



OPEN ACCESS

EDITED BY

Hans De Loof,
University of Antwerp, Belgium

REVIEWED BY

Umberto M. Musazzi,
University of Milan, Italy
Caijun Yang,
Xi'an Jiaotong University, China

*CORRESPONDENCE

Laëtitia Belgodère
✉ laetitia.belgodere@ansm.sante.fr

RECEIVED 12 September 2023

ACCEPTED 06 November 2023

PUBLISHED 17 November 2023

CITATION

Belgodère L, Emmerich J, Albin N, Bacon T, Daynes P, Vignot S, Vial T, Renaud G, Le Saulnier C, Maillard-Couvreur C, Cachet M, Veyries M-L, Youdarene R, Oualikene-Gonin W, Ratignier-Carbonneil C and Maison P (2023) Prevention and management of health products shortages by the French national agency (ANSM), 10 years of experience. *Front. Public Health* 11:1293110. doi: 10.3389/fpubh.2023.1293110

COPYRIGHT

© 2023 Belgodère, Emmerich, Albin, Bacon, Daynes, Vignot, Vial, Renaud, Le Saulnier, Maillard-Couvreur, Cachet, Veyries, Youdarene, Oualikene-Gonin, Ratignier-Carbonneil and Maison. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Prevention and management of health products shortages by the French national agency (ANSM), 10 years of experience

Laëtitia Belgodère^{4*}, Joseph Emmerich^{1,2}, Nicolas Albin^{1,3}, Trystan Bacon^{1,4,5,6}, Pascale Daynes^{1,7}, Stéphane Vignot^{1,8}, Thierry Vial^{1,9}, Guillaume Renaud¹, Carole Le Saulnier¹, Corine Maillard-Couvreur¹, Mélanie Cachet¹, Marie-Laure Veyries¹, Rym Youdarene¹, Wahiba Oualikene-Gonin¹, Christelle Ratignier-Carbonneil¹ and Patrick Maison^{1,10,11}

¹Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), Saint Denis, France, ²Hôpital Saint Joseph Paris (Médecine Vasculaire), INSERM 1153 CRESS, Université de Paris Cité, Paris, France, ³Groupe Hospitalier Mutualiste de Grenoble, Institut Daniel Hollard, Grenoble, France, ⁴General Practitioner, Montmerle-sur-Saône, France, ⁵Collège universitaire de médecine générale, Université Claude Bernard Lyon 1, Lyon, France, ⁶Groupe de travail "Thérapeutique", Collège de la médecine générale, Paris, France, ⁷Union Francophone des Patients Partenaires, Faculté de Médecine, Centre Hospitalier Universitaire Grenoble Alpes, La Tronche, France, ⁸Institut Godinot, Reims, France, ⁹Hospices Civils de Lyon, Lyon, France, ¹⁰EA 7379, Epiderme, Faculté de Santé, Université Paris-Est Créteil, Créteil, France, ¹¹CHI Créteil, Créteil, France

Shortages of drugs and medical devices have tended to increase in France and worldwide, with consequences for patients and healthcare professionals. Preventing shortages of health products has become a priority for regulatory authorities, including the French National Agency for Medicines and Health Products Safety (ANSM). To highlight perspectives for a better prevention, we described and analyzed the management of shortages in the availability of health products in France over the last 10 years. The supply chain was mapped to identify the main causes of shortages and stakeholders involved in managing shortages throughout the supply chain. National and European initiatives and regulatory measures were reviewed. A retrospective nationwide data analysis from the French reporting system of health product shortage reports was conducted over 10 years for drugs (2013–2022) and over an 18-month period for medical devices, from 1st March 2022 to 31st August 2023. An increase in drug shortage reports was observed, rising from 404 in 2013 to 3,761 in 2022 for drugs, with a relatively constant distribution of affected therapeutic classes. In 2022, the main reported causes of drug shortage risk were insufficient production capacity (27.1%), increased sales volume (21.5%), or lack of supply (13.6%). Over half of the reports on medical devices (55.4%) were objectified as indispensable, and their causes were mainly due to a lack of supply (48.2%), discontinuation of marketing (14.9%), increased sales volume (13.2%), and regulatory reasons (9.6%). ANSM and French authorities have engaged a public health policy for prevention and management of health product shortages including financial penalties, minimum safety stocks for Major Therapeutic Interest drugs, and a shortage management plan. Based on 10 years of experience, four priority measures have been identified to anticipate the risk of health products shortages based: the importance of a national coordination from raw materials to local market, the implementation of new prevention and management actions in the supply chain, strengthening European cooperation and regulation including the establishment of a list of critical drugs, and promoting transparency and information.

KEYWORDS

shortage, regulatory science, medical device, drug, health policy

Introduction

Over the last decade, an increasing trend of drug and medical device shortages has been observed in countries all over the world, independently of their income levels or geographical area (1–4). Increasingly frequent, these health products shortages have a significant impact on patients, healthcare professionals, and the economy (5–10). Regulatory authorities may also allocate huge amounts of resources to manage health products shortages. Therefore, the prevention of shortages has become a priority for authorities worldwide (11–19). This global problem requires the implementation of specific measures to improve prevention, anticipation, and ensure better coverage of medical needs.

In the US, at the height of the drug shortage crisis, the number of new shortages quadrupled, rising from 61 shortages in 2005 to a peak of 251 in 2011 (4). The number of new drug shortages has been decreasing since 2011, reaching 49 in 2022 driven by preventive measures taken by many groups including the FDA (4).

In Europe, the number of drug shortages has grown 20-fold between 2000 and 2018, compromising European healthcare systems (20, 21). The COVID pandemic has highlighted the vulnerability of health products availability in a public health emergency situation (6, 22–24). European Medicine Agency's (EMA), whose role has been strengthened by a new European regulation (25), took up the issue of managing health products shortages at the time of the health crisis with coordination actions (11, 16). France has been addressing this concern for several years. Various measures have recently been implemented at national level, including financial penalties, minimum safety stocks and shortage management plan for major therapeutic interest drugs (articles L5121-29 to L5121-34 of the Public Health Code) (13, 26).

