COVID-19 vaccine: Post-authorisation safety surveillance – Challenges in assessing long term effects of COVID vaccines

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Contents

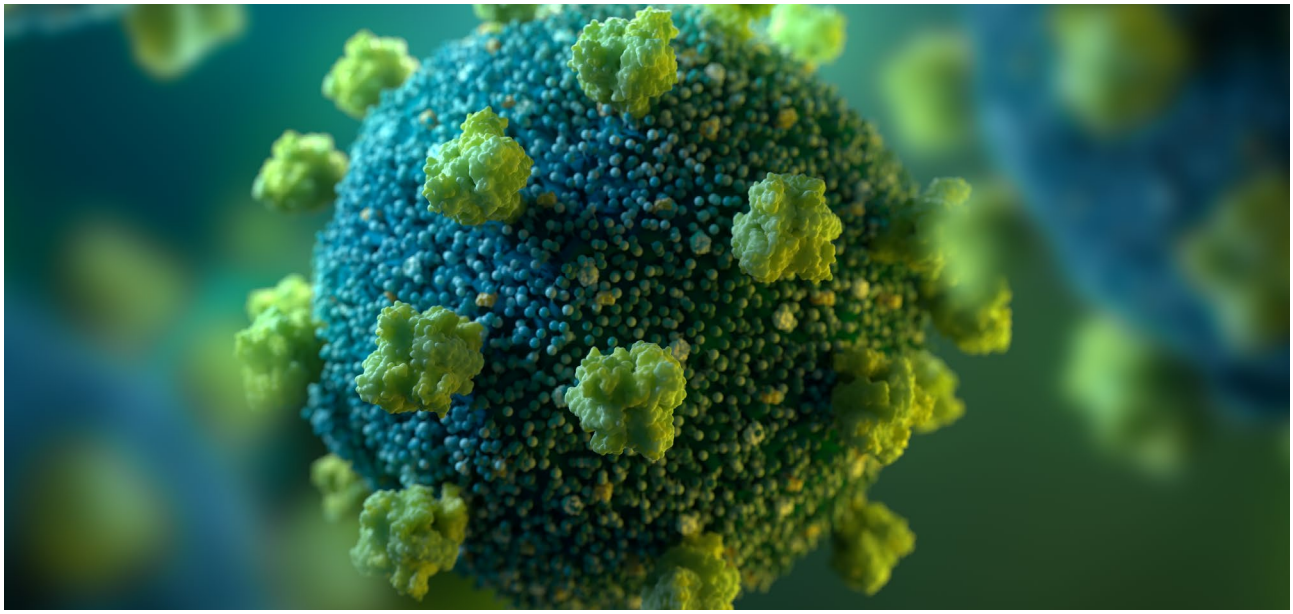
Executive summary

The COVID-19 pandemic disrupted life across the globe and has severely impacted the healthcare and clinical research industry, from overburdened hospitals and healthcare providers to complex challenges associated with responding to the disease. The global pandemic has officially ended, though the coronavirus and its variants are still prevalent, as are its lingering long-term effects and the side effects of the vaccines that slowed its spread and reduced its harm.

In this whitepaper we:

- Present the challenges associated with monitoring COVID-19 (COVID) vaccine safety in light of the accelerated approval, and the difficulty in distinguishing between vaccine side effects and long COVID symptoms
- Outline the available assessment methods and numerous post-authorisation safety surveillance methods employed to capture good quality data, as well as the challenge of assessing the large volume of associated data to generate critical insights
- Describe the clinician's perspective based on experience with the types of side effects reported by patients and the complications of long COVID in determining what is a true vaccine side-effect

Introduction



The coronavirus disease 2019 (COVID-19) pandemic was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly discovered virus closely related to the bat coronavirus, pangolin coronavirus and SARS-CoV.

The World Health Organisation (WHO) monitored the situation and provided guidance as the threat to global public health continued to rise. On 11 March 2020, alarmed by the rapid spread and severity of the virus-induced disease and the hesitancy from global leaders, WHO officially characterised COVID-19 as a pandemic.

As of 7 September 2023, there have been 770,437,327 confirmed cases and 6,959,900 deaths.[1]

The pharmaceutical industry raced toward a vaccine to abate the devastating spread even as the world seemed to shut down. Near the end of 2020, as the pandemic reached its peak, several clinical trials with vaccine candidates showed favourable results. Just months later in 2021, the first vaccines were administered.

Despite the widespread vaccination programs, COVID-19 remains prevalent, and we are still discovering the extent of its impact. Vaccines and boosters are still being administered while we continue to work on developing a better understanding of long COVID as well as the long-term side effects of the vaccines despite the challenges of collecting and assessing the vast amounts of safety data required.

770,437,327 cases
As of 7 September 2023

6,959,900 deaths
As of 7 September 2023

Vaccine development

By March 2020, COVID-19 cases and deaths were rising dramatically. The number of people testing positive for and developing severe forms of COVID-19 resulting in hospitalisation had increased to levels that threatened to collapse healthcare systems around the world. Every aspect of hospital care was impacted by the increasing need to provide care for COVID patients. This placed overwhelming pressures on even well-funded and well-resourced healthcare systems and devastated those with less robust support structures.

To add to concerns, reducing social interaction and staying home has had a devastating economic impact. This has been apparent in the service sector such as aviation, travel, tourism, hospitality, and personal small businesses, with many companies having to close permanently[2]. Restrictions needed to reduce the spread of this virus significantly reduced social interactions (work, schools, sporting and fitness clubs), and the pressure of the situation, especially for health care professionals, has also resulted in a significant effect on mental health across all age groups.[3]

The world needed an urgent response to curb the rising death toll associated with COVID-19 infection. In response, the scientific research and pharmaceutical industries worked to develop a vaccine.

13,500,122,024 vaccine doses
Have been administered as of 7 September 2023

Accelerated approval

Clinical studies with proposed candidates were accelerated to meet the urgency of the vaccine need. On 9 November 2020, Pfizer and BioNTech[4] were the first to announce that interim data from their Phase 3 clinical study with their mRNA candidate demonstrated significant efficacy and safety. Very soon after, three other companies announced successful Phase 3 results for efficacy: Moderna Inc.[5] on 16 November 2020, the AstraZeneca and University of Oxford collaboration[6] on 23 November 2020 and on 29 January 2021, Johnson & Johnson (J&J)[7] announced significant efficacy.

