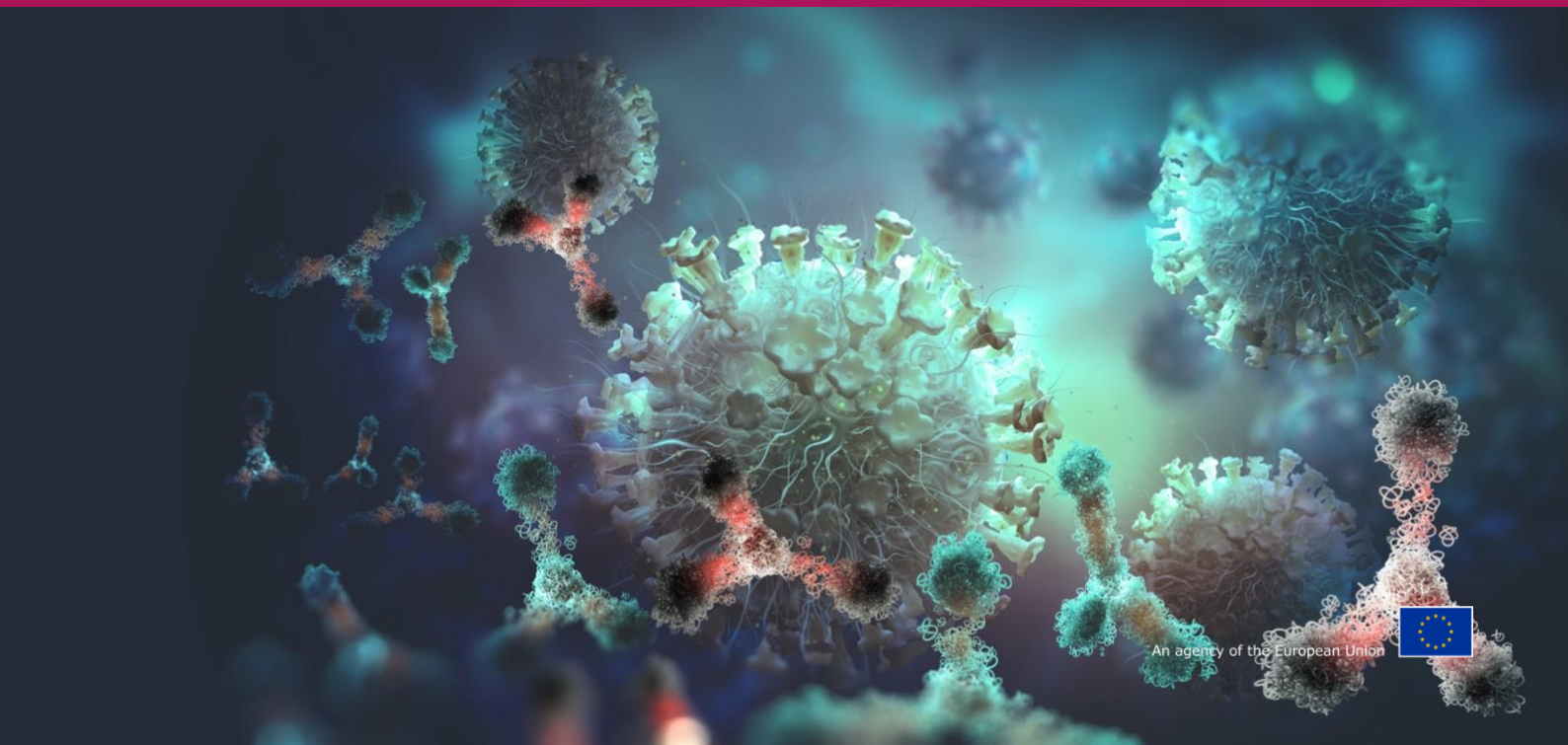
HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

COVID-19
Lessons learned

Joint report on the response to the Public Health Emergency



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Executive summary

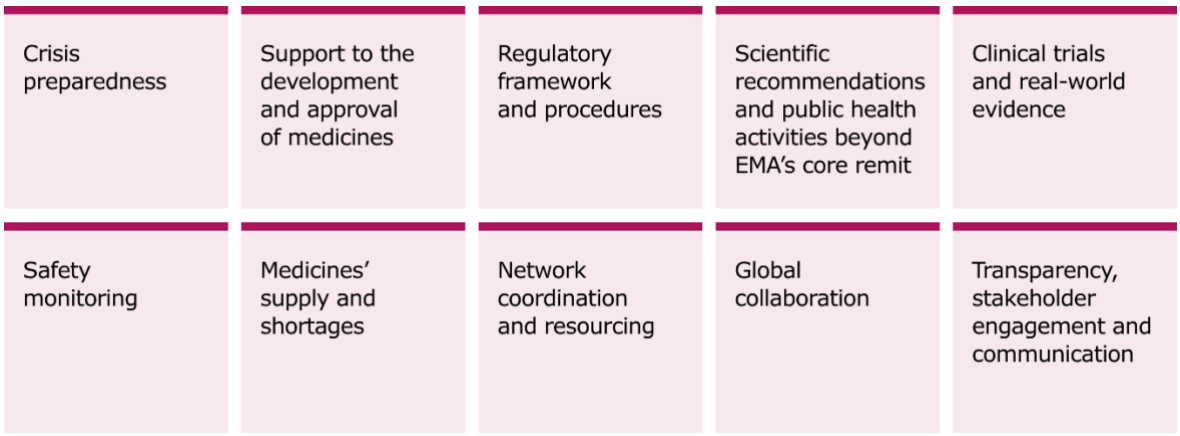
The World Health Organization (WHO) formally declared COVID-19 a public health emergency of international concern on 30 January 2020 and characterized the outbreak as a pandemic on 11 March 2020. It has been one of the longest and most intense health crises the EU has had to face in its entire existence.

The European Medicines Regulatory Network (EMRN or 'the EU Network') is the collaborative network comprised of the European Medicines Agency (EMA or 'the Agency'), the medicines regulatory authorities of the Member States (or National Competent Authorities, NCAs) and the European Commission (EC). During the pandemic, the EMRN has been a key player, not only due to its central role in authorising pandemic vaccines and therapeutics and monitoring their safety, but also due to additional tasks that were undertaken, such as crisis coordination activities, management of medicines shortages, provision of information on COVID-19 medicines and generation of reliable real-world evidence (RWE).

This report reflects the findings from a joint review of the activities and overall response to the emergency of the EU Network, which was carried out by EMA and the Heads of Medicines Agencies (HMA) of the NCAs. The report covers all areas relevant to crisis management and response (Figure 1), and offers learnings for improvements in the future through legislative and non-legislative actions to be implemented by the EMRN. Some actions are already being implemented as part of the revised EU legislation that extended EMA's mandate. Others are being followed-up as part of the broader ongoing review of the EU pharmaceutical legislation.

The report covers activities during the public health emergency phase of the pandemic, i.e., between 30 January 2020 and 5 May 2023. The ultimate goal of the lessons learned presented here is to draw from the experiences of the emergency phase of the COVID-19 pandemic to strengthen the EMRN's crisis preparedness and its ability to respond rapidly if the EU were confronted with another pandemic or health crisis of this magnitude, as well as to improve other future activities.

Figure 1: Areas where learnings have been identified to improve the EMRN's crisis response



The COVID-19 emergency context

The critical emergency phase of the COVID-19 pandemic extended over three years and was characterised by an intense prolonged crisis in terms of lives lost and pressure on healthcare systems. By September 2023, nearly 7 million official deaths had been reported to WHO, while over 26 million estimated excess deaths worldwide were linked to the pandemic. The pandemic created an unprecedented demand for safe and effective medicines to address the public health emergency, including existing medicinal products to treat severely ill patients and novel vaccines and therapeutics to prevent and treat COVID-19. Medicines shortages, which already existed in the EU before the pandemic, became much more acute and urgently required formal EU-wide coordination to oversee availability.

The EU Network initially relied on the pandemic preparedness plans and crisis management structures set up during previous public health emergencies and other health threats. However, the scale of the COVID-19 crisis necessitated extension of these structures and introduction of new elements to be able to coordinate and deliver an effective response. The majority of the EMRN's operations had to be conducted remotely during the height of the crisis. Although the switch to remote working was implemented successfully, it changed the Network's work dynamics and came at a particularly challenging time for EMA, as it was still settling in its new host country and rebalancing its human resources following the relocation to the Netherlands as a result of Brexit. Another challenge was the need to mobilise and coordinate large numbers of resources, such as assessors from the medicines regulatory authorities of the Member States, to cope with the fast-track assessment of new pandemic medicines while avoiding backlogs in procedures for non-COVID medicines. Public interest in EU regulators' work and demand for information and transparency also increased exponentially and regulators introduced additional transparency measures to meet these expectations, in order to build trust among EU citizens regarding the new medicines and vaccines authorised.

All these efforts created unprecedented challenges in terms of resource capacity and sustainability over such an extended crisis. Given the global and multifaceted impact of COVID-19, it became imperative to work closely with other EU bodies and international regulators, in particular through the International Coalition of Medicines Regulatory Authorities (ICMRA), a forum to support strategic coordination and international cooperation among global medicine regulatory authorities.

