Master of Public Health

Master de Santé Publique

POLICY ANALYSIS OF THE COVID-19 PANDEMIC IMPACT ON THE EUROPEAN UNION REGULATION OF THE MEDICINE SHORTAGES

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Master of Public Health 2020-2022

Health Policy and Management

Location of the practicum

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ACKNOWLEDGMENTS

I would like to express my deepest gratitude to my academic advisor, Dr. Matthias Brunn for his guidance and advice in the process of writing the thesis.

I would like to extend my sincere appreciation to my professional advisor, Dr. Rosa Castro, for her hard work and the opportunity to do this internship on Access to Medicines in Europe. I am grateful for her kindness, trust and invaluable advice throughout this internship. I would also like to thank Marcin Rodzinka-Verhelle for his valuable knowledge of the European Policy Affairs and help during the thesis writing.

I would like to express my sincere gratitude to my colleagues of the European Public Health Alliance (EPHA) who made this experience possible and supported me during this internship. I am thankful for their warm welcome, goodwill and inspiring devotion for public health and advocacy.

I also had the great pleasure to work with the Members of the European Alliance for Affordable Medicines and Responsible R&D who provided me with precious knowledge about the access to medicines in Europe. I had the chance to work in close collaboration with Charlotte Roffiaen which contributed to my interest in and knowledge of the medicine shortages.

Last but not least, I would like to share my sincere appreciation to Julie Gagnon and Marie Dinh for their friendship and everlasting support.

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LIST OF ACRONYMS

API	Active Pharmaceutical Ingredient
CSOs	Civil Society Organisations
EC	European Commission
ECMP	Exceptional Change Management Process
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
HCPWP	Healthcare Professional Working Party
HMA	Heads of Medicines Agency
ICU	Intensive Care Unit
i-SPOC	Industry Single Point of Contact
MEPs	Members of the European Parliament
SPOC	Single Point of Contact
PCWP	Patient and Consumer Working Party

ABSTRACT

Title: Policy analysis of the Covid-19 pandemic impact on the European Union regulation of the medicine shortages.

Introduction: In Europe, the number of medicine shortages increased 20-fold between 2000 and 2018. Medicine shortages are widespread and put substantial risk on patients' continuity of care and healthcare providers' practice. The civil society organisations have been key stakeholders to raise awareness and advocate for strengthened EU regulation on medicine shortages, despite the limited interest from the European policymakers before March 2020. However, the pandemic has exacerbated the need for a coordinated European response to cope with the vulnerabilities of the global supply chain and ensure the fair allocation of medicines across the EU Member States. This study aims to explore the impact of the pandemic on the European agenda-setting to address and mitigate the impact of medicine shortages.

Methods: A triangulation method was used to develop a comprehensive understanding of the policy-development. The study includes a grey literature review and 9 semi-structured interviews with representatives of the civil society.

Results: The COVID-19 contributed to place the medicine shortages high in the European agenda. The European Health Union Package includes the New Pharmaceutical Strategy and the EMA extended mandate and the forthcoming revision of the EU general pharmaceutical legislation.

Conclusion: The COVID-19 pandemic has reframed the perception of medicine shortages in the society and catalysed the European policy-development. Furthermore, the sense of urgency has exacerbated the power imbalance between the civil society and the pharmaceutical industry. This study highlights the need for the systematic involvement of the civil society to ensure the representation of the public-interest, even in time of crisis.

Key words: Medicine shortages, EU legislation, COVID-19, civil society

INTRODUCTION

Access to safe, effective and quality medicines and vaccines is a global concern and one target of the Sustainable Development (United Nations, 2015). Even the wealthiest countries face difficulties to secure the availability and access of medicines for all. Since 2007, medicine shortages and essential medicines stockouts have increased in the European Member States (Technopolis Group, 2021b) that put additional pressure on healthcare systems.

Definition and trends of shortages in Europe

Defining the medicine shortage is complex since all medicine shortages are not alike or as critical for the patients, the pharmacists, and the healthcare system. The European Union (EU) Member States have set multiple definitions that vary in terms of stockouts duration, therapeutic importance of the medicines and availability of substitutes. This has led to discrepancies between the EU Member States' reporting systems and data collection and cross-country comparative analysis (Technopolis Group, 2021b). In an harmonisation effort the European Medicines Agency (EMA) and the Heads of Medicines Agency (HMA) convene that "'shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level' (European Medicines Agency, 2019b). However, one year later, on 11 EU Member States studied, only 50% aligned with the EMA definition (Troein et al., 2020).

According to the European Parliament's Committee on the Environment, Public Health and Food Safety, the number of shortages notifications increased 20-fold between 2000 and 2018, and have increased 12-fold since 2008 (ENVI Committee, 2020). The pharmacists' awareness on medicine shortages and the improved reporting systems do not explain alone the surge in the shortages notifications overtime (Technopolis Group, 2021b). Despite limited comparability, some EU countries are more affected than others and the shortages across Europe vary 10-fold (Troein et al., 2020). In 2019, Portugal, Netherlands, Belgium, Norway and France ranked as the top-five countries recording the highest number of shortages notifications (Technopolis Group, 2021b).

The shortages mainly affect off-patents and low-profit margins medicines. Indeed, over half of reported shortages involve generic medicines (Troein et al., 2020). The shortages also affect all type of products forms but tablets, injectable or infusion medicines are more likely to be under shortages (Technopolis Group, 2021b). Moreover, the shortages affect almost all therapeutic areas with a tendency for the treatment of the central nervous and cardiovascular systems (Technopolis Group, 2021b). In 2019, 47% of hospital pharmacists declared that

oncology medicines stockouts were the most frequent in their facility (European Association of Hospital Pharmacists, 2019).

Root causes of the shortages

The shortage causes are multi-factorial and country dependent (Chapman et al., 2022; Technopolis Group, 2021b). First, they might be caused by manufacturing issues such as reduced capacity or non-compliance with the regulatory standards for quality and composition. The manufacturing and quality- related factors account for more than 60% of cases of shortages (ERPS, 2021). Secondly, pharmaceutical industries also face distribution and supply issues depending on their production site location and Active Pharmaceutical Ingredients (API) suppliers. Changes in supply, quality and regulation of APIs could cause medicines stockouts (ERPS, 2021). Regulatory factors to comply with one country's Market Authorisation (MA) can also explain the medicine shortages. The sudden increase in demand ensued from a change in reimbursement conditions, new therapeutic guidelines but also the spill-over effects of an alternative treatment to an ongoing shortage may also be responsible (Technopolis Group, 2021b). Shortages may also occur for commercial reasons when pharmaceutical industries decide to withdraw a medicinal product from the market due to its low-profit margins, new reimbursement negotiations or a company's repurposing of business strategies. In 2019, shortages caused by commercial withdrawals of medicines represented 63% of all shortages in Romania, 47% in Croatia, and 37% in Italy (ECL Access to Medicine Task Force, 2021).

Impact on patients and healthcare providers

Little to no peer-reviewed evidence exists on the impact of the medicine shortages on european patients, but one study was found on American patients (Kim et al., 2015). However, Civil Society Organisations (CSOs) have been key stakeholders in documenting the patients and healthcare providers experience with the medicine shortages (BEUC, 2020; Bochenek et al., 2018; ECL Access to Medicine Task Force, 2021; European Association of Hospital Pharmacists, 2019; La ligue contre le cancer, 2021; No es Sano, 2020; Pharmaceutical Group of the European Union, 2021) Medicine shortages are widespread and put substantial risk on patients' continuity and safety of treatment. Respectively 46% and 40% of Portuguese and Spanish consumers have been unable to get their medicine at least once in 2018-2020 (BEUC, 2020) while 45% of the French population underwent a change in their treatment plan as a result of the shortages in medicines (France Assos Santé, 2018). Shortages are associated with anxiety, worsening symptoms and suboptimal quality of care due to increased risks of medical errors and drug interactions (Kim et al., 2015).

Medicine shortages are also impacting the community and hospital pharmacists' daily practice. According to the Pharmaceutical Group of the European Union (PGEU), all pharmacist from the 27 EU countries surveyed, experienced medicine shortages in 2020 and spent on average 5,1 hours per week mitigating them (Pharmaceutical Group of the European Union, 2021). Shortages affect the services delivery and imply financial loss due to the time invested in mitigating the shortage effects or increased sourcing pricing (Pharmaceutical Group of the European Union, 2021). They ultimately results in higher costs for the healthcare systems due to increase length of stay or the use of more expensive alternatives (Kim et al., 2015).