From a clinical research perspective, the accelerated speed of the vaccine development was lauded as an exceptional achievement and resulted from the concerted efforts of stakeholders at every level, from sites to sponsors and regulators. However, the exceptional speed with which the studies were conducted and approved raised public concerns – how could vaccinations have been developed this fast, and were they safe? Concerns regarding safety were the biggest drivers of vaccine hesitancy, while significant portions of the surveyed population indicating hesitancy also believed the risk of COVID-19 was exaggerated[8,9].

These are fair questions and concerns. The Benefit-Risk (BR) perception for the patient may be lower, given that the acceptable level of risk is lower when a product is given to a healthy population as opposed to a treatment medicine given to sick patients. Regulators responded across various media platforms in daily briefings regarding the data and their assessment to dispel vaccine hesitancy.

What is the main determinant of COVID-19 vaccine hesitancy?

Lack of info on safety	45%
Lack of info on efficacy	8%
Lack of confidence health syst	18%
Freedom deprivation	29%

Regulatory fast-track for viable vaccines

Many of us in the pharmacovigilance and regulatory industry will have served as ad hoc educators for friends and family during the pandemic, explaining how scientific research into these viruses pre-dates this pandemic. Research data and possible candidates for the virus family were already available to allow for developing a viable candidate with speed. Research into a treatment for COVID-19 was not starting from scratch, as the associated scientific technology was under research already,[10,11,12] specifically regarding mRNA vaccines.

With the mRNA foundation, researchers could begin studies promptly. In general, the vaccine trials benefitted from a vast pool of subjects, facilitating quick recruitment. The subsequent acceleration of the study was also aided by regulations that fast-track the approval process for medicines under extenuating circumstances, such as treatments for global pandemics. This allowed parallel processes to take place, including overlapping study phases. Additionally, the data was submitted as a 'rolling review' – regulators reviewed it as it became available instead of in complete, aggregated reports.

It is correct to state that the vaccination program has been successful, with additional vaccines being approved and distributed to millions of people across the globe. Subsequently, multiple significant variants of the virus have emerged, namely Delta and Omicron*, with Omicron being the most prevalent. The pharma industry continues to assess the efficacy of the currently authorised and developing vaccines against these variants. As we develop a clearer picture of how the coronavirus will continue to impact public health through variants, we will likely see a recurring vaccination program aligned with the influenza vaccine – annual vaccinations with boosters provided to vulnerable and at-risk populations.

As of 7 September 2023, 13,500,122,024 vaccine doses have been administered (5,589,911,197 persons vaccinated with at least one dose, and 5,149,988,830 persons with a complete primary series).

*Note the naming convention as used by the WHO has been amended and the Omicron variant is now known as XBB1.5.

Post-authorisation safety surveillance

Like all medicines, vaccines must prove to be safe as well as effective. Vaccines are regulated and monitored across the globe to ensure all possible information regarding efficacy and safety is collected and understood, the benefit-risk balance remains favourable, and any concerns are identified and acted upon appropriately to ensure patient safety.

Information from the authorised use of a vaccine or any marketed drug is not as readily available and cannot be collected as easily as information generated during a clinical study. Additionally, data collected from authorised use may not always contain all the critical details required to perform accurate safety assessments. The information collected must allow for the accurate evaluation of a causal relationship and distinguish between the underlying disease, co-morbidities effects and vaccine side effects. A particular challenge is the distinction between these and long COVID, as information continues to emerge around its symptoms and effects.

In this section we discuss the challenges associated with acquiring data from the post-marketed environment, ensuring the quality of the data, and processes and procedures are in place to facilitate data collection and safety monitoring.

Signal management: Data collection

Processes are in place to facilitate data collection and safety monitoring, from collecting individual case reports, signal detection, data analysis for periodic aggregate safety reports and regular literature screening.

Passive surveillance, individual cases

Individual cases form the building blocks for broader aggregate analysis and understanding of the emerging safety profile of a product. The industry depends upon these cases being reported to the regulators and the Marketing Authorisation Holders (MAH) by Health Care Professionals (HCP) and patients, neither of whom are obligated to do so.

HCPs do not always have the time to report, especially given the time and resource strain they incurred during the COVID-19 pandemic. Patients may not be aware they can report cases or may not provide all the information required once they do. Despite the potential paperwork burden, cases reported by HCPs are more accurate than patient reports. As such, patients should be made aware of the available routes to reporting a side effect, prioritising reporting through their HCPs.

While the information received from the marketed environment via passive surveillance may be incomplete and often represents a fraction of what could be available, what is collected must be used in safety assessments and will feed into subsequent decisions and actions. The subsequent vaccinations, collection and assessment of any safety issues related to the vaccine use need to be performed, as far as possible, in real-time to make quick assessments and determine resulting actions.

Active surveillance – Post-authorisation safety studies, interventional and non-interventional

Regulators can authorise medicines, including vaccines, with the condition to facilitate further collection of information about safety in an active manner (active surveillance) via Post-Authorisation Safety Studies (PASS). MAHs can also pre-empt requests of such conditions by proposing PASSs within the authorisation approval. These studies support collection of further information regarding known safety concerns.

As part of the Conditional Marketing Authorisation, regulators required studies to investigate the safety, tolerability, immunogenicity and efficacy of the vaccines to determine if there is any vaccine-associated enhanced disease, particularly in severe COVID cases[13,14].

PASS studies in progress

PASS studies can be grouped under two main categories: **interventional** and **non-interventional**. Non-interventional studies rely on real-world data and provide results which are more generalisable. Different PASS study designs have been implemented as part of the pharmacovigilance activities for COVID-19 vaccines.

