PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The French reporting system for drug shortages: description and trends from 2012 to 2018. An observational retrospective study
AUTHORS	Benhabib, Amine; Ioughlissen, Saïd; Ratignier-Carbonneil, Christelle; MAISON, Patrick

VERSION 1 - REVIEW

REVIEWER	Bocquet François University Public Hospitals of Paris, France Faculty of Law and Political Science of Nantes, France
REVIEW RETURNED	16-Oct-2019

GENERAL COMMENTS	I find this paper rather interesting. Indeed, the subject is topical and the theme is globally well treated by the authors. The authors carry out a retrospective analysis of the ASNM databases which contain useful information on drug shortages and particularly their causes. The ANSM database is particularly rich insofar as the pharmaceutical companies have been obliged for several years in France to transmit to ANSM all this information on a proven or potential risk of drug shortages. The publication of these data is essential for the scientific and medical community but the central question with these drug shortages remains full: How to fight against them? Here are my comments/questions: Methods: It might be interesting to have more information on the causes of drug shortages. Indeed, the authors group causes into 'categories of causes' without giving more details. Perhaps, these causes transmitted by the pharmaceutical companies could be made available in Supplementary Materials. Results: This is about drug shortages in France. In my opinion, it is necessary to specify whether they are shortages at the international level or not. It would probably be necessary to have international visibility/experience and at least European on this. Discussion: Drug shortage for an INN does not mean a shortage for all the drugs in the INN, right? Please clarify this point. 'Since 2012, marketing authorization holders are required to report shortages and otherwise subjected to financial sanctions since 2016.' Have economic sanctions really been applied in France to date? I don't think so. Conclusions: What is probably missing in this descriptive paper are some proposals for trying to effectively fight these drug shortages and may be a lack of perspective on that.

	Figure 1: 'Trends in shortages by numbers of pharmaceutical products and International Nonproprietary Name drugs (INN) (2012-2018)' … in France. To be added.

REVIEWER	Aukje Mantel-Teeuwisse Utrecht University, the Netherlands
REVIEW RETURNED	22-Oct-2019

GENERAL COMMENTS	BMJ open review Benhabib et al. Benhabib et al. have assessed trends in reporting of shortages in France over the period 2012-2018. As they indicate, most of the research in this area stems from the US. Data on shortages in Europe could be a welcome addition. Their analyses are relatively simple and straightforward. The manuscript could be further strengthened in a number of ways to make it more meaningful. Major comments: • The term MTI needs better explanation. In the introduction MTI is defined as 'drugs for which unavailability would be life threatening or representing a loss of treatment opportunity'. Later, the valsartan case is mentioned as an example. Although I fully acknowledge that changing from valsartan to another angiotensin II inhibitor may not be very patient-friendly, from a pure pharmacological perspective the other pharmaceutical products in this class offer(ed) an acceptable treatment opportunity. Who decides on what is considered an MTI and what not? For patients who need to switch from a brand to a generic the shortage of a brand product may be as impactful, but I such a shortage would be seen as a MTI if a generic is still available…. • Both actual and expected shortages need to be reported according to the legislation. In the analysis, these are grouped which seems to suggest that the authors do not know if expected shortages become actual shortages or not. If this is the case, this is a major limitation which deserves (much) more attention in the discussion section. If it is known whether expected shortages become actual shortages, I suggest to present data separately. Also I would like to know how the authors would then deal with expected shortages which become reality. • The data source is one of the major limitations since data from authorities capture only part of what at least patients may perceive as a shortage (see Postma et al. Front Pharmacol 2018;9:1243). This needs further discussion. • Some of the data could be better interpreted if percentage could be compared to market share in France. For example, 18% of the shortages concerned antiinfectives. This percentage would gain meaning if the reader would know which percentage of all marketed drugs is an antiinfective. This pertains to all data in Table 1. • Abstract, conclusion: the authors suggest preventive measures should be taken and targeted. I would expect a more thorough discussion of (im)possibilities in the discussion section Minor comments: • Although (or because) I am not a native speaker, some terminology seemed a bit odd to me. Examples are effective shortages instead of actual or real shortages and former products which is defined as products with a marketing authorization > 10