Methodology for analysis of lessons learned

EMA and HMA used a variety of methods to collect and analyse data and information on the response to the public health emergency. These included an internal analysis, dedicated workshops between EMA and HMA and discussions with EMA's Management Board and the newly-created Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG). The MSSG comprises representatives from EU Member States, a representative from the European Commission and an EMA representative, as well as observers. Other activities included EMA's contribution to the EC's lessons learned exercise which became the basis for the new regulation on EMA's reinforced role. In addition, the impact assessment process for the revision of the pharmaceutical legislation carried out by the EC through interaction with regulators, among other stakeholders, prompted a thorough analysis of the situation by all NCAs. Interaction with the European Centre for Disease Prevention and Control (ECDC) also took place, and other fora included the newly created informal EMA-HMA Tactical Group on resourcing. In parallel, the Agency discussed its early learnings and lessons learned exercise with NCAs and civil society representatives, including patients, citizens, healthcare professionals and industry stakeholders.

The EMRN's activities and lessons learned during COVID-19

In the context of the pandemic, the EMRN carried out a wide range of tasks that cover ten main areas and include preparedness, medicines regulation and other activities. The lessons learned are summarised below.

Crisis preparedness

EMRN's activities

Based on the learnings from the 2009 influenza H1N1 pandemic and the 2014 Ebola outbreak, EMA had already carried out work to prepare for an emergency before the COVID-19 pandemic started. EMA triggered its emerging health threats plan on 4 February 2020, after the WHO declared the novel coronavirus outbreak a public health emergency on 30 January 2020. This plan foresaw that if a large-scale emergency were declared, EMA would activate the pandemic Task Force (now called Emergency Task Force or ETF) to initiate the scientific and regulatory activities within the EMRN to support development, approval and safety monitoring of new therapeutics and vaccines. The ETF brought together the best expertise from the EMRN, including experts from NCAs and EMA. At those early stages of the pandemic, coordination with other EU bodies, international regulators and public health authorities (e.g., WHO) was already initiated by EMA before the ETF was set up. Based on the actions defined in the emerging health threats plan, EMA and NCAs established regular interactions with vaccine/therapeutic developers and experts. In addition, the interaction between the EU expert network on shortages (the SPOC network) and EMA was strengthened, as was the interaction of EMA-HMA with the EC and other EU bodies, stakeholder groups and international partners.

However, in view of the scale and duration of the global and sudden crisis affecting healthcare systems and society at all levels, further actions needed to be taken at the EMRN level in addition to the crisis structures foreseen under EMA's emerging health threats plan and Incident Management Plan. Specific new governance structures (e.g., EMA COVID-19 Steering Group) and additional discussion fora (e.g., EMRN meetings or discussions with the Chairs of EMA's scientific committees) were set up and some EU crisis structures, including the Health Security

Committee (HSC, a group of Member States on health security at European level led by DG-SANTE), intensified their activities and organised regular interactions with EU Member States, the EC, ECDC and National Immunization Technical Advisory Groups (NITAGs).

Analysis of crisis preparedness

The EU Network was ready to deal with the novel emerging health threat, and EU medicines regulators prioritised tasks and managed to carry out successfully all core regulatory activities despite the challenges and disruption brought about by the pandemic.

Early into the crisis it became clear that it was necessary to formalise some of the measures being put in place to provide a clear pathway for the EMRN's decision making on COVID–19–related matters, as well as for sharing information and supporting alignment of positions across the EU Network. To address this, the mandate of the Agency was extended in January 2022 to formalise the role of EMA and its interaction with the NCAs in the analysis and response to shortages across the EU. In addition, the ETF's role in supporting the therapeutic response was reinforced and formalised through this Regulation. The reinforced mandate is also critical to anticipate potential health threats that may escalate into a crisis.

The EU Network acted as promptly as possible on all the required actions while safeguarding its regulatory role. It is, however, also acknowledged that a crisis situation necessitates a specific regulatory framework and sufficient resources to sustain the rapid response. Proactive engagement in the research and development of medicinal products before an actual crisis is paramount to deliver regulatory decisions with public health impact as rapidly as possible. In the future, it is important to consider that crises like a pandemic can extend for a long period. The need to ensure that the European regulatory system is resilient and capable of responding to potential crises in the future is also being addressed in the review of the pharmaceutical legislation.

Key learnings

CRISIS PREPAREDNESS

- Crisis management processes, escalation routes and structures for preparedness to respond to future crises are being updated based on learnings from the COVID–19 public health emergency. This includes non-legislative and legislative actions, some of which are already reflected through EMA's extended mandate and the proposed revisions of the pharmaceutical legislation.
- It is important to further strengthen horizon scanning of potential health threats and relevant medical countermeasures, which is being pursued as part of the ETF's role in crisis preparedness.
- It is essential to have in place a leading structure (the ETF) to centralise relevant expertise from across the Member States to enable agile scientific and regulatory work; this has now been formalised through EMA's extended mandate. Prompt dissemination of the outcomes from this group to other relevant groups and Member State authorities is important, including relevant documentation upon request. Additional crisis structures may be needed, depending on the specific situation and the extent of the public health emergency.

- Coordination and information exchange with partners remains key and is established with other EU bodies, international regulators and public health authorities (e.g., the EC, ECDC and WHO).
- In preparedness for future crisis, the EU Network needs to have the capacity to ensure a sustainable response to an extensive crisis. A joint EMA-HMA tactical group on resourcing has been set up to work on reinforcing the capacity of the network, which is a crucial aspect of crisis management.

Support to development and approval of medicines

EMRN's activities

The EU Network rapidly activated a set of agile support measures for research and development of medicines via early teleconferences with the ETF, including an enhanced and proactive pre-submission dialogue with developers of COVID-19 medicines, and waived fees for scientific advice (SA). Through early interactions with developers, the ETF provided preliminary informal feedback on development plans and sufficiently mature medicinal products benefited from an expedited formal EMA scientific advice. Timelines for SA were reduced from the standard 40-70 days to no more than 20 days.

Developers also received guidance on the best methods and study designs to generate robust data for their investigational medicine or vaccine. Interactions with academic consortia and international bodies, discussing clinical trials (including platform clinical trials) and aspects such as endpoint and population selection, supported the advancement of repurposed and new medicinal products. A fast-track procedure was provided also for the evaluation of paediatric investigation plans (PIPs), which are compulsory plans describing how a medicine will be studied in children. PIPs must be approved before companies submit a marketing authorisation application. The timeline for PIP reviews was reduced from 120 to 20 days. In total, throughout the emergency phase of the pandemic, EMA successfully completed over 500 procedures, as indicated in Figure 2.

Figure 2: Numbers of rapid procedures during the public health emergency

	2020	2021	2022	2023	**Total**
Rapid SA completed	73	77	51	15	**216**
Rapid PIPs completed	6	41	27	20	**94**
ETF discussions with developers	50	37	44	14	**145**
Rolling review packages	9	31	12	6	**58**
Initial Marketing Authorisation Applications	2	6	4	1*	**13**
Extensions of indications	1	4	10	5	**20**

(*) application was withdrawn

The exceptional context of the pandemic required special regulatory considerations for fast–track approval of medicines, while ensuring they still met the same quality, efficacy and safety standards. In order to clarify requirements for development of COVID-19 vaccines, EMA also published guidance, outlining the clinical evidence required for the approval of vaccines (see section on Regulatory framework procedures).

Approval of vaccines

Figure 3: COVID-19 vaccines and indications approved

Vaccine	Platform*	Strain	Population ≥6 months	Population ≥5 years	Population ≥12 years	Population ≥18 years
Comirnaty (BioNTech)	mRNA	Original strain	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)***			✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Omicron XBB.1.5 variant (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
Spikevax (Moderna)	mRNA	Original strain	✓ 6 months to 5 years	✓ 6-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)***		✓ 6-11 years	✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Omicron XBB.1.5 variant (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
Vaxzevria (AstraZeneca)	Adenoviral vector	Original strain				✓
Jcovden (Janssen)	Adenoviral vector	Original strain				✓
Nuvaxovid (Novavax)	Protein	Original strain			✓	✓
		Omicron XBB.1.5 variant (adapted**)			✓	✓
COVID-19 Vaccine Valneva (Valneva)****	Inactivated	Original strain				✓ 18-50 years
VidPrevtyn Beta (Sanofi Pasteur)	Protein	Beta variant***				✓
Bimervax (HIPRA Human Health S.L.U.)	Protein	Alpha + Beta variants***			✓ 16-18 years	✓

* Available platforms: See Figure 4 below

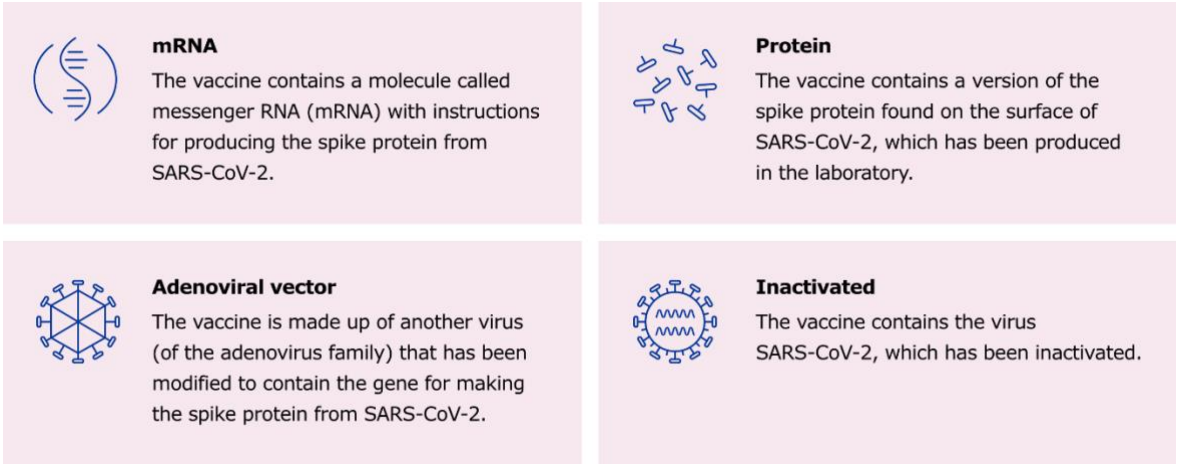
** Adapted vaccines

*** Only used as boosters

**** The marketing authorisation for COVID-19 Vaccine Valneva was withdrawn on 1 December 2023 following a request from the marketing authorisation holder

From 2020 to 2023, eight COVID-19 vaccines have been approved in the EU (Figure 3), including several using novel platform technologies. The initial vaccines targeted the original Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) and, later, its variant strains. The evaluation and approval of these vaccines in very short timeframes, while maintaining strict regulatory oversight, represents a milestone for the EMRN. It not only highlights the value of pooling resources among the EU Network and collaborating in an emergency context, but also enabled prompt availability of vaccines for citizens in all Member States.