The majority of the mandated PASSs for approved COVID-19 vaccines remain in progress or have been completed as is the case at this time, for example:

- Association between Moderna COVID-19 vaccine and paediatric safety outcomes in children and adolescents aged 5-19 in the Nordic countries: thromboembolic and thrombocytopenic outcomes, myocarditis and pericarditis
- Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine[15]
- To assess safety and immunogenicity in pregnant women with exploratory objectives including:
  - (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy
  - (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy (Cominarty)

Similarly, various PASS studies have been ongoing, and are near completion, in the US including:

- To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population (all ages), pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System (Cominarty)
- A study using secondary data from administrative claims/electronic medical records for military and civilian personnel and their families in the Department of Defense Military Health System (Cominarty)
- To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine (Cominarty)
- VAC31518COV4001: An observational post-authorisation safety study to assess the safety of Ad26.COV2.S using health insurance databases in the US
- Observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy, using an administrative claims data source in the US that includes capture of longitudinal data on diagnoses, procedures, medications and vaccines used across all applicable healthcare settings

Further results and conclusions from many of the PASSs are expected to be published in 2023.

In addition, the European Medicines Agency (EMA) funded the ACCESS project in the EU to monitor vaccines. The EMA worked with EU partners, such as the University Medical Center Utrecht, on behalf of the Vaccine Monitoring Collaboration for Europe Consortium research team VAC4EU[15]. This project began in May 2020 and ended in February 2021 and resulted in delivery of methods and tools to support safety surveillance, including a list of Adverse Events of Special Interest (see below) and template protocols for different post-authorisation study types. These products have passed through a review process by an advisory committee, consisting of members of the EMA, and approved products are available on the VAC4EU website.

Collection and monitoring of Adverse Events of Special Interest

The EMA had requested that vaccine-associated Adverse Events of Special Interest (AESI) be monitored. They refer to the following sources in the Core RMP requirements for COVID-19 vaccines: Brighton collaboration SPEAC list[16], ACCESS project list of AESI and case definitions[17] and CBER surveillance program-List of AESIs.[18] The finalised Brighton collaboration list is reviewed and updated regularly on a quarterly basis. The EMA also has a list of Designated Medical Events[19] containing medical concepts and terms that are often related to medicine – and these can also be flagged.

Additionally, seven US government agencies have participated in active monitoring of data related to vaccine administration, including rapid-cycle analyses (RCA) or "near real-time surveillance" to monitor up to 20 or more pre-specified safety outcomes of interest.[20]

Sophisticated customisation of databases and data capture aids have been implemented to support collection of these events. The Centres for Disease Control (CDC) have implemented VSafe[21] – an after-vaccination health checker, which is available on smartphones.

Text messaging or web surveys are used to provide personalised health check-ins after receiving the vaccination and can be used quickly to inform the CDC of any side effects based on the survey responses.

Signal detection, data sources

Signal detection is mandated for marketed products and involves assessing all available data regarding the product and the information in the MAH's safety database, including the individual case reports. If multiple studies are conducted in parallel for the authorised product, then non-safety-databased non-serious study cases should also be assessed in an aggregated manner on a routine basis as part of the signal detection process.

Careful analysis of individual case information during processing will allow for identification of more obvious safety concerns, while aggregate analysis will facilitate the identification of more subtle indications of safety concerns, even underlying severe problems and those which develop with long-term use.

In addition to the assessment of individual case safety reports (ICSRs) at case receipt, there are further requirements for signal detection for the vaccines. These include frequent periodic aggregate review of cases for trends and disproportionality analyses as well as observed-to-expected analysis.

Information from literature, products in class, publicly available and more extensive databases (VigiBase[22], FAERS[23], VAERS[24]) and many other competent authority websites containing alert information are considered and evaluated as part of the signal detection process.

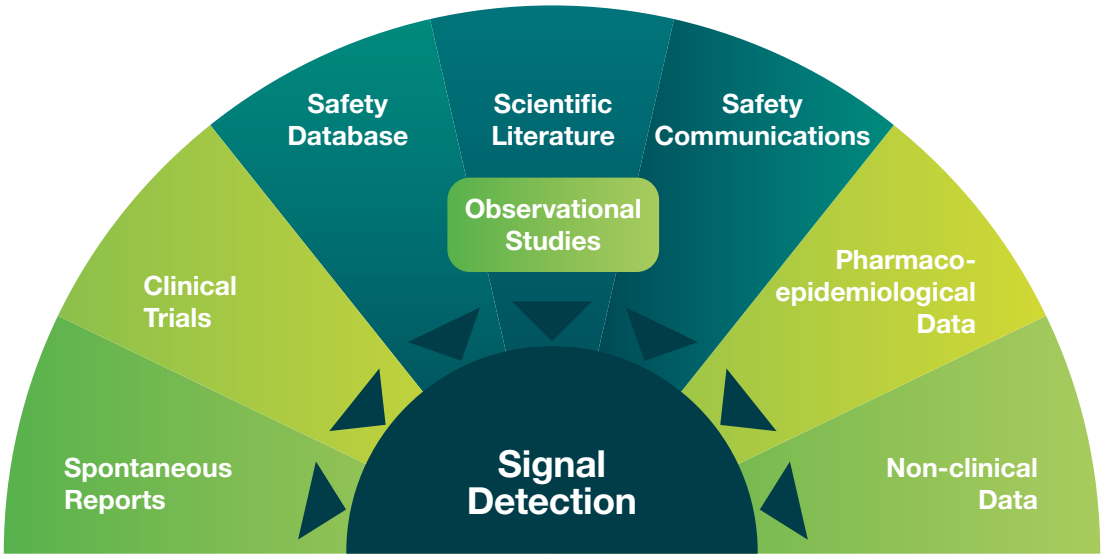
The signal detection activities should be able to detect differences in the vaccine's safety profile containing replaced or added strains, as compared with the original formulation approved.

Increased frequency for aggregate data analysis

MAHs periodically perform aggregate analysis of information from the safety database, in the context of the exposure data (how many patients have had the vaccination administered). They submit this analysis as mandated per regulations for authorised products in the form of Periodic Benefit-Risk Evaluation Reports (PBRER), Periodic Safety Update Reports (PSURs), or Periodic Adverse Drug Experience Reports (PADERs). These must be submitted at regular intervals.