In this context, the aim of this paper is to describe and analyze the reported data on shortages in the health products availability in France over the last ten years, and to highlight strategies for a better prevention.

Analysis of the management of shortages in the availability of health products in France

Mapping the risk of shortages within the health products supply chain

Figure 1 depicts a mapping of the supply chain and identifies the main causes of shortages. The map was carried out, following stakeholder exchanges, using Miro software, version 0.7.37. This

overview provides insight into the extent of action required and emphasizes the involvement of various stakeholders across the health products supply chain: industrials at the manufacturing level, regulators, and other stakeholders impacting the market.

The identified causes are categorized according to the different stages of the supply chain. These include weaknesses in the production chain, such as insufficient supply, manufacturing failures, and non-compliance with regulatory requirements. Distribution issues, such as storage or shipping problems, also contribute to shortages. Other factors, that may affect the health products market, include delays due to tenders and public contracts as well as imbalances between supply and demand. In addition, logistical difficulties may arise at any stage of the supply chain.

Data from the French health products shortage notification system

Our observational retrospective study analyzed reports of health products shortages from the French national system.

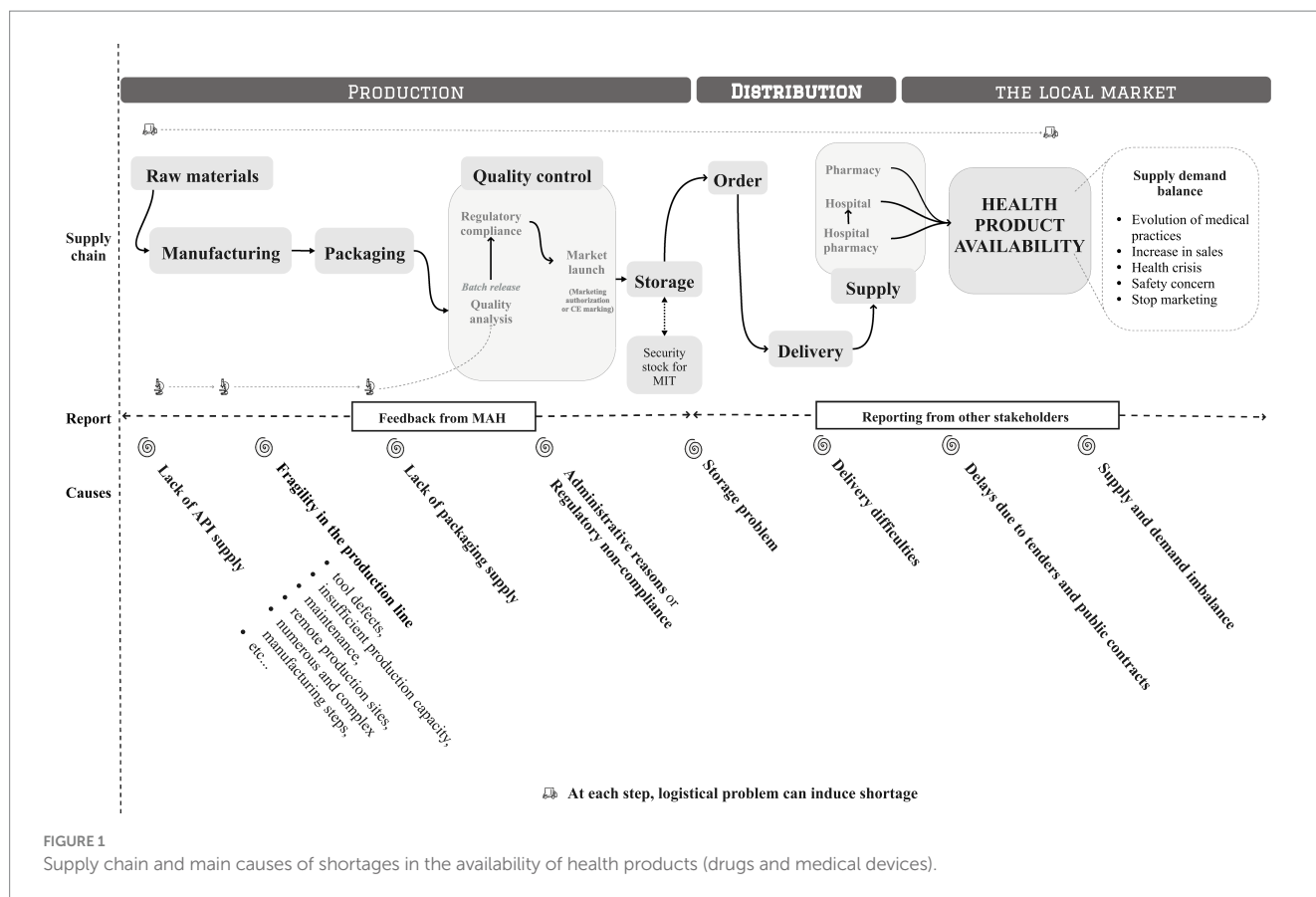
In France, the Public Health Code defines a shortage as the impossibility of manufacturing or using a medicine (CSP Art. R. 5124-49-1). Pharmaceutical companies, which are responsible for ensuring the availability of the medicines they market in France, notify ANSM of the risk of stock shortage or actual stock shortages. Since 2012, manufacturers of major therapeutic interest drugs have been required to promptly notify the ANSM of any potential or actual supply chain shortages that could lead to or have resulted in a shortage or to face financial penalties (Decrees 2012-1096 of 28th September 2012 and 2016-993 of 20th July 2016). The reporting system database contains information reported by Marketing Authorization Holder (MAH) through completed declaration forms. The following data were analyzed over a ten-year period between 2013 and 2022: number of reports, type of declaration (shortage or shortage risk), and ATC codes of the major therapeutic interest drug concerned (according to the WHO Collaborating Centre for Drug Statistics Methodology) (27). The causes for major therapeutic interest drugs have been reported since 2021 from reports declared in the new e-portal (Trustmed), and they were analyzed over the year 2022.