Figure 4: Available platforms



Approval of therapeutics

Eight therapeutics were approved between 2021 and 2022, including 5 new or repurposed monoclonal antibodies (MABs) or MAB combinations, as well as 2 new antivirals (Figure 5).

Figure 5: Therapeutics approved for COVID-19

Mechanism of action	Treatment	Status
Monoclonal antibodies targeting the Spike protein	**Evusheld** (tixagevimab / cilgavimab)	Marketing authorisation granted: 25/03/2022
	Regkirona (regdanvimab)	Marketing authorisation granted: 12/11/2021
	Ronapreve (casirivimab / imdevimab)	Marketing authorisation granted: 12/11/2021
	Xevudy (sotrovimab)	Marketing authorisation granted: 17/12/2021
Antivirals	**Paxlovid** (PF-07321332 / ritonavir)	Marketing authorisation granted: 28/01/2022
	Veklury (remdesivir)	Marketing authorisation granted: 03/07/2020
Immunomodulators	**Kineret** (anakinra)	Marketing authorisation for COVID-19 indication granted: 17/12/2021
	RoActemra (tocilizumab)	Marketing authorisation for COVID-19 indication granted: 07/12/2021

Scientific opinions on investigational medicines needed by Member States

During the public health emergency, EU-wide scientific opinions were prepared to support national decision making on the possible use of certain medicines before a formal authorisation was issued (under compassionate use, Art. 5.3 or Art. 18 reviews). This was warranted in light of rising rates of infection and deaths due to COVID-19 and the need to communicate rapidly the official scientific views to the public and the Member States. These opinions were generally based on preliminary data from ongoing studies at the time.

Figure 6: Number of procedures on investigational medicinal products before authorisation was granted

Compassionate use	**1**
Art. 5.3	**7***
Art. 18	**1**

(*) an Art. 5(3) was also done for Vaxzevria in the post-authorisation phase

Analysis of support to development and approval of medicines

Through early dialogue with developers, the EMRN had a good oversight of the COVID-19 medicines pipeline so that the EU Network's resources could be directed to the most mature and promising candidates. Developers requested and rapidly received the advice needed. However, providing such intense early support required considerable EMRN resources from the NCAs and EMA. Rapid sourcing of specific expertise became challenging due to workload, which also impacted other procedures (e.g., scientific advice for non-COVID medicines).

EMA had set up internal processes for information exchange and coordination between the ETF and EMA's Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC). However, due to urgency, at times the coordination and information flow was difficult, and this is being adapted based on experience (e.g., the refined role of the ETF in the scientific advice process under EMA's extended mandate). Availability of data for regulatory decision making was crucial and presented its own challenges (see section on Clinical trials and real-world evidence).

In addition, it's well established in the medical literature that pandemic viruses leave sequelae beyond the acute phase. SARS-CoV-2 infections have demonstrated to cause a wide range of long-term health problems and organ damage (long COVID or 'Post-Acute Sequelae Condition (PASC)') in substantial numbers of people. This still poses challenges regarding the definition of the condition(s), establishing its pathophysiology and identifying treatments.

Key learnings

SUPPORT TO DEVELOPMENT AND APPROVAL OF MEDICINES

- Obtaining comprehensive and systematic information relevant to the development of medicines is key for providing additional development support efficiently. This is being further strengthened through the ETF's work in preparedness and in cooperation with partners.
- In crisis situations, it is important that regulators provide agile feedback and engage in regular dialogue with medicines developers, and this is now strengthened and formalised through the ETF in EMA's extended mandate. Informal communications with developers, academic groups and international stakeholders are crucial to adequately triage the level of regulatory support needed.
- To maintain efficient use of available resources, it is necessary to prioritise, in consultation with the ETF and EMA's scientific committees, the rapid assessment of

the most promising candidate medicines, taking into account the urgency for public health.

- Further reflections are warranted on how to ensure that the level of maturity of product developments and any potential major blocking factors are considered up front, to avoid premature reviews or slow progress of applications (e.g., due to low-quality data) that take away available resources from other assessments. Steps are being considered also as part of the revision of the EU pharmaceutical legislation.
- There is a need to plan for work also beyond the emergency period, to address long-term effects of the pandemic, such as the need for medicines for long COVID.

Regulatory framework and procedures

EMRN activities

The public health emergency demanded fast-track assessment of medicines and rapid approval. For these cases EMA had already foreseen an appropriate tool for exceptional cases in its health threats plan: the rolling review. It was used throughout 2020-2023 and allowed EU experts to scrutinise the data from ongoing studies on a medicine or vaccine as soon as it became available, and before a formal marketing authorisation application was submitted. Once it was established that sufficient data were available, the company submitted a formal application, which was then processed under an exceptionally shortened timetable, much faster than the standard 210 days, as most of the data had already been assessed during the rolling review.

The EU legislation allows medicines to be authorised based on less comprehensive clinical data when they address an unmet medical need and available data show a positive benefit-risk profile. During the public health emergency such a conditional marketing authorisation (CMA) was used to expedite the approval of urgently needed treatments and vaccines. Rather than collecting the results of all the studies supporting an application that are normally required over a period of years, a marketing authorisation can be obtained as soon as enough data become available to demonstrate that a medicine's benefits outweigh its risks. While a CMA is a tool to speed up the approval process, it also guarantees that medicines assessed comply with EU standards of quality, safety and efficacy with robust safeguards. The remaining data are detailed in specific obligations and are required to be provided by the company post-authorisation, giving the EU authorities the confidence to recommend population–wide roll-out across the EU.

Analysis of regulatory framework and procedures

The use of CMAs and rolling reviews resulted in expedited authorisation of new COVID-19 medicines, including vaccines. However, workload increased considerably due to the very short assessment timelines and intense effort to review data as they became available on a continuous basis. This exceptional situation placed additional workload pressure on assessors from the NCAs who were managing several procedures simultaneously. This was made more challenging in cases where applications were filed prematurely and reviews started but did not progress because companies were unable to provide key data required for a formal marketing application and subsequent evaluation.

The CMA is a valuable tool. However, it would be desirable to expand the regulatory tools available in emergencies to enable further flexibility. An emergency use authorisation route that could allow even earlier access to medicines is currently not available at EU level, and in some instances Member States used their own provisions (based on Art.5 of Directive 2001/83) to grant access to a treatment in emergency settings before formal approval in the EU. This was sometimes supported by EMA's review of the data at EU level (see section on Support to development and approval of medicines).

Regulatory flexibility was successfully applied to ensure timely availability of medicines (e.g., waiving certain compulsory language requirements in the labelling or facilitating the introduction of certain changes to increase supply capacity, see section on Medicines supply and shortages).

EU regulatory procedures to implement changes to the original marketing authorisation post-marketing (e.g., adding a new indication or a new pharmaceutical form) were also fast-tracked. Pharmacovigilance procedures focused on safety aspects and the need for broader discussion around the benefit-risk profile resulted in another procedure being triggered on one occasion (i.e., an Art 5.3 procedure). In order to address this, cooperation between CHMP and PRAC was enhanced further, including the participation of leading experts in the discussions of the other committee and the involvement of committee Chairs from both scientific committees in crisis-response discussions.

Key learnings

REGULATORY FRAMEWORK AND PROCEDURES

- Earlier medicines availability might be enabled by the introduction of an EU level mechanism such an emergency use authorisation, which would provide more flexibility and complement the regulatory tools available for use during a crisis. A Temporary Emergency Marketing Authorisation (TEMA) is currently under consideration in the review of the EU pharmaceutical legislation. Such an authorisation mechanism, which would complement the CMA, should still maintain the safeguards that are part of the CMA.
- The rolling review has proven to be a key tool enabling prompt regulatory assessment outcomes. The use of this tool should be maintained in future crises, using more selective criteria to determine the pace of rolling review for different investigational products and excluding premature submissions, to ensure optimal use of available resources at NCAs and EMA.
- Outside the context of public health threats, the stepwise early review of available data may also be considered for a limited number of high priority medicinal products that address unmet patient needs (e.g., PRIME). Also in this context, it will be critical to define and use selective criteria and exclude premature submissions, to ensure optimal use of available resources at NCAs and EMA.
- A further update of EMA's health threats plan is foreseen. It will revisit the process for rolling review and other accelerated procedures to be used in a crisis context to maximise the speed and efficient use of available resources.