For the COVID-19 vaccine, these periods are more frequent – safety information is assessed more often due to the nature of the vaccine. The accelerated approval was associated with a safety profile which was incomplete, as pertaining to data collected in association with long term safety and missing information, as compared with data acquired and assessed during standard approval.

Aggregate analysis is mandated by the requirement for monthly summary safety reports in addition to six monthly Periodic Safety Update Reports (PSURs). The focus of these PBRER/PSUR reports is ensuring that new information reported in the period is in keeping with the known benefit and risk profile of the vaccine as outlined in the product information. The safety data is analysed from the company safety database and includes severe and applicable non-serious AESI cases from studies and serious and non-serious cases from the post-marketed environment.

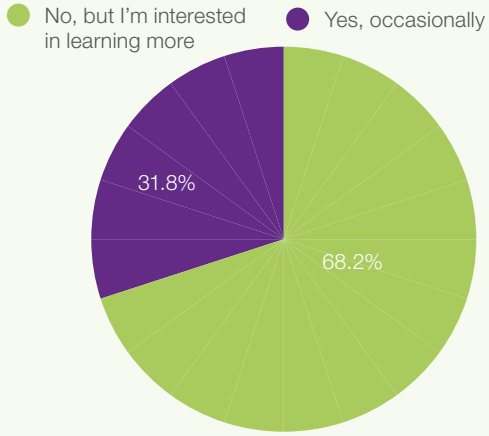


Signal management: Data assessment

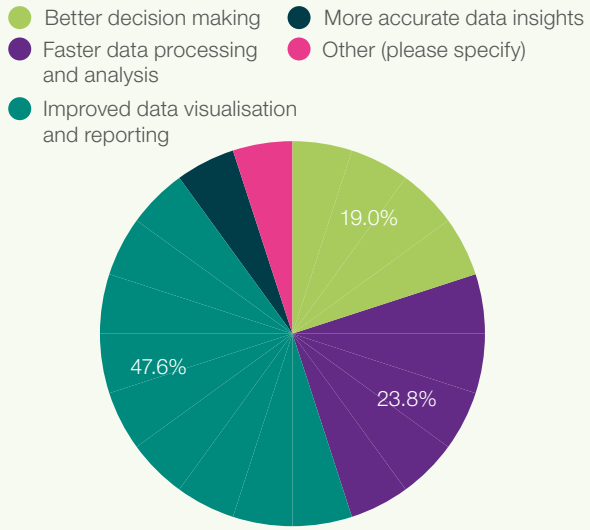
Business intelligence tools

During a recent webinar ICON hosted exploring the "Challenges in assessing long-term effects of COVID and COVID vaccines", we polled attendees on their usage of business intelligence tools to assist in analysing large public data sets. We found that, among respondents, there was significant interest in using these tools and that their primary benefits include improved data visualisation and reporting, faster processing and analysis, and improved decision-making.

Have you ever utilised a business intelligence tool to analyse a public data set?



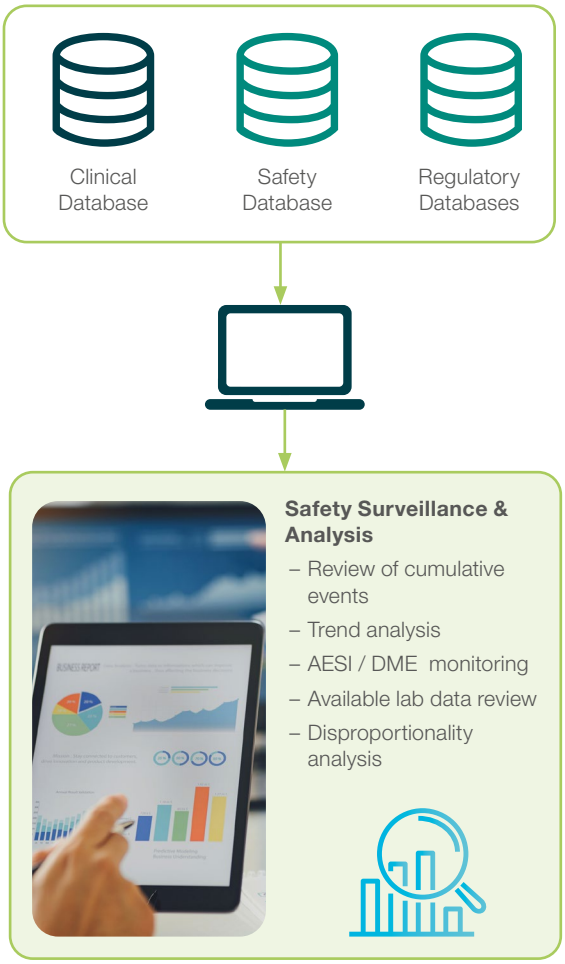
What is the benefit you have seen from using business intelligence tools for analysing public data sets?



Challenges with large data volume

As mentioned earlier, assessment of large datasets is part of signal management. It can pose several challenges, including data heterogenicity, data complexity and data volume. The volume of COVID related safety data is vast given the available data source – the vaccinated global population.

To address these challenges, various methods are used, including data mining, machine learning and statistical analysis. New technology such as ICON's SIGNET enhances all three methods and, by taking data from the safety, clinical or public safety databases, enables faster and more accurate analysis of safety data from a variety of data sources. Overall, a combination of these methods is essential to effectively manage and analyse large data in pharmacovigilance.