The civil society and the EU framework to ensure the supply of medicines

The civil society defines non-state, not-for-profit, voluntary organisations formed by people in that social sphere (Greer et al., 2017). At the European level, the Civil Society Organisations (CSOs) are umbrella organisations, that gather regional and national organisations.

From a top-down perspective, patients, healthcare users and professionals' organisations have contributed to inform and reassure their members through information-sharing. From a bottom-up one, they have contributed to raise awareness on the impact of medicine shortages in the society by depicting the experience of patients and healthcare providers. At the European level, they secure the representation of public-interest in the health policy proposals made by the European Commission, co-legislated by the European Parliament and the Council of the European Union and enforced by the EU Member States.

As established by the Better-Making Law (European Parliament et al., 2016), civil society organisations are consulted by different European Institutions, since their contribution allows the development of informed and patient-centric health policies that are coherent with the field needs. In Europe, the Directive 2001/83/EC legislates the use of medicines for human use. However, only two articles are dedicated to the medicine shortages (European Parliament & Council of the European Union, 2001). The Article 23a requires the Marketing Authorisations Holders to notify the National Competent authority at least two months in advance of their intent to suspend the marketing of a product it has placed on that market. Article 81 mandates that after entering the market, the manufacturer is responsible for ensuring the continuous and appropriate supply of their medicines on the market.

The European Medicines Agency (EMA) also plays an important role in coordinating and harmonising the response to prevent and mitigate the shortages in the remit of its mandate (European Parliament and the Council, 2004). Traditionally, representatives of the patients and healthcare provider's organisations seat in the different EMA's working groups.

Impact of COVID-19 on the medicine shortages

While medicine shortages are a longstanding problem in European countries, the COVID-19 outbreak in Europe has raised the general population awareness on this issue. The pandemic has been characterised by a sudden increase in demand for Intensive Care Unit (ICU) medicines that included medical oxygen, anaesthetics, antibiotics, muscle relaxants as well as resuscitation, anti-diuretics, or cardiac medicines (European Commission, 2020e; European Medicines Agency, 2020a). The unpredicted surge in demand resulted in manufacturing delays as well as rearrangement of production lines to maximise the availability of the ICU-related medicines, sometimes at the expense of other therapeutics (Technopolis Group, 2021b). The first month of COVID-19 were also characterised by the stockouts of certain chronic diseases treatments due to the repurposing of these medicines to find a treatment against COVID-19 (European Commission, 2020e).

Moreover, the COVID-19 pandemic has exacerbated the need for coordinated European measures to cope with the vulnerabilities of the global supply chain (European Parliament, 2021b; Technopolis Group, 2021b). On the one hand, the European Union depends on a limited number of Active Pharmaceutical Ingredients (API) producers in East Asian countries. Indeed, 61% of APIs production sites are located in China and India. (European Medicines Agency, 2017). The quarantine measures and international export bans respectively undermined the manufacturing and distribution capacities to ensure the supply of medicines in the EU (Technopolis Group, 2021b). Additionally, protectionism, such as stockpiling of essential medicines, constrained the equitable allocation of supply across all EU Member States (European Commission, 2020a).

OBJECTIVES AND RESEARCH QUESTIONS

While the impact of COVID-19 on medicine shortages has been described (ERPS, 2021; European Parliament, 2021b; Technopolis Group, 2021b), little is known about the consequences of the pandemic on the European agenda-setting to address the medicine shortages in the long-term.

This policy analysis aims to answer to the following research question: How has COVID-19 impacted the European agenda-setting to prevent and mitigate the medicine shortages?

To answer to this research question, the following sub-questions were explored:

1. How has the problem perception of medicine shortages evolved with the COVID-19 pandemic?

2. What legislative and non-legislative measures to prevent and mitigate the shortages have been implemented by the European Institutions, before and after March 2020 ?
3. How has COVID-19 impacted the contribution of civil society organisations to the policy-making process?

METHODS

For this policy analysis, the Kingdon's Multiple Stream Framework (1984) informed the research process. The Multiple Stream Framework explains the role of policy entrepreneurs inside and outside government who take advantage of agenda-setting opportunities, the policy windows, to move them onto the government's formal agenda (Buse et al., 2005). The models suggests that the problem, the policy and the politics streams intertwined and lead to the opening and closing of policy windows. These policy windows can result in governmental action and the development of concrete policy solutions.

For this exploratory policy analysis, the triangulation of qualitative data source was used. Triangulation refers to the use of multiple data source to develop the understanding of a comprehensive phenomena (Patton, 1999). First, a grey literature review was performed to collect evidence on the European pharmaceutical legislative and non-legislative measures to prevent and mitigate the shortages in Europe, before and after March 2020. Secondly, semi-structured interviews were performed to contextualise the findings of the grey literature. It helped to gain a deeper understanding on the impact of the pandemic on the European legislative and non-legislative measures addressing the medicine shortages. Plus, it allowed to explore the impact of the COVID-19 pandemic on the problem perception of the medicine shortages and how different stakeholders have contributed to the policy-making process. Civil Society Organisations (CSOs) have been actively engaged in the European policy development. Hence, they are key stakeholders for this research question.

GREY LITERATURE

This secondary data analysis gathered policy recommendations, policy briefs, informative papers, technical reports, reviews on medicine shortages that were collected from February 2022 to mid-June 2022. The data collection inclusion criteria were the following: 1. The document is published in the Publications office of the European Union; 2. The document has been published between 2012 and 2022; 3. The document was written by the European Commission, the European Parliament or the Council of the European Union; 4. The document is in English; 5. The document is available as PDF, HTML or DOC; 6. The document is available within the 20 first pages of the data search which is classified by relevance. The key terms were "medicine shortages" or "medicinal products" AND shortages. They were

deliberately kept very narrowed as access and availability of medicines can refer to a broader concept. Exclusion criteria included: 1. Titles that addressed antimicrobial resistance, veterinary medicinal products shortages, shortages in the UK, Malta or Cyprus (national exception), shortages of medical devices only, or regulation of the paediatric use. Additional policy papers were collected from the "Availability of medicines" webpage to document the EMA's role in addressing the medicine shortages. An article selection flow chart is available in Annex 1.

QUALITATIVE STUDY

Sampling method

Participants were European civil society representatives from patient, healthcare users and professionals' organisations. 7 out of 9 were sampled using the purposive method and 2 out of 9 through the snowball one. They were identified after Google searches to identify the CSOs specialised in the medicine shortages but also thanks to informal meetings organised with european public health stakeholders as part of the internship. Participants were invited via emails exchanges. Up to three kindly reminders for this study enrolment could be sent. Participants all received an information form that fully explained the purpose and process of the study, verbal consent was obtained before the beginning of the interview. 14 representatives from 11 organizations were invited to participate. 4 healthcare professionals and 5 patient's representatives were enrolled. In the results section, they are respectively identified as HCP# and P#. For more information, refer to the participants demographics (Annex 2). Lack of time, CSOs turnovers and lack of information on the topic justified the refusal to participate. The interviewer already had professional meetings with 2 patients' representatives and 1 healthcare professional organisations.

Data collection

Data collection occurred from 2 to 17 May 2022. All interviews were conducted and video-recorded on Teams/ Zoom. All the interviews were conducted in English, except for the first 2 participants. Due to the nationality of the researcher, this did not constrain the analysis of the interviews. The quotes were then translated in English. 5 participants connected from their home while 4 participants did from their workplace. Each participant was interviewed once and by the same interviewer. The order of data collection did not present significant differences in the analysis of the interview transcripts. A semi-structured interview guide (Annex. 3) was used to collect inputs from the participants. It was composed of 9 questions and additional probes. The questions were pilot-tested with two external CSOs representatives familiar with the European policy-making process. The interview guide was slightly modified after the first two interviews with the real participants. The interviews were transcribed verbatim on Microsoft Word and transcripts were proofread while watching the video tape.