Scientific recommendations and public health activities beyond EMA's core remit

EMRN activities

When EMA, through its scientific committees, completes its evaluation of a marketing authorisation application and, with an EC decision, the medicine is approved for use, the conditions of use for the medicine are reflected in the EU product information, which contains the prescribing information (or Summary of Product Characteristics) and the patient leaflet. When needed, EMA also issues an accompanying public health communication to patients and healthcare professionals. During the public health emergency, it became necessary for EMA to issue public health communications on the use of medicines outside of regulatory procedures and before sufficient data were available to justify a change to the product information. In some cases, this need was triggered by external requests for EMA to address issues beyond the formal core mandate of the Agency (e.g., vaccination decisions or emergency use of a novel medicine before its evaluation was concluded by EMA). For example, an ETF review of scientific evidence was used to agree on an EU-level scientific position on the use of hydroxychloroquine or chloroquine to treat COVID-19 patients off-label. Another example concerns requests for analysis of real-world data from vaccination of different target groups to guide decisions on the use of Vaxzevria in national vaccination programmes. In these instances, the ETF reviewed the available data and contributed to public health communications, often jointly with ECDC. Cooperation was also developed through ECDC with NITAGs to work jointly on questions received by EMA concerning vaccination policies. Such policies fall under national remit, but considering the extraordinarily large vaccination campaigns and the often diverse recommendations across Member States, an EU-level scientific opinion was warranted to align recommendations and address any uncertainties.

Analysis of recommendations and activities outside regulatory procedures

EMA, sometimes in collaboration with ECDC, provided timely recommendations on very important public health aspects that went beyond its core mandate when a single EU scientific voice was needed (e.g., timing of booster doses, vaccine effectiveness against new variants, repurposing of existing medicines for COVID-19 indications). The availability of information on such issues was often limited and sometimes the Agency had to rely on data from non-EU countries, academic studies or preliminary studies. Engaging in activities beyond the formal legal mandate in an emergency setting (i.e., for providing public health advice or for the approval of a medicine for emergency use without the full data package usually required for regulatory approvals; see also section on Support to development and approval of medicines) deviates from the usual assessment based on standard data requirements. This at times posed challenges for assessors of the national regulatory agencies (i.e., members of EMA's CHMP and PRAC). In this context, the ETF was pivotal in making recommendations outside of the formal regulatory authorisation procedures and in areas where the Committee's mandate was limited. The role of the ETF in providing sufficient flexibility to respond to these demands outside of regulatory procedures was subsequently formalised in EMA's extended mandate.

Key learnings

SCIENTIFIC RECOMMENDATIONS AND ACTIVITIES OUTSIDE REGULATORY PROCEDURES

- Finalising, through the ETF, an EU scientific position on urgent matters not subject to formal regulatory procedures was key for an agile EU response. This possibility should be maintained and further developed for future crises, but also in a broader public health context. It is important to provide the ETF with an adequate mandate to support such recommendations.
- Engagement in activities beyond EMA's core regulatory activities might be needed, also in the future, when dictated by urgent and critical public health needs. Increased interaction with academia, governmental bodies and non-governmental organisations should be foreseen.
- Ongoing work should continue to further strengthen the framework for cooperation with the EC, ECDC, and national non-regulatory bodies, including NITAGs, as well as other decision makers such as Health Technology Assessment bodies (HTAs).

Clinical trials and real-world evidence

EMRN activities

In March 2020, a large number of clinical trials were taking place across Europe when COVID-19 restrictions were imposed. Limitations in hospital access for patients with non-COVID diseases meant that study protocols had to be changed, requiring regulatory approval. The EMRN provided developers of medicines with urgent guidance on how to conduct clinical trials in these circumstances, such as in a situation where participants could no longer attend follow up appointments in person. EMA, through the work of its working parties and scientific committees, also provided guidance on methodological aspects with respect to acceptance of data generated in an emergency context to ensure data integrity.

COVID-19 trials took place during the transition phase from the Clinical Trials Directive 2001/20/EC to the Clinical Trials Regulation (EU) 536/2014. This, however, did not pose major issues in practice since most trials during the pandemic were conducted under the directive.

Due to the urgency and extent of public health needs during the pandemic, evidence on COVID-19 medicines stemming from real-world settings became pivotal to drive regulatory and policy decisions. EMA used real-world data from clinical practice to monitor the safety and effectiveness of COVID-19 treatments and vaccines and of other medicines used for COVID-19. EMA contracted academics specialised in observational research to conduct several independent studies, including early safety monitoring studies of COVID-19 vaccines (ACCESS project), studies assessing the impact of COVID-19 infection and medicines in pregnancy (COSIGN project) and studies on coagulopathies and use of antithrombotic agents in patients with COVID-19. In addition, different NCAs also conducted pharmacoepidemiological studies on COVID-19 vaccines at national level, for which references are collected in the EU PAS Register. For instance, several studies have been conducted using BIFAP, the Spanish database of

electronic medical records, and the French National Health Data System linked to the COVID-19 vaccine database.

This context provided a strong case for the DARWIN EU project and also highlighted the need for more publicly funded post-authorisation studies, in particular on vaccines. Such studies are key to generate adequate evidence to continuously re-assess the benefits and risks of the vaccines and inform decision making on their use in national or regional vaccination strategies for different populations. As a first step, EMA signed a contract with academia in 2020 to set up an infrastructure to analyse real-world data. In 2021, EMA and ECDC agreed on a new initiative aimed at coordinating these studies jointly. A further step was taken in 2022 with the launch of the Vaccine Monitoring Platform, which is now part of EMA's extended legal mandate.

Analysis of clinical trials and real-world evidence

Continuing ongoing clinical research for non-COVID medicines was challenging. Clinical research for COVID-19 medicines was frequently fragmented, with small, underpowered studies, or otherwise sub-optimally designed for providing robust results, and on occasion developers did not follow the recommendations provided during EMA's scientific advice. Furthermore, large multinational clinical trials that could have been impactful started too late. This emphasises the importance of enhancing coordination of EU-funded initiatives and the approval process of clinical trials of medicines targeting COVID-19, including the prioritisation of investigational medicines and vaccines for inclusion in clinical trials, with support from the EMRN. Regulatory delays were caused in particular by a lack of coordination between national ethics bodies and between those bodies and NCAs. A workshop on clinical trials in public health emergencies was hosted by the EMRN in June 2023 and revealed key learnings for operating in emergencies. Improvements in coordination of clinical research in emergency situations are being tackled through several ongoing initiatives on clinical trials, such as the acceleration of clinical trials through ACT EU, the ETF's cooperation with the Clinical Trials Coordination Group (CTCG), the European Partnership on Pandemic preparedness and the discussions on Clinical Trials in Public Health Emergencies.

Further discussions on trial methodology, in particular for adaptive platform trials, will need to be pursued in preparation for possible future emergencies through ACT EU and at the ETF.

The pandemic also exposed the crucial need for more and better data and scientific evidence to guide decision making, e.g., regarding the use of vaccines and therapeutics in the different populations and age groups, the duration of protection or vaccine effectiveness against newly-emerged virus variants. During the public health emergency, it was difficult to gather mass vaccination campaign data promptly to confirm safety and effectiveness of the new vaccines in the routine care setting, for example to support use in special populations, such as immunocompromised individuals or pregnant women. The options for prompt new subgroup analyses based on individual patient data from clinical trials were also limited. Crucial data often came from stakeholders other than companies, for example from healthcare providers with advanced data collection systems outside the EU (e.g., Israel or USA) and from independently funded academic studies. In the EU, not all Member States were able to collect data and when they did, there were differences in the type and format of data collected which made analysis at EU level difficult. RWE studies from the EU were often completed later than those from the USA or Israel as the governance, data access, contracts and methods for effectiveness studies were only put in place after the start of the pandemic. There were a few large studies (including an EMA-funded study coordinated by the Danish Medicines Agency (DKMA)), but these came late.

It is critical to proactively establish RWE networks, with appropriate governance (including data access agreements), study methods and contracts in place, as once a public health emergency starts, results are required before these can be put in place.

Looking ahead, as collection of real-world data and public procurement of studies (e.g., through DARWIN EU and the Vaccine Monitoring Platform) is strengthened, it will be important to prioritise and coordinate studies between EMA, ECDC, Health Emergency Preparedness and Response Authority (HERA) and national bodies.

Another important learning from the crisis is the need to anticipate potential pandemic trails and disease sequelae that can lead to a demand for clinical trials on new medicines or repurposing of existing ones. Increased interaction with academy-led clinical trial networks is needed to make sure such clinical trials will satisfy regulatory requirements and preparatory activities should be initiated before a public health emergency starts.

Key learnings

CLINICAL TRIALS AND RWE

- Conduct of large clinical trials that are sufficiently powered and methodologically sound remain indispensable for prompt and well-informed regulatory decision making. Therefore, efforts are continued to facilitate and support them, in cooperation with Network partners (e.g., CTCG, ACT EU and workshop on clinical trials during emergencies).
- Regular interactions with clinical trial networks in the EU and more globally are needed to agree on the design of platform clinical trials in inter-epidemic periods.
- It is important to proactively put infrastructure in place for RWE studies and identify early the need for such studies.
- It is important to continue developing the framework and planning for obtaining the necessary EU data from sources beyond companies (e.g., healthcare data). Proactive investment in data, networks and methods is needed to prepare for future public health emergencies, as well as long-term funding for independent vaccine studies. This is being pursued in initiatives such as DARWIN EU and the Vaccine Monitoring Platform.
- Particular efforts should focus on obtaining data post-authorisation in a timely manner and in populations where generation of evidence was challenging during the pre-authorisation phase (e.g., immunocompromised individuals, pregnant women or specific paediatric populations).
- Due to the increased use of real-world data and evidence, it is necessary to continue increasing expertise on their use in the EMRN, including investing in human resources.
- It is also desirable to pursue ongoing efforts to develop capacity to have access to and analyse individual patients' data from clinical trials.