	years. These I would not call former products – which suggests that they have been taken off the market – but old(er) products. • The role of the (changing) regulation is not very clear either. Part of it was introduced in 2012 and may be seen as the reason for this study. Part of it was introduced in 2016. Did the authors intend to study its effects? If so, this needs to be clarified and better addressed. Changing legislation may influence results, especially since it stimulates reporting as far as I understand, and as such needs more attention in the discussion section. In the abstract, conclusion the first sentence 'along with a reinforced regulation' is also unclear to me in this respect. • The definition of pharmaceutical products on page 4 suggests that if 2 different strengths of the same products are (expected to become) unavailable this counts as 2 shortages. Is that correct? That raises the question this affects the analyses for e.g. figures 2-4. • I was surprised by the number of approved and marketed INN drugs in France (N=800) versus the number of 400 real or expected INNs in shortage. This again raises the question whether these were all actual shortages in the end or that the legislation just stimulates reporting and industry is reporting everything if there might be a little chance they will run into problems. Also, I suppose that although 50% of the INNs may be affected by shortages, it does not imply that all of these were completely unavailable in the country (e.g. if a certain amoxicillin generic is unavailable, there will probably be many other brands which are still available. Correct?) • Both the discussion (page 7, line 53) and conclusion (p.9, lines 53-59) contain new information which better fits within the results and discussion section, respectively. • Table 1: data per category do not sum up to 3530, suggesting there is either missing data or a category "other", e.g. for marketing authorization procedures • Figure 4: readability of the legend needs to be improved. • STROBE statement: study design not mentioned in title, for missing data: see bullet above – this is unclear from the methods section.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Bocquet François

Institution and Country: University Public Hospitals of Paris, France; Faculty of Law and Political Science of Nantes, France

Please state any competing interests or state 'None declared': None declared

I find this paper rather interesting. Indeed, the subject is topical and the theme is globally well treated by the authors. The authors carry out a retrospective analysis of the ASNM databases which contain useful information on drug shortages and particularly their causes. The ANSM database is particularly rich insofar as the pharmaceutical companies have been obliged for several years in France to transmit to ANSM all this information on a proven or potential risk of drug shortages. The publication of these data is essential for the scientific and medical community but the central question with these drug shortages remains full: How to fight against them?

Here are my comments/questions:

Methods: It might be interesting to have more information on the causes of drug shortages.

Indeed, the authors group causes into ‘categories of causes’ without giving more details. Perhaps, these causes transmitted by the pharmaceutical companies could be made available in Supplementary Materials.

We thank you for raising this important point. In the declaration forms sent to the ANSM, marketing authorization holders are asked to describe the causes of shortages (open question). The answers are very heterogeneous and narratives. The problems encountered during the manufacture of drugs were often described in several lines. Therefore, we may not provide a list of the detailed “causes” in supplementary materials which would be unclear and heterogeneous. The categories of causes were created for the present study. A more accurate classification of the causes of shortage is being evaluated to be suggested in a further version of the declaration form.

Results: This is about drug shortages in France. In my opinion, it is necessary to specify whether they are shortages at the international level or not. It would probably be necessary to have international visibility/experience and at least European on this.

We thank you for your comment. Information regarding other countries affected by shortage or availability of drugs in other countries was not requested from pharmaceutical companies neither collected in the present database. Yet, the issue of drug shortage in other countries was addressed in the discussion section.

Discussion: Drug shortage for an INN does not mean a shortage for all the drugs in the INN, right? Please clarify this point.

We thank you for this suggestion. The following sentence was added at the end of the methods page 6 of 43 line 22 & 23 ? “Therefore, a shortage of a pharmaceutical product does not necessarily imply shortages of all drugs with the same INN”.

‘Since 2012, marketing authorization holders are required to report shortages and otherwise subjected to financial sanctions since 2016.’ Have economic sanctions really been applied in France to date? I don't think so.

