVID-19 and first among Spanish scientific institutions. 13% of all COVID-19-related Spanish scientific production is associated with the Institute.
- Among the main international institutions publishing on COVID-19, the ISCIII ranks fifth in terms of publications in the top 10% of the world's most cited publications on this subject. 37% of the ISCIII's scientific production on COVID-19 is included in the top 10% of the world's most cited papers (the Spanish average for COVID-19 publications is 26%).
- 9% of the ISCIII's scientific production on COVID-19 is included in the top 1% of the world's most cited papers on the subject (Spain's average for COVID-19 publications is 5%).
- 69% of the ISCIII's scientific production on COVID-19 was published in the world's most important journals in the field or in the first quartile (Q1), with the Spanish average for COVID-19 publications being 58%.
- 48% of the ISCIII's scientific production on COVID-19 was published in collaboration with other institutions worldwide. Its main international partners were the Institut National de la Santé et de la Recherche Médicale (Inserm, France), Harvard University, King's College (London) and the Karolinska Institutet (Stockholm).
- 51% of the ISCIII's scientific production on COVID-19 was published in collaboration with other institutions in Spain, mainly Universitat de Barcelona, Universitat Autònoma de Barcelona and Universidad de Madrid.

TOP TEN COUNTRIES IN THE WORLD IN SCIENTIFIC PRODUCTION ON COVID-19. 2020-2022

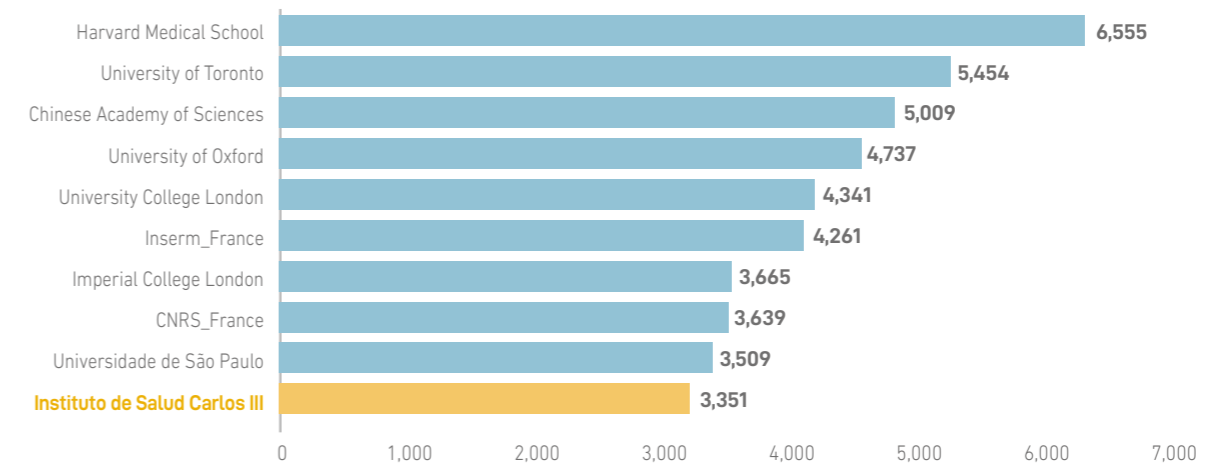


Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

The ISCIII in the context of international scientific production on COVID-19

The Institute ranks 10th in the world in publications on COVID-19 and is the leading institution in Spain in terms of scientific production on this disease.

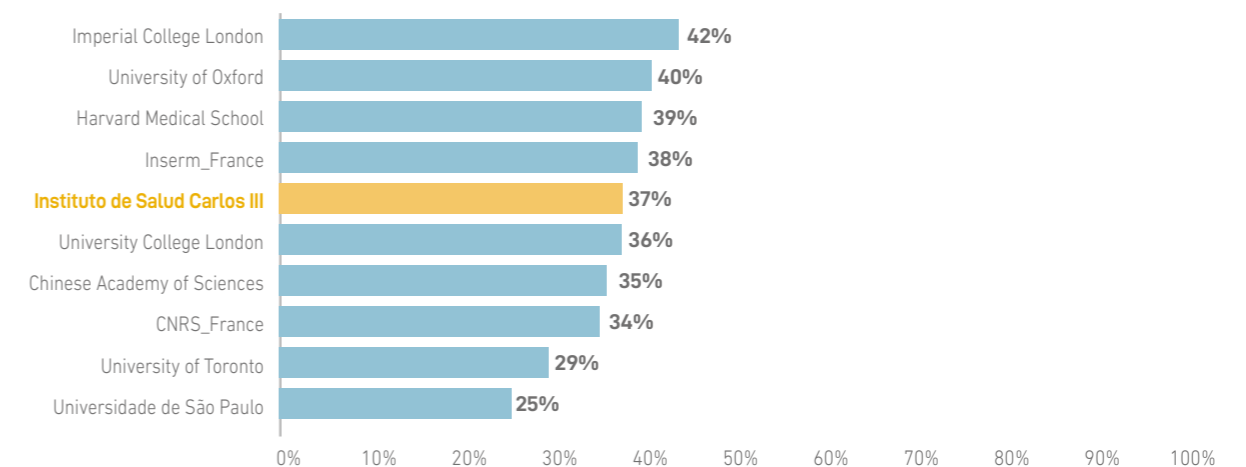
TOP TEN INSTITUTIONS IN THE WORLD IN COVID-19 PUBLICATIONS. 2020-2022



Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

To put Spanish production and the ISCIII's work into context, it is advisable to make a comparative analysis of the main bibliometric indicators of scientific production on COVID-19 published by the world's top ten institutions producing work on topics related to the causes, symptoms and consequences of this disease. Firstly, in terms of the documents on COVID-19 of excellent scientific quality, measured by belonging to the top 10% most cited articles in the world in this field, the ISCIII is in fifth position, with 37% of its publications being included among the top 10% most cited internationally.

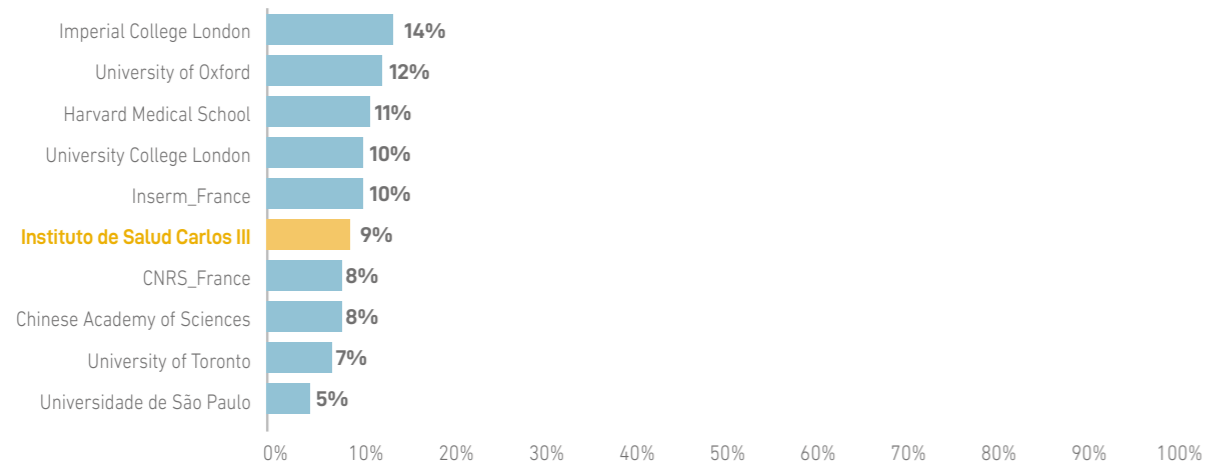
COVID-19 PUBLICATIONS IN THE TOP 10% OF THE WORLD'S MOST CITED PUBLICATIONS BY LEADING INTERNATIONAL INSTITUTIONS (%). 2020-2022



Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

Secondly, the percentage of COVID-19 publications belonging to the exclusive group of the top 1% of the world's most cited publications between 2020 and 2022 has been analysed. We have found that 9% percent of the ISCIII's COVID-19 publications belong to this group, and the Institute ranks sixth among the international institutions analysed.

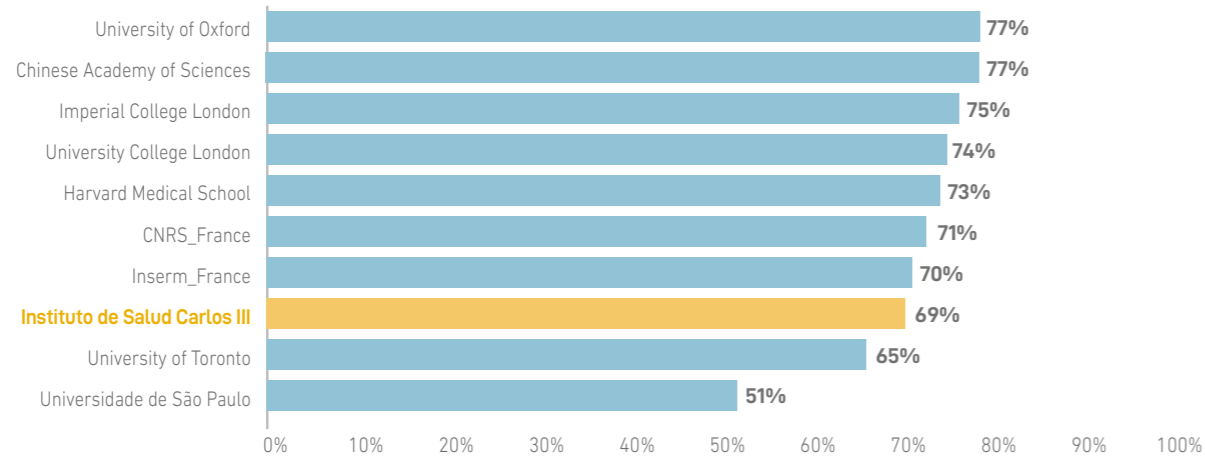
COVID-19 PUBLICATIONS IN THE TOP 1% OF THE WORLD'S MOST CITED PUBLICATIONS BY LEADING INTERNATIONAL INSTITUTIONS (%). 2020-2022



Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

Thirdly, COVID-19 papers that have been published in the top 25% of the world's leading journals, or in the first quartile (Q1) in this field, have been evaluated. 69% of the ISCIII's COVID-19 publications belong to this group and it ranks eighth among the international institutions analysed.

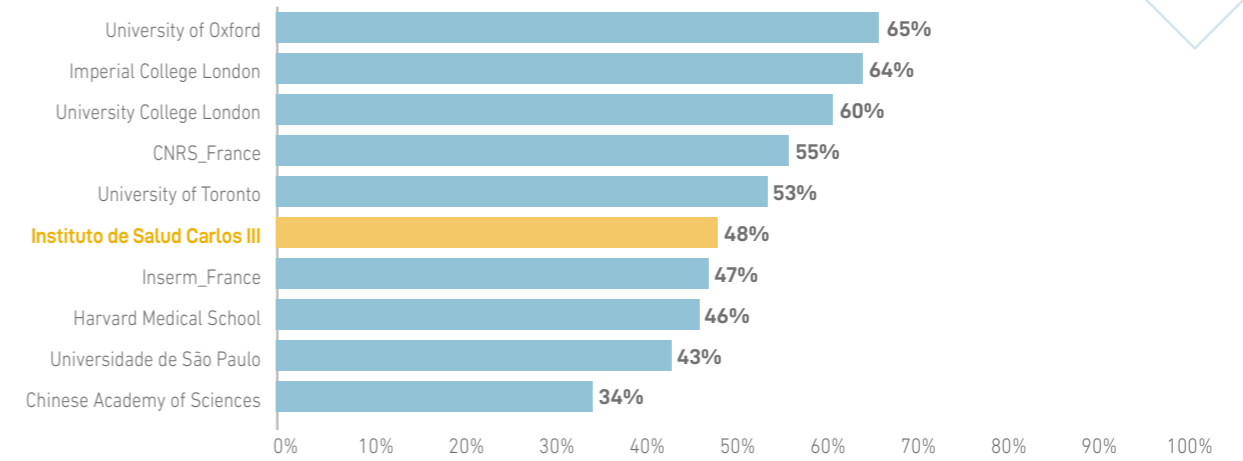
COVID-19 PUBLICATIONS INCLUDED IN THE TOP 1% OF THE WORLD'S MOST CITED PUBLICATIONS BY LEADING INTERNATIONAL INSTITUTIONS (%). 2020-2022



Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

Finally, the international collaboration involved in the scientific production of the world's leading institutions generating COVID-19 publications has been studied.

COVID-19 PUBLICATIONS IN Q1 JOURNALS FROM LEADING INTERNATIONAL INSTITUTIONS (%). 2020-2022

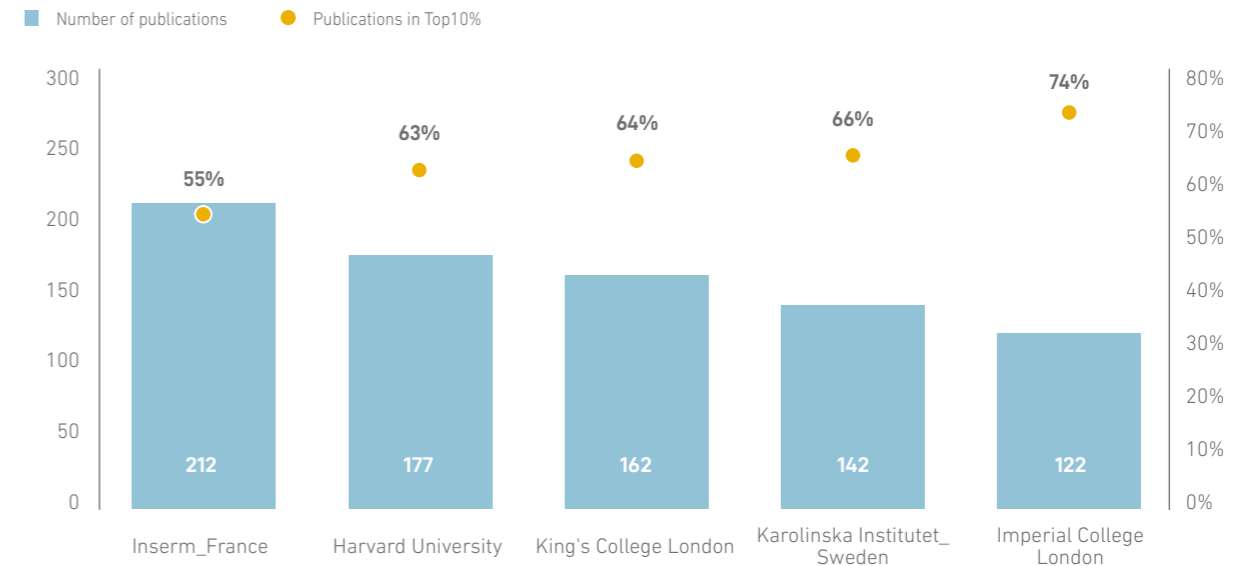


Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

The pandemic is global. Although the field of scientific research has always had an international dimension, this dimension grew across the board during the COVID-19 pandemic. This was in terms of the inclusion of the international dimension in scientific policies, the multiple parties involved, the scientific activities, the methods for producing knowledge, the dissemination of results and the impacts associated with it.

As a result, 48% of the ISCIII's scientific production has been published in collaboration with other international institutions. The main collaborators of the ISCIII in COVID-19 publications and the percentage of these included in the top 10% most cited in the world in the field are shown below.

LEADING INTERNATIONAL INSTITUTIONS WITH WHICH THE ISCIII HAS COLLABORATED IN COVID-19 PUBLICATIONS AND % OF THE COLLABORATION IN THE TOP 10%. 2020-2022



Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023



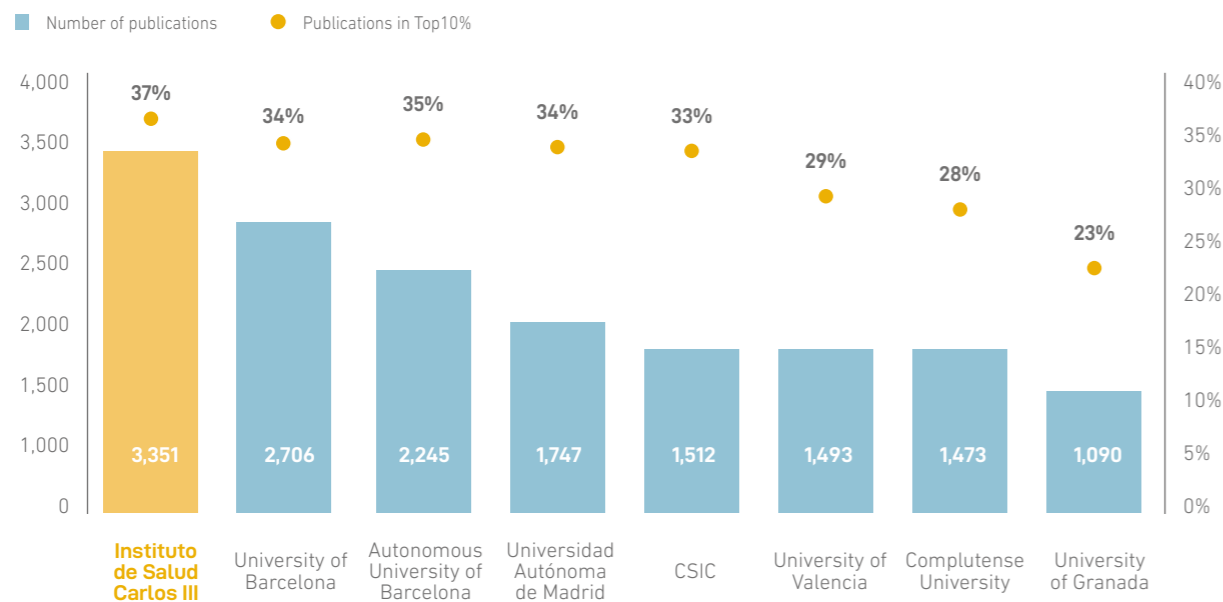
The ISCIII in the context of Spanish scientific production on COVID-19

Between 2020 and 2022, the ISCIII's scientific production amounted to 28,975 documents, representing 9% of Spain's scientific production in that period (327,589 publications).