For medical devices, reports of risks of shortages or disruptions in availability were received following the implementation of a non-mandatory procedure specific to medical devices established by ANSM, and analyzed over an 18-month period from 1st March 2022 to 31st August 2023. This procedure, for the shortages management by anticipation, is based on the principle of an early exchange of information.

The categories of causes were elaborated on the basis of a working group involving the various stakeholders. All available reports have been analyzed to describe the production phase. Data were presented as numbers or percentages of major therapeutic interest drugs or medical devices reported on shortage or risk shortage.

Figure 2 displays the number of reports of shortage risk and shortage for major therapeutic interest drugs in France between 2013

Abbreviations: ANSM, French National Agency for Medicines and Health Products Safety; CHESSMEN, Coordination and Harmonization of the Existing Systems against Shortages of Medicines, European Network; EMA, European Medicine Agency; MAH, Marketing Authorization Holder; MSSG, Executive Steering Group on Shortages and Safety of Medicinal Products; SMP, Shortage Management Plan; SPOC, Single Point of Contact.



and 2022 (from 404 to 3,761). Figure 3 indicates a relatively constant distribution of therapeutic classes affected by shortages over time with cardiovascular system, nervous system, and anti-infective drugs accounting for approximately 50% of reports. In 2022, 4,372 causes of shortage risk or shortages of major therapeutic interest drugs were reported, mainly due to insufficient production capacity and increased sales volume (27.1 and 21.5% respectively), and 13.6% due to a lack of supply (raw material and/or packaging material) (Figure 4A).

Although less impacted, medical devices are also concerned about shortages. Over an 18-month collection period in 2022–2023, 184 shortage risks and shortages in availability were reported in France. Among these, 102 were objectified as indispensable for the continuity of care. 52.9% were reported by manufacturers or distributors. Shortages in availability were mainly due to a lack of supply (48.2%), discontinuation of marketing (14.9%), increased sales volume (13.2%), and regulatory reasons (9.6%) (Figure 4B). Class IIa and III medical devices are more affected by shortages (37.1 and 28.9% respectively) than class I and IIb medical devices (15.5 and 17.5% respectively).

Actionable recommendations

Based on our ten-year period and taking into account the mapping of stages, our results and the review of initiatives and regulatory measures taken since 2012, four priority measures have been identified to anticipate the risk of health products shortages, following the roadmaps of the French government (26) and the European Commission (28).

Importance of a national coordination

To date, the monitoring of the downstream supply chain is not complete and centralized (Figure 1). National coordination from raw materials to the local market allow to facilitate their management and anticipate shortage risks more effectively. To manage shortages and limit their impact, regulatory actions could be granted, such as allowing the importation of therapeutic alternatives, extending batch expiration dates, or authorizing hospital preparations (e.g., cisatracurium during the COVID crisis) (6).

Effective coordination requires the centralization of knowledge on issues related to all stages of the supply chain (Figure 1), including manufacturing data, logistics, needs, and use, but also agreements and contracts concluded by stakeholders. National governance can play a key role in coordinating decisions and actions needed at national and territorial levels for the day-to-day management of health products shortages.

Economic factors such as price, reimbursement, and monopoly as well as therapeutic recommendations, consumption, and off-label use are important determinants of the availability and the balance between production and needs.

Implementation of new prevention and management actions during the supply chain

Since September 2021, French regulations require the MAH to maintain a minimum safety stock of two months for major therapeutic interest drugs reserved for the national market to prevent shortages more effectively. Decree 2021–349 of 30th March

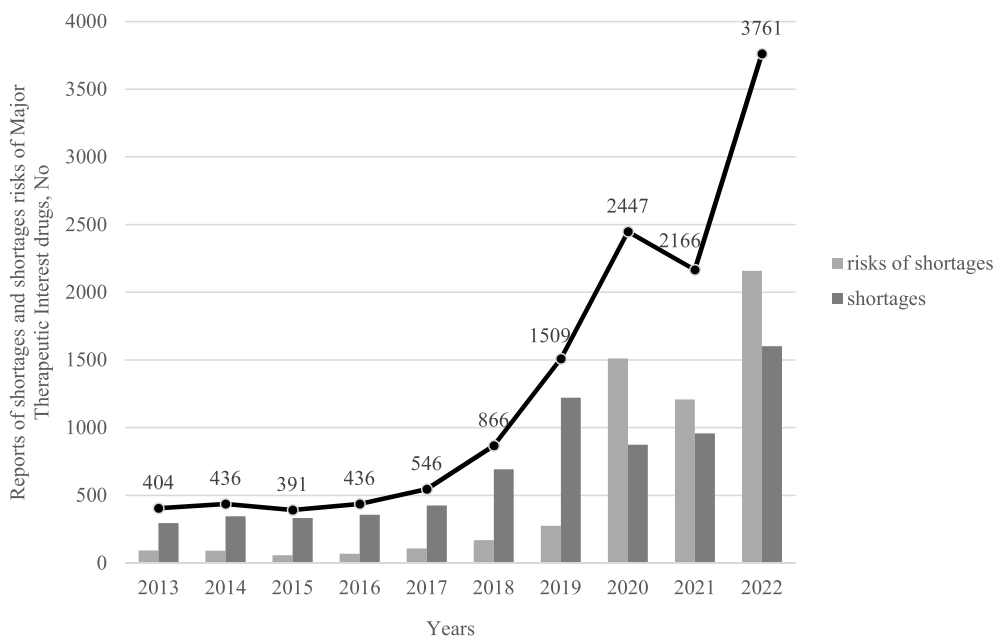


FIGURE 2
Number of reports of risks of shortages and shortages for major therapeutic interest drugs between 2013 and 2022 in France.