Data analysis

An inductive content analysis was performed. Memos were written after each interview to identify the main themes, patterns, discrepancies that could be developed in the study. A first open-coding phase was initiated to analyse the main themes. The data was segmented in 4 topical codes “Pre-Covid”, “First wave”, “Post-Covid”, “Shortages” with subcodes and 2 interpretative codes derived from the data: “Power balance” and “EU4Health”. The codebook is available in the Annex 4.

RESULTS

PART A: PROBLEM STATEMENT AND POLICY RESPONSE TO THE SHORTAGES BEFORE THE COVID-19 OUTBREAK

1. The role of civil society organisations in addressing the medicine shortages

a. Documenting the medicine shortages

For the last decade, Civil Society Organisations (CSOs) have been key stakeholders in depicting the scale of medicine shortages and their impact on patients’ continuity of care and well-being. Interviews with the participants outlined that most of them initially reported the shortages as a micro-scale issue for certain category of chronic patients in a limited number of Member States.

> *“Back in 2010-11, some of our members, especially from smaller countries at first but also followed shortly after from bigger countries, started to raise the topic as a topic of common interests that could be looked into with the entire membership.” – HCP4*

> *“It started on HIV because patients started to realise that they could not find their treatment in yeah… in the pharmacy where they used to buy it” – P3*

As this phenomenon was undocumented, 3 out of the 9 representatives of the European civil society organisations mentioned that they initiated surveys among their national members. While patient organisation aimed to evaluate the scope of the problem, healthcare professionals’ representatives depicted the drawbacks on community and hospital pharmacists’ daily activity.

> *“We want to have an understanding of the situation on the ground because we are very well aware from our members that shortages are having [..] a significant impact on patient’s health and on pharmacy practice. So, every year, we do this survey”.*

- *HCP3*

Besides documentation, CSOs are actively engaged in European Union policy debates around shortages. All participants mentioned the need for European policymakers to "put a face on a problem" through the experience-sharing of healthcare users, patients and healthcare providers as cooperation between the civil society organisations and the European Policy makers lead to more understanding of the shortages consequences.

"We need a patient-centric approach and a systematic involvement of patients in all decision-making schemes, I think, because you cannot address a problem if you don't know from those who suffer from this problem, the size of the problem, what exactly what are the details of the problem" – P2

Not only do they advocate for the representation of public interests in legislative and non-legislative measures, but they also feedback on the policy effectiveness and outcomes.

"They [civil society organisations] understand the impact of it on patients. They can collect this information and feed it back to the policymakers, so that policymakers have a better understanding of the impact. […] of course, they have to be involved in policy decisions. Especially when you deal with something like shortages, you have to make sure that the policy solution you are going for will have the desired impact […] It needs to have the experience and the perspective or knowledge of users." – P1

2. The premises of the EU debates on the medicine shortages

Legislative measures on medicine shortages

The premises of the reflexion on the medicine shortages could be glimpsed in this literature review but the medicine shortages were considered as a minor subcategory of the whole debate on the availability and access of medicines. First, the EU Commission launched a study on the EU pharmaceutical product pricing that briefly highlighted the impact of low-pricing and reimbursement practices on medicine shortages (Vogler et al., 2015). This was echoed by the "workshop on EU Options for Improving Access to medicines" (European Parliament, 2017a, 2017b). Finally, the medicine shortages have been in several Council of the European Union's agenda during formal and informal debates, working groups and conferences under the Bulgarian, Dutch, Slovak, Romanian and Portuguese Presidencies (Council of the European Union, 2019a; Technopolis Group, 2021b). In 2020, the Council held a debate on how to strengthen cooperation and coordination to improve access to medicines (Council of the European Union, 2016, 2019a)

Anecdotal solutions could be promoted through different records but no structured reflexion on the shortages was made available. Different Commission's studies mentioned the use of

Supplementary Protection Certificates, off-label medicines, export bans or notification procedures to mitigate the supply disruption or (European Commission, 2018; Vogler et al., 2015; Weda et al., 2017). The need to report medicine shortages across the EU on an annual basis (European Parliament, 2017b), strengthened cooperation among EU Member States through information sharing, implementation of a notification system and market surveillance (Council of the European Union, 2019a) or relocation of medicines production back to EU were mentioned (Council of the European Union, 2019b).

Complexification of the non-legislative measures to address the medicine shortages

Before the pandemic, disruption in the medicine supply due to economic or commercial reasons were not within the EMA mandate. The premises of the EMA action was to prevent and mitigate the medicine shortages due to Good Manufacturing Practices (GMP) defects through harmonisation and communication procedures (European Medicines Agency, 2012b, 2012a, 2013a, 2013b, 2016c, 2016b, 2016a). From 2012 to 2016, the working documents emphasizes that EMA and the Heads of Medicines Agency elaborated their comprehension of shortages issues. First, the Agency underlined that the variation in medicine shortages definition still varied across the EU Members States. The Agency published common trigger points for harmonised notification across the EU (European Medicines Agency, 2015). Though not within the remit of their mandate, the EMA and the HMA identified the commercial reasons responsible for the medicines market withdrawals. However, both agencies remained evasive on their concrete legislative proposals to address the shortages while National Competent Authorities were invited to implement policies to mitigate the shortages in their country.

Over the years, the topic of medicine shortages gained importance at the EMA which complexified the type of measures and guidelines to ensure coordination, communication, and harmonisation across the EU Member States. In 2016, the EMA published a public catalogue on ongoing and resolved shortages for all type of causes and merged with the HMA into the Task Force on the Availability of Authorised Medicines for Human and Veterinary Use (European Medicines Agency, 2016c). It aims to determine the root causes of for all type of shortages, provide a standardized definition and indicators allowing to accurately and timely report shortages but also develop communication guidelines and systems to increase the flow of information between the different EU stakeholders (Technopolis Group et al., 2021).

Initiated by the Parliament's call (European Parliament, 2017b), the EMA and the HMA declared the availability of medicines as a priority in their EMA/HMA strategy to 2020 and work plan (European Medicines Agency, 2018). As requested during the Task force multi-stakeholder workshop on the availability of authorized medicines (European Medicines

Agency, 2018), the Task Force published a «Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)» (European Medicines Agency, 2019b) and «Good practice guidance for communication to the public on medicines' availability issues» (European Medicines Agency, 2019a). These papers both contribute to providing an harmonized definition of medicine shortages and the collection of the information provided in national shortages catalogues. They also encourage information-sharing across the EU Member States, with the healthcare providers and patients. Since 2019, the Task Force has implemented a pilot programme to establish a Single Point Of Contact (SPOC) network on shortages (Technopolis Group, 2021) where representatives of the National Competent Authorities reports current or anticipated shortages to the EMA.

3. Two-way stream between the Civil Society Organisations and the European Institutions

The EMA has a long tradition of collaborative work with the civil society organisation (Greer et al., 2017). Among the interviews, 4 participants belonged to the Patients and Consumer Working Party (PCWP) while 2 belonged to the Healthcare Professionals Working Party (HCPWP). Participants mentioned working parties were venue for dialogue and a "two-way stream" where the civil society experience and technical inputs can feed the EMA's activity. The 2 members of the HCPWP highlighted that the EMA would sometimes require technical inputs on a specific type of medicines under shortages or best-practices to report and cope with the shortages in different EU Member States.

> *"Through membership in the Healthcare Professional Working Party, we've been putting a lot on different […] shortage exercises. They were guidance documents that were drafted, EMA also consulted us on the work that they were doing, or are still doing, with the Heads of Medicines Agency on the availability of medicines […], there have also been like smaller consultations […] linked to specific products" – HCP4*

Three out of five patient representatives mentioned that the EMA would consult them to document the patient experience on medicine shortages.

> *"The EMA, as I mentioned, has a Working Party for Patient and Consumer organisations. It's a forum for exchange of views and input. The Medicines Agency basically seeks the input of civil society into its various policies and activities. […] It's also for sharing information. […] In these last years, the agenda has included a specific item on medicine shortages. So, the EMA updates us on its work and then we comment" – P1*

All participants outlined that they liaised with the European Commission (EC) and the different Members of the European Parliament (MEPs), especially the Environment, Public Health and

Food Safety (ENVI) Committee. They sent joint letters, position papers or response to the EC's public consultation. Participants stressed that before the pandemic, the interest in medicine shortages was rather limited, as echoed by the literature review. 4 participants mentioned a joint letter sent to the ENVI Committee in 2019 asking for a study on the root causes of shortages.