In relation to COVID-19 publications, 25,668 publications relating to COVID-19 were published in Spain, with 13% of Spanish scientific production on this disease being associated with the ISCIII (3,351 documents). The ISCIII's COVID-19 publications accounted for 12% of total scientific production between 2020 and 2022.

Looking at the leading Spanish institutions with the greatest scientific production on COVID-19, and the percentage of these that are included in the top 10% most cited in the world in the field, the ISCIII - with its various organisations - not only appears as the most relevant Spanish institution in publications on COVID-19, but also as the one with the highest percentage of these in the top-10 most cited in the world on the disease.

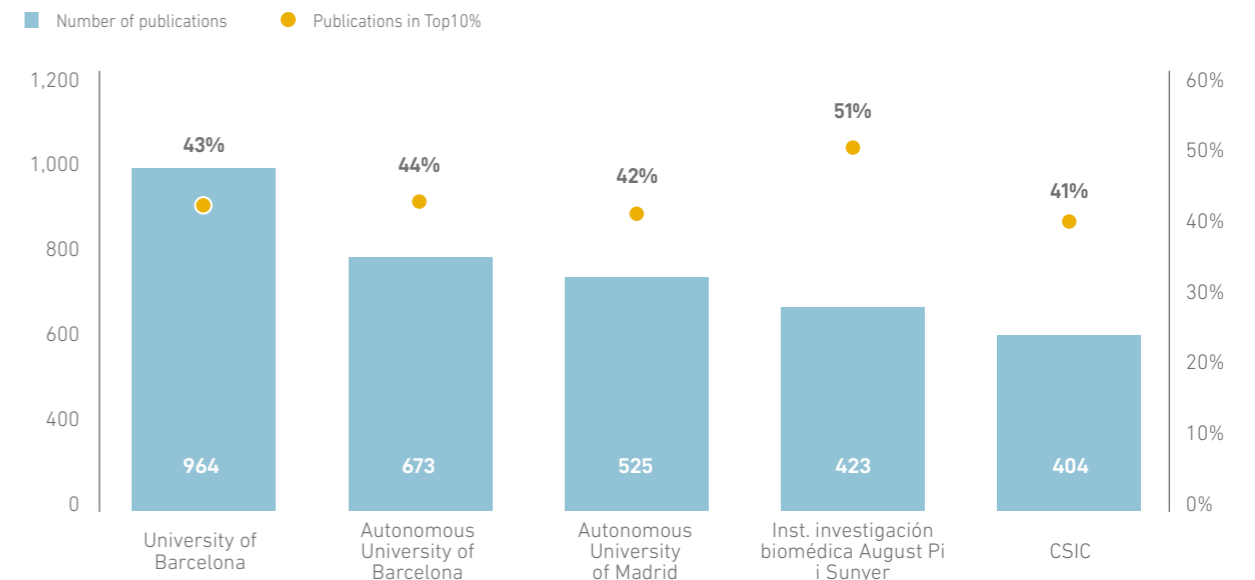
SPANISH INSTITUTIONS WITH THE HIGHEST SCIENTIFIC PRODUCTION IN COVID-19 AND % IN TOP 10%. 2020-2022



Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

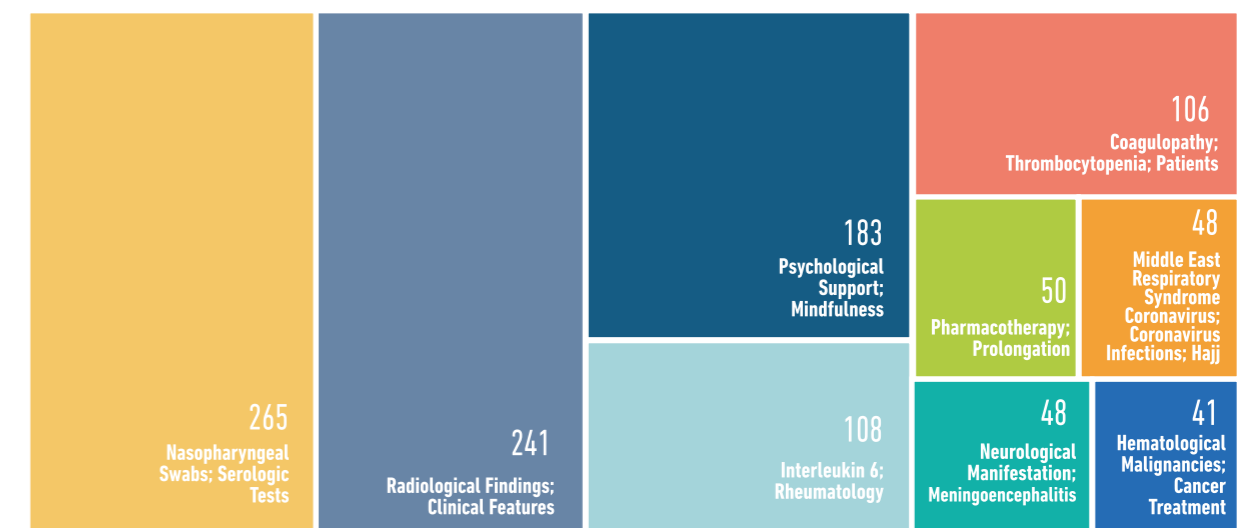
With regard to the ISCIII's collaboration with other institutions in Spain, 51% of the Institute's scientific production has been published in collaboration with other national institutions.

LEADING SPANISH INSTITUTIONS WITH WHICH THE ISCIII HAS COLLABORATED IN COVID-19 PUBLICATIONS AND % OF THE COLLABORATION IN THE TOP 10%. 2020-2022



Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

THEMATIC GROUPINGS WITH THE HIGHEST PRESENCE IN ISCIII COVID-19 PUBLICATIONS. 2020-2021



Source: FECYT from Scival with Elsevier's Scopus data. Consulted between 26 and 28 January 2023

ANNEX I

Top 25 COVID-19 publications in Spain with the highest number of citations received as of 31 January 2023

Title	Year	Full date	Scopus Source title	Citations
The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2	2020	2020-04-01	Nature Microbiology	4,079
Remdesivir for the treatment of COVID-19 — Final report	2020	2020-11-05	New England Journal of Medicine	3,896
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure	2021	2021-09-21	European Heart Journal	2,107
COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review	2020	2020-06-16	Journal of the American College of Cardiology	1,814
Compassionate use of remdesivir for patients with severe Covid-19	2020	2020-06-11	New England Journal of Medicine	1,780
Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study	2020	2020-12-22	Journal of the American College of Cardiology	1,762
Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study	2020	2020-08-01	European Archives of Oto-Rhino-Laryngology	1,553
Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2	2020	2020-05-14	Cell	1,348
Repurposed antiviral drugs for COVID-19 — Interim WHO solidarity trial results	2021	2021-02-11	New England Journal of Medicine	1,306
Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis	2020	2020-01-01	JAMA – Journal of the American Medical Association	1,288
Autoantibodies against type I IFNs in patients with life-threatening COVID-19	2020	2020-10-23	Science	1,275
A global survey of potential acceptance of a COVID-19 vaccine	2021	2021-02-01	Nature Medicine	1,213
Hepatocellular carcinoma	2021	2021-12-01	Nature Reviews Disease Primers	1,167

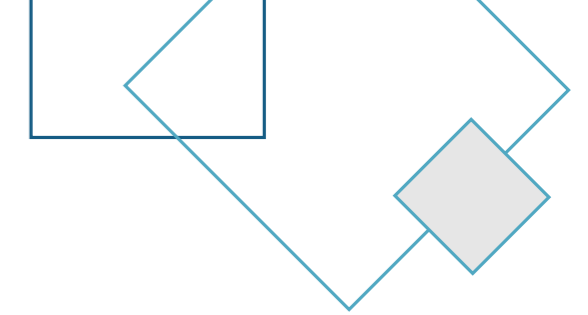
Title	Year	Full date	Scopus Source title	Citations
Inborn errors of type I IFN immunity in patients with life-threatening COVID-19	2020	2020-10-23	Science	1,125
Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study	2020	2020-08-22	The Lancet	1,025
Genomewide association study of severe covid-19 with respiratory failure	2020	2020-10-15	New England Journal of Medicine	1,021
Effects of COVID-19 home confinement on eating behaviour and physical activity: Results of the ECLB-COVID19 international online survey	2020	2020-06-01	Nutrients	1,015
Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study	2020	2020-06-20	The Lancet	1,005
Mortality and pulmonary complications in patients undergoing surgery with perioperative sars-cov-2 infection: An international cohort study	2020	2020-07-04	The Lancet	974
Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis	2020	2020-09-01	The BMJ	859
Remdesivir for 5 or 10 days in patients with severe covid-19	2020	2020-11-05	New England Journal of Medicine	833
Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases	2020	2020-07-01	British Journal of Dermatology	797
Transplantation of ACE2 – Mesenchymal stem cells improves the outcome of patients with covid-19 pneumonia	2020	2020-01-01	Aging and Disease	764
Mental health consequences during the initial stage of the 2020 Coronavirus pandemic (COVID-19) in Spain	2020	2020-07-01	Brain, Behavior, and Immunity	747
Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: Data from the COVID-19 Global Rheumatology Alliance physician-reported registry	2020	2020-07-01	Annals of the Rheumatic Diseases	718

ANNEX II

Top 25 ISCIII COVID-19 publications with the highest number of citations received as of 31 January 2023

Title	Year	Full date	Scopus Source title	Citations
COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review	2020	2020-06-16	Journal of the American College of Cardiology	1,814
Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study	2020	2020-12-22	Journal of the American College of Cardiology	1,762
Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2	2020	2020-05-14	Cell	1,348
Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis	2020	2020-01-01	JAMA – Journal of the American Medical Association	1,288
Autoantibodies against type I IFNs in patients with life-threatening COVID-19	2020	2020-10-23	Science	1,275
Inborn errors of type I IFN immunity in patients with life-threatening COVID-19	2020	2020-10-23	Science	1,125
Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study	2020	2020-08-22	The Lancet	1,025
Genomewide association study of severe covid-19 with respiratory failure	2020	2020-10-15	New England Journal of Medicine	1,021
Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis	2020	2020-09-01	The BMJ	859
Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition) ¹	2021	2021-01-01	Autophagy	716
COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study	2020	2020-09-01	The Lancet Child and Adolescent Health	703
How mental health care should change as a consequence of the COVID-19 pandemic	2020	2020-09-01	The Lancet Psychiatry	699
Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial	2020	2020-04-24	JAMA network open	696

Title	Year	Full date	Scopus Source title	Citations
Practical recommendations for the management of diabetes in patients with COVID-19	2020	2020-06-01	The Lancet Diabetes and Endocrinology	510
Miller Fisher syndrome and polyneuritis cranialis in COVID-19	2020	2020-08-04	Neurology	467
Drug treatments for covid-19: Living systematic review and network meta-Analysis	2020	2020-07-30	The BMJ	439
Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report	2020	2020-09-01	Chest	419
“Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study”	2020	2020-10-01	Journal of Steroid Biochemistry and Molecular Biology	397
Preventing problematic internet use during the COVID-19 pandemic: Consensus guidance	2020	2020-07-01	Comprehensive Psychiatry	360
Prevalence of depression during the COVID-19 outbreak: A meta-analysis of community-based studies	2021	2021-01-01	International Journal of Clinical and Health Psychology	358
Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality among Patients with COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial	2021	2021-04-27	JAMA – Journal of the American Medical Association	347
First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020	2020	2020-03-05	Eurosurveillance	346
COVID-19 in solid organ transplant recipients: A single-center case series from Spain	2020	2020-07-01	American Journal of Transplantation	306
Impact of coronavirus syndromes on physical and mental health of health care workers: Systematic review and meta-analysis	2020	2020-10-01	Journal of Affective Disorders	304
The Effect of Age on Mortality in Patients With COVID-19: A Meta-Analysis With 611,583 Subjects	2020	2020-07-01	Journal of the American Medical Directors Association	302



RESEARCH AT THE ISCIII DURING THE PANDEMIC

The ISCIII has become one of the top ten international institutions with the most publications on COVID-19 during the pandemic, and the leading institution in terms of the number of publications on a national level. It also stands out as a body of scientific excellence, with 37% of its scientific publications appearing in the top 10% most cited publications, and 9% of its publications in the exclusive top 1% most cited articles.

During the course of the pandemic, the ISCIII has reinforced its scientific and technical services with the aim of providing evidence to facilitate public health decision-making during the most critical moments of the pandemic.

COVID-19 projects: five examples

It is difficult to include in this report all the projects, activities and scientific publications promoted by the ISCIII in relation to SARS-CoV-2 and COVID-19. The work of the ISCIII as a leading national organisation can be seen through five examples that are representative of the wide range of COVID-19 projects carried out over the last three years. These are the ENE-COVID, ENE-COVID-Senior, COSMO-Spain, COMBIVACS and CIBER-POST-COVID studies. They have yielded results that are highly significant for the scientific community and which, moreover, have continued to evolve and adapt as the pandemic has progressed.

ENE-COVID

In 2020, after the declaration of the State of Alarm and as the weeks of lockdown passed, the need arose to understand the real rate of SARS-CoV-2 infection among the Spanish population as this would facilitate public health decision-making.

In collaboration with the Ministry of Health, the Ministry of Science and Innovation and the autonomous communities, the ISCIII launched the ENE-COVID study in April 2020. Its aim was to identify the percentage of the population that had developed antibodies up to that precise moment in the pandemic. More than 68,000 people participated in the ENE-COVID study. For the study and diagnosis, some 200,000 rapid tests were performed and about 175,000 blood samples were taken from all the participants.

To give an idea of the scale of the project, it was the first international study to provide accurate population-level infection rates, and the first to provide information on infection by age group. In addition, it subsequently allowed the characterisation of the population of asymptomatic people, i.e. those who had been infected with the disease but had no symptoms or very mild symptoms, and proposed an index of diagnostic probability in symptomatic people.

Cross-checking with available population data also provided the best estimate of virus lethality to date. The study was carried out in four phases and allowed the information to be broken down by autonomous community, introducing the geographical variable into the transmissibility of the virus.

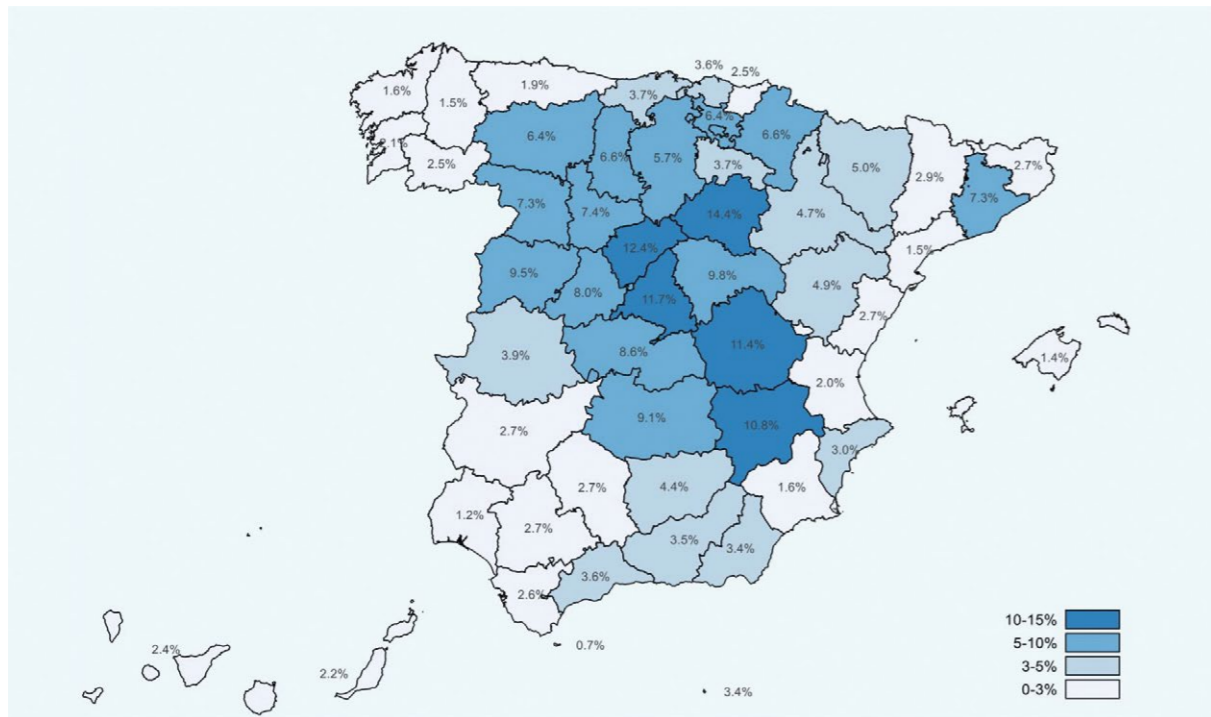




The first three phases of the ENE-COVID study were carried out in the first half of 2020, between 27 April and 11 May, from 18 May to 1 June and from 8 to 22 June, in all the autonomous communities and in the cities of Ceuta and Melilla. The report concluded that 5% of the Spanish population had developed SARS-CoV-2 antibodies. The percentage of the Spanish population acquiring these coronavirus antibodies did not vary greatly across the three periods analysed, with the first wave estimated at 5% and the second and third waves at 5.2%. These figures were published during the first half of 2020 and soon made it possible to rule out herd immunity as a solution. This had initially been one of the ideas most frequently debated during the pandemic.