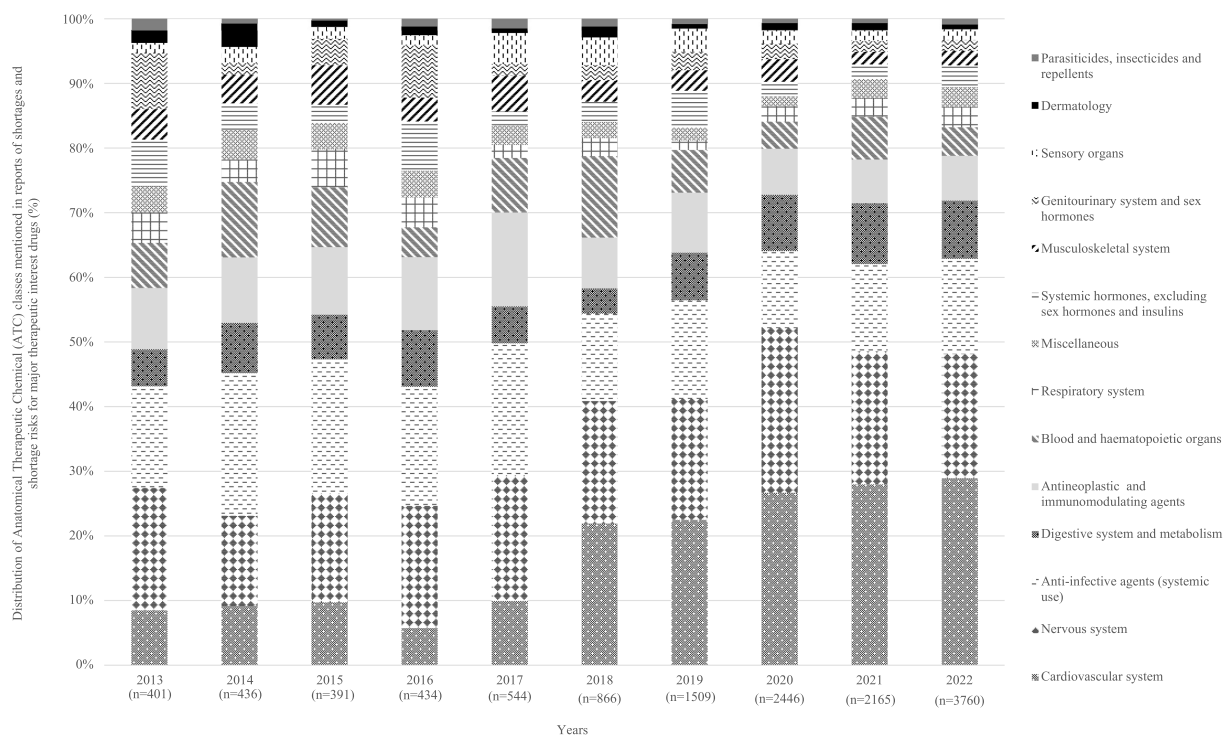
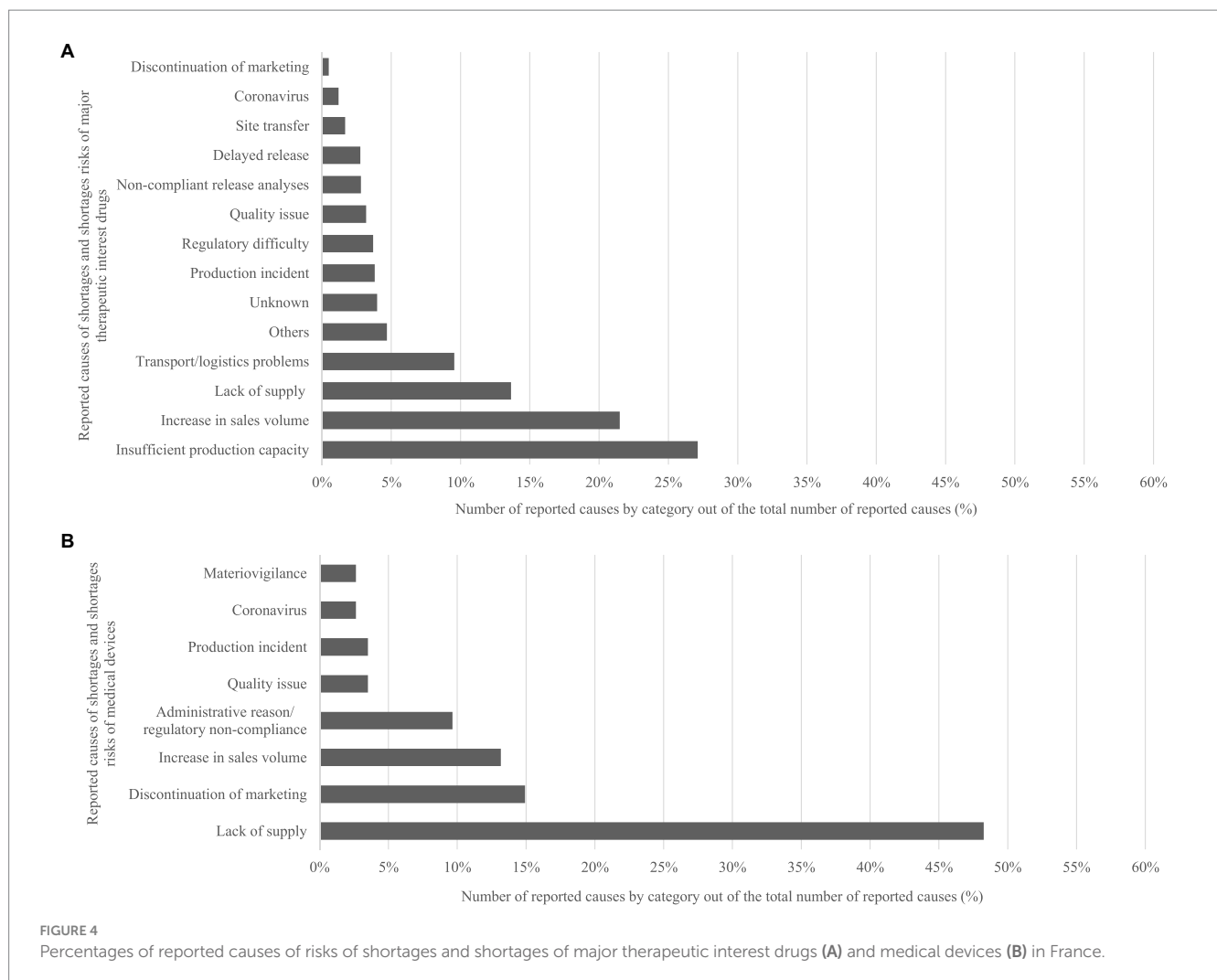