1

This is indeed an interesting question but we believe that this issue is beyond the scope of the present study. There have been several financial sanctions since the application of this law, accounting for up to 350,000 euros.

Conclusions: What is probably missing in this descriptive paper are some proposals for trying to effectively fight these drug shortages and may be a lack of perspective on that.

We thank you for your relevant remark, yet the present study aimed to provide a quantitative description of drug shortages in France. The only proposal that we seemed suited to our results were presented in the conclusion : “Preventive measures, including contingency plans, should particularly target former old drugs, injectables, antiinfectives, nervous system, cardiovascular system drugs as well as antineoplastic and immunomodulating agents”.

Figure 1: ‘Trends in shortages by numbers of pharmaceutical products and International Nonproprietary Name drugs (INN) (2012-2018)’ … in France. To be added.

This comment was taken into consideration and “in France” was added to the legend of Figure 1.

Reviewer: 2

Reviewer Name: Aukje Mantel-Teeuwisse

Institution and Country: Utrecht University, the Netherlands

Please state any competing interests or state ‘None declared’: None declared

BMJ open review Benhabib et al.

Benhabib et al. have assessed trends in reporting of shortages in France over the period 20122018. As they indicate, most of the research in this area stems from the US. Data on shortages in

Europe could be a welcome addition. Their analyses are relatively simple and straightforward. The manuscript could be further strengthened in a number of ways to make it more meaningful.

Major comments:

• The term MTI needs better explanation. In the introduction MTI is defined as ‘drugs for which unavailability would be life threatening or representing a loss of treatment opportunity’. Later, the valsartan case is mentioned as an example. Although I fully acknowledge that changing from valsartan to another angiotensin II inhibitor may not be very patient-friendly, from a pure pharmacological perspective the other pharmaceutical products in this class offer(ed) an acceptable treatment opportunity. Who decides on what is considered an MTI and what not? For patients who need to switch from a brand to a generic the shortage of a brand product may be as impactful, but I such a shortage would be seen as a MTI if a generic is still available….

We thank you for raising this point which needed to be clarified.

Major therapeutic of interests (MTI) drugs were defined by the French Health law. This definition relates to some ATC classes and thus comprises all drugs from the same therapeutic class, whether they are generics or brand names. The list of the ATC classes covered by the definition of MTI drugs published in the ministerial order from the 27th of July 2016 was added in the supplementary materials. We have also added the following sentence in the manuscript in page 4 of 43 lines 41 to 48:

The shortage of a MTI drug has to be reported by the marketing authorization holder (MAH) to the ANSM even when another competing equivalent MTI drug is available. MAHs are not aware of the productions capacities of other MAHs and thus of the availability of equivalent MIT drugs at the time of the report. The impact of a shortage in terms of public health and production is estimated by the ANSM."

• Both actual and expected shortages need to be reported according to the legislation. In the analysis, these are grouped which seems to suggest that the authors do not know if expected shortages become actual shortages or not. If this is the case, this is a major limitation which deserves (much) more attention in the discussion section. If it is known whether expected shortages become actual shortages, I suggest to present data separately. Also I would like to know how the authors would then deal with expected shortages which become reality.

We thank you for allowing us to clarify this point. Effective and predicted shortages are indeed grouped in the definition but are both managed the same manner by the MAH. In practice, when a MAH encounters a problem that could have an impact on a production of a drug, he must report the shortage. At the time of the report, depending on the stocks, the shortage may be predictive or become effective in a few hours and vice versa. We added a paragraph in the method section of the manuscript page 5 of 43 lines 44 to 46: « At the time of the report of shortage, depending on the stocks, the shortage may be predictive or become effective in a few hours and vice versa."

• The data source is one of the major limitations since data from authorities capture only part of what at least patients may perceive as a shortage (see Postma et al. Front Pharmacol 2018;9:1243). This needs further discussion.

We thank you for mentioning this point. According to Postma & al. ,"Combining data from both authorities and pharmacy practice seems to be necessary in order to gain a more complete overview and maximum insight in potential drug shortages at a national level".