"We started working together with a group of healthcare professionals and healthcare users within EPHA, in 2019. We drafted 2 letters. One was for the Parliament […], we got just one answer which was "we're not interested" [B: ok], it was in 2019. We did the same with European Commission and the answer was different. We had gathering with the European Commission which invited all stakeholders […]. The conclusion was "We're not sure, what we can do". Our request at that time was still very simple, it was "We want a European report, in order to evidence the problem at European level and to better know how to deal with it". So, so there was no opposition but a quite cautious interest." - P3

However, mixed results regarding the Members of the European Parliament's interest have been highlighted which could be explained by their personal interest for a specific health topic, like cancer.

"- Interviewer : Why has the Parliament decided to take actions on medicine shortages in 2017 ? Interviewee: I think it was a push from the civil society organisations because we for sure spoke with different MEPs on this matter […] and they organised the different meetings [B: ok] with these MEPS and also discussions." – Patient representative (P2)

PART B: EU RESPONSIVENESS DURING THE FIRST WAVE OF COVID-19

1. COVID as a wakeup call

Medicine shortages are a longstanding problem in the European countries, but participants described the early months of the COVID-19 crisis as a "wakeup call" that set the medicine shortages high in the EU policy agenda. It modified the perception of medicine shortages among the general population and the European policymakers.

"- Interviewer: How important did the shortages seem to be for the European Commission or the European Parliament, before the pandemic ? - Interviewee: My impression is that to some extent, they seemed to be important already. It was

recognised that shortages were a problem, but I think the pandemic really triggered this topic and put it to the top of the policy agenda." – P1

Participants acknowledged that health, and the ill-health drawbacks suddenly became visible in the EU citizen's everyday life whereas they usually only affected a specific category of chronic ill patients.

"With COVID, everybody has been impacted and I think that's a big change in people's mind and maybe also in the in the Commission, that "One day, it could be me"- P5

The COVID-19 triggered the debate of strategic autonomy and dependency of the European States on East Asian Countries.

"All of a sudden, we noticed that we were dependent, for more than 60% of active ingredient, […] on India, Asia, etc. It's true that it came out suddenly during the pandemic in newspaper articles, on TV in shows etc. Whereas it had been underlined in a lot of reports since 2013" – HCP2

Furthermore, the pandemic has both unveiled the EU Member States protectionism and the lack adequate legislative framework to coordinate response the EU Members States to ensure the fair distribution of medicines under shortages.

"I think everybody was caught off guard, didn't have proper preparedness plan and then Member States realised the need to have a coordination at European level. Then, they realise that the EMA didn't have the powers they wish it could have so… And then that's why the discussion to expand the EMA's mandate started." – HCP3

"I would not say that there has been a radical change, what changed is that the European Commission realised that […] fighting shortages was a priority and that the pharmaceutical legislation regulation, which was the basis for the management of shortages, was not adequate anymore." – P3

2. Coordination of the European response to mitigate the impact of ICU-related medicine shortages

a. European Commission and the Member States

The European Commission has been reactive to the COVID-19 outbreak and calls on different measures to undermine the impact of shortages for ICU-related and other medicines facing risks of shortages.

The Commission encouraged Member States to reduce protectionists measures (European Commission, 2020a). Export bans for medicines and unnecessary national stockpiling by wholesalers and pharmacies were asked to cease in solidarity with the most vulnerable health systems (European Commission, 2020a). The Commission also called for the use of public procurement framework and invited central purchasing bodies to buy essential medicines for hospitals to ensure fair distribution of supply. The Commission also enhanced national medicine agencies and health authorities to share timely and accurate information with healthcare providers to provide optimal patient care. They set guidance to undermine the impact of shortages in the hospital setting (European Commission, 2020a).

The European Commission spurred Member States to be flexible towards the pharmaceutical industries and wholesalers. Recommendations included provide protective equipment for all employees of the supply chain and lift travel restriction for wholesalers in order to avoid the disruption of the supply chain and ensure the maximum workforce capacity (European Commission, 2020a). Additionally, the Commissions called Member states to support industry through fiscal incentives to increase the manufacturing capacity (European Commission, 2020a).

b. European Commission and the Industry

Box. 1 The Industry's positions on medicine shortages

In Europe, the pharmaceutical industries are represented by the EFPIA, for innovative medicines manufacturers, and Medicines for Europe, the generic medicines manufacturers. Both industry types acknowledge the dreadful impact of shortages on patients (EFPIA, 2019a; Medicines for Europe, 2017a).

While they acknowledged their share of responsibility in certain root causes for the shortages, such as the economical and manufacturing factors (AESG et al., 2019), industries called on the the EU Member States to be held accountable (AESG et al., 2019; EFPIA, 2019b). Indeed, they identified regulatory time lags and national requirement as root causes of shortages (AESG et al., 2019; EFPIA, 2019b). The generic industries also voiced their dissatisfaction regarding the cost-containments measures considered as financially unsustainable to maintain some medicinal products on the market (Medicines for Europe, 2017a, 2017b, 2019).

Since 2017, the pharmaceutical industries have stated their willingness to comply with the EU regulations and mitigate the shortages. For instance, the EFPIA mentioned the implementation of market forecasting methods and inventory management techniques to overcome the shortages (EFPIA, 2019b). As seen with the CSOs, the industry representatives also proactively formulated recommendations for the European Commission. These included a study on the root causes and definition of shortages, and a harmonised reporting system in all EU competent authorities to report potential risk of shortages (EFPIA, 2019b). Overall, both the innovative and generic medicine industries asked for more regulatory flexibilities and incentives to prevent and mitigate the shortages (AESG et al., 2019; EFPIA, 2019b; Medicines for Europe, 2017a). Medicines for Europe recommended national market predictability and the acceptance of multi-country packages in case of confirmed shortages to facilitate the movement of products between countries.

The Commission also required industries to monitor their stocks in critical products and production capacity and reorganise their production lines to produce critical medicines. These information were shared during weekly meetings with the pharmaceutical industries representatives (European Commission, 2020e).

During the first wave of the pandemic, the Commission, the Heads of Medicines Agencies and the EMA set regulatory flexibilities to the industries known as "Exceptional Change in Management Process (ECMP)" and VAT exemptions (European Commission, 2021a). The

ECMP were exclusively applied to critical medicines to treat COVID-19 patients and aimed to minimise their disruption, facilitate the re-purposive line production, and boost manufacturing capacity.

Box 2. Example of the Exceptional Change in Management Process (ECMP)

Marketing Authorisations (MA) are granted National Competent Authorities and delivered for a specific production site, supplier, and composition of a medicinal product. During the pandemic, the EU Institutions enabled fast-track procedures to expand national marketing authorisations to new Member States who needed these medicinal products. The renewal submission procedures could be postponed while medicines remained available on the market and diversified suppliers could be used, regardless of the MA specificities.

The **Good Manufacturing/Distribution Practices (GMP and GDP**) certificates for the manufacturing or distribution of active substances and/or finished products are delivered after an onsite control (European Medicines Agency, n.d.). These controls investigate the compliance with quality, efficacy, safety and marketing authorisation requirements (European Medicines Agency, n.d.). During the crisis, the EMA network could conduct a remote assessment or an extension of GMP certificates for the importation and manufacturing of medicinal products.

For medicines that enter a national market, **labelling and packaging** must comply with the official language and norms for packaging. During the pandemic, the European Institutions agreed to grant full or partial exemptions to certain labelling and packaging requirement to ensure availability of medicines (European Commission, 2020a). However, manufacturers still needed to provide a website link with information in the correct language.

c. The EMA as a central coordinator of the supply in medicines

Besides the flexibilities granted for control processes, the EMA became a central coordinator between Member States, National Competent Authorities, and pharmaceutical companies.

In March 2020, the Commission, the EMA and Member States set up an EU Executive Steering Group on Shortages of Medicines Caused by Major Events (Technopolis group, 2021). This group was an attempt to coordinate action at the European level to avoid the disruption in the supply chain due to the COVID-19 pandemic and ensure effective communication with healthcare providers and patients. The Steering Group focused on ICU medicines for ventilated and non-ventilated COVID patients and further worked on essential medicines for non-COVID hospitalised patients.