FIGURE 3
Distribution of Anatomical Therapeutic Chemical (ATC) classes mentioned in reports of shortages and shortage risks for major therapeutic interest drugs (2013–2022).

2021 allows the ANSM to adjust stocks if necessary. In 2022, the minimum safety stock was increased to four months for 422 drugs. In addition, MAHs are required to submit shortage management plan (SMP) to the ANSM which identifies risks in the supply chain

and outlines measures to mitigate them. It describes therapeutic alternatives allowing the continued patient treatment under the best possible conditions and actions to be taken if the shortage cannot be avoided. Non-compliance with these national obligations



is subject to financial penalties, with reinforced guidelines from 2022.

In addition, to ensure the supply of health products, the shortage prevention system needs to be strengthened. Actions should be taken to improve compliance with shortage management plans and the respect of security stocks for major therapeutic interest drugs. Regulatory authorities should be empowered to require manufacturers to take all necessary measures to reduce and manage the risks of shortages of all health products, including medical devices.

Although reports of medical devices shortages are currently limited, a legislative lever has just been introduced (articles 27 of law no 2023-171 of 9th March 2023). The decree will enable the implementation of reporting obligations for operators. A regulatory framework will be established to consolidate the definition of the risk situation for patients caused by the unavailability of medical devices.

French legislators point out that French pharmaceutical production has declined, leading to a loss of French health sovereignty (29). Maintaining or even relocating active pharmaceutical ingredients and health products manufacturers in France and Europe would help to limit supply chain difficulties, which have been identified as a major source of shortages. Actions should be taken to promote and improve the attractiveness of France and Europe. A map of active and potential production sites in Europe should be shared in order to identify points

of vulnerability in the production chain. Discussions on joint procurement, in particular for essential vaccines or other drugs at the European level, will be pursued.

Strengthening European cooperation and regulation to better prevent health product shortages

A strategy to secure the supply of health products is being implemented at the European level (16, 23, 30–33).

To reinforce the EMA role in crisis preparedness and management for health products, a new regulation has been implemented in 2022 (25). This could also provide a framework for dealing with shortages more broadly. A comprehensive crisis management plan also covers medical devices, which have not been taken into account at EMA level until now. A network of contact points was created (SPOC), and European working groups were set-up: the CHESSMEN joint action (Coordination and Harmonization of the Existing Systems against Shortages of Medicines, European Network), Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG), a European collaboration by the EMA (Task Force) in 2016, and EU4Health program. To strengthen Europe's ability to prevent, detect, and rapidly respond to cross-border health emergencies, the European Commission has established a Health Emergency Response Authority

(HERA). A draft reform of the European Commission's pharmaceutical legislation is currently being prepared (28). This would introduce enhanced monitoring of drug shortages across the European Union, including the establishment of a list of critical drugs (31). The ANSM is actively participating in the work on this issue European level and in the drafting of the new European regulation.

The establishment of a database on drug supply within the EMA allows for the regulation and facilitation of data consolidation. With regard to medical devices, the ANSM supports common measures and positions, in particular with regard to the provisions adopted at national level.

The COVID crisis has demonstrated the importance and feasibility of solidarity within the European Union (34–37) to reduce competition between member states in fighting shortage situations.

Promoting transparency and information to prevent the consequences related to health products shortages and enhance confidence

To enhance transparency, stakeholder interactions and access to information on health products availability at all stages of the supply chain, efforts must be made to improve in accordance with trade secrets. At the European level, efforts have been made to publish and share information on shortages (38).

There is also a need to share information in real time on the availability of health products, from suppliers to pharmacists and physicians, as soon as a significant shortage is identified and confirmed.¹

All stakeholders, including health professionals and patient representatives, have a key role in managing the crisis induced by health products shortages, and should be involved in the decision-making process. In particular, they are consulted to identify real needs in the field, to establish national recommendations, and, where appropriate, to prioritize treatment indications (39–41).

As part of its policy of data sharing and transparency, the ANSM has developed a digital application² intended for the general public and healthcare professionals. This application provides access to the history of reports and annual analyses.

Public understanding of the context is necessary for the proper management of health products shortages and compliance with the measures put in place. Public education and awareness should be raised through transparent communication, information campaigns, and integrating patient decisions in the management of drug shortages, in order to improve their confidence in the healthcare system for positive outcomes.

The impact of health products shortages on the care pathway and the loss of opportunity for patients should be objectively assessed and more precisely defined, whether in terms of treatment delays, risk of reduced efficacy, occurrence of adverse effects, or medication errors (42). The multifactorial and proactive approach in France aims to minimize the impact of shortages on patients and health professionals. Our work highlights the need to monitor the targets set by the ANSM to address this public health priority, and therefore to strengthen or develop existing indicators.

Discussion

To our knowledge, this is the first analysis of both drugs and medical devices availability shortage reports over a long period of time and at a national level. The mapping process highlighted the fact that the shortages occurred at the same stage in the supply chain, for both drug and medical device. Tensions over drug availability are much more frequently reported than for medical devices.