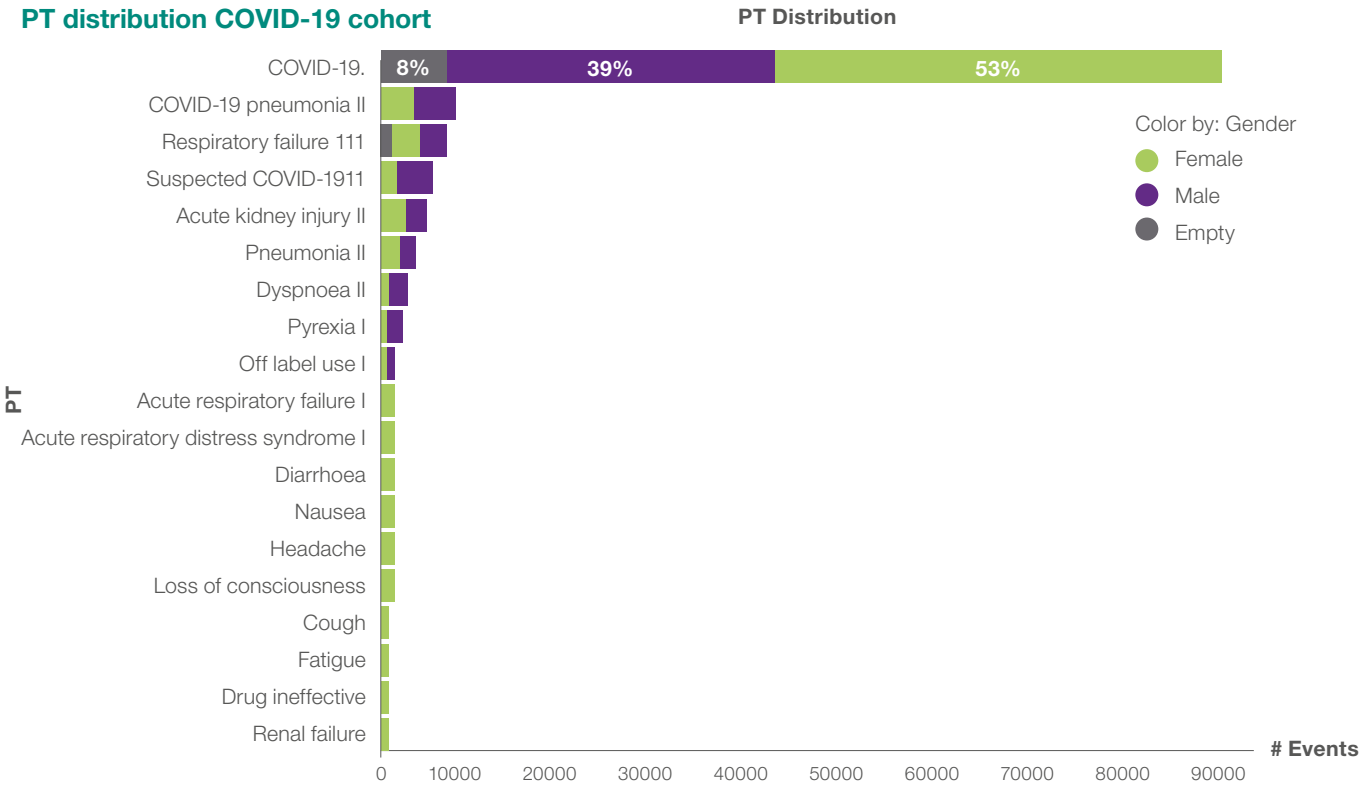
Assessment of large data volume – Automated solution use case

A good example of the methods and technology used for assessing large data sets is the use case presented during the webinar on “Challenges in assessing long-term effects of COVID and COVID vaccines” presented on 29 March 2023.

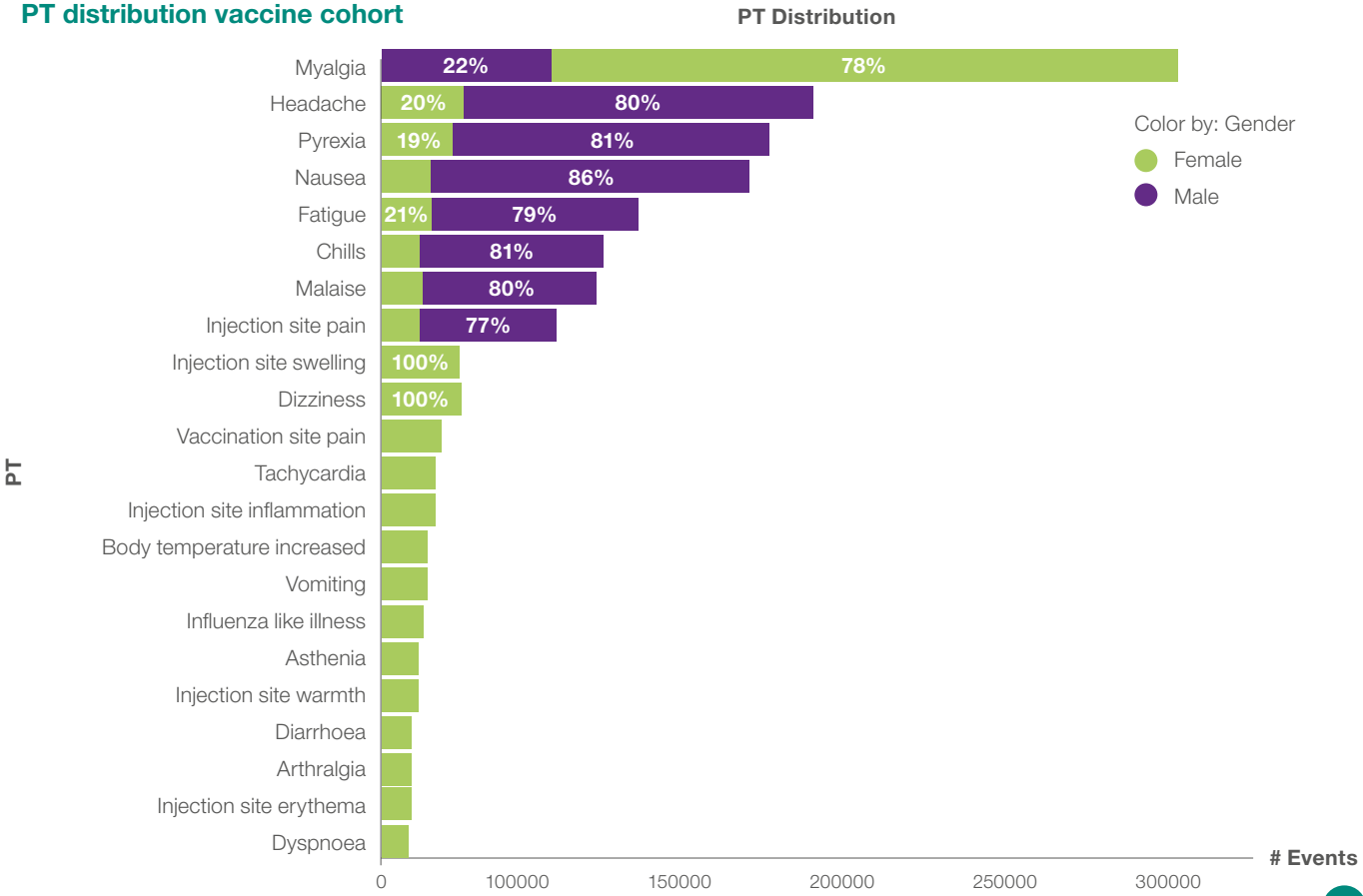
Our starting point was a very large VigiBase data set. The first step was to model the data and make sure we have a good overview of the data architecture, and that data is loaded properly in the system. Using clear natural language processing (NLP) criteria in SIGNET, we managed to identify the cohorts of interest. The interactive visuals provided us with an advantage to examine the data instantly and seamlessly with high granularity. Additionally, the system allowed us to create custom filters to better define cohorts or topics of interest.