Safety monitoring

EMRN activities

The EU has a comprehensive safety monitoring and risk management (pharmacovigilance) system, which ensures measures are in place for detecting any potential new risks, conducting rigorous scientific assessments of all safety data and introducing any necessary mitigating actions early on. The safety of all EU medicines is monitored according to guidance set out by EMA and NCAs in the good pharmacovigilance practices (GVP). After COVID-19 medicines, including vaccines, were first approved and introduced in clinical use, regulators needed to ensure close safety and effectiveness monitoring of these new medicinal products. Thus, a strengthened system was put in place to collect and monitor the unprecedented volumes of safety data. To ensure that all new information, collected post-marketing from extensive vaccination campaigns worldwide, was promptly reviewed and any emerging new information was shared with the public in a timely manner, EMA and NCAs agreed on an additional pharmacovigilance plan for COVID-19 vaccines. This included additional measures for companies, who had to submit monthly summary safety reports (SSRs) in addition to the periodic safety update reports foreseen by the legislation, given the mass vaccination campaigns launched across the EU.

EMA's pharmacovigilance system enabled the EU network to take necessary actions as new data emerged, confirming that it is robust and fit for purpose. One example is the prompt identification of a very rare and serious thrombotic adverse events associated with Vaxzevria, which triggered immediate regulatory action from EU regulators.

EMA also issued guidance (coreRMP19) to support pharmaceutical companies' preparation of risk management plans (RMPs) for COVID-19 vaccines. It covers specific aspects such as vaccine safety in special populations, including pregnant women, elderly or patients with co-morbidities. EMA leveraged different types of data for the post-authorisation safety follow-up of COVID-19 vaccines by companies, ranging from spontaneous reports from patients and healthcare professionals to real-world data. Such real-world data were obtained through the above-mentioned academic studies and private partners (e.g., ACCESS and COSIGN projects) and EMA also funded independent safety studies to further support swift regulatory action to protect public health when needed.

Analysis of safety monitoring

Strategies to help tailor existing pharmacovigilance measures (such as SSRs reviewed monthly in addition to PSURs and near-real-time review of spontaneous reports) enabled timely assessment of rapidly accumulating safety information. Monthly SSRs supported monitoring of Adverse Events of Special Interest (AESIs), which are very rare but serious adverse events (e.g., myocarditis/pericarditis or anaphylaxis). Some of these very rare and potentially fatal adverse events required dedicated expert meetings, in particular with academia and clinicians, to elucidate the pathophysiology and better understand these events (e.g., Thrombosis with thrombocytopenia syndrome (TTS) and myocarditis workshops).

The functionality of available IT tools for analysing Eudravigilance data could be enhanced to better customise the reports and allow automatic data searches. The unprecedented volumes of safety reporting (Individual Safety Case Reports, ICSRs), over a short period of time, led to challenges in processing ICSRs, both by national regulators and industry, which required

mitigation measures. EMA and the wider EMRN worked intensively and deployed additional resources to tackle the high workload.

Once COVID-19 medicines were used in millions of people outside the controlled setting of clinical trials, detection and evaluation of potential safety signals allowed the identification of very rare side effects. Out of the millions of safety reports submitted by citizens and healthcare professionals to the national pharmacovigilance systems and by companies, all of which are collected in Eudravigilance, only a few were confirmed as new safety signals not detected during clinical trials (2022 Annual pharmacovigilance report; 2021 Annual pharmacovigilance report). Real-world evidence also proved critical in the evaluation and contextualisation of safety issues. However, the spontaneous reporting programme remains the main pillar on which the detection of new risks is based, and the Network needs to continue investing resources in such programmes.

Key learnings

SAFETY MONITORING (PHARMACOVIGILANCE)

- The EU pharmacovigilance system is robust, fit for purpose and has been particularly efficient in promptly identifying and dealing with emerging issues during the pandemic.
- Spontaneous safety reports submitted by vaccinated individuals and healthcare professionals were crucial for early detection of emerging safety concerns. Work should continue to raise awareness and strengthen the spontaneous reporting programme.
- Access to high quality and fit-for-purpose real-world data (e.g data from EU healthcare systems) in a timely manner in various EU countries should be further reinforced to complement the monitoring of vaccines' safety, risk contextualisation and rapid evaluation on the impact of the risk-benefit balance.
- COVID-19 emphasized the value of a robust yet flexible signal management process, from data analysis to committee discussion and communication on a particular signal.
- There is room to further modernise EU Pharmacovigilance IT tools for increased data integration to support advanced analytics, group risk assessment, data visualisation and communication.
- For safety studies, preparedness necessitates networks of data sources in place (e.g., Vaccines Monitoring Platform) to monitor safety and effectiveness of pandemic vaccines. This requires collaboration of industry with public health bodies, ECDC, EMA, etc.
- Besides observational studies to determine the incidence of adverse reactions, studies to ascertain the pathophysiological mechanisms leading to AESIs need to be conducted to provide adequate management and mitigation strategies.

Medicines supply and shortages

EMRN activities

Ensuring the continued availability of medicines for European patients during the pandemic posed difficulties. Most medicine shortages are normally dealt with at national level. However, during the pandemic, as medicine shortages reached exceptional levels, an executive steering group was established within the Agency to ensure a robust response to major events and to coordinate urgent actions related to the supply of medicinal products. Newly created in March 2020 in response to the emerging crisis, the EU Executive Steering Group on Shortages of Medicines Caused by Major Events (now called the Executive Steering Group on Shortages and Safety of Medicinal Products or MSSG), composed of a representative of the Agency, a representative of the Commission and one representative of each Member State, provided strategic leadership for urgent and coordinated action. The MSSG's role on medicines shortages is supported by the Medicine Shortages Single Point of Contact (SPOC) Working Party, composed of single points of contact for medicines shortages from the NCAs of EU Member States responsible for human and veterinary medicines.

In April 2020, the EU Executive Steering Group launched an enhanced fast-track monitoring system, initially focused on medicines for COVID-19 patients in intensive care units (e.g., anaesthetics, antibiotics, resuscitation medicines and muscle relaxants). This system allowed regulators to detect and monitor common issues across Member States, spot patterns in medicines supply and demand, anticipate future supply disruptions early and identify EU/ European Economic Area (EEA)-wide measures to address disruption issues. Each pharmaceutical company concerned had to appoint an industry single point of contact (i-SPOC) responsible for reporting on ongoing or anticipated shortages of medicines used to treat COVID-19 patients. EMA compiled information from the i-SPOCs and shared it with the steering group to inform decision making. Pandemic measures, including lockdowns, travel restrictions and quarantines, prevented inspection of facilities and there were concerns about the impact on supply chains given the explosion in the demand for medicines. Forecasting demand of medicines during COVID-19 was also undertaken and a reflection paper on the topic was prepared in 2021.

Analysis of medicines supply and shortages

Despite lacking a formal legal mandate at the time, action taken by HMA and EMA on shortages during the pandemic provided significant support to Member States' activities on medicines availability. This resulted in the formal recognition of this new role for EMA by the legislators, who subsequently extended EMA's legal mandate. Some of the tangible benefits of EMA's coordinating role in preparation for or during public health emergencies include the close engagement with companies on their plans to expand manufacturing and prevent or mitigate shortages, the substantial reduction of assessment timelines for changes to boost supplies from several months to days or weeks, the proactive planning of Good Manufacturing Practice (GMP) compliance checks, the use of remote assessments and reliance on international partners, the extensive use of existing flexibilities (e.g., post approval change management protocols (PACMP), labelling) and new regulatory flexibility tools (e.g., Exceptional Change Management Process (ECMP), and the additional labelling flexibilities mechanism agreed for COVID-19 vaccines). All these efforts resulted in rapid expansion of supply capacity, in particular for COVID-19 vaccines. The SPOC Network shared information on the impact of the pandemic on supply chains, shortages and coordinated actions to prevent and manage shortages. Despite the

many advantages, numerous challenges remained, such as a considerable increase in workload, challenges in identifying inspectors and performing inspections in third countries due to limited resources and travel restrictions. Alternative routes to verify compliance with good practice, regulations and guidelines for pharmaceuticals (GxP), e.g., through remote assessments, still required substantial additional effort from the EU Network as the assessments were as resource intensive as physical inspections.

Key learnings

MEDICINES SUPPLY AND SHORTAGES

- The MSSG established within EMA plays a key role as a central EU coordinator on medicines availability and shortages, in preparation of or during public health emergencies.
- It may be necessary to maintain measures for extending supply capacity and additional regulatory flexibility tools (e.g., ECMP, labelling flexibilities) for future crisis situations needing rapid expansion of supply. This is being further considered by the MSSG.
- When prioritising resources for additional support to increase supply capacity, it is important to balance resource capacity with the expected public health impact.
- Improving efficiency of GMP compliance assessment, by complementing remote assessments with stronger reliance on inspections conducted by trusted international partners (either under Mutual Recognition Agreement or a hybrid approach), is important.

Network coordination and resourcing

EMRN activities

Working closely as a Network comprising 27 EU Member States, the EC and 3 EEA countries, close collaboration and coordination was essential to promptly reach harmonised positions on COVID-19-related matters. Strengthened engagement took place through the creation of dedicated fora to align EU positions on scientific matters (via the ETF) and to discuss strategic matters to the extent possible, particularly when differing positions were sometimes held at national level.

The unprecedented mobilisation of experts through the European network, including from NCAs, proved to be one of the key success factors supporting fast-track development and authorisation of medicines and vaccines for COVID-19. The ETF brought together the best expertise from the EMRN on topics including infectious diseases, vaccinology, antivirals, clinical trials, virology, immunology and immunotherapy. The ETF was instrumental in conducting exploratory reviews of investigational products and issuing EU-level scientific positions, in identifying the most appropriate regulatory pathway to ensure that potential treatments and vaccines were approved and made available as swiftly as possible, and in providing rapid scientific advice, endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP),

on questions from medicine developers on their development plans. The ETF was also centrally involved in interactions with academia or sponsors/ investigators of clinical trials not funded by industry and advised on the start of rolling reviews and timing of applications.