The EU Executive Steering group has developed a monitoring and forecasting model to help predict and match the demand and supply of medicines used in intensive care units across the EU Member States (European Medicines Agency, 2020c). This involved sharing of best

practices regarding the estimation of future needs by different Member States and explore how joint principles for data collection and analysis. Their method has been published a "reflection paper on forecasting demand for medicinal products in the EU/EEA" (European Medicines Agency et al., 2021). The forecasting of demand/supply was further extended to other medicines therapeutics types (European Medicines Agency, 2020d).

In April 2020, the EMA launched an industry Single Point of Contact System (i-SPOC) to monitor the root causes of ongoing and expected shortages in critical medicines to treat COVID-19 (European Medicines Agency, 2020b). The system was built on the existing SPOC network implemented to communicate with the National Competent Authorities: here, a pharmaceutical spokesperson is responsible for reporting to the EMA. The i-SPOC monitors nationally authorised medicines based on the list of essential medicines to treat COVID-19 patients. This monitoring and coordinating role in case of emergency paved the way for the draft regulation of the EMA mandate proposed by the European Parliament (European Parliament, 2020a).

3. The role of the civil society during the pandemic

a. Civil Society consultation in time of crisis

The first months of the COVID-19 pandemic were characterised by a sense of urgency that resulted in the swift implementation of measures by the EC and the EMA. Due to short deadlines, the public consultation and structured dialogue of all stakeholders has been undermined. Ultimately, this has constrained the ability of healthcare and patient organisations to contribute to the development of policy solutions.

"Usually also, it takes quite some time for stuff to be adopted, but especially at the beginning of the pandemic like for instance the guidance document linked to ICU medications […]. That one went extremely quickly which was also been challenging for associations like us, to be consulted which was great, but to be consulted with extremely short deadlines…" – HCP4

The interviews highlighted mixed results regarding the direct contacts between the CSOs and the EC during the first months of the pandemic. Healthcare professionals working on ICU-related medicines seemed to be more consulted than others. However, some members were unable to remember if they had participated in any formal or informal consultation.

"It's difficult to say. It's true that I've had a closer look at my colleague's problems in European hospitals. I saw some texts passing on, mostly for national competent authorities and industrials but I don't think that we had nor time nor resources to consult" – HCP2

"For the civil society, it has not been optimal. […] It's true that the relationships that we could have with members of the Commission facilitated the individual solicitations but there has not been […] this collective process" – HCP1

Participants depicted the direct contacts between the Commission, the EMA, the National Competent Authorities, and the pharmaceutical industries. Most participants underlined that the pharmaceutical industry was more consulted than them, as depicted with the EMA COVID-19 Task Force.

"The communication channel was very much between the National Health Authorities and the EMA or like.. Industrials." – P5

"This second Task Force involved Member States and the industry [B nods], it was a constant dialogue with industry because obviously the objective was to make sure that the industry could increase production and provide as much medicines as possibly needed. Um so… It makes sense but both patients, or healthcare users organisations and healthcare professionals organisations have been completely excluded from this dialogue" – P3

The EMA's HCPWP and the PCWP became the venue to raise some concerns and voice their opinion on policy measures and certain flexibilities given to the industry.

"One of the things they consulted us on PCWP, yes, you know for the industries there were some flexibilities on the packages. […] We said, "we want to be consulted on this […]". So, they shared with us a document that they published about allowed flexibility for the packages […] and we could make some points, little points there. Other than that, I don't remember that they consulted us." – Healthcare user representative (P4)

b. Factors inducing different consultation methods

First, the pharmaceutical industry has been portrayed as a more legitimate actor during the first months of the crisis. 4 out of 9 interviews legitimised the differences in consultation mode with the pharmaceutical industry as they were considered as the most knowledgeable stakeholder at the time. The Commission directly contacted the pharmaceutical industry for their technical input on the European market, status of medicines stock or vulnerabilities of the supply chain.

"Industry was more consulted than us because there were practical problems like, bringing medicine by planes from or active pharmaceutical ingredient from third countries, or lorries blocked at the borders of Bulgaria for example." – HCP3

Participants also expressed that the public image of the pharmaceutical industry had improved due to the dependency of the EU Member States on the private sector.

" For all institutions, Member States, the European Commission, even the European Parliament until a certain extent, not all MEPs, industry has been considered as saviours in some way. They developed vaccines in record time, also treatments and so all doors opened to the industries […]. We felt like there was no caution anymore" – P3

As a result, most participants, in particular healthcare users and patients, felt that the Commission considered them as "secondary stakeholder" during the crisis.

"The perception you have is that they don't value you as a stakeholder as much as the industry. You know what I mean? It's a bit like, and understand, we need the industry especially in this situation [...] but I mean… […] It gives a bit impression that maybe they did not consider our input as necessary and valuable which is, I think, problematic." – P4

Secondly, the perception of the pharmaceutical industry as a more legitimate actor to mitigate the medicine shortages of ICU-related medicines has been reinforced by COVID-19 putting significant strain on patient organisations.

"There has been an enormous strain and burden of COVID-19 on our civil society organisations. A lot of them have seen reduced funding, resource problems with capacity. So, it's just become in a way harder to engage them in advocacy" – P1

Participants stressed that generic medicine shortages became a secondary as they had to cope with competing priorities, such as sharing of guidelines and information with the healthcare providers and patients.

"We did not see patient associations in this period because, there is no ICU-patient association. But they have been more active regarding delayed care, actually" – HCP1

Regardless of the COVID-19 crisis ad as compared to the pharmaceutical industries, all the interviews highlighted a structural imbalance in the economic, financial, and human resources. This structural imbalance leads to an over-representation of the pharmaceutical industry's private interest at the EU level and a minimisation of the CSOs' policy recommendations.

"We don't have huge teams like pharmaceutical industry and that can work non-stop on one specific project, we have a small team, and we have many things to checkout. So, in this regard I would say it's more difficult to... for civil society organisations to have their voices heard." – HCP4

PART C: RESILIENCE OF THE EU DEBATES ON MEDICINE SHORTAGES

1. Extension of the European Health Union Package

COVID-19 has impacted the EU Health Union Health Package and gave room for several legislative and non-legislative measures to address the shortages of medicines. In September 2020, the Parliament published “The shortage of medicines – how to address an emerging problem” (European Parliament, 2020b) that put medicine shortages as a priority of different EU legislative and non-legislative measures. They include the new pharmaceutical strategy, the revision of the EU pharmaceutical legislation, the extension of the EMA statutory basis and the EU4 Health Programme.

a. The New Pharmaceutical Strategy

In November 2020, the European Commission adopted the new Pharmaceutical Strategy for Europe (European Commission, 2020d) which aims to secure the supply of medicines and avoid shortages, by the pillar 'Enhancing the resilience of the pharmaceutical supply chains' (European Commission, 2020g). It consists in building the EU’s strategic autonomy by diversifying and securing the pharmaceutical supply chain, promoting strategic stockpiling and increased production and investment in Europe (ERPS, 2021).

Civil society organisations have been able to participate in the public consultation (European Commission, 2020b, 2020f). Multiple back-and-forth after the adoption of the Pharmaceutical Strategy with a specific mention on medicine shortages outlines the interest of the European Parliament, the Commission and the Council (Council of the European Union, 2021a; European Commission, 2021d; European Parliament, 2021a; Sacrédeus, 2021; Schaffenrath, 2021).

Part of this Pharmaceutical Strategy, the Commission hold a Structured Dialogue on security of medicines supply. The multiple stakeholders included all the actors of the supply chain, civil society representatives and the researchers to understand the global supply chains and identify vulnerabilities. The Council of the EU invited all Member States to provide inputs to the Structured Dialogue to develop a better understanding of the global supply chains (Council of the European Union, 2021a).

b. Revision of the EU general pharmaceuticals legislation

In 2021, the Commission announced that they would revise the EU general pharmaceutical legislation by the end of the annual quarter 2022. One objective of the revision is to enhance the security of supply and address the shortages (European Commission, 2021c)(Council of the European Union, 2021a).