Our data confirm an increase in reports of concerns about the availability of major therapeutic interest drugs in France over time. Regulatory changes over the study period make it difficult to interpret the data and make comparisons over the years. The implementation of the anticipation policy in 2020 may have contributed to the more than fourfold increase in reports, from 866 in 2018 to 3,761 in 2022. To compare our data quantitatively and qualitatively, and more specifically the number of drug reports, we need to take into account changes in regulations. This also highlights the fact that regulations can have an impact on the reporting system.

Similar increases have also been observed in other European countries, including Finland, the Netherlands, and Germany (3, 12). The therapeutic classes most affected were generally the same across different countries, particularly the nervous system and cardiovascular system (3, 14, 15). More international information and data are becoming available on this topic, although they cover shorter periods of time (38). However, comparisons are difficult due to the lack of common criteria for defining shortages and criticality (1). Indeed, there is a lack of standardization in the definition of shortages between the different European member states (1). Even if a harmonized definition within Europe has been agreed in 2019 (11), each member state has its own notification system with different characteristics (43). Consequently, our results give only visibility on shortages and their causes inherent to the production stages. To date, there is no systematic monitoring of the downstream supply chain. As a result, our data on shortages do not include the distribution chain failure (non-delivery of a pharmacy or internal-use pharmacy), and supply disruptions (inability of a pharmacy to dispense a drug to a patient within 72 h).

The issue of shortages and their management in the field of medical devices is a recent concern. With a year and a half's hindsight, this analysis is preliminary and there is little data available from other countries. As reporting on medical devices was not mandatory for the industrials, declarations provided from a variety of sources (patients, healthcare professionals, industrials...), whereas drug shortages are declared by the marketing authorization holders or the pharmaceutical companies operating them. Furthermore, reports from the professionals and patients have been essential so far, accounting for over a third of the reports. As a result, manufacturers' and distributors' statements are not exhaustive, as is probably the case with drugs. Moreover, quantitative comparisons between reports on shortages of medical devices and drugs are not straightforward, due to the difference in term of regulations and type of declarant.

The European level is a framework for exchange, with the aim of fostering cooperation, encouraging dialog and promoting harmonization and use of preventive practices to reduce shortages between member states. Management including legislation, price negotiations and market issues are at the national level. To extend the efforts made at the national level, ANSM is a driving force at the EMA

1 <https://ansm.sante.fr/disponibilites-des-produits-de-sante>

2 <https://data.ansm.sante.fr/>

level in the CHMP and in the working groups. In particular, the agency shares its experience of the national pilot phase for medical devices at EMA level, with the aim of strengthening regulatory measures to anticipate future developments.

Reporting and data analysis allow us to characterize shortages, adapt actions, and evaluate their impact. Comprehensive data on the entire chain and on the characteristics of drug production will make it possible to model and anticipate disruptions.

The fact that the study does not describe all factors that may affect the availability of health products may be a limitation. Price is often mentioned as a determining factor in dealing with shortages of health products. However, pharmaceutical pricing policies are not part of the European framework, but are the result of national decisions. Negotiations, managed at the national level, are a weakness of the European system.

This integrated approach includes: a well-coordinated approach and management in the face of a shortage, an improvement in communication and operations within all the stakeholders, changes in government policy (at the national and European level to achieve a harmonized policy); and by education and training of healthcare professionals but also of patients.

The implementation of such a strategy at the national level, targeting all different measures together, should hopefully reduce the impact of health products shortages. Similar measures to reduce the impact of shortages appear to have been successful in the US (4).

It should be kept in mind that the existing gaps between supply and demand are another critical parameter in the balance of the global health system and particularly in France where the consumption of health products is known to be high (44–48).

Conclusion

Within the European framework, France has implemented a new mitigation strategy regarding drugs and medical devices supply chain tensions and shortages. The ANSM is involved in a broad public health policy to improve the prevention, management, and response to health products supply tensions and shortages, which is based on 4 priorities: coordination, prevention/management actions, European cooperation, and transparency. The aim of this strategy is to reduce the occurrence of health products shortages and the ensuing consequences for patients. The ANSM therefore supports all initiatives at national and European level in line with this strategy. Manufacturers, MAHs, hospitals, health-care professionals, patients, and regulators

References

- Shukar S, Zahoor F, Hayat K, Saeed A, Gillani AH, Omer S, et al. Drug shortage: causes, impact, and mitigation strategies. *Front Pharmacol.* (2021) 12:426. doi: 10.3389/fphar.2021.693426
- Benhabib A, Ioughlissen S, Ratignier-Carbonneil C, Maison P. The French reporting system for drug shortages: description and trends from 2012 to 2018: an observational retrospective study. *BMJ Open.* (2020) 10:e034033. doi: 10.1136/bmjopen-2019-034033
- Sarnola K, Kari H, Koskinen H. Medicine shortages: product life cycle phases and characteristics of medicines in short supply—a register study. *Front Pharmacol.* (2022) 13:249. doi: 10.3389/fphar.2022.943249
- Drug Shortages for Calendar Year 2022 (Required by Section 506C–1 of the Federal Food, Drug, and Cosmetic Act). Available at: <https://www.fda.gov/media/169302/download> (accessed June 15, 2023) (2023).
- Huss G, Barak S, Reali L, Magendie C, Carrasco-Sanz A, Somekh E, et al. Drug shortages in pediatrics in Europe: the position of the European pediatric societies. *J Pediatr.* (2023) 261:113472. doi: 10.1016/j.jpeds.2023.113472
- Chapuis C, Collomp R, Albaladejo L, Terrisse H, Honoré S, Bosson J-L, et al. Redistribution of critical drugs in shortage during the first wave of COVID-19 in France: from operating theaters to intensive care units. *J Pharm Policy Pract.* (2022) 15:28. doi: 10.1186/s40545-022-00425-z
- Atif M, Sehar A, Malik I, Mushtaq I, Ahmad N, Babar Z-U-D. What impact does medicines shortages have on patients? A qualitative study exploring patients' experience and views of healthcare professionals. *BMC Health Serv Res.* (2021) 21:827. doi: 10.1186/s12913-021-06812-7
- Kruijtbosch M, Floor-Schreuderling A, van Leeuwen E, Göttgens-Jansen W, Bouvy ML. Moral reasoning perspectives of community pharmacists in situations of drug

must all be involved to strive against shortages of drugs and medical devices.