As the regulatory response to COVID-19 was highly important at both the EU and national level, an EU executive level forum was established, first informally and then as the MSSG with a formal mandate, as part of EMA.

In addition, there was the need to manage an increased workload and the negative impact of COVID-19 restrictions on the activities of the Network. EMA and the NCAs had to adapt activities and processes to ensure a rapid response to the pandemic whilst maintaining core regulatory activities for human and veterinary medicines. Nevertheless, substantial limitations in the EU Network's resourcing were noted mainly for scientific advice and authorisation procedures. Business continuity plans were put in place to meet the demands, prioritising procedures related to COVID-19 and safety, applying additional measures for operating core activities, and reallocating existing resources.

Analysis of Network coordination and resourcing

Normally, scientific assessors from NCAs allocate their evaluation teams based on the projected submission dates communicated by applicants and take on new assessments based on their planned work. During COVID-19, frequent changes to submission dates, especially late and/or multiple changes, including for rolling reviews, meant that evaluation teams were not able to take on other assessments. The situation was further complicated by the overall increase and urgency of the workload, affecting some specific areas in particular (e.g., vaccine assessment). Although some delays were observed in the appointment of scientific evaluation teams, no significant delays occurred in terms of starting and completing most authorisation procedures for both COVID-19 and non-COVID-19 products, and for COVID-19 products an unprecedented acceleration of timelines was achieved. Nevertheless, the signs of resource limitations across the EMRN continued to persist, resulting in a back-log for non-COVID-19 scientific advice procedures observed during later phases of the pandemic.

Key learnings

NETWORK COORDINATION AND RESOURCING

- It is necessary to maintain a common executive level forum for EMA, HMA and the EC, as well as a dedicated scientific forum for preparedness and crisis situations. These have now been formalised as the MSSG and ETF under the extended EMA mandate.
- In future crises, ensuring close coordination with EMA's scientific committees and their early strategic input into a crisis response will remain essential. During the COVID-19 response, this was ensured through the work of the ETF and involvement of the Chairs of scientific committees in relevant discussions.
- It will also remain necessary to adjust the way of working during future crises, to prioritise medicinal products requiring resource-intensive rapid procedures and additional support, to ensure the right balance between public health impact and resource use. In addition, it is key to identify the procedures that need to be safeguarded to avoid delays and ensure business continuity.

- It is necessary to raise and maintain awareness of the EMRN's resourcing issues and work jointly with other partners to ensure appropriate resourcing and expertise in the EU Network in the long term. It is also warranted to maintain ongoing efforts (e.g., ad hoc EMA-HMA tactical and operational groups on resourcing) to improve coordination and planning of resource allocation.

Global collaboration

EMRN activities

The COVID-19 pandemic was a global challenge for public health, which required the urgent development of new treatments and vaccines for use worldwide. International collaboration brought multiple benefits to regulatory authorities, aligned requirements for medicines developers globally and, ultimately, facilitated patient access to medicines.

Collaboration and exchange of information with other international regulators significantly increased during the pandemic and played a pivotal role in the assessment of COVID-19 products. Existing and new ad hoc confidentiality agreements allowed EMA to receive and share information in real time on important issues and enabled an unprecedented collaboration with regulators across the globe. Additional measures were put in place to obtain more information directly from international regulators (more extensive information sharing and/or new partners) and to facilitate an international level discussion on scientific matters. Regular exchanges with international partners, including discussions through ICMRA, took place, such as biweekly calls with WHO. EMA and EU Network experts participated in various WHO advisory groups, such as those related to WHO's Research and Development (R&D) Blueprint that led the initial activities for therapeutics and vaccines (e.g., WHO R&D Blueprint – novel Coronavirus (nCoV)), in cooperation with international stakeholders. These contributions allowed rapid mapping of ongoing initiatives to advance and investigate medical countermeasures for COVID-19. In addition to numerous bilateral discussions, the COVID-19 Vaccine Global Access (COVAX) regulatory advisory group, chaired by WHO and the Coalition for Epidemic Preparedness Innovations (CEPI), provided an additional opportunity for sharing views across regulators on a global scale.

Importantly, the EU Network's efforts were also directed to promote vaccine access equity for third countries, with six WHO Emergency use listings of COVID-19 vaccines based wholly or partly on EMA's assessment.

At the end of 2020, EMA started piloting the OPEN initiative to increase international collaboration on the evaluation of COVID-19 vaccines and therapeutics. The collaboration allowed sharing of scientific expertise during the evaluation of COVID-19 products among several international regulators who were facing common challenges. The outcome concluded that the OPEN pilot had facilitated the assessment of the same data by multiple authorities and recommended the initiative to be continued after the crisis for high-impact areas, while international agencies maintained full scientific and regulatory independence.

The Agency also led efforts to align regulatory requirements with international regulators, in particular under the umbrella of the ICMRA, thereby further facilitating medicine development and approval. There was a strong need to support harmonised regulatory outcomes globally, based on the same information available at the time. The alignment on clinical trial design for vaccines and the minimal data needed to start clinical trials were notable examples of the

harmonisation achieved on a global scale via ICMRA discussions. This has continued with respect to strategies to update vaccines composition and represents a far-reaching level of global regulatory convergence.

Analysis of global collaboration

This crisis resulted in unprecedented collaboration at international level, given the inherent global nature of medicines development and supply chains. New collaboration agreements were established with new partners, in addition to strengthening existing ones. International alignment was achieved on many regulatory requirements and, in some cases, also at individual medicine level. The EU Network's work to promote access equity contributed to reducing regulatory barriers and to ensuring that more people in third countries could receive COVID-19 vaccines.

International collaboration had many benefits, including the sharing of more extensive and sometimes critical information directly between international partners (for example, discussions at the ICMRA Vaccine Pharmacovigilance Network which helped provide additional knowledge on COVID-19 vaccines during pregnancy and lactation).

EU experts identified reciprocity of information exchange and more active participation of regulators under the OPEN initiative in EMA's scientific evaluation as areas for further improvement, as well as improvements in communication, document management systems and adapted IT tools to further facilitate the flow of documents exchanged.

For EMA, the most useful initiative was the sharing of the international regulator's assessment reports, feedback received on EMA's evaluations and receiving advanced notice of regulatory actions/communications. In terms of challenges, international regulators at times still reached different outcomes or completed an assessment at a different time due to differences in regulatory frameworks. However, a good alignment was reached on main regulatory requirements.

It is also important that the collaboration with international partners is extended to support preparedness in future crises for and conduct of large observational studies that would enable capturing rarer outcomes, as well as to share expertise and resources, ultimately ensuring a better crisis preparedness and response at a global level.

Key learnings

GLOBAL COLLABORATION

- During future crises, it is important to maintain efforts to facilitate global alignment of regulatory requirements. Use of established cluster collaboration with some Agencies (e.g., the US Food and Drug Administration (FDA) and Health Canada (HC)), coupled with more global discussions at fora such as ICMRA or COVAX, provides invaluable opportunities for regulatory alignment and increased confidence in regulatory decisions.
- The strengthened international cooperation (e.g., continuation of OPEN, bilateral arrangements on exchange of confidential information, alignment and convergence of requirements and expanding regulatory reliance, including through ICMRA) is being expanded to cover non-crisis and other crisis situations.

- Further collaboration with international partners (e.g., through ICMRA) should be developed on conduct of large observational studies in future public health emergencies.
- There is a need for development of IT tools to share information more efficiently among international regulators and fostering reciprocity of information exchange would facilitate further international cooperation.
- Strengthening of expertise can be supported by real-time exchanges with partner regulators.

Transparency, stakeholder engagement and communication

EMRN activities

The EU network was committed from the start of the pandemic to enhancing transparency of regulatory activities and increasing the public understanding of the scientific data underpinning the approval of new medicines and vaccines to build public trust. Due to the vast amount of new scientific evidence that was continuously emerging, coupled with an unprecedented level of public attention and demand for information, this was a challenging task. In particular, communicating the scientific developments and evolving uncertainties over time was a challenge, as was addressing the rise in misinformation and disinformation being disseminated.

EMA's communication approach relied on three main pillars: communicating proactively, engaging with the public, media and healthcare professionals, and enhancing transparency on EMA's regulatory processes and outcomes. Workflows were adapted to ensure rapid decision–making on crisis communication, with the involvement of the COVID-19 Steering Group. Weekly meetings with the EC and ECDC were introduced to share information and align communications, as well as with the HMA working group of NCA communication professionals.

Overall, the Agency increased its proactive communication, anticipating the need to provide factual information on the fast-track approval of COVID-19 vaccines and on the novel platform technologies utilised in some of these vaccines. EMA also strengthened its engagement with stakeholders and the media as an important reputable information source during the crisis via the dissemination of factual scientific information on social media. Patient, consumer and healthcare professional representatives became members of the ETF, contributing to discussions and providing input from their perspective as needed. All these activities increased public awareness of EMA and the Network's role in fighting the pandemic, helping to convey reliable information to the public. EMA also reached out to the public to respond to their questions and concerns in four dedicated public stakeholder meetings and liaised with media through regular press briefings and media interviews. Dissemination of communication materials via the EMA and NCA websites and targeted mailing to stakeholders were also critical to deliver public health information and advice.

Key communication materials on COVID-9 vaccines were subject to user testing to increase the effectiveness of these public health communications. An overview of key communication and engagement activities is provided in figure 7.