After thoroughly comparing that data, two of the cohorts provided the best comparison; “Vaccine cohort” which included all patients who received one of the COVID vaccines. Defining this cohort presented a challenge, due to the numerous ways of coding the vaccine name, and we overcame this by applying the NLP search. The other cohort “COVID/COVID related symptoms” included all patients who have been reported to experience COVID and/or COVID related symptoms. SIGNET’s ability to create a custom filter allowed researchers to intersect the cohorts and have a glimpse in the profiles of patients who had a vaccine and experienced COVID. Overall, although we have not yet discovered any ground-breaking insights, this exercise helped us prove that with methods mentioned earlier and state of the art technology, we are able to tackle one of the main challenges in modern pharmacovigilance which is data size, type and availability.

PT distribution COVID-19 cohort



PT distribution vaccine cohort



Risk management and minimisation

The EMA requires Risk Management Plans (RMPs) to be submitted with the Marketing Authorisation Application. The RMPs contain information on the product's safety profile and how any known risks will be prevented or minimised in patients. They also outline any plans for routine and additional pharmacovigilance activities including studies (refer to Active surveillance – post-authorisation safety studies, interventional and non-interventional), plans to obtain more information about the product's efficacy and safety and details of how to evaluate the risk-minimisation measures.

Routine Risk Minimisation Measures (RMMs), and additional RMMs for some of the vaccines as per the risks associated with each individual vaccine, are in place to try to prevent the occurrence of any risk and to minimise the impact if it does occur. Relevant sections in the product information (SmPC, USPI) guide HCPs how to use the product appropriately and help to minimise the risks.

The Pfizer vaccine has the RMM for Myocarditis and Pericarditis, and the AstraZeneca vaccine required an update to the SmPC regarding the risk of thrombocytopenia and coagulation disorders.[25,26] Furthermore, a Direct Healthcare Professional Communication has been developed by both companies and published to alert healthcare professionals on the signs and symptoms of these risks.[26]

During post-marketing safety surveillance, MAHs may implement additional Risk Minimisation Measures to address any newly identified safety concerns and minimise risks to the vaccinated population.

For most approved vaccines, the safety concerns and additional Risk Minimisation Measures, per the approved EMA RMPs, are as follows:

Known risks per RMPs Module SVIII. Summary of safety concerns

Risk Type	Risk Name	Comirnaty	COVID-19 Vaccine Janssen	Nuvaxovid dispersion for injection	Spikevax	Vaxzeviria
Important Identified	Anaphylaxis	x			x	x
	Myocarditis and Pericarditis	x			x	
	Thrombosis with thrombocytopenia syndrome		x			x
	Guillain-Barré syndrome		x			x
	Thrombocytopenia, including immune thrombocytopenia		x			x
	Venous thromboembolism		x			
Important Potential	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	x	x	x	x	x
	Thrombosis					x
	Nervous system disorders, including immune-mediated neurological conditions					x
	Myocarditis and Pericarditis			x		
Missing Information	Use in pregnancy and while breast feeding	x	x	x	x	x
	Use in immunocompromised patients	x	x	x	x	x
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	x	x	x	x	x
	Use in patients with autoimmune or inflammatory disorders	x	x	x	x	x
	Interaction with other vaccines	x	x	x	x	x
	Long term safety data		x	x	x	x

Risk minimisation measures RMPs part V.3

Risk Type	Risk Name	Comirnaty	COVID-19 Vaccine Janssen	Nuvaxovid dispersion for injection	Spikevax	Vaxzeviria
Important Identified	Anaphylaxis	Routine			Routine	Routine
	Myocarditis and Pericarditis	Routine & aRMM			Routine	
	Thrombosis with thrombocytopenia syndrome		Routine & aRMM			Routine
	Guillain-Barré syndrome		Routine			Routine
	Thrombocytopenia, including immune thrombocytopenia		Routine & aRMM			Routine
	Venous thromboembolism		Routine & aRMM			
Important Potential	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	None	None	None	None	None
	Thrombosis					Routine
	Nervous system disorders, including immune-mediated neurological conditions					Routine
	Myocarditis and Pericarditis			None		
Missing Information	Use in pregnancy and while breast feeding	Routine	Routine	Routine	Routine	Routine
	Use in immunocompromised patients	Routine	Routine	Routine	Routine	Routine
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	Routine	None	Routine	Routine	None
	Use in patients with autoimmune or inflammatory disorders	None	None	None	Routine	None
	Interaction with other vaccines	Routine	Routine	Routine	Routine	Routine
	Long term safety data		None	None	None	None

Competent authority role

The information collected by the MAH is also mandated to be shared with the medicines regulators, routine signal detection and also monthly safety summary reports in addition to six monthly PSURs so they are kept informed and can also undertake their own assessments. Additionally, individual cases can be reported directly to the regulators, who will in parallel assess the data and perform their own analysis.