In addition, the study results showed that 28.7% of SARS-CoV-2 infections during the first wave were asymptomatic. This gave rise to the development of a predictive model for the presence of infection through a scoring system based on the symptoms described in the seroprevalence study, with an estimated effectiveness of 70%.

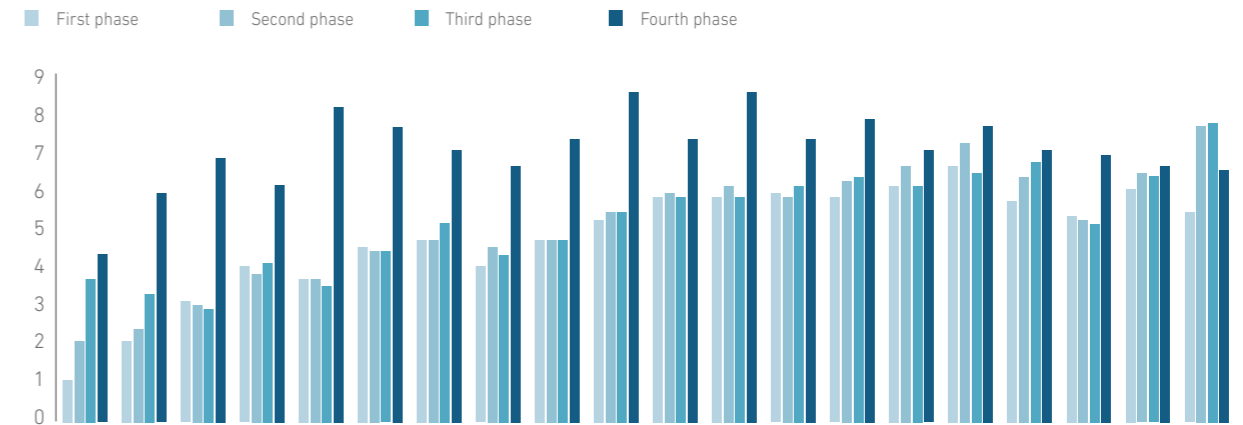
The geographical differences in seroprevalence data were significant. While some provinces had figures of between 2% and 3%, others were above 10%, with a higher percentage being found in the central part of the peninsula. Contact with the virus was higher in urban areas, so the seroprevalence percentage was also higher in cities with more than 100,000 inhabitants compared to smaller cities (6% and 4% respectively).



Map of the third phase of the report, with seroprevalence percentages by province obtained through a rapid test. <https://www.isciii.es/Noticias/Noticias/Paginas/Noticias/ENECOV19resultadosfinales.aspx>

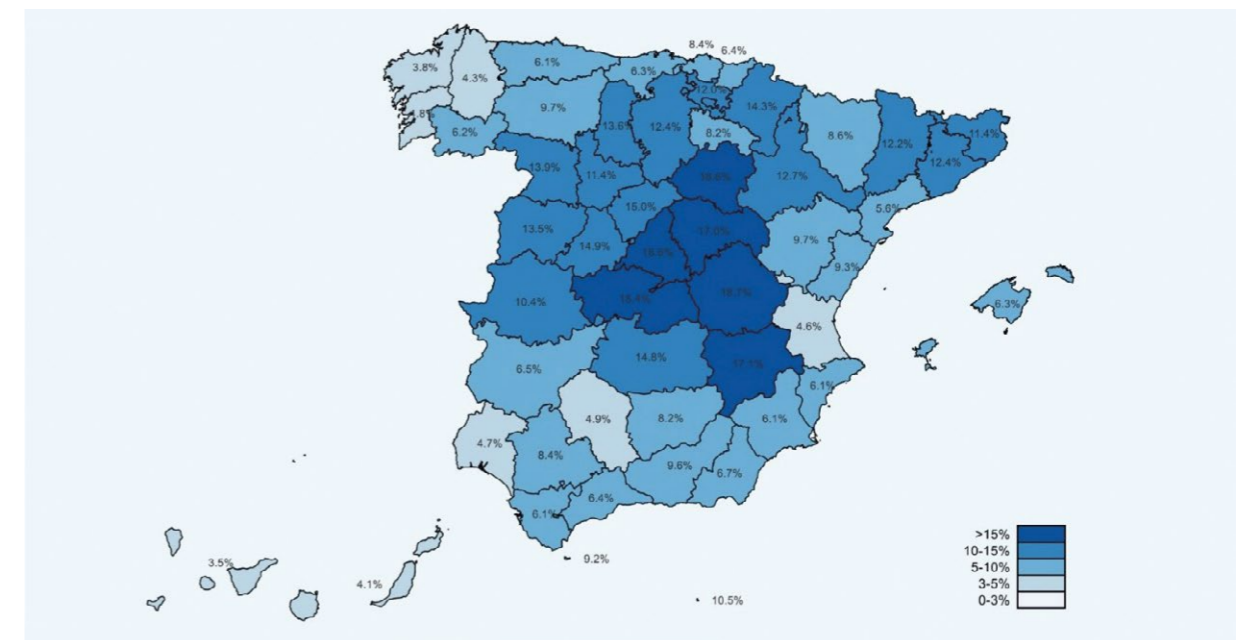
In relation to other socio-demographic variables, SARS-CoV-2 seroprevalence was found to be somewhat lower in children and adolescents, at around 3.5%, with little variation in the adult population. Because of their close contact with the virus during the early stages of the pandemic, a higher prevalence of antibodies was observed among health care and elderly care workers, with percentages of over 10% and 7%, respectively.

SEROPREVALENCE PERCENTAGE BY AGE GROUP

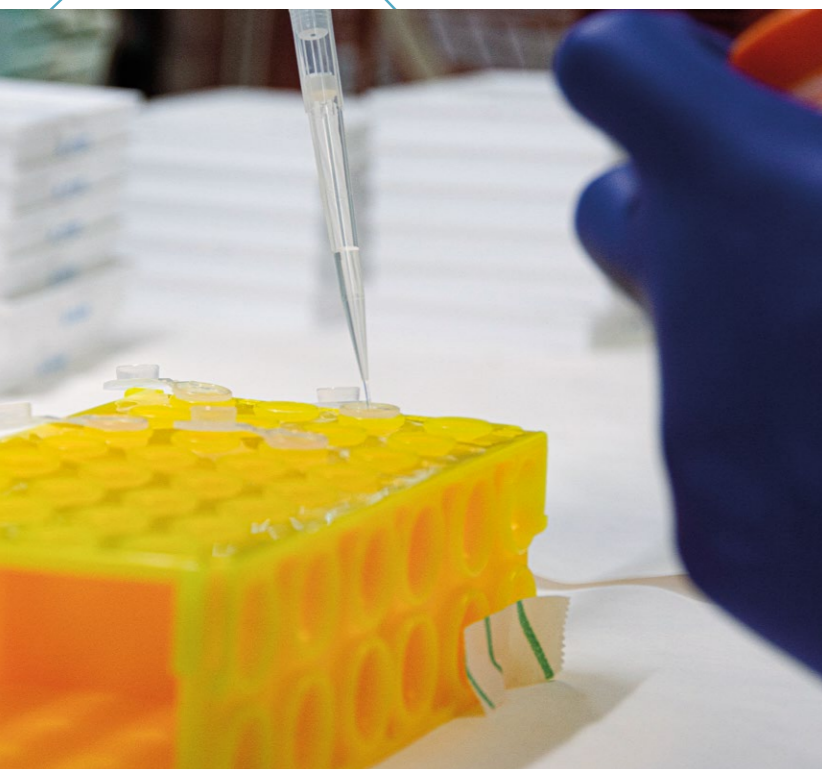


The [fourth phase of the study](#) took place between 16 and 29 November 2020, when the second wave of the pandemic was over and the third wave was just around the corner. A higher estimated prevalence of 9.9% was detected. In other words, since the start of the pandemic, one in ten people had been infected with the coronavirus. A total of 51,409 people participated in this phase. Three out of every four participants in the previous phases of the study participated in this latest one.

The results also showed significant geographical differences between autonomous communities, with some provinces having a prevalence of more than 15% and others having a prevalence of only 5%. A comparison with the other phases of the study, conducted between April and June 2020, showed a greater dispersion of the virus during the second wave of the pandemic.



Overall prevalence of anti-SARS-CoV-2 IgG antibodies (cumulative prevalence Phases 1-4). Rapid test results.



As was the case with the results obtained in the previous rounds, health care and elderly care workers (16.8%) and women caring for dependent persons at home (16.3%) had the highest overall prevalence figures at the end of the study.

There was also an increase in the percentage of people who were seronegative during the first phase and developed detectable antibodies, with a figure of 3.8%. This was higher than the 0.7% and 0.9% figures detected in the preliminary phases.

In terms of the scientific production resulting from this study, we can highlight the publication of the results from the first phase of ENE-COVID [in the prestigious journal The Lancet](#). This demonstrated that it was impossible to reach herd immunity quickly and it also provided a more accurate measurement of those people who had developed antibodies while being infected with the coronavirus but had no symptoms.

Using other complementary information sources - deaths in confirmed cases - (RENAVE) and excess mortality (MoMo), [an article was published in The British Medical Journal](#) with estimates of the lethality of the SARS-CoV-2 virus in Spain.

In addition, and as mentioned above, ENE-COVID enabled the creation of a predictive model of infection among people with symptoms compatible with COVID-19, as well as the characterisation and measurement of asymptomatic infection and estimates of its prevalence in people with chronic health problems. All this was published [in an article in The Journal of Clinical Epidemiology](#).

In April 2022, ISCIII researchers published a study in the *Journal of Clinical Virology* on the evolution of SARS-CoV-2 antibodies taken from the fourth round of the seroprevalence study. This study took advantage of the ENE-COVID project to analyse in depth the evolving trends in IgG antibody detection.

Two important findings came out of this study. First, the data suggested that up to one-third of the coronavirus-infected population could have negative serological test results, months after infection. Second, it could be concluded that heterogeneity in the immune response was observed with respect to the production of IgG against the N or S RBD protein of SARS-CoV-2, as well as being conditional on the severity of the disease. Thus, this study shows a tendency not to detect IgG antibodies after 7 months in 43.3% of the participants who were infected after the first phase of the ENE-COVID study.

The ENE-COVID study continues to contribute knowledge. In March of this year, the *American Journal of Public Health* published two articles, as part of a monograph on epidemiological surveillance and COVID-19 studies based on representative samples of the population, led by a team from the ISCIII. In addition to reviewing the study methodology and summarising how the knowledge generated supported the health strategy, both articles reveal new results from the joint analysis of the first two waves, and establish that in the second wave, socio-economic differences emerged that led to a greater impact on vulnerable groups.

References:

Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet* 2020;396:535-44. [https://doi.org/10.1016/S0140-6736\(20\)31483-5](https://doi.org/10.1016/S0140-6736(20)31483-5).

Pastor-Barriuso R, Pérez-Gómez B, Hernán MA, et al. Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. *BMJ* 2020;371:m4509. <https://doi.org/10.1136/bmj.m4509>.

Pérez-Gómez B, Pastor-Barriuso R, Pérez-Olmeda M, Hernán MA, Oteo-Iglesias J, Fernández de Larrea N, Fernández-García A, Martín M, Fernández-Navarro P, Cruz I, L Sanmartín J, León Paniagua J, Muñoz-Montalvo JF, Blanco F, Yotti R, Pollán M. ENE-COVID nationwide serosurvey served to characterize asymptomatic infections and to develop a symptom-based risk score to predict COVID-19. *J Clin Epidemiol*, 2021, Vol 139, Pages 240-254, ISSN 0895-4356. <https://doi.org/10.1016/j.jclinepi.2021.06.005>.

Pérez-Gómez B, Pastor-Barriuso R, Pérez-Olmeda M, Hernán MA, Oteo-Iglesias J, Fernández de Larrea N, Fernández-García A, Martín M, Fernández-Navarro P, Cruz I, Sanmartín JL, León Paniagua J, Muñoz-Montalvo JF, Blanco F, Yotti R, Pollán M; ENE-COVID Study Group. ENE-COVID nationwide serosurvey served to characterize asymptomatic infections and to develop a symptom-based risk score to predict COVID-19. *J Clin Epidemiol*. 2021 Jun 11:S0895-4356(21)00183-9. <https://doi.org/10.1016/j.jclinepi.2021.06.005>.

Pérez-Olmeda M, María Saugar J, Fernández-García A, Pérez-Gómez B, Pollán M, Avellón A, Pastor-Barriuso R, Fernández-de Larrea N, Martín M, Cruz I, Sanmartín JL, Fedele G, León Paniagua J, Muñoz-Montalvo JF, Blanco F, Yotti R, Oteo-Iglesias J, ENE-COVID Study Group. Evolution of antibodies against SARS-CoV-2 over seven months: Experience of the nationwide seroprevalence ENE-COVID study in Spain. *J Clin Virol*. 2022 Apr, Vol 149, 105130, ISSN 1386-6532. <https://doi.org/10.1016/j.jcv.2022.105130>.

Roberto Pastor-Barriuso, Beatriz Pérez-Gómez, Jesús Oteo-Iglesias, Miguel A. Hernán, Mayte Pérez-Olmeda, Nerea Fernández-de-Larrea, Marta Molina, Aurora Fernández-García, Mariano Martín, Israel Cruz, José L. Sanmartín, José León-Paniagua, Juan F. Muñoz-Montalvo, Faustino Blanco, Raquel Yotti, Marina Pollán, and on behalf of the ENE-COVID Study Group. Design and Implementation of a Nationwide Population-Based Longitudinal Survey of SARS-CoV-2 Infection in Spain: The ENE-COVID Study. *American Journal of Public Health* 0, e1_e8. <https://doi.org/10.2105/AJPH.2022.307167>.

Beatriz Pérez-Gómez, Roberto Pastor-Barriuso, Nerea Fernández-de-Larrea, Miguel A. Hernán, Mayte Pérez-Olmeda, Jesús Oteo-Iglesias, Pablo Fernández-Navarro, Aurora Fernández-García, Mariano Martín, Israel Cruz, José L. Sanmartín, José León-Paniagua, Juan F. Muñoz-Montalvo, Faustino Blanco, Raquel Yotti, and Marina Pollán. SARS-CoV-2 Infection During the First and Second Pandemic Waves in Spain: the ENE-COVID Study. *American Journal of Public Health* 0, e1_e12. <https://doi.org/10.2105/AJPH.2023.307233>.



A first-hand account

Marina Pollán

National Centre of Epidemiology

In the first wave of the pandemic, when all the professionals in the regional or state public health services, including the National Centre of Epidemiology, were recording the COVID-19 cases diagnosed in their area of responsibility, the daily mortality monitoring system soon showed the impact of the pandemic in terms of the number of deaths. The health services in Madrid and other autonomous communities were being overwhelmed and diagnostic tests were restricted to serious cases and essential personnel.

Seroprevalence studies are particularly useful when it is impossible to diagnose all cases and it is suspected that there are asymptomatic infected people. At the National Centre of Epidemiology, we convinced the director of the ISCIII, Dr Raquel Yotti, that we needed to carry out a study that would give us a more accurate picture of the intensity of the pandemic across the region.

In collaboration with the Ministry of Health, the design proposal we submitted and the diagnostic tests that the National Centre of Microbiology proposed after analysing the reliability of those available, allowed us to work with all the health services in the autonomous communities and cities to carry out a population-based seroepidemiological study. In other words, we wanted to ensure the representativeness of the data we were collecting.

With the country in lockdown and the health services overwhelmed, we were able to deploy all the logistics necessary to carry out the study, preparing an online training system at the National School of Public Health for the professionals doing the fieldwork and setting up an IT platform developed by the Ministry of Health that collected the required information.

ENE-COVID has been an international example of what can be done, and is seen as a benchmark in different countries, including the United States. In addition to giving a snapshot of the penetration of the virus in our country, we were the first to estimate the proportion of asymptomatic people at that time and the fatality rates for the new virus.