Part of this revision, several studies have been commissioned such as the one on the root causes of the shortages (Technopolis Group, 2021b, 2021a), as recommended by the civil society organisations, and the forthcoming review of potential solutions to address the medicine shortages (Jongh et al., 2021).This initiative has been welcomed by the EP and the Council (Council of the European Union, 2021a; European Parliament, 2020b).

c. EMA extended mandate

In November 2020, the European Commission published the lessons learnt from COVID-19 in an attempt to reinforce the EU's resilience for cross-border threats (European Commission, 2020c). These proposals have been legislated by the European Parliament in January 2022 (European Parliament & Council of the European Union, 2022) after numerous forth-and-back with the different EU Institutions (Council of the European Union, 2021b, 2021c, 2022; European Commission, 2021d; European Parliament and the Council, 2020, 2022a, 2022b; Sacrédeus, 2021; Varkardakastanis, 2021).

The EMA extended mandate aims to turn the ad-hoc solutions set up by the EMA during the first wave of the COVID-19 into permanent structures to monitor and mitigate shortages of medicines and medical devices caused by major events. The mandate stipulates the creation of a EU Executive Steering Group on Shortages of Medicinal Products (MSSG) to deal with emerging issues, coordinate and monitor the supply of medicines and ensure the communication channel between manufacturers and competent national authorities (European Commission, 2020c).

d. Transversality of medicine shortages

Medicine shortages have been integrated in the EU4Health Programme for the period 2021-2027 (European Parliament & The Council of the European Union, 2021). The 2021 EU4Health Programmes allocated a specific budget of 12M€ within the crisis preparedness item that aims to mitigate the shortages of medicines and improve the security of supply including COVID-19 therapeutic. However, the shortages of medicines are not mentioned in the 2022 EU4Health Programmes 2022 (European Commission, 2022). It will be interesting to see if a specific budget in the 2023 EU4Health Programmes will be allocated to the shortages after the revision of the EU general pharmaceutical legislation.

Additionally, the Europe's Beating Cancer Plan specifically addresses the shortages of cancer medicines and the initiatives developed through the Pharmaceutical Strategy to ensure the access to innovative and generic medicines (European Commission, 2021b).

2. Return to the civil society's structured consultation

a. Contribution to the legislative process

Participants mentioned that after the first wave of the pandemic, the Commission returned to structured and public consultations of all the stakeholders.

"I don't really know the impact on the European Commission or the Parliament during the pandemic. However, I can observe that civil society organisations, patient representatives, hospitals, payers, healthcare professionals, are represented in the consultations. May that be in small groups or or for public consultations" – HCP2

Participants were able to participate in the Structured Dialogue but depicted it as "an example of the power imbalance". 5 out of 6 participants that attended this event explained the flaws in the organisational process that lead to an over-representation of the industrial interests. Participants also outlined that the Commission recognised the bias and reconvene a meeting with CSOs to balance the representation of interests.

"There was a Structured Dialogue [B: yes] and there was an imbalance in terms of representation of interests […]. There were 50 representatives from the industry, because there is EFPIA and then all the companies or the consultancies and then only one representative from the doctors, one patient organisation. Of course, the discussion was dominated by industry. Also, because the Commission gave them the rapporteurship of the working group and by being a rapporteur, you… you guide the discussion." – HCP3

"The Commission listened to us well because they had in order to mitigate a bit this problem, […] they had organised just one dedicated meeting only with civil society without the industry, so that was quite good." – HCP4

As opposed to this Structured Dialogue, the study on the root causes of shortages was considered as a success for the civil society representatives.

"This study has been done now, the Technopolis one. It was interesting. For us, also it's means that we've achieved something, it's the civil society that asked to do this report." – P5

Despite problems in the inclusion of stakeholders, participants approved the consultancy methods, such as bilateral interview, and the good balance of recommendations.

" When the people from Technopolis were doing the consultations they were very good in the sense that we actually participated in a bilateral interview with them. They came back and asked us for more information. I think there are some recommendations about civil society involvement in the report which is what we asked for." – P1

The Structured Dialogue and the study on the root causes of shortages reflects the mixed views of the participants on the quality of the Commission's consultation of the CSOs. Patients representatives explained that the technocratic consulting methods and the limited time frame for capacity-building within umbrella organisations, like CSOs, were major constrains.

"[The Covid-19 pandemic] has accelerated the process [of collaboration between CSOs and the different European Institutions], for sure. I don't think it would have gone that fast, that there would have been such process on the stakeholder consultation without the COVID-19" – HCP1

"Our proposals seem not sufficient for them [The European Commission], what they are asking is only data. We produce data but on the impact of shortages on patients. Obviously, that's much more difficult to produce data on how the measures we propose could impact shortages at EU level. So, it seems that they do not understand the way we work, and they do not seem to be in a position to transform our proposal in legislative proposal, which is quite surprising because with the European Parliament, it worked very well." – P3

Finally, while interest in the medicine shortages was present for the MEPs before the pandemic, participants mentioned that their interest has grown.

"If you compare let's say those in the ENVI committee before COVID pandemic and now, I think you have a few that might not have had such a great interest in health beforehand and that might have now a bit more interesting in the topic." – HCP4

b. Contribution to the non-legislative process

Participants mentioned that the CSO inclusion in the different EMA's working parties was not impacted during or as a result of the COVID-19 pandemic. After a push from the CSOs, some of their representatives will attend as "observers" of the COVID-19 Steering Group set within the new EMA extended mandate. This highlights the resilience of the EMA in terms of inclusion of CSOs in case of major events, like COVID-19.

"Within HCPWP, we know that they are also going to keep us engaged, so I think there's room for us to contribute. Um and so far, I see that the EMAs also like liaising with us on what this Steering Group is doing. […] So, I see a lot of room for let's say trying to shape a little bit of how this extended mandate… […] I think the PCWP secretariat and people working there, they really tried to liaise as much as they can. […] As I say we can bring very useful inputs at the EMA. We pushed for the Steering Groups to have representatives of the PCWP and the HCPWP and that's there." – P4

c. Contribution to the European Health Union

The interviews underlined the momentum for health and echoed the transversality of medicine shortages across the European Union Health Package, particularly to ensure the access to oncology medicines.

"It was not just COVID, it was also the fact that institutions want to work more on health and cancer is a specific case […]. We also had in 2021, the European Beating Cancer Plan, there is also a momentum for cancer." – P2

The Health Union is high in the European agenda which has legitimised and eased the involvement of the civil society organisations in the policy-making process.

"Interviewer: How could have the COVID-19 pandemic influence the way civil service organisations now collaborate with different European institutions? Interviewee – Uh… More legitimacy, I would say. That's the first word that comes to my mind. You know when I started here, […] I said "you know, health is never on the top of the political agenda". It's wrong now." – P5

"Some MEPs wanted to hear from us […] on the Extended Mandate. It was easier because you could have online meetings and so it felt like more accessible." - HCP3

DISCUSSION

The main objective of this study was to understand the impact of the COVID-19 pandemic on the European agenda-setting to address the medicine shortages. The triangulation approach was used to collect evidence from the policy papers and contextualise them with 9 semi-structured interviews with civil society representatives.

MAIN RESULTS

This study has highlighted the impact of COVID-19 on the EU regulation of the medicine shortages. Before the pandemic, the EU framework was limited to the Directive 2001/83/EC and the EMA could only address shortages due to GMP non-compliance and quality defects. Civil society organisations had been key advocates to raise awareness on this issue though the European Institution's interest was limited to develop concrete solutions.

The COVID-19 pandemic has underlined the lack of coordination between EU Member States, the limit of the current EU general pharmaceutical legislation and the need for EU's strategic autonomy. While the European Commission set regulatory flexibilities to ensure the provision of supply during the crisis, the EMA has created several ad-hoc activities to monitor and forecast the shortages of medicines during major events.

The COVID-19 has catalysed the emergence of a European Health Union package, based on the problems outlined during the first month of the pandemic, where medicine shortages are transversal. However, concrete legislative measures to address the long-term root causes of shortages are expected for the fourth quarter of 2022, within the new EU pharmaceutical legislation.

THE MULTIPLE STREAM FRAMEWORK

As seen in the methods, the results of this study may be observed in the light of the Multiple Stream Framework.