As mentioned above, the EMA also funded the ACCESS project (vaccine COVID-19 monitoring readiness) and works in collaboration with the University Medical Centre Utrecht, under which 22 organisations work together to monitor the benefits and safety of the new vaccines under a master protocol. In this regard, ACCESS has published background incidence rates for 26 AESI for COVID-19 safety monitoring. Processes have also been put in place by the FDA to monitor the safety of the vaccines with required post-marketing and pharmacoepidemiologic studies and the recommendation of a Pharmacovigilance Plan (PVP). The PVP documents the actions which will be taken to address all important identified and potential risks and missing information.[27]

Clinical perspective

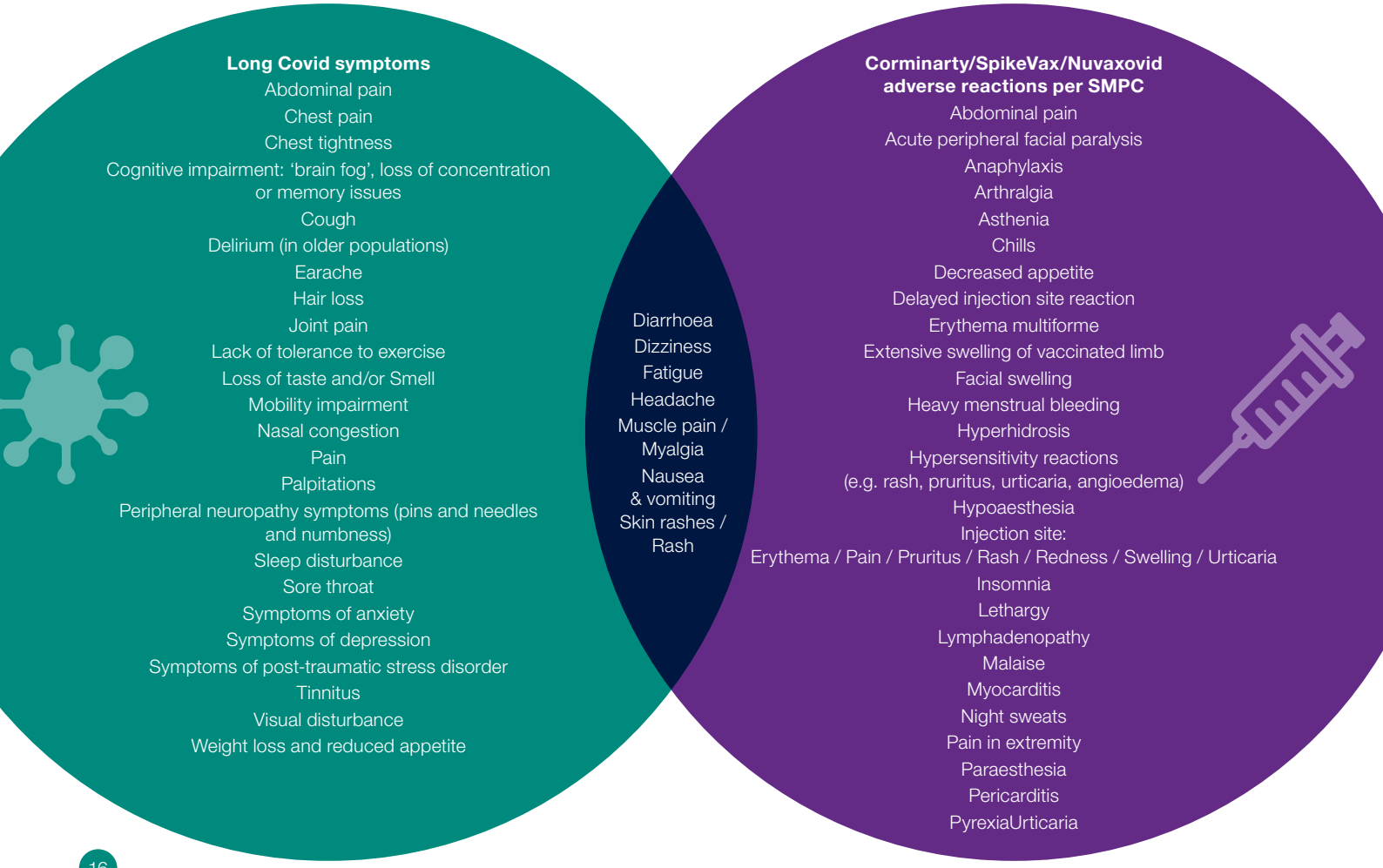
Although most patients who have suffered a COVID-19 infection recover fully within a few weeks, a proportion of patients continue to have symptoms for many months after the acute phase, known as long COVID. Clinicians face a number of challenges in assessing the effects of both conditions.

On the one hand, COVID-19 infection emerged suddenly as a new disease and the medical profession did not have clarity in how to respond. As clinical researchers became busy with identifying viable vaccines, HCPs were flooded with patients needing urgent care and were receiving disease and treatment advice in waves. As the various aspects of the disease became better understood, the advice given to patients adapted and changed over time.

Similarly, the new vaccines were distributed under emergency use authorisations, and we as healthcare providers lacked the years of experience we have with other vaccines. As such, we were unsure of the long-term implications – and we face difficulty in understanding them. For example, as most of the population has been vaccinated and has had COVID-19 infection, if a new symptom arises, we lack a control group to clearly identify the cause.

In addition, information on symptoms associated with COVID-19 may be missing as there are many patients who did not take the COVID test if their symptoms were mild. This may have been to avoid the self-isolation or may now be attributed to the cost of testing.

Furthermore, there are common and overlapping symptoms between long COVID and vaccine side effects, such as chest pain, increased risk of thrombosis and neurological symptoms.



Information overload and uncertainty

The media have played a crucial role in shaping the public's response to the pandemic, to the extent that they have become one of the biggest challenges for clinicians. The amount of information disseminated regarding COVID and COVID vaccines has been overwhelming. Continuous news stories tracking the number of infections and deaths or picturing the near collapse of hospitals around the world has fuelled public fear and anxiety. Additionally, the vast amount of misleading and non-evidence-based information circulating on the web stoked anxieties and vaccine hesitancy. This created great uncertainty among the population, which led to distrust in researchers, in the medical profession, in journalists and even in reputed institutions.