It gave me real satisfaction to have this unique opportunity to take on the scientific coordination of this study which, without the efforts of all the professionals involved and without the overwhelming response from the public (seen in the high participation rates), would not have been possible.

In all the reports, scientific articles and presentations about the study, we try to reflect this multi-faceted aspect, along with conveying the gratitude of those of us who have in some way been the visible face of this collective effort.

ENE-COVID-Senior

With the arrival of the COVID-19 vaccine between late 2020 and early 2021, the ENE-COVID study needed to be adapted to a scenario in which a large part of the Spanish population had been vaccinated. As a result, the seroprevalence study proposed through ENE-COVID evolved into the ENE-COVID Senior study. It was aimed at analysing the efficacy and immunological duration of doses of the SARS-CoV-2 vaccine in the population most affected by the pandemic, which was people aged over 65 years. This study analysed the immune response to the third dose, its ability to deal with new variants and the evolution of cell-mediated immunity.

Likewise, with approval by the public health authorities of the recommendation for a fourth dose of the vaccine for people over 60 years of age and those at risk, it became essential to continue with the study in order to analyse the impact of this latest dose on the group.

This study began in September 2021 and was adapted to changing circumstances, such as the emergence of new variants like omicron and the drastic increase in cases during Christmas 2021 and early 2022. [The first results](#) linked to these analyses shed light on the efficacy of a third dose in the vaccination schedule. Research led by the CNM confirmed that total antibody titres increase after inoculation of this third dose, that neutralising antibodies against the omicron and delta variants also increase and that cellular immunity is maintained for a certain period of time.

Following the recommendation of the public health authorities to administer a fourth dose for older people and those at risk, the ENE-COVID-Senior study continues to monitor and analyse the immunological evolution of the programme participants.

References:

Martín-Galiano AJ, Díez-Fuertes F, McConnell MJ and López D (2021) Predicted Epitope Abundance Supports Vaccine-Induced Cytotoxic Protection Against SARS-CoV-2 Variants of Concern. *Front. Immunol.* 12:732693. <https://doi.org/10.3389/fimmu.2021.732693>.

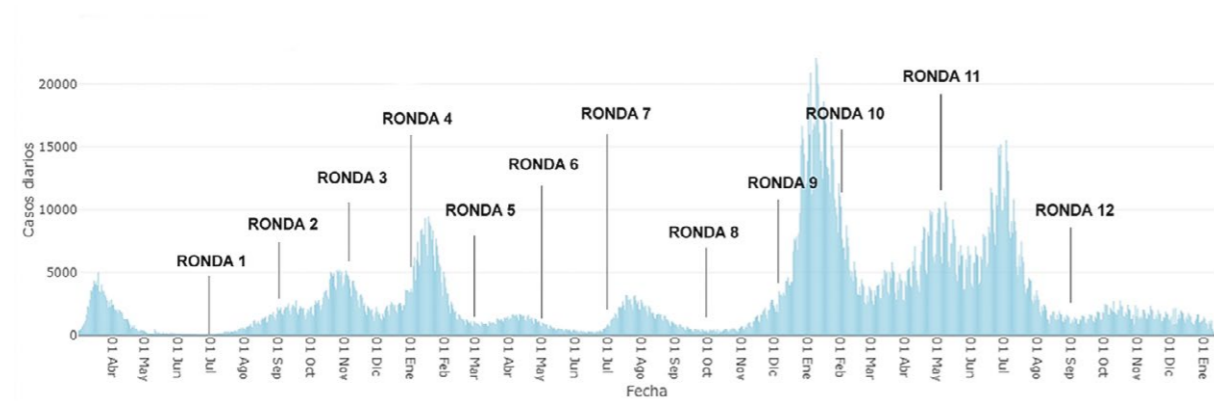
**There are still no ENE-COVID-Senior publications as we are awaiting the study on the fourth dose.*



COSMO-Spain

In May 2020, the ISCIII coordinated the launch in Spain of the COSMO-Spain study, a project promoted by the WHO and supported by the Ministry of Health. This has provided information, on a bi-monthly basis, on the population's knowledge and opinion of the COVID-19 pandemic.

Throughout 2020, 2021 and until the end of 2022, with the presentation of the final phase of the study last November, COSMO-Spain has allowed us to estimate how the Spanish population has been responding to preventive measures, the information sought on the coronavirus, vaccines and public health measures, among other aspects.

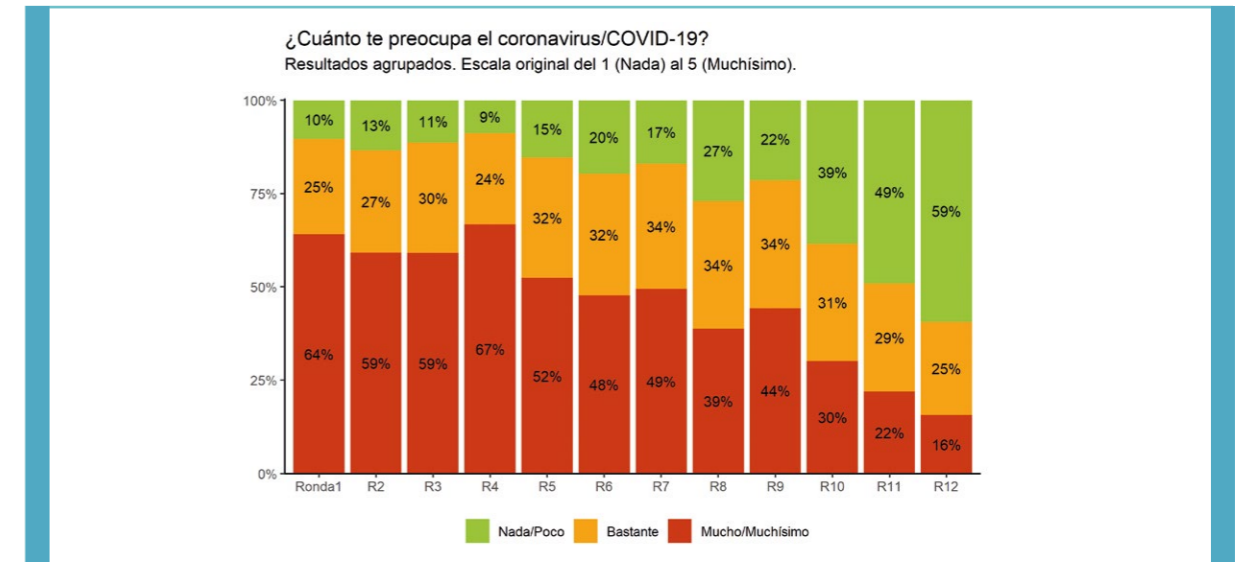


Date of the different phases of the COSMO-Spain study, based on the evolution of the number of Covid-19 cases in Spain

The study had a total of 12 phase, in which a representative demographic cross-section of Spanish society was analysed. This involved a total of more than 12,000 people during the entire length of the study. The analysis of the data according to the evolution of the pandemic has made it possible to observe different trends and changes in public opinion about different aspects. It has also confirmed the importance of studying public opinion and public knowledge of a public health crisis.



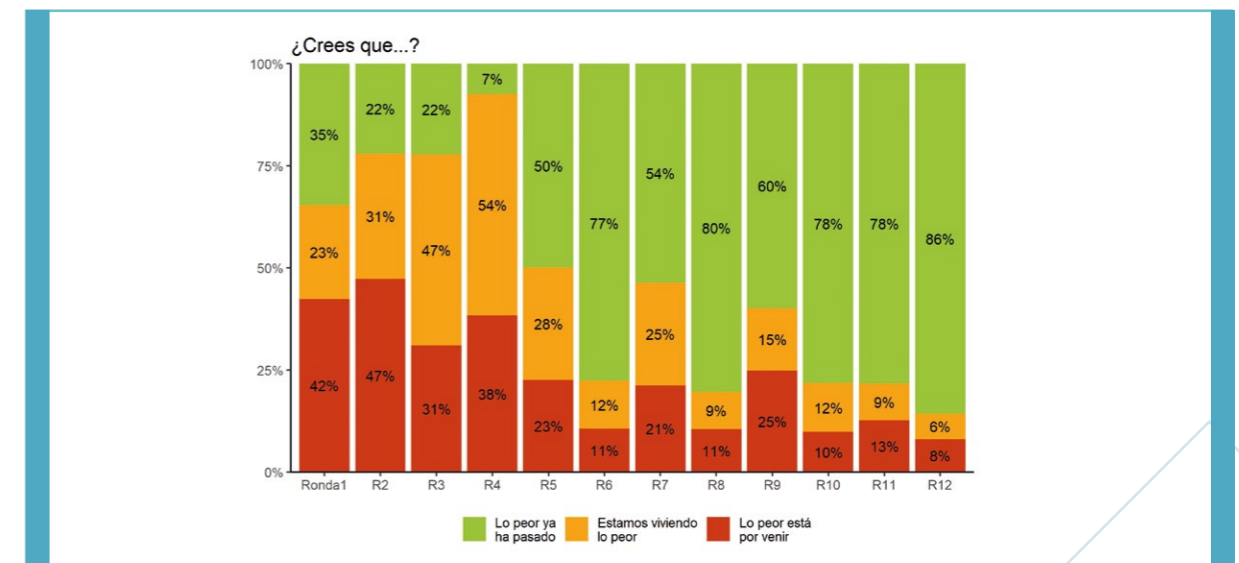
For example, there has been a decrease in the Spanish population's concern about the coronavirus disease. In September 2022, the date of the last survey conducted, only 16% of the population were very/extremely worried about Covid-19. The respondents' concern peaked during the first phase, conducted in May 2020, when the country was in full lockdown and with the State of Alarm still in force, and during the 4th phase, during the peak of the third wave during Christmas 2020. At this time, only 10% of respondents showed little or no concern about the virus.



Levels of fear about the pandemic have also been falling. While after the third wave, nearly 80% reported being afraid of the coronavirus, more than eighteen months later, 59% are still somewhat afraid of it, but only 26% reported high levels of fear (a score of 4-5 on a scale from 1 to 5).

As concern about and fear of SARS-CoV-2 have decreased over time, public perception of the severity of the pandemic has also fallen. During the early phases of the study, around 80% of the population said they were experiencing the worst or expecting the worst of the pandemic, a perception that reached its highest peak at Christmas 2020 (around 93%).

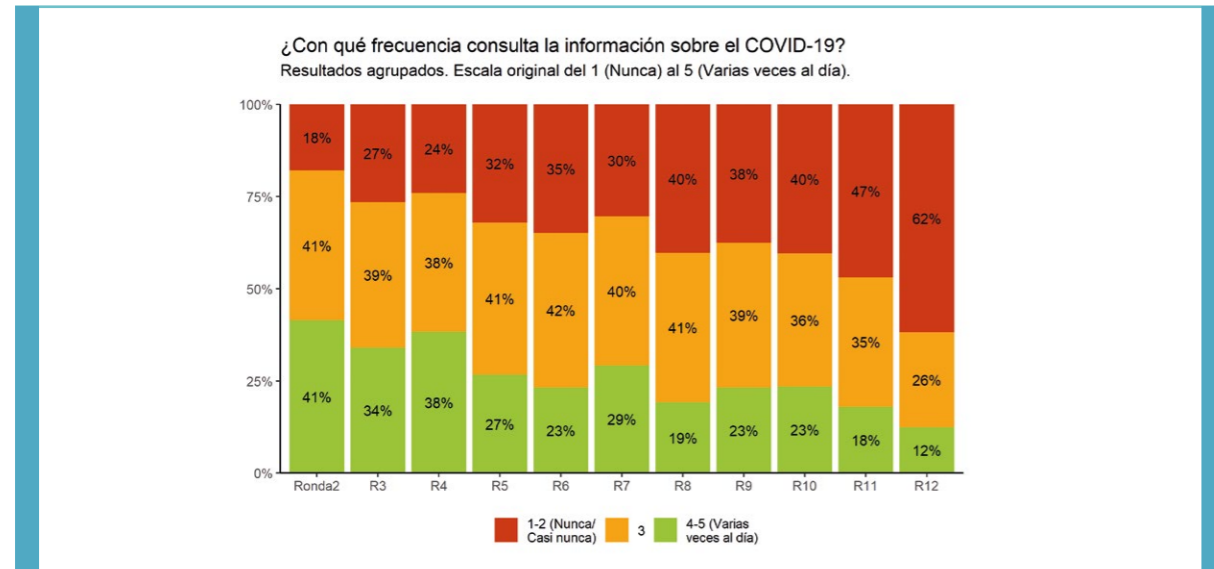
However, once the so-called third wave of the pandemic was over, 50% of respondents said that they thought the worst of the pandemic was over. This turning point coincided with the start of the vaccination programme in Spain.



The study also reflects how the pandemic may have influenced various issues in people's lives. While most say it has not caused any major disruption beyond needing to manage the pandemic situation itself, 47% say it has had negative effects on their access to health care, 33% say it has worsened their social life, 32% say it has aggravated their mental health, and 28% say it has had a negative impact on their physical condition.

The Spanish population's knowledge of the characteristics and preventive measures against SARS-CoV-2 infection has remained fairly high and stable throughout the evolution of the pandemic. There were, for example, some differences at the beginning of the pandemic with regard to knowledge about the transmissibility of the virus through aerosols and whether asymptomatic people were contagious. The use of masks has been confirmed as the most commonly-used preventive measure.

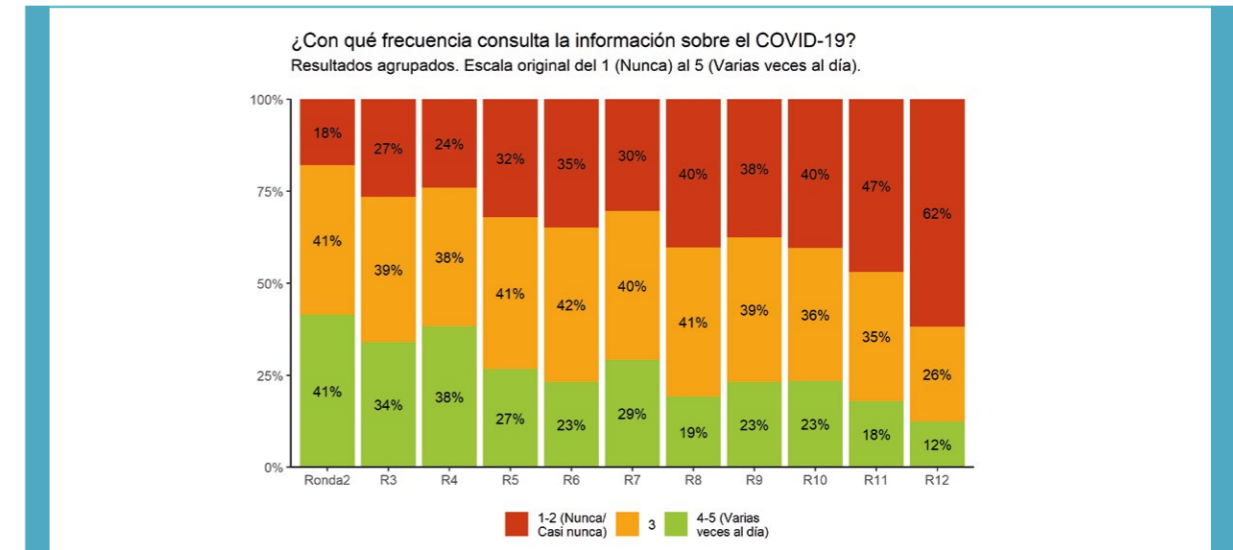
The levels of perceived risk of catching COVID-19 with some severity have also fallen over time as people have learned more about the disease and its symptomatology and the vaccination programme has progressed. While at the beginning of the study, 43% and 39% of the population, respectively, considered that they might have a *severe* or *normal* level of sickness with the disease, these percentages had changed to 13% and 43% by September 2022.



As the pandemic progressed, self-protection measures against COVID-19 infection were also relaxed, including the use of masks and hand gel and hand-washing. Masks, ventilation and hand gels were the most frequent self-protection measures.