The problem stream

The problem stream is the recognition of a public matter as a problem for the society that requires the government action. It is influenced by previous efforts of government to respond to them (Buse et al., 2005). The results illustrated that civil society organisations have raised awareness on the impact of the medicine shortages on patient continuity of care and healthcare professional's occupational activity. However, before the pandemic, advocacy has not been sufficient to promote concrete policy proposals. The EMA published its first documents on the shortages in 2013 but the problem was concretely considered in 2017 by the European Parliament. This could be related to three main limitations. First, the medicine shortages issue is a phenomenon that has been undocumented by the researcher community and entitled to opacity of data on the root causes and trends in shortages before the pandemic. Data collection on medicine shortages was performed by the National Competent Authorities or civil society organisations and characterised by a low permeability through the European and general population sphere. Secondly, European healthcare systems are fragmented and the Directive 2001/83/EC can be transposed in varying national policies. Some EU Member States, like France, might be more inclined than others to implement concrete measures to prevent and mitigate the shortages. European action could have been limited by the prevailing idea that EU Member States should be independent rather than submitted to a strict coordination of their national medicines agencies and interoperability of their reporting systems.

The COVID-19 pandemic has changed the public perception of medicine shortages. First, the type of medicines under shortages, paracetamol and ICU-related medicines among others, were either widely used or associated with mortality risks. Mass media coverage has raised awareness on the severity of the phenomenon. Secondly, the pandemic has highlighted EU’s dependency on East Asian countries to supply Active Pharmaceutical Ingredients which renew the debate of strategic autonomy. Finally, the pandemic has highlighted the lack of

coordination between the Member States and the limitation of the legislative tools to prevent and mitigate the medicine shortages.

The policy stream

The policy stream refers to the ongoing analyses of a problem and their proposed solutions with debates surrounding these problems and possible responses (Buse et al., 2005). Regardless of the Directive 2001/83/EC, no European legislative measures was enforced at the European level before the pandemic. The EMA mandate was restricted to the management, coordination, and harmonisation of shortages due to GMP non-compliance and quality defects. From 2015 to 2019, the EMA's working parties were the venue for discussing policy options to address this issue and set new guidance to report and communicate on all types of shortages. The European Commission and the European Parliament progressively acknowledged the need for action, but no policy proposal was on the table. The results highlighted that the civil society organisations were key stakeholders in advocating for the development of patient-centric policies. As mentioned during the interviews but not developed in this study, the national policy-setting intertwined with the European one, and Member States encouraged the European policymakers to act. With the first wave of the COVID-19 pandemic, the cross-border health threats have urged the European bodies to promote swift solutions while constraining the structured and public consultation process. Our results also highlighted how the structural power imbalance impacts the policy stream. According to the CSOs, the resources gap between them and the pharmaceutical industry as well as the sense of urgency resulted in the over-representation of the industrial policy options in the debate, as seen during the Structured Dialogue.

The politics stream

The politics stream refers to unpredicted events, changes of government and campaigns by interest groups (Buse et al., 2005). The results highlighted that most civil society organisations became "invisible participants" from the medicine shortages politics and policy stream during the first wave of the pandemic.

With COVID-19, the public perception of the medicine shortages has gained importance. Moreover, the pandemic and the use of new tools, such as remote meetings, facilitated the contacts between the civil society organisation and the different European Institutions. Another fundamental aspect depicted in the interviews was the importance given to the European Health Union Package thanks to the change in the new Commission in 2019. The medicine shortages have become transversal to the Europe's Beating Cancer Plan or the crisis and preparedness plans which might explain the interest from the Commission and several MEPs to address this issue.

The COVID-19, and potential other politics stream, has opened a policy window and catalysed the European response and political agenda. Supply of medicinal products is the fourth pillar of the European Pharmaceutical Strategy and a key piece of the upcoming European Pharmaceutical revision. The European Commission published a study on the root causes of medicine shortages in 2021, hosted the Structured Dialogue and another study on the policy proposal impact assessment is expected for Q4 2022. The EMA extended mandate for emergency crisis has entered into force in March 2022. Whereas many non-legislative measures have been launched since the COVID-19 outbreak, concrete legislative proposals are still on the making. However, the fading sense of urgency could deter EU Member States to allocate more budget and power to the European Institutions.

Strengths and limitations

To the author's knowledge, this research study is the first one that has specifically studied the impact of the COVID-19 pandemic on the European agenda for preventing and mitigating the medicine shortages considering the Multiple Stream Framework. In addition, this study has stressed the contribution of the civil society to the policy-development whereas their role is often disregarded in the scientific literature.

This study has several limitations. First, the analysis of the impact of the COVID-19 pandemic was not exhaustive due to the lack of hindsight on the policy proposals within the revision of the European Pharmaceutical legislation that will be made by the end of the year 2022. Given the limited time frame, the study mainly focused on the relationship between the European Commission, the EMA and the civil society organisations while other actors are also involved in the policy-setting of the EU agenda. Further studies could investigate the role of pharmaceutical industries or Member States in the policy-development. The researcher has previous professional relationship with three participants which might have led to certain biases such as assumptions about the role attributed to the civil society organisation by the European Commission and the EMA. The study has not reached data saturation since only 9 participants were interviewed. Two participants had less-than-two years seniority in their organisations and 3 participants mentioned that medicine shortages were not a priority topic for their organisations before the pandemic. It could have limited their comparison for the pre- and post-COVID era, though all of them already worked on European health organisations before the pandemic. Therefore, further studies with a larger sample could explore the role given to civil society organisation on health topics in time of crisis.

CONCLUSION

The COVID-19 pandemic has reframed the public perception of the medicine shortages in Europe and urged European Institutions to consider medicine shortages as an agenda priority. The EMA extended mandate and the New Pharmaceutical Strategy aim to ensure the fair allocation of medicinal products during major events and restore EU's strategic autonomy. Despite the initiative to revise the EU general pharmaceutical legislation, the relevance of the policy proposals and their transposition at the national level is still to be determined. Whereas medicine shortages preceded the COVID-19 pandemic, the political will to implement strong prevention and mitigation measures might weaken as the cross-border health threats fades. Additionally, the pandemic has exacerbated the structural power imbalance between different stakeholders. This study highlights the need for the systematic involvement of the civil society organisations to ensure the representation of the public-interest, even in time of crisis.

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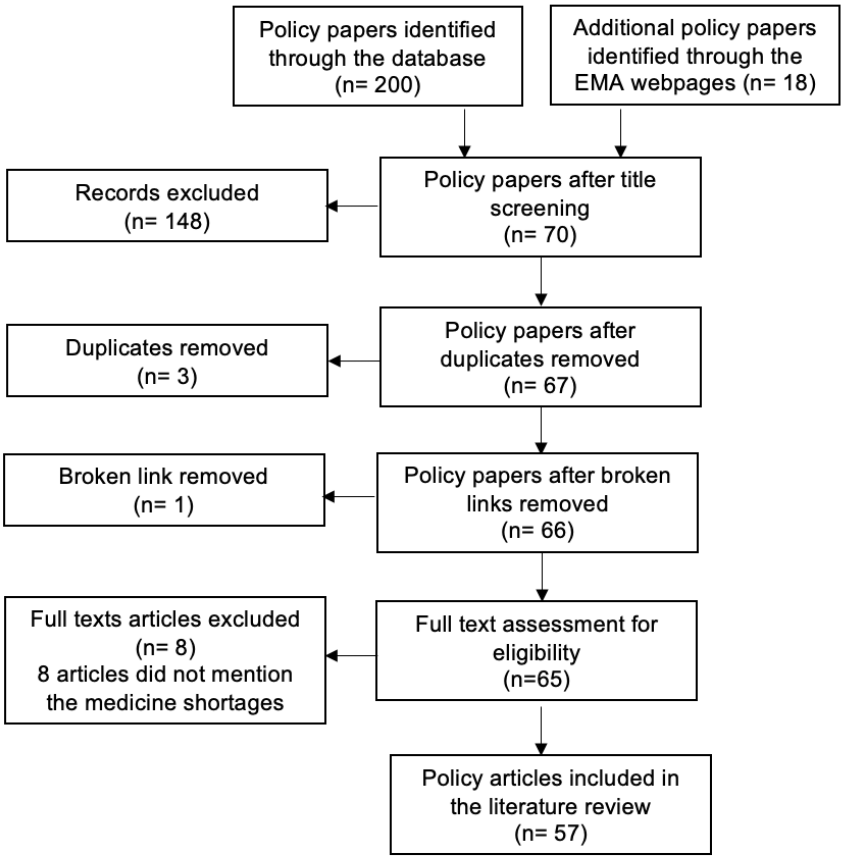
APPENDICES

Annex 1. Grey literature selection flow chart



Annex 2. Participants demographics

Participant	Sex	Organisation type	Seniority (y)	Position	EMA Working Party
HCP1	M	Healthcare professional	17	Director	No
HCP2	F	Healthcare professional	2	Policy Officer	No
P1	F	Patient / Healthcare users	12	Director	Yes
HCP3	F	Healthcare professional	4	Director	Yes
P2	F	Patient / Healthcare users	2	Policy & Advocacy Officer	Yes
P3	F	Patient / Healthcare users	10	Policy & Advocacy Officer	Yes
HCP4	F	Healthcare professional	5	Director	Yes
P4	F	Patient / Healthcare users	3	Policy & Advocacy Officer	Yes
P5	F	Patient / Healthcare users	3	Policy & Advocacy Officer	No

Note: For anonymisation purposes, the nationality of the participants has not been specified in this table. The number of Brussels civil society organisations advocating on medicine shortages and part of the EMA's working parties being already limited.