Patients harboured strong fears around death or prolonged illness, though some were afraid of COVID infections while others were afraid these symptoms would result from the new vaccines. Consequently, these fears shaped the ideas, concerns and expectations (ICEs) that patients bring to consultations with their clinicians.

Collecting and understanding patients' ICEs is a necessary though time-consuming process. It allows clinicians to address them and educate patients with facts on a scientific basis to help manage their uncertainty.

Diagnosis

Clinicians then proceed to make a diagnosis based on the symptoms described, the physical examination and the diagnostic tests. Special attention is paid to the timing of the events to correlate the reported symptoms with the administration of the vaccine or with the onset of the acute COVID-19 infection.

Clinicians compare the symptoms described by a patient with the summary of product characteristics of the vaccine and the symptoms recognised as long COVID and proceed to rule out any other possible explanation for them. As such, clinicians make a diagnosis of exclusion. It is critical to be certain that there is no other medical explanation for the patient's symptoms before attributing them to a side effect of the vaccine or to long COVID so that no medical conditions are missed. If any other medical explanation for the patient's symptoms is found, clinicians treat it accordingly.

Patients with suspected long COVID are referred to the post-COVID clinic for further investigation and/or support as appropriate.

Reporting side effects

Suspected side effects to the vaccines should be reported via the Yellow Card System in the UK. This is very important as the industry relies on the post-marketing reporting of side effects to continue safety surveillance.

There are many reasons why clinicians do not report as much as would be desirable:

– lack of time
– complexity of reporting
– fear of unnecessary reporting
– lack of feedback and understanding of the surveillance and safety process

For most of the clinicians, the clinical research industry behind the development of the vaccines is completely different than the one they operate in, so in their daily work, these reporting procedures may not be prioritised.

In the wake of the pandemic, we have discovered a key opportunity to improve communication between the clinical research industry and clinicians to enhance mutual collaboration for the benefit of our patients. Because, ultimately, the patient is always the highest priority.

Conclusion

The accelerated development and approval processes for the COVID-19 vaccine has enabled faster distribution of vaccinations against the virus, helping to reduce the burdens on global healthcare systems by curbing infection and hospitalisation rates. The vaccine allowed the world to begin recovering from the devastating pandemic but we are still working to understand the full extent of the wider health implications.

As the world adjusts to a 'new normal', work remains ongoing to monitor vaccine effectiveness against genetic variants, their evolving safety profile and the long-term safety of vaccine use. Acquisition and assessment of the associated large volumes of data are important determinants in ensuring the most accurate and up-to-date information is available so conclusions can be reached and appropriate actions taken.

Several post-authorisation safety surveillance studies are currently underway across the US and Europe and will be concluding this year with results that will bring us closer to understanding the long-term health impacts posed by the COVID-19 pandemic, including the nuances between long COVID and potential vaccine side effects.

Contact us

To learn more about how ICON can help you navigate the increasingly complex pharmacovigilance landscape.

Conclusion

Further reading

Whitepaper: Taking safety reporting to the next level with automation

Learn how combining pharmacovigilance expertise and deploying rule-based automation can drive timely delivery of drug safety information.

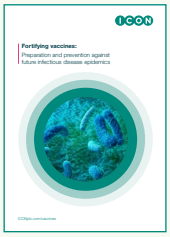
ICONplc.com/safety-reporting

Whitepaper: Pharmacovigilance affiliate model

Explore the benefits in adopting an outsourced model for pharmacovigilance that is centrally managed and geographically dispersed, ensuring efficient and compliant delivery whilst retaining the effectiveness of a local presence.

ICONplc.com/affiliatesolution
ICONplc.com/PSP

Whitepaper: Fortifying vaccines: Preparation and prevention against future infectious disease epidemics



Read to learn infrastructural and strategic considerations for strengthening vaccine development, in addition to strategies to improve the efficiency of vaccine clinical trials, including responsive trials, technology, and master protocols and adaptive trials.

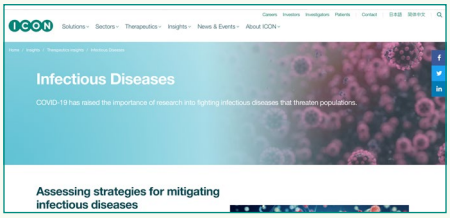
ICONplc.com/fortifying-vaccines

Factsheet: Rapid mobilisation advancing vaccine development

When fighting infectious diseases, speed is of the essence. Learn how ICON's ability to quickly mobilise without compromising on quality has been crucial in supporting clients to develop vaccines for a wide range of highly contagious and dangerous infectious diseases.

ICONplc.com/factsheet_Vaccines
ICONplc.com/therapeutics/vaccines

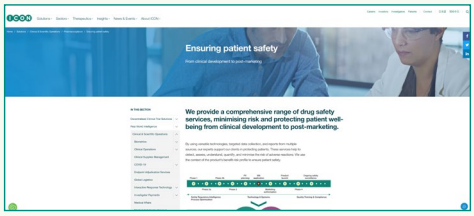
Webpage: Infectious diseases



The complex nature of regulatory safety reporting requirements demands a high level of expertise to ensure instant access to critical intelligence.

ICONplc.com/IDinsights
ICONplc.com/covid

Webpage: Ensuring patient safety



Learn how ICON's comprehensive range of drug safety services can minimise risk and protect patient well-being from clinical development through post-marketing.

ICONplc.com/patient-safety

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Together, we improve outcomes.

Our pharmacovigilance team bring together safety services into a seamless delivery solution that focuses on transparency, easy to review outputs, and with a strong focus on continuous quality improvement and operational efficiency.

ICON and You.
Partners making a difference.

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About ICON

ICON is the world's leading clinical research organisation, powered by healthcare intelligence. From molecule to medicine, we advance clinical research providing outsourced development and commercialisation services to pharmaceutical, biotechnology, medical device and government and public health organisations. We develop new innovations, drive emerging therapies forward and improve patient lives. With headquarters in Dublin, Ireland, ICON operates from 111 locations in 53 countries and has approximately 41,150 employees as of 1 August 2023.