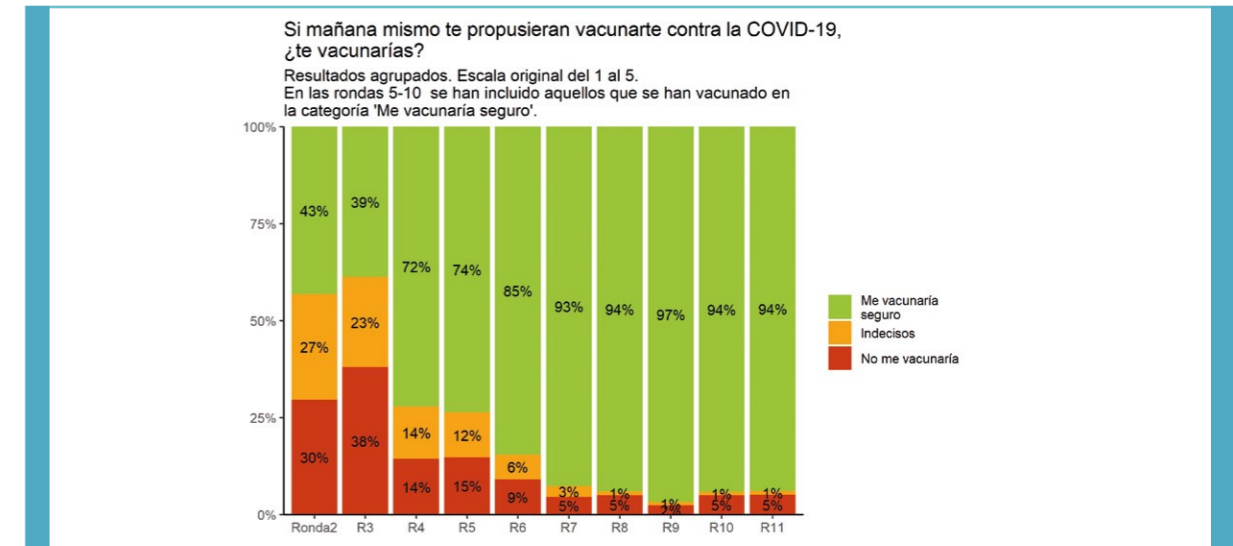
The COSMO-Spain study also assessed the way in which the Spanish population found information about the pandemic. This makes it possible to draw some conclusions about the trust Spanish people have in the media and in public and health institutions. The frequency with which Spanish people search for information on COVID-19 has been decreasing as their levels of concern about the pandemic have fallen. So, while 82% of respondents said they regularly searched for information about the virus at the start of the pandemic, only 38% did so after the summer of 2022.

Among the most trusted sources or channels of information for the population are information from health professionals, with a high degree of confidence compared to other sources of information (an average of 4 on a 5-point scale), and information from official and institutional channels, more specifically from the WHO and the Ministry of Health (with scores close to 3.0-3.2). Slightly less trust is placed in the traditional media: radio, television and the press, with scores of around 2.6-2.8. The social media and Internet are in last place, with the lowest levels of trust.



The trust of the Spanish population in their health professionals as a source of information also led to greater confidence in health institutions. Hospitals and health centres have been widely trusted throughout the pandemic. Science, which together with the SNS, has played a key role in the fight against the SARS-CoV-2 pandemic, has been recognised by the surveyed population, who have reported having the utmost confidence in it throughout the pandemic.

Similarly, confidence in the vaccine has increased as more information has become available. In the early days, when vaccines were first being developed but were not yet available, only 4 out of every 10 people said they felt confident about being vaccinated. By the end of the third wave, and as vaccination was being extended to all demographic levels, only 15% of survey respondents reported their intention not to be vaccinated. It is from phases 6 and 7 of the study, with 37-80% of the population having received at least one dose of the vaccine, that the highest levels of confidence in the safety of the vaccine were observed.



In the final study phases, respondents were also asked whether they would accept an additional dose of a vaccine if that were recommended. Confidence in this case remained at high levels, above 70%, but with a slight tendency towards a possible rejection of further additional doses.

The COSMO-Spain study has also analysed a panel of non-vaccinated individuals, with the aim of detecting and describing population groups that are reluctant to accept the COVID-19 vaccination, as well as studying their attitudes and perceptions. During the month of October 2021, more than 1,000 people with an average sample age of 30 years were surveyed, 963 of whom had not received any doses. Some of the reasons for not being vaccinated most mentioned by respondents were that they *were not safe or were experimental* (55%). The second most mentioned reason was that *vaccines were big business* (28.5%), followed by *I am healthy and do not need to be vaccinated* (22.3%). A similar percentage, 22.2% thought that *vaccines were bad for their health* or said they *were concerned about their side effects*. 30.6% said that they would be vaccinated in the future and 43.5% were undecided. Among the conditions for deciding to have the vaccine, 57.3% of respondents said they would do *so once enough time had passed for them to be convinced that the vaccine was safe*, and 22.7% would do so *if it were required to travel*.

Referencias:

Romay-Barja M, Pascual-Carrasco M, De Tena-Dávila MJ, Falcón M, Rodríguez-Blázquez C, Forjaz MJ, Ayala A, Molina-de la Fuente I, Burgos A, Muñoz A, Benito A. How patients with COVID-19 managed the disease at home during the first wave in Spain: a cross-sectional study. *BMJ Open*. 2021;11(5):e048702. <https://doi.org/10.1136/bmjopen-2021-048702>.

Rodríguez-Blázquez C, Romay-Barja M, Falcón M, Ayala A, Forjaz MJ. The COSMO-Spain Survey: Three First Rounds of the WHO Behavioral Insights Tool. *Front. Public Health*. 2021;9:678926. <https://doi.org/10.3389/fpubh.2021.678926>.

Beca-Martínez MT, Romay-Barja M, Falcón-Romero M, Rodríguez-Blázquez C, Benito-Llanes A, Forjaz MJ. Compliance with the main preventive measures of COVID-19 in Spain: The role of knowledge, attitudes, practices, and risk perception. *Transbound Emerg Dis*. 2021 Nov 3. <https://doi.org/10.1111/tbed.14364>. Epub ahead of print. PMID: 34730277.

De Bruin M, E Suk J, Baggio M, Blomquist SE, Falcon M, Forjaz MJ, Godoy-Ramirez K, Leurs M, Rodríguez-Blázquez C, Romay-Barja MJ, EUiters, Kinsman J. Behavioural insights and the evolving COVID-19 pandemic. *Eurosurveillance* 2022;27:2100615. <https://doi.org/10.2807/1560-7917.ES.2022.27.18.2100615>.

Falcón M, Rodríguez-Blázquez C, Fernández-Gutiérrez M, Romay-Barja M, Bas-Sarmiento P, Forjaz MJ. Measuring COVID-19 health literacy: validation of the COVID-19 HL questionnaire in Spain. *Health Qual Life Outcomes*. 2022;20(1):138. <https://doi.org/10.1186/s12955-022-02050-5>.

Rodríguez-Blázquez C, Romay-Barja M, Falcon M, Ayala A, Forjaz MJ. Psychometric Properties of the COVID-19 Pandemic Fatigue Scale: Cross-sectional Online Survey Study. *JMIR Public Health Surveill*. 2022;8(9):e34675. <https://doi.org/10.2196/34675>.

Beca-Martínez MT, Romay-Barja M, Ayala A, Falcon-Romero M, Rodríguez-Blázquez C, Benito A, Forjaz MJ. Trends in COVID-19 Vaccine Acceptance in Spain, September 2020-May 2021. *Am J Public Health*. 2022 Nov;112(11):1611-1619. <https://doi.org/10.2105/AJPH.2022.307039>.



A first-hand account: Maria João Forjaz National Centre of Epidemiology.

***Representing the whole COSMO-Spain team.**

During the lockdown, I received a call from the director of the National Centre of Epidemiology to tell me about the request from the World Health Organisation (WHO) to conduct a study on "behavioural insights" or public perceptions of the pandemic.

We quickly formed the COSMO-Spain team. It was made up of the following members: a researcher from Universidad de Murcia (UMU), María Falcón, an expert in health literacy; María Romay Barja, from the National Centre for Tropical

Medicine (CNMT-ISCIII), with experience in this type of study and who had conducted a similar survey during the lockdown; and Carmen Rodríguez-Blázquez, from the CNE, a psychologist researching person-centred health outcomes.

Over more than two years, we launched a total of twelve phases, surveying samples from nearly one thousand people every two months to gather their opinions about the pandemic, concerns, knowledge, search for information, pandemic fatigue, preventive behaviours and vaccination, among other aspects.

We were supported by the WHO and worked with the European Centre for Disease Prevention and Control (ECDC). This support from the international community made us feel even more motivated. In addition, we worked closely with the Ministry of Health and were pleased to be able to participate in meetings with the Autonomous Communities, where we provided concrete data on pandemic fatigue and young people's opinions about the pandemic. This made it possible to develop more effective communication strategies. We also had technological support from the Telemedicine and Digital Health Research Unit (UITeS-ISCIII) in the preliminary study, conducted during the months of the lockdown, and in specific surveys on the reasons for non-vaccination.

The results of the COSMO-Spain study are available to everyone from the project's website and have been widely disseminated through press releases and numerous interviews in different media channels. In addition, we have analysed the data in more detail, identifying vulnerable groups and factors associated with the behaviours, attitudes and effects of the pandemic. So far, the results have been disseminated in eight scientific publications and at several conferences. We have generated knowledge and applied a methodology that can be extended to many areas of health to improve health-related policies, services and communication outcomes.



COMBIVACS

The turning point in the pandemic was undoubtedly the appearance of the vaccines. The first vaccines were approved at the end of 2020 and they were increasingly administered throughout 2021 and until 2022 through booster doses. The picture of the first patient receiving the first dose in our country, on 27 December 2020, in a nursing home in the province of Guadalajara, will forever be etched on our memories.

According to estimates by the European Centre for Disease Prevention and Control (ECDC), in [an article published in November 2021](#), with the collaboration of the CNE, vaccines saved almost 90,000 lives among people aged over 60 in Spain and almost 470,000 across Europe. That was with the vaccines only having existed for twelve months.

In April 2021, the ISCIII launched the COMBIVACS trial, one of its most important contributions to the pandemic. Evaluation of the use of the combined vaccination schedule using the Comirnaty vaccine (Pfizer/BioNtech) as a second dose in patients who had already received a first dose of Vaxzevria (AstraZeneca) concluded that the combined use of vaccines produces a powerful immune response.

This clinical trial was designed in response to the public health authorities' suspension of the use of the Vaxzevria vaccine in people under 60 years of age following unusual

safety concerns in younger age groups. This situation meant that several million people worldwide had received a first dose but their planned vaccination schedule could not be completed.

COMBIVACS was launched in five Spanish university hospitals: Hospital Universitario de Cruces in Bilbao; Hospital Clinic and Hospital Vall d'Hebron in Barcelona, and Hospital Clínico and Hospital La Paz in Madrid. A total of 676 people took part in the study, 450 of whom were in the intervention group, i.e. they received a second dose of the Comirnaty vaccine to complete their vaccination schedule, and 226 people were in the control group. The latter group did not receive the full schedule initially but were given Pfizer's second vaccine after the study had been successfully completed.

This study was the first of its kind in the world. It provided very important information on the use of heterologous schedules (a combination of different vaccines) at a time of huge uncertainty about the right decision to be made by the public health authorities, who needed scientific evidence to support solutions and alternatives to the single-vaccine schedule (always using the same type of vaccine).

The first results of the study [were published in The Lancet](#) in June 2021, marking a milestone in vaccine strategies. Since then, a large part of the population has received the third dose of their vaccination schedule following a heterologous schedule. COMBIVACS demonstrated, firstly, that immunogenicity against coronavi-

rus was very high and, secondly, that reactogenicity (side effects) was very similar to that observed in other vaccination schedules.

This study confirmed the important finding that a heterologous vaccination schedule induces a powerful humoral and cellular response. No serious cases were reported during the trial and adverse reactions were mild to moderate, similar to inoculation with other vaccines. None of the participants had to be hospitalised.

Once the study had been completed, the initial control group members were vaccinated with a second dose to complete their schedule and continue with the analysis and comparative study. In August 2022, one year after the publication of the article in *The Lancet*, ISCIII researchers published [another article in eClinical Medicine](#) describing the decrease in antibody levels six months after completing the vaccination schedule. This supported the use of a third dose. It reported that while antibodies declined, levels remained neutralising.

However, it was also reported that these might not be sufficient for the beta and omicron variants of the virus, which were becoming more prevalent at that stage of the pandemic.

Once this new vaccination of the control group had been completed, the humoral and cellular immune response was analysed 1 month, 3 months and 6 months after the second immunisation. After 180 days, only 20% of all participants had sufficient levels of neutralising antibodies to block the new beta and omicron variants. Inoculation with a third dose of the vaccine was therefore highly recommended.

COMBIVACS, which ended in December 2022 after monitoring the patients who had been inoculated with a third dose for six months from the time of vaccination, has provided a wealth of data that will be published in the near future.

References:

Javier García-Pérez, María González-Pérez, María Castillo de la Osa, Alberto M. Borobia, Luis Castaño, María Jesús Bertrán, Magdalena Campins, Antonio Portolés, David Lora, Mercedes Bermejo, Patricia Conde, Lourdes Hernández-Gutierrez, Antonio Carcas, Eunate Arana-Arri, Marta Tortajada, Inmaculada Fuentes, Ana Ascaso, María Teresa García-Morales, Humberto Erick de la Torre-Tarazona, José-Ramón Arribas, Natale Imaz-Ayo, Eugènia Mellado-Pau, Antonia Agustí, Carla Pérez-Ingidua, Agustín Gómez de la Cámara, Jordi Ochando, Cristóbal Belda-Iniesta, Jesús Frías, José Alcamí, Mayte Pérez-Olmeda. Immunogenic dynamics and SARS-CoV-2 variant neutralisation of the heterologous ChAdOx1-S/BNT162b2 vaccination: Secondary analysis of the randomised CombiVacS study, *eClinicalMedicine*, Volume 50, 2022, 101529, ISSN 2589-5370, <https://doi.org/10.1016/j.eclinm.2022.101529>.

Alberto M Borobia, Antonio J Carcas, Mayte Pérez-Olmeda, Luis Castaño, María Jesús Bertrán, Javier García-Pérez, Magdalena Campins, Antonio Portolés, María González-Pérez, María Teresa García Morales, Eunate Arana-Arri, Marta Aldea, Francisco Díez-Fuertes, Inmaculada Fuentes, Ana Ascaso, David Lora, Natale Imaz-Ayo, Lourdes E Barón-Mira, Antonia Agustí, Carla Pérez-Ingidua, Agustín Gómez de la Cámara, José Ramón Arribas, Jordi Ochando, José Alcamí, Cristóbal Belda-Iniesta, Jesús Frías, on behalf of the CombiVacS Study Group. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial, *The Lancet*, 2021. ISSN 0140-6736. [https://doi.org/10.1016/S0140-6736\(21\)01420-3](https://doi.org/10.1016/S0140-6736(21)01420-3).



A first-hand account

Mayte Pérez-Olmeda

National Centre of Microbiology

The COVID-19 pandemic has transformed our lives in ways we could not have imagined. In my case, it caught me in the middle of a professional move, with the State of Alarm preventing a "normal" transition. On 16 March I experienced a day full of uncertainty, in an almost unknown laboratory and with no technical personnel, but grateful to Management for considering me an essential staff member in the fight against this unknown virus.

Throughout the pandemic, the Serology Laboratory was available to meet the needs of authorities, companies and researchers. Initially, it validated the serological trials necessary for the diagnosis and study of the evolution of the disease.

In the first wave of the epidemic, we took part in the ConPlas-19 study, financed by the ISCIII, whose main objective was to identify whether the hyperimmune serum generated after severe infection could fight the virus and minimise lung damage, which we were able to confirm.

A few weeks later, we set up a COVID laboratory with the infrastructure and serological tests needed to process more than 60,000 samples for the first National Seroepidemiological Study (ENE-COVID), launched by the Ministry of Health and the ISCIII. This study was of great international importance and established that 5% of the Spanish population had been exposed to the virus in the first wave of the epidemic.

Then came the vaccines and, with them, the dreaded onset of side effects, forcing the suspension of the 2nd dose of the AstraZeneca vaccine. We urgently needed to understand whether a second dose with another vaccine would be effective and safe. That is why we designed the CombiVacS study, the first to demonstrate the efficacy and safety of heterologous vaccination. The arrival of more aggressive variants and the decline in antibodies was of particular concern to us in the population hardest hit by the pandemic, the over-65s. As a result, we designed the ENE-COVID Senior study with the aim of finding out how this population was being protected against SARS-CoV-2 and understanding the evolution of their immune response after the third and fourth doses were administered.

In our lives, we are all constantly making decisions. In my case, accepting the directorship of the Serology Laboratory months before the start of the pandemic was a turning point in my professional career and work environment. The task has been arduous, with little rest and enormous pressure, but tremendously rewarding, not only because of the scientific challenges and achievements, but also because of the camaraderie and experiences we have had at the CNM among the essential staff. It is something I will always remember.

Long COVID

The ISCIII, through its Centre for Biomedical Research Network (CIBER) Consortium, launched the CIBER-POSTCOVID project in November 2021. This research project, addressing what is known as "Long COVID", was commissioned by the Ministry of Health and run in coordination with the Ministry of Science and Innovation. In July 2022, [we saw the presentation of the first results from the study](#). These allowed us to reach an agreed definition of Long COVID, come closer to defining a common range of symptoms and outline new lines of research in this area. The first part of the study addresses how to define Long COVID.

The first part of the study addresses how to define Long COVID.

This study arose from the need to reach a consensus in the absence of agreement in the SNS on what exactly Long COVID is and how to assess and identify its severity in patients. The lack of a common definition was making it difficult to implement patient monitoring strategies and interventions following a multidisciplinary approach, as well as to correctly code data in information systems. In fact, different terms existed at that point, including those such as "Long COVID", "Long-term COVID", "Post-COVID" and "Chronic COVID", all used to describe the persistence of symptoms or changes 12 weeks after the acute infection phase.

The first phase of CIBERPOSTCOVID included representatives of patients and relatives, CIBER researchers and researchers from other state networks, health and clinical management professionals and health planning professionals. After this first phase, agreement was reached on the following definition of the term "Long COVID": "A set of multi-organ symptoms not attributable to other causes that persist after the acute phase of the infection". This definition is in line with existing international definitions.