Author contributions

LB: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. JE: Conceptualization, Writing – review & editing. NA: Writing – review & editing. TB: Writing – review & editing. PD: Writing – review & editing. SV: Writing – review & editing. TV: Writing – review & editing. GR: Writing – review & editing. CS: Writing – review & editing. CM-C: Writing – review & editing. MC: Writing – review & editing. M-LV: Writing – review & editing. RY: Writing – review & editing. WO-G: Writing – review & editing. CR-C: Writing – review & editing. PM: Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors are very grateful to the following ANSM officers for their invaluable inputs: J. Chong, C. Leleu, and N. Gueddoudj.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

- shortages. *Res Soc Adm Pharm RSAP*. (2022) 18:2424–31. doi: 10.1016/j.sapharm.2020.11.012
9. Biedermann F. New Dutch regulations to alleviate drug shortages. *Lancet*. (2022) 400:349–50. doi: 10.1016/S0140-6736(22)01421-0
10. Postma DJ, Notenboom K, De Smet PAGM, Leufkens HGM, Mantel-Teeuwisse AK. Medicine shortages: impact behind numbers. *J Pharm Policy Pract*. (2023) 16:44. doi: 10.1186/s40545-023-00548-x
11. Musazzi UM, Di Giorgio D, Minghetti P. New regulatory strategies to manage medicines shortages in Europe. *Int J Pharm*. (2020) 579:119171. doi: 10.1016/j.ijpharm.2020.119171
12. Vogler S, Fischer S. How to address medicines shortages: findings from a cross-sectional study of 24 countries. *Health Policy*. (2020) 124:1287–96. doi: 10.1016/j.healthpol.2020.09.001
13. Bocquet F, Degrasat-Théas A, Peigné J, Paubel P. The new regulatory tools of the 2016 health law to fight drug shortages in France. *Health Policy*. (2017) 121:471–6. doi: 10.1016/j.healthpol.2017.03.007
14. Videau M, Chemali L, Stucki C, Saavedra-Mitjans M, Largana S, Guerin A, et al. Drug shortages in Canada and selected European countries: a cross-sectional, institution-level comparison. *Can J Hosp Pharm*. (2019) 72:7–15. doi: 10.4212/cjhp.v72i1.2863
15. Ravela R, Lyles A, Airaksinen M. National and transnational drug shortages: a quantitative descriptive study of public registers in Europe and the USA. *BMC Health Serv Res*. (2022) 22:940. doi: 10.1186/s12913-022-08309-3
16. Cooke E. Preparing Europe for future health threats and crises — the European medicines agency; ensuring safe and effective medicines and medical devices. *Eur Secur*. (2022) 27:2200798. doi: 10.2807/1560-7917.ES.2022.27.42.2200798
17. Han JED, Ibrahim H, Aiyegbusi OL, Liu X, Marston E, Denniston AK, et al. Opportunities and risks of UK medical device reform. *Ther Innov Regul Sci*. (2022) 56:596–06. doi: 10.1007/s43441-022-00394-0
18. Mazer-Amirshahi M, Pourmand A, Singer S, Pines JM, van den Anker J. Critical drug shortages: implications for emergency medicine. *Acad Emerg Med*. (2014) 21:704–11. doi: 10.1111/acem.12389
19. de La Provôté S, Cohen L. Commission d'enquête sur la pénurie de médicaments et les choix de l'industrie pharmaceutique française. [Rapport de commission d'enquête]. Sénat Available at: <https://www.senat.fr/travaux-parlementaires/structures-temporaires/commissions-denquete/2022-2023-ce-penurie-de-medicaments.html> (accessed October 24, 2023) (2023).
20. Colin-Oesterlé N REPORT on the shortage of medicines – how to address an emerging problem | A9-0142/2020 | European Parliament. (2020). Available at: https://www.europarl.europa.eu/doceo/document/A-9-2020-0142_EN.html (accessed October 13, 2023).
21. Miljković N, Batista A, Polidori P, Kohl S, Horák P. Results of EAHP's 2019 medicines shortages survey. *Eur J Hosp Pharm Sci Pract*. (2020) 27:202–8. doi: 10.1136/ijpharm-2020-002341
22. Peres D, Monteiro J, Boléo-Tomé J. Medical masks' and respirators' pattern of use, adverse effects and errors among Portuguese health care professionals during the COVID-19 pandemic: a cross-sectional study. *Am J Infect Control*. (2022) 50:618–23. doi: 10.1016/j.ajic.2021.10.002
23. Abed I, Gonzalez-Quevedo R, Mura M, Dias M, da Rocha DS, García BJ. Commentary on the European medicines Agency's extended mandate: protecting public health in times of crisis and improving availability of medicines and medical devices. *Br J Clin Pharmacol*. (2023) 89:5–10. doi: 10.1111/bcp.15567
24. Bohand X, Jordan D, Dubois F. Managing the risk of shortages and medication errors with curares during the COVID-19 pandemic: a hospital pharmacy experience. *Eur J Hosp Pharm*. (2021):2605. doi: 10.1136/ijpharm-2020-002605
25. Regulation (EU). 2022/123 of the European Parliament and of the council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices (2022). doi: 10.5040/9781782258674,
26. Buzyn A Feuille de route ministérielle 2019–2022 pour lutter contre les pénuries et améliorer la disponibilité des médicaments en France. (2019). Available at: https://solidarites-sante.gouv.fr/IMG/pdf/31142_dicom_pe_nurie_de_me_dicamentsv8.pdf (accessed November 21, 2022).
27. WHO collaborating Centre for drug statistics methodology. (2023). ATC/DDC Index Available at: https://www.whocc.no/atc_ddc_index/ (accessed July 28, 2023).
28. Reform of the EU pharmaceutical legislation Available at: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en (accessed May 22, 2023) (2023).