Annex 3. Interview guide

Time	Main question
PRE-PANDEMIC	Before March 2020, how has your organisation contributed to the problem perception of medicine shortages in Europe ?
	Before March 2020, how important did the shortages seemed to be in the European agenda-setting or policy discussion ?
	Before March 2020, how were civil society organisations involved in the formulation of solutions and the European policy development to address the medicine shortages?
6 MONTHS AFTER THE COVID-19 OUTBREAK	As compared to the pre-pandemic period, what differences have you noted in the type of measures implemented by the European Commission or the EMA to respond to the pandemic?
	What advocacy work did your organisation conduct on the medicine shortages during the pandemic?
	How were the civil society organisations involved on the formulation of emergency measures by different European Institutions to respond to the shortages?
>6 MONTHS AFTER THE COVID-19 OUTBREAK	What legislative or non-legislative measures to address medicines shortages have been implemented as a result of the pandemic ?
	As compared to the pre-pandemic period, how has the European agenda-setting evolved to address the medicine shortages?
	How has or could have COVID-19 influenced the way civil society organisations collaborate with the European Commission, the European Parliament or the EMA ?

Annex 4. Codebook

Topical or Interpretative	Code	Subcode	ID	Definition
Topical	Pre-Covid	General	T1A	Use this code to capture any general information about the dynamics between different stakeholders, recommendation and policies made before March 2020 that would not fit into any subcode.
		Member Advocacy	T1B	Use this code to capture information related to the inputs and activities produced by the different civil society organisations for capacity-building purposes or advocacy at the national level before March 2020. This code can also capture the lack of activity done on medicine shortages before March 2020.
		EU Advocacy	T1C	Use this code to capture information related to civil society organisations participation or non-participation to European Commission consultation, EMA workshop or any solicitation of a Member of the European Parliament before March 2020. This code can also capture the lack of activity at the European level before March 2020.
		Added value	T1D	Use this code to capture information linked to the role and added-value of civil society organisation representativeness in the European health policy-making process for the medicine shortages.
		Agenda	T1E	Use this code to capture information linked to the perception of the medicine shortages problem in the European Union and legislative and non-legislative measures implemented by the different European Institutions before March 2020
Topical	Crisis	General	T2A	Use this code to capture any general information about the dynamics between different stakeholders, recommendation and policies made before March 2020 that would not fit into any subcode.
		Window of opportunity	T2B	Use this code to capture information related to the impact of COVID-19 on the framing of the medicine shortages problem, the reaction from the general population, Member States and the European Union and the reflection about preparedness and reactiveness in the European Union.
		Responsiveness	T2C	Use this code to capture information related to European Institutions responsiveness to the COVID-19 crisis and legislative or non-legislative measures implemented to prevent and mitigate the impact of medicine shortages between March and August 2020.
		Consultation	T2D	Use this code to capture any information related to way different European Institutions consulted the pharmaceutical industries or civil society organisations on legislative and non-legislative measures from March to August 2020.

Topical	Post-Covid	General	T3A	Use this code to capture any information about the COVID-19 pandemic and its impact on the medicine shortages that would not fit into any subcodes
		EU Event	T3B	Use this code to capture any information relative to the Structured Dialogue or the Technopolis consultancy rounds mandated by the different European Institutions, their topic, format, strengths, weaknesses, and outcomes to address the medicine shortages after March 2020
		Policies	T3C	Use this code to capture any information about policies, legislative or non-legislative measures implemented by the different European Institutions to address the medicine shortages after August 2020. This code can also capture their absence.
		CSO & EU	T3D	Use this code to capture any information on the impact of COVID-19 on the way civil society organisation may or may not collaborate with or be included in the different European Institutions and reflection about the dynamic between these stakeholders. This code can also the absence of change in the collaboration because of the COVID-19 pandemic.
		Multi-stakeholderism	T3E	Use this code to capture any information link to the differences in the way different civil society organisations, patients, healthcare professionals or consumers and actors of the supply chain may collaborate address the medicine shortages because of COVID-19.
Topical	Shortages	General	T4A	Use to code to capture general facts about the medicine shortages, their trends, root causes and key facts about them and how they are dealt with at the national and the European level.
		Recommendations	T4B	Use this code to capture any information related to the lesson learnt from COVID or potential recommendations that participants have made to prevent and address the medicine shortages.
		Member States	T4C	Use this code to capture any information about policies implemented in specific Member States to address the shortages, actions taken by the member States to deal with the problem at the European level.
Iterative	Power Balance	Differences	I1A	Use this code to capture any factors that could explain the difference in consultation mode between the civil society organisations and the pharmaceutical industries by the different European Institutions after March 2020 such as time and professionalisation. Resources are excluded from this section.
		Resources	I1B	Use this code to capture any information relative to the difference in financial, human and time resources between the pharmaceutical industries and the civil society organisations and how this can influence their respective advocacy work at the European level.
		Priorities	IAC	Use this code to capture any information related to the competing priorities and work done by the civil society organisation on healthcare delivery or access to medicines and their potential impact on the medicine's shortages advocacy during the first wave of the COVID pandemic.
Iterative	EU 4 Health	General	IB1	Use this code to capture any information related to other factors than COVID-19 that may explain a window of opportunity for taking actions to address the medicine shortages in the European Union (Pharmaceutical Strategy, EU Pharmaceutical legislation, EU Beating Cancer Plan)

RÉSUMÉ

Titre : Analyse politique de l'impact de la pandémie de COVID-19 sur la régulation européenne des pénuries de médicaments.

Introduction : En Europe, le nombre de pénuries de médicaments a augmenté de 20 fois entre 2000 et 2018. Les pénuries de médicaments sont étendues et causent des risques substantiels sur la continuité des soins des patients et la pratique des professionnels de santé. La société civile a été un acteur majeur dans la sensibilisation aux pénuries de médicaments et le plaidoyer pour un renfort de la régulation européenne. Cependant, la pandémie a exacerbé le besoin d'une réponse européenne coordonnée afin de contrebalancer les vulnérabilités de la chaîne d'approvisionnement mondiale et assurer la distribution équitable des médicaments entre les États Membres européens. Cette étude vise à comprendre l'impact de la pandémie dans le développement d'un agenda européen permettant de réduire l'impact des pénuries.

Méthodologie : Une méthode de triangulation a été utilisée afin de développer une compréhension exhaustive de la construction politique. Cette étude comprend une revue de littérature grise et 9 entretiens semi-structurés avec des représentants des organisations de la société civile.

Résultats : La pandémie a contribué à placer les pénuries de médicaments en tête de l'agenda politique. L'union européenne de la santé comprend la nouvelle Stratégie Pharmaceutique, l'extension du mandat de l'Agence Européenne des Médicaments, ainsi que la prochaine révision de la législation européenne pharmaceutique.

Conclusion : La pandémie de COVID-19 a redéfini la perception du problème des pénuries de médicaments dans la société et catalysé le développement de la politique européenne. Le sentiment d'urgence a également exacerbé la balance du pouvoir entre la société civile et l'industrie pharmaceutique. Cette étude illustre le besoin de la représentation des intérêts commun au travers de l'implication systématique de la société civile, et ce, même en temps de crise.