Some of the symptoms that have reached the highest degree of consensus and that appear in the available literature are:

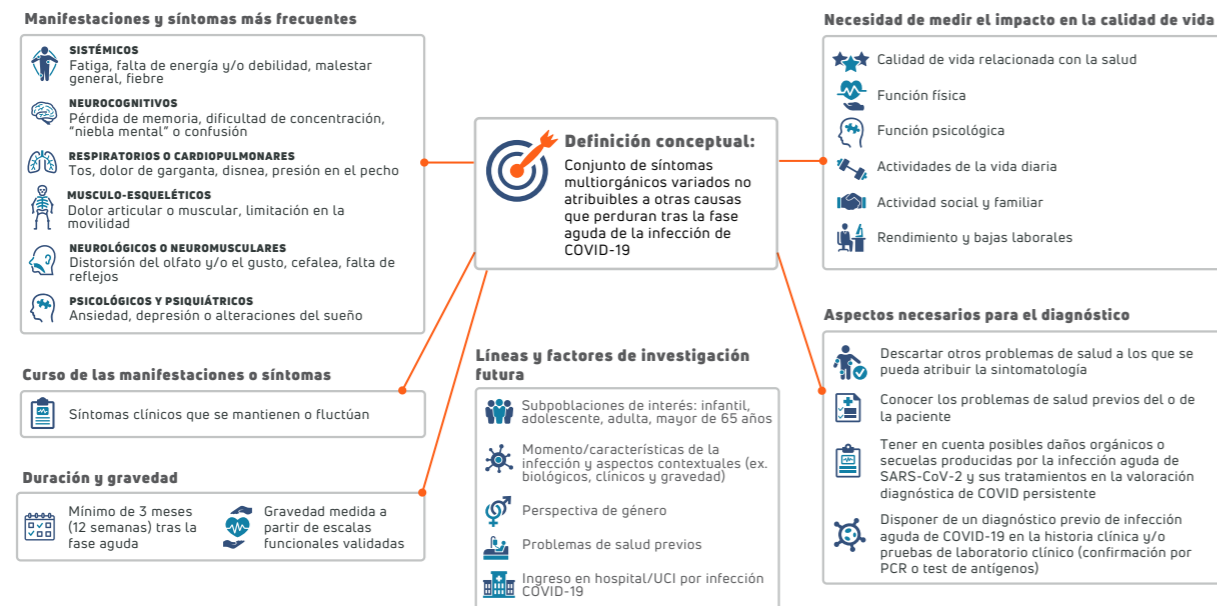
- **Neurocognitive symptoms:** memory loss, difficulty concentrating and confusion.
- **Musculoskeletal symptoms:** joint or muscle pain and limited mobility.
- **Systemic symptoms:** fatigue, weakness, fever and general malaise.
- **Síntomas neurológicos y neuromusculares:** olfato y gusto distorsionado, cefalea y falta de reflejos.
- **Psychological and psychiatric symptoms:** anxiety, depression and sleep problems.
- **Respiratory and cardiopulmonary symptoms:** cough, sore throat, shortness of breath and chest tightness.

The variability of these symptoms, their persistence beyond the acute phase of SARS-CoV-2 infection and their duration for more than three months are three of the key aspects most frequently observed during the course of the study.

In addition, the researchers concluded that other factors need to be taken into account for the proper measurement of the impact of Long COVID, such as the relationship with overall health, physical function, the patient's psychological state, the level of daily activity, their social relationships and their work performance. Measuring the social and work impact was a key element for the informants in both the qualitative study and the consensus study.

In order to perform future quantitative studies and establish a possible Long COVID diagnosis, the authors of the study believe there is a need to have an initial diagnosis of acute infection (with laboratory tests or clinical history), identify and rule out any other possible health problems of the patient and establish potential organ damage caused by acute SARS-CoV-2 infection and its treatment.

DEFINICIÓN OPERATIVA DE COVID PERSISTENTE Y ELEMENTOS CLAVE EN EL CIBERPOSTCOVID



The study attempts to identify other risk factors that could influence a Long COVID diagnosis, such as age, being female (a factor that also appears in the systematic review), the presence of comorbidities and hospitalisation during the acute phase.

CIBERPOSTCOVID examines the difficulty in establishing a strong consensus and addressing Long COVID in the paediatric population and proposes new lines of research in this field. It could also be interesting to conduct population stratification studies to identify affected groups, along with studies taking into account the gender perspective, looking at prior health problems, studying ICU admissions linked to acute infection and addressing other clinical, biological and contextual decisive factors. The study is currently continuing to provide further information on the different areas linked to the management of Long COVID.



A first-hand account

Vicky Serra

Epidemiology and Public Health Department at CIBER

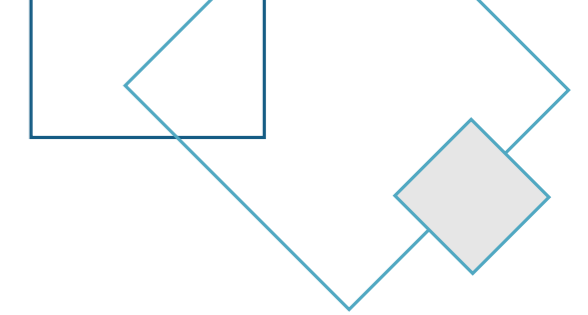


At the end of 2021, we were commissioned by the Ministry of Science and Innovation and the Ministry of Health to improve our understanding of Long COVID, including what it is and its characteristics and predisposing factors. The CIBERPOSTCOVID project began under the leadership of two thematic networks forming part of the Centre for Biomedical Research Network (CIBER) Consortium, namely the respiratory diseases network (CIBERES) and the epidemiology and public health network (CIBERESP). Within this framework, as a researcher at CIBERESP and the Agency for Health Quality and

Assessment of Catalonia (AQuAS), it has been an honour and a great learning experience to co-lead the first phase of this project with Antoni Serrano. I see it as being somewhere between science and consultancy and it has generated tools for clinical decision-making and planning.

The main challenge we faced was the lack of scientific evidence and agreement. So we moved forward in a collaborative and multidisciplinary way, collating the opinions of expert professionals and the vision and experience of patients, as well as reviewing the literature and performing a consensus study. Thanks to this collaboration, consensus has been reached on the most frequent signs and symptoms of Long COVID, its duration and clinical course, its impact on daily activity and the restrictions it places on the functioning of the affected individuals.

Being able to shed a little more light on the jumbled mass of information we needed to study has been a great learning experience. How have we done it? Through collaboration; joining forces; science; adopting a clinical and multidisciplinary approach; management; multidisciplinary again, but from the perspective of citizenship; communicating the results in a clear and understandable way throughout the process; and the teamwork of all those involved in the commissioned project.



PROVISION OF SCIENTIFIC AND TECHNICAL SERVICES

Introduction

Along with its research, financing and training roles, the fourth main role of the ISCIII is the provision of scientific and technical services to the R&D system and the SNS. It played a special role during the pandemic which is no surprise given the Institute's experience in the fields of microbiology and epidemiology, both key areas over the last three years.

From the start of COVID-19, when the ISCIII offered a sample analysis and confirmation of cases service until many more centres and organisations could start to perform these tasks, the ISCIII has remained at the forefront of providing services to the scientific and health community. Some examples of the services that the ISCIII has provided over the last three years include: the task of sequencing SARS-CoV-2 and making it available to researchers; training and consultancy work for ministries, autonomous communities and other organisations involved in the management of the pandemic; and the collection, analysis and publication of indicators and data for monitoring the pandemic over time.

Action taken at the start of the pandemic: crisis microbiology

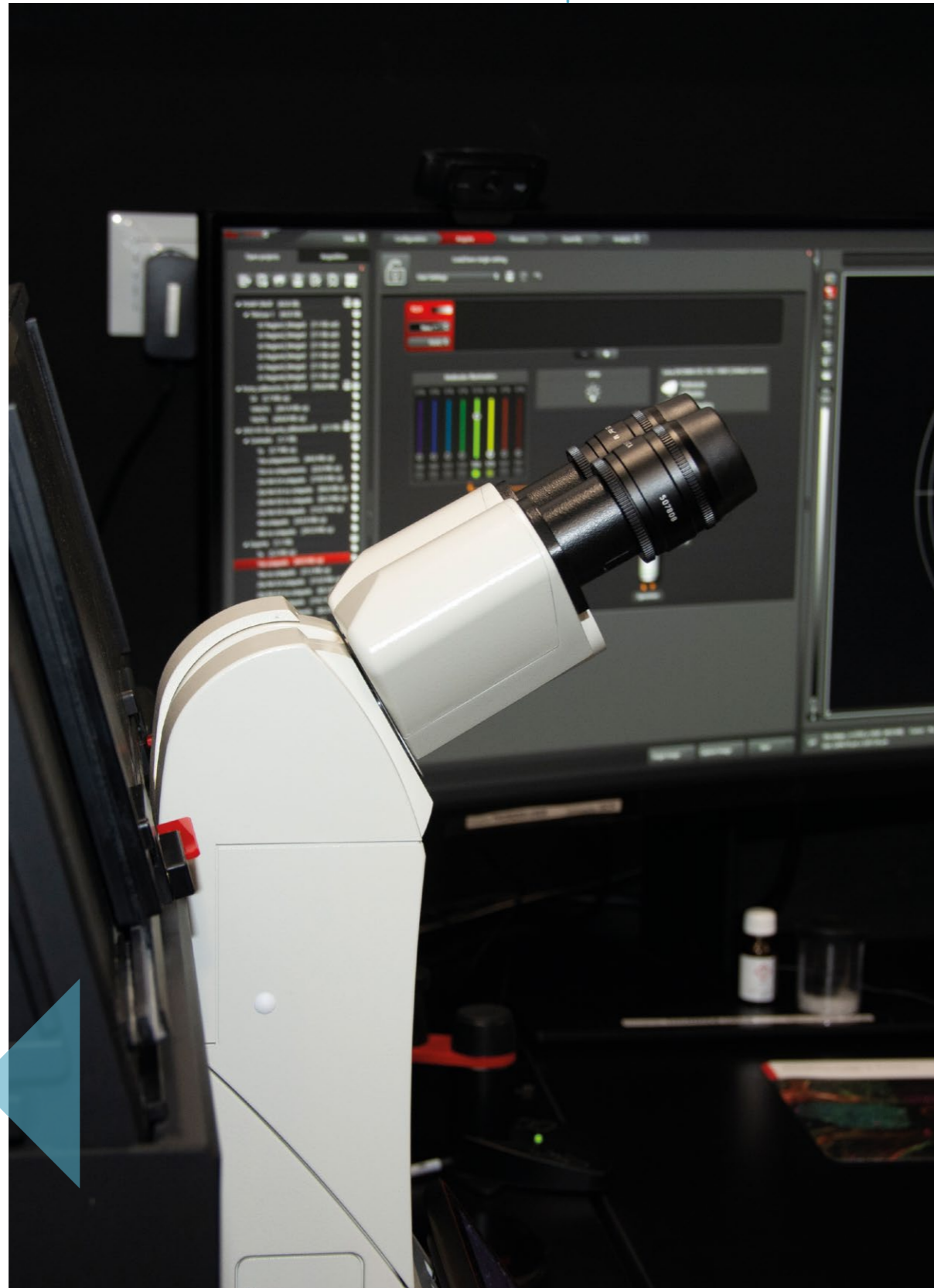
On 11 March 2020, the World Health Organisation declared COVID-19 a pandemic. SARS-CoV-2, a new coronavirus, caused a health crisis that was unprecedented in our recent history. This crisis has continued in constant waves right up to the present day.

The first wave of this epidemic took place between February and June 2020, two months after the effects of SARS-CoV-2 were detected in late 2019. The following waves appeared between August and October 2020 and the third wave started in the middle of the Christmas period. The fourth was in spring 2021 and the fifth came with the summer. The infection rate during the sixth wave started to rise during the early days of November 2021 and the seventh wave, with a more controlled infection rate, appeared in spring 2022.

From the outset, the pandemic put science in a difficult position, creating a race against time to understand the nature of the new coronavirus and how to treat the disease. From the very first moment, the ISCIII has been committed to strengthening its research work, service provision and financial support for the scientific activity of the SNS.

The CNM launched several initiatives and made all its tools available in order to try to contain the epidemic. Initially, all SARS-CoV-2 samples were tested at the CNM, so all confirmations of suspected cases were handled by it. To improve its diagnostic capacity, it reorganised 13 laboratories into a single combined laboratory, which allowed for joint working to support the SNS.

In addition, the CNM implemented the PCR test for diagnosis; established a validation programme for commercial PCR tests for the detection of SARS-CoV-2 in clinical samples; coordinated reliability studies of antigen detection tests; generated devices for the production of reliability studies on serological tests; and provided advice to other research centres and universities.





It is worth noting that the CNM established a specific PCR test (RT-q PCR) that allowed it to rule out or confirm suspected cases more quickly, thus increasing the diagnostic capacity of the system at a time when hospitals were overwhelmed.

In late March 2020, researchers at the CNM Respiratory Virus Laboratory [succeeded in fully sequencing the virus](#) from respiratory samples. This achievement allowed us to comprehend the nature of the virus, analyse possible specific changes that define its behaviour, and understand its circulation and spread in the population.

The CNM has also developed a number of tools to produce various epidemiological predictions for future scenarios. In addition, it provided researchers with daily updates on the progress of the pandemic.



A first-hand account

Jesús Oteo National Centre of Microbiology

In September 2019, following my appointment as director of the National Centre of Microbiology (CNM), I reflected on one of the centre's main objectives: "Pathogenic micro-organisms have the ability to evolve very quickly, which forces us to constantly adapt if we are to deal with the threats they can generate in the best possible conditions". At that time I had no idea how soon we would need to demonstrate this, responding to the worst health crisis any of us have ever experienced.

The critical need was to guarantee diagnostic capacity. This took place in an initial scenario where the methodology was not yet developed in most hospitals and commercial PCR kits were scarce and not well evaluated. The CNM had been working on the development of a diagnostic PCR test since the end of 2019, and this was fully operational by February 2020. The big challenge was to scale up our diagnostic capacity in just a few days so that we could meet the huge demand. We modified the CNM's operating structure, which at that time was organised into thirteen Reference Laboratories, into a single large, networked laboratory made up of different teams working in a coordinated manner. This operation involved more than 60 professionals from different areas of microbiology and it was continuously adapted to the needs generated by the pandemic.

Those were weeks of stress, of haste, of trial and error, and of uncertainty. I remember them for the great pressure and endless hours of work, but also with pride for the work done, both by the CNM as a whole and by each of my colleagues.

We had a continuous stream of offers from ISCIII volunteers to help with this work. However, one aspect that especially concerned me was ensuring the optimisation and structuring of the work in order to achieve the coordination level required for the best possible efficiency. As a result, my priority was to maintain a controlled team that would work in a coordinated fashion as opposed to having a larger team that was more difficult to coordinate.

In addition, this had to be combined with other objectives that became more important as the pandemic progressed, such as the national seroprevalence study and the evaluation of both PCR and rapid diagnostic tests.

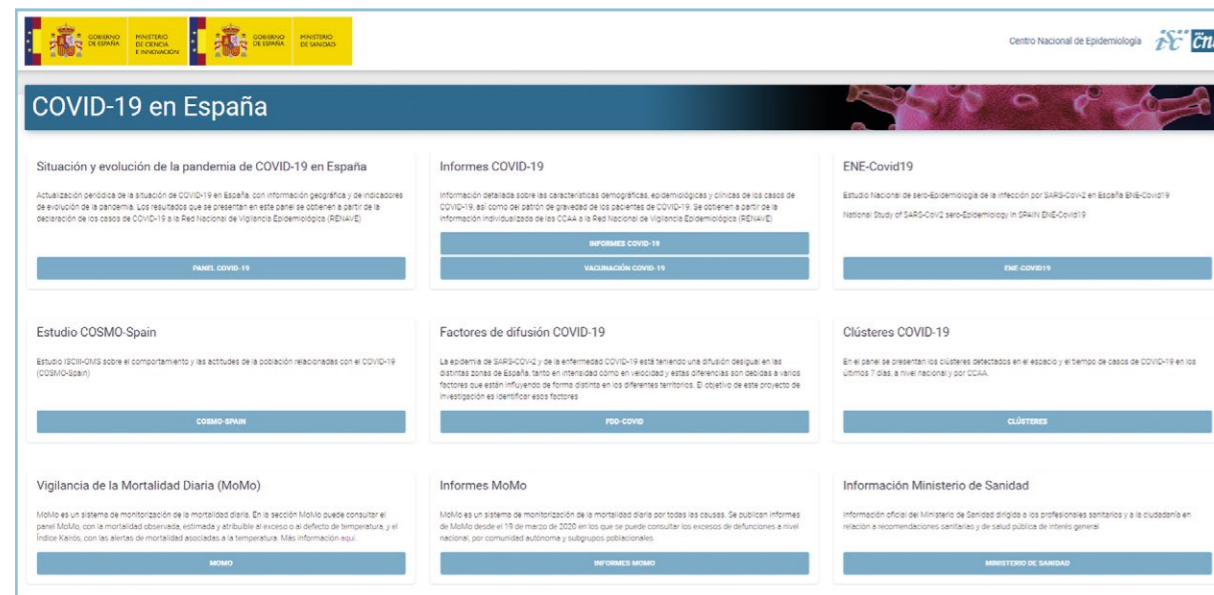
These were months spent engaged in emergency microbiology, when we had to adapt to new needs and setbacks every day. It was not an easy task, as the situation forced us to take immediate decisions with no guiding precedents. What I remember most is the involvement and excellent attitude of the CNM staff, even in the darkest moments.