29. Dharréville MP, Dufeu A, Touraine J-L, Berta P, Biémouret G, Christophe P, et al. Rapport d'information déposé en application de l'article 145 du règlement, par la commission des affaires sociales, en conclusion des travaux d'une mission d'information sur les médicaments (Mme Audrey Dufeu et M. Jean-Louis Touraine). [Rapport d'information]. Assemblée Nationale Available at: https://www.assemblee-nationale.fr/dyn/15/rapports/cion-soc/115b4275_rapport-information (accessed October 21, 2022) (2021).
30. EMA HMA. Good practices for industry for the prevention of human medicinal product shortages. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practices-industry-prevention-human-medicinal-product-shortages_en.pdf (2023).
31. EMA. Recommendations of the executive steering group on shortages and safety of medicinal products on the availability of a subset of antibiotics. Available at: https://www.ema.europa.eu/en/documents/other/recommendations-executive-steering-group-shortages-safety-medicinal-products-availability-subset_en.pdf (2023).
32. EMA. Joint statement by executive steering group on shortages and safety of medicinal products (MSSG) shortages antibiotic medicines. Eur Med Agency Available at: <https://www.ema.europa.eu/en/news/joint-statement-executive-steering-group-shortages-safety-medicinal-products-mssg-shortages> (accessed October 13, 2023) (2023).
33. CHESSMEN Coordination and harmonisation of the existing systems against shortages of medicines – European network. CHESSMEN. (2023). Available at: <https://www.ja-chessmen.eu> (accessed October 27, 2023).
34. Beetsma R, Burgoon B, Nicoli F, de Ruijter A, Vandenbroucke F. Public support for European cooperation in the procurement, stocking and distribution of medicines. *Eur J Pub Health*. (2021) 31:253–8. doi: 10.1093/eurpub/ckaa201
35. Burni A, Erforth B, Friesen I, Hackenesch C, Hoegl M, Keijzer N. Who called team Europe? The European Union's development policy response during the first wave of COVID-19. *Eur J Dev Res*. (2022) 34:524–39. doi: 10.1057/s41287-021-00428-7
36. Greer S, de Ruijter A. EU health law and policy in and after the COVID-19 crisis. *Eur J Pub Health*. (2020) 30:623–4. doi: 10.1093/eurpub/ckaa088
37. Plank K. German state aid for Covid-19 medicinal products: a risk for solidarity in the European Union. *Eur J Health Law*. (2022) 29:53–78. doi: 10.1163/15718093-bja10061
38. Abed I, Burgos JG, Knudsen Y. Public information on shortages in the EU/EEA: improvements made between 2018 and 2020. *Eur J Hosp Pharm*. (2023):554. doi: 10.1136/ijpharm-2022-003554
39. EMA and HMA. Good practice guidance for patient and healthcare professional organisations on the prevention of shortages of medicines for human use (2022). Available at: https://www.ema.europa.eu/en/documents/other/good-practice-guidance-patient-healthcare-professional-organisations-prevention-shortages-medicines_en.pdf
40. Neuzillet Y, Leon P, Seisen T, Allory Y, Audenet F, Loriot Y, et al. A prospective descriptive 1-year study in France of all BCG therapy dispensations for non-muscle-invasive bladder cancer. *BJU Int*. (2022) 131:611–6. doi: 10.1111/bju.15941
41. Rollin P, Xylinas E, Lanz C, Audenet F, Brunelle S, Compérat E, et al. Intravesical adjuvant regimen of epitubicin for intermediate risk NMIBC: Feasibility study from CC-AFU vessie. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol*. (2022) 32:326–31. doi: 10.1016/j.purol.2021.12.008
42. Bourneau-Martin D, Babin M, Grandvillemin A, Mullet C, Salvo F, Singier A, et al. Adverse drug reaction related to drug shortage: a retrospective study on the French National Pharmacovigilance Database. *Br J Clin Pharmacol*. (2022) 89:1080–8. doi: 10.1111/bcp.15550
43. Turbucz B, Major M, Zelko R, Hanko B. Proposal for handling of medicine shortages based on a comparison of retrospective risk analysis. *Int J Environ Res Public Health*. (2022) 19:4102. doi: 10.3390/ijerph19074102
44. Taine M, Offredo L, Weill A, Dray-Spira R, Zureik M, Chalumeau M. Pediatric outpatient prescriptions in countries with advanced economies in the 21st century: a systematic review. *JAMA Netw Open*. (2022) 5:e225964. doi: 10.1001/jamanetworkopen.2022.5964
45. Drusch S, Le Tri T, Anki J, Zureik M, Herr M. Decreasing trends in potentially inappropriate medications in older people: a nationwide repeated cross-sectional study. *BMC Geriatr*. (2021) 21:621. doi: 10.1186/s12877-021-02568-1
46. Taine M, Offredo L, Dray-Spira R, Weill A, Chalumeau M, Zureik M. Paediatric outpatient prescriptions in France between 2010 and 2019: a nationwide population-based study. *Lancet Reg Health*. (2021) 7:100129. doi: 10.1016/j.lanepe.2021.100129
47. La France encore trop consommatrice d'antibiotiques. (2022). Available at: <https://www.santepubliquefrance.fr/presse/2022/la-france-encore-trop-consommatrice-d-antibiotiques> (accessed February 14, 2023).
48. Tubiana S, Sibide J, Herlemont P, Drouin J, Picone O, Duval X, et al. Trends in anti-infective use during pregnancy in France between 2010 and 2019: a nationwide population-based study. *Br J Clin Pharmacol*. (2022) 89:1629–39. doi: 10.1111/bcp.15638