Figure 7: Number of communications, engagement activities and webpages issued during the public health emergency

Figure 7a: Number of communications

Public health communications	**166**
Media queries	**9467**
Media interviews	**193**
Joint communications with ECDC	**8**

Figure 7b: Number of COVID-19 webpages new/updated during 30 January 2020 - 05 May 2023

Topic pages[1]	31
Medicine-related pages	42
News	301
Patient safety news	20
Press briefings	33
CHMP extraordinary meetings	16
Public stakeholder meetings	4
Other events	11
Total	**456**

Figure 7c: Number of medicine-related pages (by medicine type)

Paediatric investigation plans (PIPs)	21
Medicine European public assessment reports (EPARs)	16
Direct healthcare professional communications (DHPCs)	10
Withdrawn applications (rolling review)	2
Total	**42**

As part of its transparency efforts, EMA reactivated its landmark policy on the publication of clinical data supporting marketing authorisations for COVID-19 medicines. This programme, which had been suspended in 2018 due to the Agency's relocation after Brexit, was

[1] COVID-19 topic pages (purple menu section) – 11 out of the 31 COVID-19 topic pages have been archived since the end of the reporting period and replaced with other published COVID-19 topic pages - changes related to the end of COVID-19 as a public health emergency of international concern declared by WHO.

exceptionally reinstated for COVID-19 medicines and vaccines (Figure 8), given the unprecedented public interest in this information.

Figure 8: Number of clinical trial data packages for COVID-19 medicines published during the public health emergency

Vaccines	44
Therapeutics	27
Total	**71**

Requests for information from the public also increased substantially during the pandemic (Figure 9), together with a surge in demand for access to data on suspected side effects recorded in EudraVigilance (the EU database for suspected adverse effect of medicines).

Figure 9: Number of requests for information and access to documents received by the Agency

Requests for information (including queries from healthcare professionals and patients)	7038
Requests for access to documents	342
Total	**7380**

Transparency concerning the evaluation of marketing authorisation applications of new medicines and vaccines was also exceptionally increased during COVID-19. The product information was published within hours after a positive opinion from EMA and publication of the summaries of the scientific evaluations (assessment reports) was also expedited (when possible, within 7 days of the issuing of the marketing authorisation, compared with the standard time of around 10 weeks). EMA also explored new approaches to communication, like the visualisation of benefits and risks for Vaxzevria, and joint communications with international regulators.

Analysis of transparency, stakeholder engagement and communication

The crisis raised the profile of EMA, the EU Network and their regulatory work, and this translated into more requests for media and stakeholder engagement. Additionally, EMA and the EMRN experienced a surge in the numbers of queries from the public, specifically concerning vaccines. This resulted in a high workload that persisted as the crisis continued, which required EMA to channel emerging information into regular press briefings to inform citizens on new developments. Press briefings and direct engagements with generalist media were impactful ways of clarifying scientific aspects related to approved vaccines and therapeutics. While most of EMA's communications take place within regulatory procedures and following scientific committee meetings, during COVID-19 it was often necessary to issue urgent ad hoc communications to support policy decision making in Member States. Particularly important were the joint communications issued with ECDC. Additionally, it soon became evident that there was a need to explain to the public the role of the different public health authorities involved in vaccine approval and vaccination policy, in particular to raise awareness of the role of regulators in this process. Messaging was coordinated at EU level, with EMA providing

consistent messages for use by all Member States and supported by the HMA Working Group of Communication Professionals (WGCP), ECDC and the EC. However, at times it was challenging to explain the different vaccination decisions taken by Member States' policy makers on the basis of available data and a single scientific regulatory assessment, which were based also on local factors at Member State level. Extensive experience was gained in crisis communication during the COVID-19 pandemic and EMA will update its crisis communication plan accordingly.

Key learnings

TRANSPARENCY, STAKEHOLDER ENGAGEMENT AND COMMUNICATION

- Extraordinary transparency measures applied during COVID-19 helped to address public needs and should also be applied in future crises. Some of the additional transparency measures are being rolled out more generally outside of the crisis setting (e.g., full RMP publication, list of medicines that received scientific advice).
- Monitoring of public concerns and mis/disinformation enabled prompt action to be taken and concerns to be addressed in proactive communications. Therefore, these activities will be maintained and work is ongoing to strengthen the Network's response to mis/disinformation.
- Underpinning urgent communication by agile assessment by the ETF/EMA's scientific committees, backed by the available evidence, was crucial for ensuring credibility and should be maintained in future crises. Prompt and timely communication may be required outside standard regulatory process timepoints (e.g., before an assessment is concluded) in case of very high public interest and interim holding communications may still need to be issued.
- Joint communications with ECDC were crucial for providing a complete perspective on public health and scientific issues by European Institutions.
- Set up of a crisis communication structure for rapid decision-making was instrumental and EMA's crisis communication plan is being updated to transfer knowledge gained from COVID-19 to prepare for future crises.
- Regular press briefings and public stakeholder meetings should be maintained as a default approach in crisis situations, and alternative routes to establish a more targeted outreach to the media, healthcare professionals and public are being explored.
- Research and user-testing activities should be continued to develop optimised tools for communicating on benefits and risks of medicines, including data visualisation.
- Knowledge among communication officers within the EMRN should be improved with trainings on crisis communication, tools and actions to increase transparency.

Conclusions

Areas performing well

Overall, the EU Network successfully carried out the required regulatory work throughout the public health emergency. This has resulted in the authorisation of eight life-saving vaccines within an exceptionally short timeframe, in some cases using completely novel platform technologies. Eight therapeutics from different classes (monoclonal antibodies, antivirals, etc.) have also been approved and many scientific recommendations were issued by the Emergency Task Force outside of formal procedures to support public health authorities in the Member States.

The EU Network also carried out a large number of procedures involving scientific advice, PIPs and post-marketing variations, and coordination of the work on shortages and supply chain expansion. Because of the emergency situation and the need for mass vaccination campaigns, in addition to the standard safety monitoring of the safety of new vaccines and medicines, the Network strengthened its pharmacovigilance process. Emerging safety signals were identified early on, based largely on suspected adverse reactions reported by vaccinated people. Scientific assessors carefully analysed all the evidence and in those cases where signals were confirmed, these were rapidly reflected in the product information.

The response to COVID-19 was achieved in very challenging circumstances for EMA and NCAs, under pandemic restrictions and adjusting to the new way of working remotely, and despite the identified resourcing constraints throughout the EMRN. Regular work on the evaluation and supervision of other medicines continued. While the Network had to apply some prioritisation, as reflected in the COVID-19 Business Continuity Plan, and while there were some serious challenging areas, notably the scientific advice for non-COVID-19 products, major delays were avoided and the authorisation of new medicines did not have to be postponed due to assessment capacity issues.

The emergency phase of the pandemic extended over three years, during which the regulatory activity of the EMRN gained unprecedented visibility and interest in its work. As a result, EMA received a substantially increased number of engagement requests and calls for communication activities. High expectations for transparency prompted the Agency to provide extraordinary measures for COVID-19 products, including reinitiating the clinical data publication activities

which had been suspended due to the Agency's relocation. Overall, the EU Network has delivered to its usual high standards while also coping with an extremely high workload. In such context, staff and experts from across the EMRN demonstrated their strong commitment to the protection of the health of European citizens.

The COVID-19 public health emergency served also to consolidate the very close and productive cooperation with EU and international partners. The latter allowed advanced notice and information exchange and enabled a degree of harmonization of regulatory requirements internationally, mainly through ICMRA.

Recognition of EMA's work, as part of the EMRN including support to public health priorities, has resulted in new legislation extending EMA's mandate in the context of crisis preparedness and management. It not only formalizes the work of the ETF and the engagement with NCAs on addressing medicines shortages, but also gives the EMA new tasks, such as the development of an European Medicines Shortage Monitoring Platform and several tasks in the field of medical devices.

Summary of areas performing well

- Ability to promptly respond to the crisis situation, including development support, assessments and safety monitoring/risk management, while avoiding major delays for non-COVID products.
- Recognition of the EMRN work during pandemic through formal extension of EMA's mandate.
- Proactive support to medicines developers through the ETF, EMA's scientific committees and working parties.
- Successful implementation of regulatory flexibilities and accelerated assessment/rolling reviews, performed by national experts from NCAs as members of EMA's scientific committees and the ETF.
- Provision of public health advice beyond the scope of core medicines regulatory approval.
- Close cooperation and coordination among EMA, national authorities in Member States, the EC, ECDC and international partners and reinforced stakeholder engagement.
- Enhanced transparency, public engagement, communication and ability to respond to high demand for information.

Areas requiring further improvement

Some areas remain where further improvements could enable better addressing public health needs.

The need to rapidly set up larger and more methodologically sound clinical studies to provide timely and meaningful results to inform regulatory decision making and clinical practice was

identified. This applies to pre-authorisation studies which EMA can support through scientific advice, but equally to post-authorisation studies to generate evidence that was not available prior to approval. It is also crucial to improve availability of multiple sources of real-world data, such as EU healthcare data, to have more efficient tools for analysis of these data and more expertise to integrate the generated RWE into regulatory assessments. For example, more granular and up-to-date vaccine exposure data are crucial for the assessment of emerging vaccine safety signals. RWE can also help assess the impact that a fast-changing situation, like the emergence of new virus variants, has on authorised medicines.