Epidemiological data: information to ensure better action

The CNE, together with the CNM, was the second core element of the ISCIII's work during the pandemic. This centre, together with the ISCIII Information and Communication Technologies Unit, adapted the Spanish Surveillance System (SiViEs) platform from the start of the crisis, overcoming the technological limitations in terms of uploading data. The need for proper decision-making and to introduce measures to contain the virus required us to have large databases of up-to-date information that would allow surveillance networks to monitor cases and the evolution of the pandemic in a much more diligent way and on a daily basis.

In addition, from the outset, work began on the progressive adaptation of Influenza Surveillance Systems into integrated respiratory surveillance systems, to take advantage of our existing experience in influenza surveillance and apply it to surveillance not only for COVID-19, but also for influenza, RSV and other respiratory viruses. This adaptation led to the implementation of a joint surveillance system, known as Acute Respiratory Infection Surveillance (SIVIRA), that will be consolidated in the current 2022-2023 season.

Since the early months of 2020, through the [public information panel on the pandemic](#), which is still active, the ISCIII has allowed all members of the public to find information and see the evolution of the pandemic with daily updated information. Throughout this time, everyone has been able to see daily updated information on the evolution of cases, hospitalisations, deaths, transmissibility, geographical spread and the demographic and epidemiological characteristics of COVID-19, among other information of interest.



Screenshot of the appearance of the Public Information Panel

The public information panel has been fed with updated data on different aspects of the pandemic and is organised into different sections, which include:

- **Status and evolution of the COVID-19 pandemic in Spain.**

This section provides a daily update on the COVID-19 situation in Spain. In this way, anyone can see the number of cases reported to the National Epidemiological Surveillance Network (RENAVE), the cumulative rate, the geographical distribution of cases, the evolution of the pandemic, the epidemic curves at national and provincial level, and data files with indicators of the evolution of the pandemic.

- **COVID-19 reports.**

During the course of the pandemic, the CNE has published a series of reports with key data on the pandemic at any given time. Thus, in 2020, a total of 59 reports on the COVID-19 situation in Spain were published; in 2021, 52 reports were uploaded to the panel; and during the course of 2022, a total of 47 reports were published.

In addition, during the lockdown, a series of reports were published on the COVID-19 situation among healthcare workers, the population group that suffered most severely from the adverse effects of the pandemic due to being the first line of defence in the fight against the SARS-CoV-2 virus.

From the moment the vaccination process began in Spain, information began to be shared about its evolution in our country. Periodically, monitoring reports on the effectiveness of the vaccination in Spain have been updated and the reports of the COVID-19 Vaccination Effectiveness Work Group ([Vaccination COVID-19](#)) have been made public. This Work Group is made up of leading figures from the Ministry of Health's Directorate-General for Public Health, the Centre for Coordination, Alerts and Health Emergencies (CCAES), the ISCIII and the Spanish Agency of Medicines and Medical Products (AEMPS).

The reports from this Work Group show the results of the COVID-19 vaccine effectiveness studies, results that have helped guide the vaccination strategy throughout the national COVID-19 vaccination programme. The effectiveness of the COVID-19 vaccine in nursing home residents and in populations of different age groups has been reported. This relates to protection against SARS-CoV-2 infection and to more severe infection outcomes such as hospitalisations and death. Information from different population-based registries, such as the national vaccination registry (REGVACU) and the national registry of laboratory tests (SERLAB), as well as COVID-19 surveillance information reported to the National Epidemiological Surveillance Network through the SiViEs platform, were used to conduct these analyses.

References:

Mazagatos C, Monge S, Olmedo C, Vega L, Gallego P, Martín-Merino E, Sierra MJ, Limia A, Larrauri A, Working Group for the surveillance and control of COVID-19 in Spain. Effectiveness of mRNA COVID-19 vaccines in preventing SARS-CoV-2 infections and COVID-19 hospitalisations and deaths in elderly long-term care facility residents, Spain, weeks 53 2020 to 13 2021. *Euro Surveill.* 2021;26(24):pii=2100452. <https://doi.org/10.2807/1560-7917.ES.2021.26.24.2100452>.

Monge S, Rojas-Benedicto A, Olmedo C, Mazagatos C, José Sierra M, Limia A, Martín-Merino E, Larrauri A, Hernán MA; IBERCovid. Effectiveness of mRNA vaccine boosters against infection with the SARS-CoV-2 omicron (B.1.1.529) variant in Spain: a nationwide cohort study. *Lancet Infect Dis.* 2022 Sep;22(9):1313-1320. [https://doi.org/10.1016/S1473-3099\(22\)00292-4](https://doi.org/10.1016/S1473-3099(22)00292-4). Epub 2022 Jun 2. PMID: 35658998; PMCID: PMC9162477.

Monge S, Rojas-Benedicto A, Olmedo C, Martín-Merino E, Mazagatos C, Limia A, Sierra MJ, Larrauri A, Hernán MA. Effectiveness of a second dose of an mRNA vaccine against SARS-CoV-2 Omicron infection in individuals previously infected by other variants. *Clin Infect Dis.* 2022 Jun 10:ciac429. <https://doi.org/10.1093/cid/ciac429>. Online ahead of print. PMID: 35687580; PMCID: PMC9214148..

Monge S, Mazagatos C, Olmedo C, Rojas-Benedicto A, Simón F, Vega-Piris L, Sierra MJ, Limia A, Larrauri A, Grupo de Trabajo de Registros, Vigilancia y Control de la COVID-19 en España. Efectividad de las vacunas frente a SARS-CoV-2 utilizadas en España: infección, hospitalización y mortalidad en personas de cincuenta a cincuenta y nueve años. *Rev Esp Salud Pública.* 2022; 96: 2 de septiembre e202209060. https://www.sanidad.gob.es/biblioPublic/publicaciones/recursos_propios/resp/revista_cdrom/VOL96/C_ESPECIALES/RS96C_202209060.pdf.

► Factors in the spread of COVID-19

In view of the varying spread of the SARS-CoV-2 virus and COVID-19 in Spain between different autonomous communities and regions, this research project, funded by the ISCIII, was launched with the aim of identifying the factors underlying the varying transmissibility of the virus in each region. It was also designed to disseminate this knowledge so that action could be taken in relation to these factors and to improve decision-making in the face of future increases in cases and new epidemic curves.

This study concluded that the most important factors in the spread of the disease were the number of residential places per 100 people over 70 years of age, the percentage of infected healthcare staff and factors related to the internal and external mobility of the communities and their relationship with Madrid and the Basque Country.

References:

García-García D., Herranz-Hernández R., Rojas-Benedicto A., León-Gómez I., Larrauri A., Peñuelas M., Guerrero-Vadillo M., Ramis R., Gómez-Barroso D. Assessing the effect of non-pharmaceutical interventions on COVID-19 transmission in Spain, 30 August 2020 to 31 January 2021. *Eurosurveillance*, 2022. <https://doi.org/10.2807/1560-7917.ES.2022.27.19.2100869>.

David, GG., Rafael, HH., Ayelén, RB. et al. Perimeter confinements of basic health zones and COVID-19 incidence in Madrid, Spain. *BMC Public Health* 22, 216 (2022). <https://doi.org/10.1186/s12889-022-12626-x>.

Rosillo N, Del-Águila-Mejía J, Rojas-Benedicto A, Guerrero-Vadillo M, Peñuelas M, Mazagatos C, Segú-Tell J, Ramis R, Gómez-Barroso D. Real time surveillance of COVID-19 space and time clusters during the summer 2020 in Spain. *BMC Public Health*. 2021 May 21;21(1):961. <https://doi.org/10.1186/s12889-021-10961-z>.

► COVID-19 Clusters

The public information panel also included a panel of COVID-19 clusters, i.e. those geographical areas where an increase in reported COVID cases was detected in a given space and time. This was at both the national and regional level.

The public information panel also included direct information from the main studies carried out by the Institute, such as ENE-COVID and COSMO-Spain, as well as official information from the Ministry of Health on health recommendations for both healthcare staff and of general interest.

► Monitoring of Estimated Daily Mortality (MoMo)

One of the tools most closely monitored throughout the pandemic has been the MoMo analysis system. This provides key information on daily mortality monitoring, making it possible to estimate the impact of COVID-19 in Spain and its autonomous communities, at a time when universal monitoring did not reflect the true scope of the pandemic.

The system for monitoring daily all-cause mortality (MoMo) was developed in 2004 under the auspices of the Ministry of Health with the aim of reducing the impact of excess temperature on the population's health. MoMo is able to detect deviations of excess daily all-cause mortality from the figures that would be expected given the historical series. Although heat waves were its initial focus, it has subsequently been used to estimate the impact on population mortality of any major public health event, such as the COVID-19 pandemic. While MoMo does not provide specific information on cause of death, the trends it identifies can help us interpret possible excess deaths such as those suffered during the pandemic, with estimates calculated on a daily basis at national, regional and provincial levels, by gender and age group.

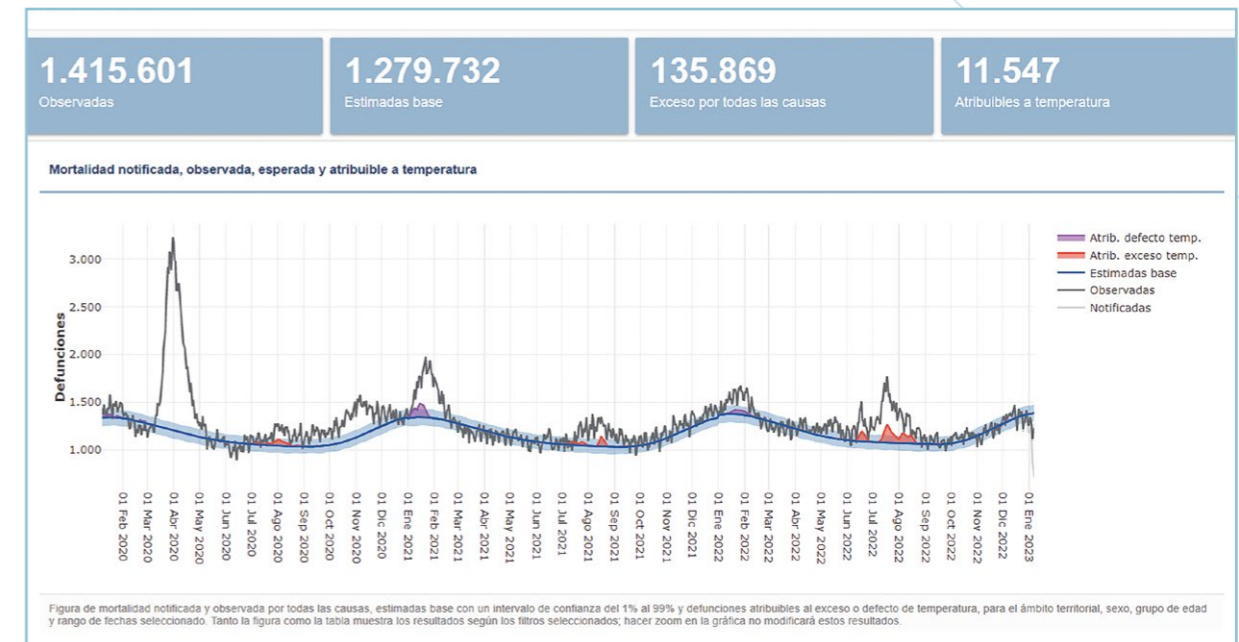


Image of the excess mortality recorded in Spain from January 2020 to January 2022.

The data collected by the mortality monitoring system have subsequently been used in other research projects relating to COVID-19. For example, the data obtained from the ENE-COVID study, the National Epidemiological Surveillance Network (RENAVE) and the Daily Mortality Monitoring System (MoMo) made it possible to estimate the lethality of SARS-CoV-2 infection in Spain.

► Joint sentinel surveillance for respiratory viruses: COVID-19, influenza and RSV

To improve monitoring of the COVID-19 pandemic and its relationship with other respiratory viruses, in 2020, work began on a comprehensive respiratory sentinel surveillance system, based on the influenza surveillance systems. The aim was to understand the evolution over time and space of influenza, COVID-19 and respiratory syncytial virus (RSV), their hospitalisation rates and pattern of severe disease, identify the different genetic variants of the viruses studied and evaluate the effectiveness of vaccines. The objective was to better respond to the epidemiological situation and address the possible simultaneous circulation of SARS-CoV-2, influenza and RSV.

The comprehensive joint surveillance model represents a paradigm shift in surveillance objectives. The aim is to adapt the existing influenza surveillance systems to be able to monitor influenza, COVID-19 and RSV through a single, more sustainable and more efficient surveillance system. In addition, the system has the capability to respond to the circulation or emergence of other respiratory viruses, following their microbiological confirmation, using the same surveillance infrastructure.

Every week, with the coordination of the CNE and the CNM, the ISCIII publishes a report on the evolution of this sentinel surveillance, which provides information on both mild respiratory infections, treated in primary care (ARIs), and severe respiratory infections, requiring hospital admission (SARI) ([Weekly SiVI-RA reports](#)). In addition, a document analysing this joint monitoring during the 2021-2022 season ([SiVIRA 2021-22](#)) was published.

In response to one of the main objectives for the comprehensive respiratory infection systems, a contribution has been made to the evaluation of viral disease prevention and control measures, in the framework of the European ECDC project "Vaccine Effectiveness, Burden and Impact Studies (VEBIS) on COVID-19 and Influenza", estimating the effectiveness and impact of influenza and COVID-19 vaccines. In addition, all the results have been shared with the SNS Interterritorial Council Vaccines and Vaccination Registry to guide action in Public Health initiatives.

References:

Mazagatos C, Delgado-Sanz C, Monge S, Pozo F, Oliva J, Sandonis V, Gandarillas A, Quiñones-Rubio C, Ruiz-Sopeña C, Gallardo-García V, Basile L, Barranco-Boada MI, Hidalgo-Pardo O, Vazquez-Cancela O, García-Vázquez M, Fernández-Sierra A, Milagro-Beamonte A, Ordobás M, Martínez-Ochoa E, Fernández-Arribas S, Lorusso N, Martínez A, García-Fulgueiras A, Sastre-Palou B, Losada-Castillo I, Martínez-Cuenca S, Rodríguez-Del Águila M, Latorre M, Larrauri A; SARI surveillance VE group in Spain. COVID-19 vaccine effectiveness against hospitalization due to SARS-CoV-2: A test-negative design study based on Severe Acute Respiratory Infection (SARI) sentinel surveillance in Spain. *Influenza Other Respir Viruses*. 2022 Jul 26:10.1111/irv.13026. <https://doi.org/10.1111/irv.13026>. Epub ahead of print. PMID: 35880469; PMCID: PMC9350393.

Sentís A, Kislalya I, Nicolay N, Meijerink H, Starrfelt J, Martínez-Baz I, Castilla J, Nielsen KF, Hansen CH, Emborg HD, Nardone A, Derrough T, Valenciano M, Nunes B, Monge S; VEBIS-Lot4 working group. Estimation of COVID-19 vaccine effectiveness against hospitalisation in individuals aged ≥ 65 years using electronic health registries; a pilot study in four EU/EEA countries, October 2021 to March 2022. *Euro Surveill*. 2022 Jul;27(30):2200551. <https://doi.org/10.2807/1560-7917>. ES.2022.27.30.2200551. PMID: 35904059; PMCID: PMC9336167.

Kissling E, Hooiveld M, Martínez-Baz I, Mazagatos C, William N, Vilcu AM, Kooijman MN, Ilić M, Domegan L, Machado A, de Lusignan S, Lazar M, Meijer A, Brytting M, Casado I, Larrauri A, Murray JK, Behillil S, de Gier B, Mlinarić I, O'Donnell J, Rodrigues AP, Tsang R, Timnea O, de Lange M, Riess M, Castilla J, Pozo F, Hamilton M, Falchi A, Knol MJ, Kurečić Filipović S, Dunford L, Guiomar R, Cogdale J, Cherciu C, Jansen T, Enkirch T, Basile L, Connell J, Gomez V, Sandonis Martín V, Bacci S, Rose AM, Pastore Celentano L, Valenciano M; I-MOVE-COVID-19 and ECDC primary care study teams; I-MOVE-COVID-19 and ECDC primary care study team (in addition to authors above). Effectiveness of complete primary vaccination against COVID-19 at primary care and community level during predominant Delta circulation in Europe: multicentre analysis, I-MOVE-COVID-19 and ECDC networks, July to August 2021. *Euro Surveill*. 2022 May; 27(21):2101104. <https://doi.org/10.2807/1560-7917>. ES.2022.27.21.2101104. PMID: 35620997; PMCID: PMC9137272.

Finally, with regard to the generation, management and publication of data and knowledge, the support work of the ISCIII National Library of Health Sciences (BNCS) has been important, especially in the first year of the pandemic, at which time it provided [a guide offering resources for accessing reliable information](#). In addition, also during 2020, the ISCIII formed a scientific analysis group on SARS-CoV-2 and COVID-19, with the aim of publishing scientific-general interest reports on the diagnosis, treatment, prevention and management of the virus and the disease, and to inform both the scientific community and the public of important information on the development of research into the virus and the pandemic.



A first-hand account

Amparo Larrauri

National Centre of Epidemiology

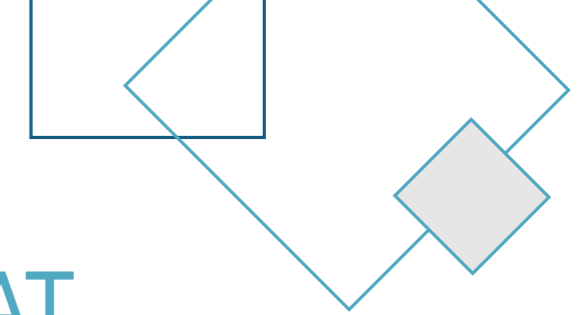
The development of inpatient influenza surveillance systems in the aftermath of the 2009 influenza pandemic allowed us for the first-time to obtain essential information on the severity of seasonal and pandemic influenza epidemics. In 2020, a new pandemic, this time for COVID-19, highlighted the need for integrated respiratory surveillance systems that could simultaneously provide information on influenza and COVID-19, with the same surveillance structure and in the same clinical act.

Since summer 2020, the Surveillance Unit for Influenza and other respiratory viruses of the National Centre of Epidemiology has coordinated the implementation of the acute respiratory infection surveillance system (SiVIRA) in Spain, with the development of sentinel respiratory surveillance systems in both primary care (ARIs) and hospitals (SARIs). This key objective was a very important challenge for our Unit because it has involved the development of complex surveillance processes, for which the relationship between the organisations in different areas of the National Health System within each autonomous community has been critical. This was during a time of heavy workloads due to the COVID-19 pandemic.

For those of us who have been involved in the evolution of historical influenza surveillance systems, this challenge became a unique opportunity to implement new surveillance systems that are more stable, efficient, resilient, capable of responding to the emergence of any respiratory agent in the future, and that can provide essential information to guide the control and prevention policies for such important respiratory diseases as influenza, COVID-19, RSV infection and many more.

In SiVIRA's third year of operation, that goal has been achieved. Most autonomous communities are participating in the systems and these have a promising future that could open up new surveillance options, in which the automation of processes and the interoperability of systems will be key aspects for the surveillance of these and many other infectious diseases.

Over the three years of the pandemic, we have continued to improve and update the COVID-19 in Spain panel in step with the evolution of the pandemic and also the Daily Mortality Monitoring (MoMo) system. Introducing estimates of excess mortality attributable to temperature, in addition to all causes (MoMo Panel), is enabling us to do more and better research on the impact of heat waves and cold snaps on mortality in the population, always with the responsibility to act in the interests of the scientific community and the general population.



PARTICIPATION AT THE EUROPEAN AND INTERNATIONAL LEVEL



In a global crisis, international collaboration and participation is fundamental. Since the beginning of the pandemic, the ISCIII has participated in several international projects, many of which are still ongoing. These are allowing us to compile scientific knowledge about the coronavirus and make progress with the research, control and monitoring of infectious diseases such as COVID-19. Internationalisation is one of the ISCIII's objectives, included among its main challenges set out in its Strategic Plan 2021-2025, and the pandemic has been a spur to, out of both desire and necessity, continue to promote the Institute's participation in transnational initiatives.

At the onset of the pandemic, the European Commission's [ERAvsCorona](#) Action Plan was created. This enabled the development of several short-term coordinated research and innovation initiatives, many of them focused on boosting research infrastructures and R&D projects in response to SARS-CoV-2. One such initiative was the [COVID-19 Data Portal](#), whose application in Spain made it possible to collect data such as those related to the COVID-19 Fund launched by the ISCIII.

In this regard, data management and global data sharing is proving to be a challenge in the pandemic. The Elixir-Converge project, which started in 2020 and is due to end this year, has been coordinating national research infrastructures to promote good data management, reproducibility and reuse. The ISCIII has participated in and funded this initiative, which has been complemented by other projects such as the 1+ Million Genomes (1+MG) project, in which the Institute is also actively taking part and which aims to improve the approach to genome sequencing applied to infectious diseases such as COVID-19.

Continuing with the area of big data, the Genomic [Data Infrastructure \(GDI\)](#) project, designed to support the European 1+MG initiative, was launched in November 2022. Specifically, GDI will promote the development, implementation and operation of sustainable data access infrastructures within each participating country. This includes the legal frameworks, operating procedures and ethical principles required to foster and maintain public trust and confidence with cross-border access to highly sensitive personal data.

This initiative, in which the Institute is also participating, will unlock a data network of more than 1 million genome sequences for research and clinical use. This will create unprecedented opportunities for routine transnational and multi-stakeholder initiatives in personalised medicine for common, rare and infectious diseases. Of the three cases detected so far where it has been used, one of them relates to infectious diseases, with an initial focus on COVID-19. In relation to 1+MG/B1MG, the BYCOVID initiative linked to the European COVID-19 data portal and associated national portals is one of the best examples to explain the need for the creation of sustainable solutions that consolidate and complement national infectious disease projects beyond COVID-19.

From the beginning of the pandemic, the ISCIII has been involved in various international projects

The ISCIII has led a Spanish consortium of 40 hospital over the last two years

Another more specific example of the ISCIII's participation in European data management projects relating to COVID-19 is PHIRI. Since 2020, this has involved working on obtaining tools to make better use of public health information, proposing the development of IT and computer systems that allow the research community to make the most of scientific information. The ISCIII is present in almost all [PHIRI](#) work packages and is strongly involved in work package 5, co-led by the CNE. This aims to review research methodologies to assess the global impact of COVID-19. The Institute also collaborates in PHIRI projects on the assessment of national and European policies, the creation of a catalogue of information sources and the development of training activities.

Together with PHIRI and [Elixir-Converge](#), the ISCIII's participation in data management projects also includes collaboration in the [I-MOVE-COVID-19](#) consortium. This aims to obtain epidemiological and clinical information on patients with COVID-19 and virological data on SARS-CoV-2. The Institute participates through the CNM and the CNE.

Another of the ISCIII's most notable participations so far in relation to the pandemic is the [VACCELERATE Project](#). This aims to accelerate clinical research on vaccines for infectious diseases, including specific initiatives for COVID-19. Two of the main activities that VACCELERATE, which grew out of the HERA Incubator, has been involved in during this time are a [register of volunteers](#) to participate in clinical trials and a [register of units](#) capable of conducting these trials. The coordination of VACCELERATE in Spain is led by the CNM, which forms part of the ISCIII.

With the move from one European R&D framework programme to another (from Horizon 2020 to Horizon Europe), many of the initiatives that began at the start of the pandemic are continuing their work with renewed efforts. For example, the HERA Incubator, whose work has now been completed, is being continued through a recently launched project called the SARS-CoV-2 Sequencing Laboratory Network ([RELECOV](#)). This focuses on improvements in microbiological surveillance and genome sequencing, with some of its efforts being directed towards infectious diseases and COVID-19.

As work prior to that to be carried out by RELECOV, over the last two years the ISCIII has led a Spanish consortium of 40 hospitals working on the "[Improvement of Sequencing Infrastructures and Capacities to respond to the COVID-19 pandemic](#)", within the framework of HERA and with the collaboration of the European Centre for Disease Control and Prevention (ECDC). This project has allowed us to strengthen sequencing and variant analysis work and accelerate a process in which the ISCIII was already directly involved: transforming and directing microbiological surveillance towards molecular surveillance based largely on the genome sequencing of microorganisms associated with different infectious diseases.

RELECOV began in January 2021 with the aim of providing information necessary for the genomic surveillance of SARS-CoV-2 variants. Funded by the ECDC and managed by HERA, it will continue through the grant that HADEA awarded to the ISCIII's CNM, which will coordinate Inmaculada Casas' team in what is known as RELECOV 2.0. The network is made up of 48 laboratories in 17 Autonomous Communities and Ceuta and Melilla.

The COVID-19 pandemic has provided lessons at both the global and national levels, generating useful knowledge and experience so that we can prepare our response to future pandemics. The ISCIII is also involved as a member of what is known as a Coordination and Support Action (CSA) for the preparation of a new European partnership, officially called the European Partnership for Pandemic Preparedness (BE READY). This aims to improve the prediction of and response to future health threats through the financing of R&D projects in coordination with the European authorities.

In short, the national activity that the ISCIII has been carrying out around the pandemic over more than three years would not make sense without the international approach exemplified by the aforementioned projects, which have strengthened the Institute's work in the European health R&D field.



A first-hand account

Inmaculada Casas National Centre of Microbiology

As an expert in respiratory viruses and their transmission, I was not surprised by the pandemic. In fact, we were expecting it. What surprised me was the specific virus involved, a second SARS-group coronavirus that has established itself as yet another respiratory virus to add to the long list.

It meant us revisiting existing virological detection and surveillance systems, both nationally and globally. The option of performing a differential diagnosis covering the new SARS coronavirus has been a key element in the response to the current epidemic season (2022-2023) and has enabled us to understand what happened in the previous two epidemic

seasons. We can recall the first case detected in La Gomera when we had some of the reagents, frozen since our experience with the first SARS coronavirus in 2003.

To take on this and future pandemics adopting a 21st century approach, we need to be continually investing in R&D and innovation. Governments must understand this. It is clear that COVID-19 research initiatives have made great strides in advancing vital issues in the control of disease and the social situation. Different researchers from distinct areas have come together to produce multidisciplinary research. An example of this occurred at the National Centre of Microbiology with the COVID Funds, whose coordination added value to my frantic work in the first two years of the pandemic.

Virology has become a big part of our society and genomics has proved vital to our understanding of the virus. With the arrival of the Alpha variant in Spain in December 2019, the network of regional SARS genome sequencing laboratories (RELECOV) was created and this is working in a coordinated manner. This coordination has encouraged me to try to convince everyone that the smartest thing to do is to join forces and share data for the common good.

With this global vision of the pandemic, the European management and financing bodies generated a programme to understand the viral evolution and circulation dynamics of different variants in Europe. The ECDC/HERA-Incubator project, coordinated by the ISCIII, has formed the framework for the RELECOV network. A new EU4Health-HaDEA project, starting in the first quarter of 2023, will now aim to strengthen this national network and extend its scope to other respiratory viruses.

For me, the pandemic has been the greatest personal commitment in my professional life.



CONCLUSIONS

Since COVID-19 is still among us, our work must go on. More than three years ago, in the first weeks of 2020, an uncertain and growing threat was looming with the arrival of an unknown airborne virus. It very quickly became a pandemic and the consequences of that are still with us today. The COVID-19 pandemic led to the public facing a situation of individual and collective risk to their health, and it required the imposition of drastic population measures, including lockdown. Both the scientific community and healthcare workers in our country faced huge amounts of stress and uncertainty over what has been a never ending challenge unlike any seen before.

While the COVID-19 pandemic health emergency highlighted some weaknesses in the system, broadly speaking, it also demonstrated that both the scientific and health sectors are up to the task of responding to the demands of complex global public health crises. In most countries, a real lack of readiness and response to the appearance of new emerging infectious agents was evident from the outset. More needs to be done to improve prevention and control of the potential negative effects of such threats on the population.

The ISCIII is a Public Research Body whose mission is to contribute to improving the health of the public and to combat diseases. It carries out this work through the promotion of research and innovation in Health Sciences and Biomedicine, the provision of services and providing training through educational programmes targeted at the SNS. Its four core functions of in-house research, R&D financing, training and the provision of scientific and technical services form a bridge between science and health, allowing it to interact with all kinds of organisations- government authorities, universities, companies, scientific societies, professional associations, health professionals and representatives of the public, among others - both nationally and internationally, with well-established participation and leadership in the European research field.

Our leadership and commitment to society have been demonstrated throughout the pandemic, from the outset providing an extensive diagnostic, information-generating and advisory service for the entire SNS. Since the early 2020s, the ISCIII has offered high-quality scientific and technical support, allocating much of its research, financing and training efforts and resources to other scientific and care systems.

The Institute, together with other national bodies, has once again demonstrated its ability to contribute knowledge, facilitating the domestic management of the pandemic and decision-making, which has not always been easy. It creates an environment of connection and collaboration between the people involved in improving our approach to the disease, individual health care and strengthening public health. It has also cemented its role as one of the leading organisations promoting collaborative actions, capable of bringing together biomedical and health research.

The Institute's work is one of the many contributions made. The efforts it has made over the last three years are adding valuable scientific and technical knowledge that will contribute, together with the work of other partners, to future improvements. The responsiveness created throughout 2020, and in subsequent years, has been enlightening, allowing for global collaboration that has allowed us to find solutions to problems as they arose. Focussing on areas where there is room for improvement must always be a key objective.

The generation of knowledge on COVID-19, designed to support decision-making at both the clinical and health planning and public health levels, has been led by the ISCIII. From the first month of the pandemic, the specific FONDO-COVID call allowed large groups of SNS researchers to undertake collaborative projects to answer questions about diagnosis, treatment, prevention and gaining a better understanding of the virus, funding 129 projects with a high impact through their transfer. In addition, the ISCIII has promoted studies that have provided unique contributions on the seroprevalence of the infection (ENE-COVID study), monitoring of public opinion about the pandemic (COSMO-Spain), the efficacy of heterologous vaccination schedules (COMBIVACS), the analysis of vaccination in the over-65s (ENE-COVID SENIOR) and the definition of Long COVID (CIBERPOSTCOVID), among others.

With regard to the provision of information sources, from the outset the existing epidemiological information systems in the CNE were made available to help deal with the pandemic. The integrated surveillance system for respiratory infections (SiVIRA), based on the existing Spanish Surveillance System (SiViEs) platform, provided the latest data on the evolution of the pandemic from the start of the first wave. Together with the daily mortality information provided by the MoMo tool, and the specific reports that allowed for continuous updates on the epidemiological situation, it provided verified information that could be used by the health authorities and society as a whole.

With regard to the provision of scientific and technical services, the Institute has been at the forefront since the start of COVID-19, when it offered its capacity for sample analysis and confirmation of cases until other centres and organisations were able to take on these tasks. The CNM had identified the complete SARS-Cov-2 sequence by the end of March 2020 and made it available to the scientific community. It also established a specific PCR test (RT-q PCR) to rule out or confirm suspected cases in a shorter time, allowing for an increase in the diagnostic capacity of the health system in the moments when high demand was overwhelming its diagnostic capabilities.

In health emergencies, public access to accurate information is essential to deal with uncertainty and avoid the impact of misinformation or fake news. For this reason, the ISCIII developed an information and consultation service available to the public, which had a massive impact and received a large number of consultations.

With a strong reputation built up over its 33 years of existence, the ISCIII's role of leadership and responsibility during the pandemic has also allowed it to improve its visibility and reputation among the public thanks to the importance of its studies, some of which were pioneering, and the engagement and commitment of professionals dedicated to problem solving and raising public awareness of their activity. All this has been a source of unprecedented motivation, and selfless pride, for all those who have been striving each day to promote the development of quality science that is accessible and meaningful to the public, aligned with collaboration and solidarity for those most in need, and linked to cooperation and the principles of solidarity, equity and social justice. This is the way forward if we are to move towards a fairer and more collaborative society.

We need to reflect deeply on all the lessons learned over the last three years. Although there is no doubt that biomedical R&D in our country is more than ready to face new challenges, it is important to make improvements in certain areas. These include encouraging and increasing international coordination and cooperation, and promoting imaginative mechanisms for preparing for and responding to future pandemics and other possible events, all with the aim of having a positive impact on public health. The foundations we have laid are encouraging, but much remains to be done. The identification of structural weaknesses and limitations is



an excellent starting point for the necessary reflection and for making the organisational improvements in our systems for responding to threats in a globalised world.

To achieve these objectives, we need to keep giving a strong boost to the development of the capacities and potential of Spanish science. Efforts to reinforce this process include preventing the loss of talent, regaining the momentum lost in previous years and implementing scientific policies such as those promoted recently, thanks to national efforts and European funds. This commitment to science in our country, highlighting the advances made, cannot be allowed to lose momentum if we want to continue to play a key role in scientific production and in the resolution of health problems, standing shoulder-to-shoulder with the industrialised countries around us. The hard work seen during the pandemic must continue.

Three years into the pandemic, the ISCIII continues to work on SARS-CoV-2 and COVID-19, with a scientific output of excellence and providing follow-up on the analysis of the available information. On the whole, the planning of its actions is confirmation of its commitment to science in our country, with a necessarily strong international collaboration for a globalised world, and a clear focus on people, both individually and collectively, to promote the improvement of health care and public health. The institution's commitment to society, the ultimate goal of our efforts, has been strengthened over this difficult and intense period of the pandemic and we are aware that we must continue to work towards our main objective: to improve people's health through science.



GOBIERNO
DE ESPAÑA

MINISTERIO
DE CIENCIA, INNOVACIÓN
Y UNIVERSIDADES



Instituto de Salud Carlos III