It is also imperative to have sufficient reserve resource capacity available that can be called upon in crisis situations like a pandemic. Some of the accelerated reviews offered for COVID-19 products, including rolling reviews, imply an increased workload and the Network must continue to prioritise the most promising medicines for which such additional support is to be reserved. To improve efficiency, EMA and HMA need to further streamline and rationalise regulatory and communication processes, while maintaining its rigorous quality standards. The need to intensify the cooperation with some partners, for instance with NITAGs, was also identified. At times it was difficult for citizens to understand the rationale for different decisions by regulatory authorities and NITAGs involved in vaccination policies at national level (e.g., Vaxzevria was not used or restricted in vaccination programs for certain target groups in some countries, considering the local circumstances and the occurrence of TTS cases). A critical challenge during the pandemic was the profuse amount of mis- and disinformation circulating in social media, particularly on vaccine safety. Efforts are needed to invest and collaborate with other public health authorities on setting up an adequate response system. Many of these shortcomings are already being considered and addressed as part of ongoing initiatives (e.g., work on the European Health Data Space (EHDS) or DARWIN EU and ACT EU).

Summary of areas for improvement

- Enable large clinical studies that can provide timely and meaningful results.
- Extend development and access of real-world data sources with relevant and granular information, improve IT systems for processing these data, and strengthen network of expertise.
- Reserve resource-intensive additional measures to the most promising medicines.
- Continue to invest in improving resourcing within the EMRN and developing more streamlined processes to deal with the increased workload.
- Earlier medicines availability might be supported by the introduction of an EU level mechanism such as the proposed TEMA.
- Build on communication and engagement approaches developed during COVID-19, work further on establishing collaborations on infodemic management and prepare a strategy to address mis- and disinformation.
- Reinforce cooperation with other partners, e.g., NITAGs.

Ongoing actions/next steps

Although the public health emergency phase of the pandemic was declared over by the WHO on 5 May 2023, SARS-CoV-2 continues spreading worldwide and evolving. The EU Network continues its work on vaccine adaptations, monitoring the long-term safety and effectiveness of COVID-19 vaccines and therapeutics, and supporting ongoing post-authorisation studies to generate valid RWE. The ETF is also working to support treatment/prevention of long COVID, considering the millions of people impacted across Europe and monitoring the long-term effects of SARS-CoV-2 infection.

Resourcing issues, clinical trials, shortages and RWE are priority areas being pursued currently within the Network. Media engagement on COVID-19 has calmed down but efforts continue to support the required communication and social media activities. The EMRN continues its strong cooperation with stakeholders, in particular with patients and healthcare professionals, who are part of the ETF as civil society representatives. The EMA will maintain its transparency and clinical data publication efforts and will continue to provide any update needed on COVID-19 to the public.

In terms of the lessons learned and recommendations in this report, EMA has already implemented a number of them as part of its extended mandate, which also includes an enhanced role on preparedness to be more proactive during public health threats. EMA and HMA have collaborated closely, particularly in the areas of resourcing, process improvement, communication and cooperation with other (regulatory and non-regulatory) authorities, and further work to address key learnings is ongoing. In addition, the review of the EU pharmaceutical legislation will provide a vehicle to bring about further changes and enhancements to the EU regulatory toolbox based on learnings from the COVID-19 public health emergency.

The intensity and duration of the COVID-19 public health emergency tested the EMRNs crisis response mechanisms and precipitated EU medicines regulators to embark on a large and unexpected learning curve. This analysis of the EMRN's response has helped consolidate an overview of the work achieved in the service of EU public health. Beyond COVID-19, the Network's role in crisis preparedness has been strengthened with horizon scanning of potential health threats and support for relevant medical countermeasures, enabling EU medicines regulators to be better prepared for the next public health crisis when it arises.

Glossary

AESI	Adverse Event of Special Interest
ACT EU	Acceleration of clinical trials in the EU
CEPI	Coalition for Epidemic Preparedness Innovations
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional marketing authorisation
COVID-19	Disease caused by the SARS-CoV-2 virus, first noted to affect humans in 2019
COVAX	COVID-19 Vaccine Global Access
CTCG	Clinical Trials Coordination Group
DARWIN	Data Analysis and Real-World Interrogation Network, a proposed EU platform to access and analyse healthcare data from across the European Union
DG-SANTE	Directorate-General for Health and Food Safety
DKMA	Danish Medicines Agency
EC	European Commission
ECDC	The European Centre for Disease Prevention and Control
ECMP	Exceptional Change Management Process
EEA	The European Economic Area, comprising the EU Member States, Iceland, Liechtenstein and Norway
EHDS	European Health Data Space
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network, the Network
ETF	Emergency task Force
EU	European Union
FDA	Food and Drug Administration
GMP	Good manufacturing practice
GVP	Good pharmacovigilance practise
GxP compliance	Good practice, regulations and guidelines that apply to organisations that manufacture medicinal products that are consumed or used by humans or animals
HC	Health Canada
HERA	Health Emergency Preparedness and Response
HMA	Heads of Medicines Agencies. A strategic and coordinating body representing the national medicines regulators of the EEA countries

HSC	Health Security Committee
HTA	Health Technology Assessment (body)
i-SPOC	Industry single point of contact
ICSR	Individual Case Safety Report
ICMRA	International Coalition of Medicines Regulatory Authorities
MABs	Monoclonal antibodies
MSSG	Executive Steering Group on Shortages and Safety of Medicinal Products
NCA	National competent authority. One of the national medicines regulators that form part of the Network
NITAGs	National Immunization Technical Advisory Groups
OPEN	Opening procedures at EMA to non-EU authorities
PACMP	Post approval change management protocol
PIP	Paediatric investigation plan
PRAC	Pharmacovigilance Risk Assessment Committee
PRIME	Priority Medicines Scheme (EMA)
R&D	Research and development
RMP	Risk management plan
RWE	Real-world evidence
SA	Scientific Advice
SPOC	Single Point of Contact
SSR	Summary Safety Report
TEMA	Temporary Emergency Marketing Authorisation
TTS	Thrombosis with thrombocytopenia syndrome
WGCP	HMA Working Group of Communication Professionals
WHO	World Health Organization

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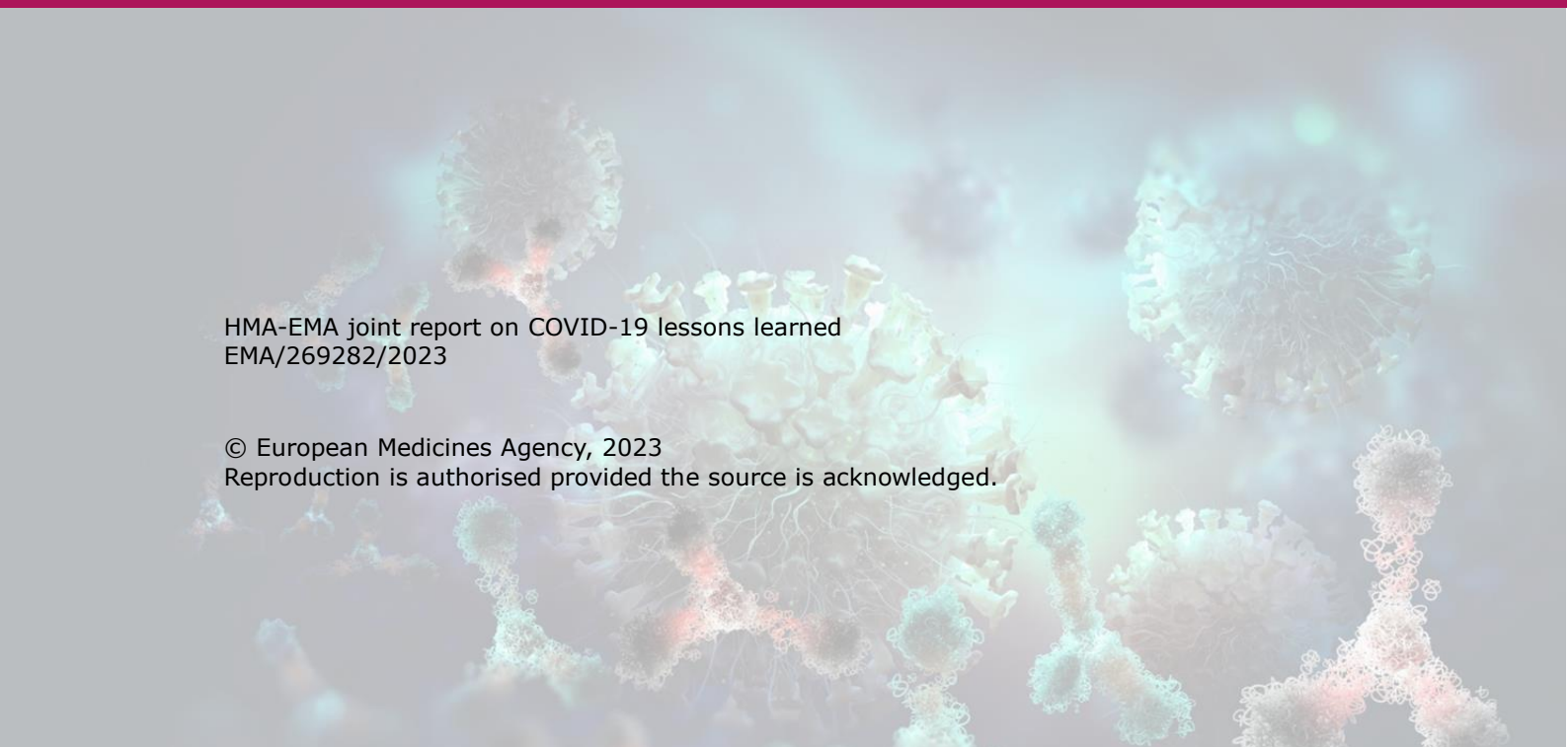

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