We added the following paragraph in the method section of the manuscript page 5 lines 50 to 56:" According to the definition of drug shortages in France, short supply was not considered in present study. A drug shortage reflects the capacity of a pharmaceutical company to produce drugs in accordance to the authorities' scope whereas a short supply assesses the sanitary risk in the scope of the pharmacy practice."

We also added in the discussion the following sentence on page 10 lines 24 to 29: "According to the definition of, drug shortages in France, short supply was not considered in the present study. The combination of data from both authorities and pharmacy practice has been suggested to improve the surveillance31. This requires a standardization of definition of drug shortages between European members."

• Some of the data could be better interpreted if percentage could be compared to market share in France. For example, 18% of the shortages concerned antiinfectives. This percentage would gain meaning if the reader would know which percentage of all marketed drugs is an antiinfective. This pertains to all data in Table 1.

We agree with your comment and we aimed to clarify this information but we were unable to provide sufficient accurate data regarding market share of MTI drugs. In order to be able to determine the market shares of antiinfectives among MTI drugs, it would have been necessary to have the list of all marketed MIT drugs. There is no list of the drugs included in the definition of MTI drugs at the moment (only a list of ATC classes), therefore such comparison would have been biased.

- Abstract, conclusion: the authors suggest preventive measures should be taken and targeted. I would expect a more thorough discussion of (im)possibilities in the discussion section

It is a relevant point, yet the present study aimed to provide a quantitative description of drug shortages in France. The only proposal that we seemed suited to our results were presented in the conclusion : “Preventive measures, including contingency plans, should particularly target former old drugs, injectables, antiinfectives, nervous system, cardiovascular system drugs as well as antineoplastic and immunomodulating agents”.

Minor comments:

- Although (or because) I am not a native speaker, some terminology seemed a bit odd to me. Examples are effective shortages instead of actual or real shortages and former products which is defined as products with a marketing authorization > 10 years. These I would not call former products – which suggests that they have been taken off the market – but old(er) products.

We took into account your remark and have modified former by old products throughout the manuscript.

- The role of the (changing) regulation is not very clear either. Part of it was introduced in 2012 and may be seen as the reason for this study. Part of it was introduced in 2016. Did the authors intend to study its effects?

We thank you for asking this question, but we believe that studying the changing regulation was not the aim of the present study and there was a lack of perspective between 2016 and 2018 to study the impact of this new regulation on drug shortages.

If so, this needs to be clarified and better addressed. Changing legislation may influence results, especially since it stimulates reporting as far as I understand, and as such needs more attention in the discussion section. In the abstract, conclusion the first sentence ‘along with a reinforced regulation’ is also unclear to me in this respect.

Although marketing authorization holders were requested to report drug shortages since 2012, it became mandatory in 2016. The present study did not aim to analyse the impact of the reinforced regulation (report of shortages becoming mandatory). To avoid this misunderstanding, we modified the abstract the discussion and the conclusion.

- The definition of pharmaceutical products on page 4 suggests that if 2 different strengths of the same products are (expected to become) unavailable this counts as 2 shortages. Is that correct? That raises the question this affects the analyses for e.g. figures 2-4.

We thank you for asking this question. The definition of pharmaceutical products indeed does not reflect the INN and a shortage of one INN may indeed relate to the shortage of several pharmaceutical products with the same INN. Pharmaceutical products had the same definition each year and the Figures 2 to 4 present the trends in shortages of pharmaceutical products, therefore the interpretation of these figures are unlikely to be impacted by the definition of pharmaceutical products.

- I was surprised by the number of approved and marketed INN drugs in France (N=800) versus the number of 400 real or expected INNs in shortage. This again raises the question whether these were all actual shortages in the end or that the legislation just stimulates reporting and industry is reporting everything if there might be a little chance they will run into problems. Also, I suppose that although 50% of the INNs may be affected by shortages, it does not imply that all of these were completely unavailable in the country (e.g. if a certain amoxicillin generic is unavailable, there will probably be many other brands which are still available. Correct?)

The number of approved and marketed INN drugs is n =2 800 and not 800.

“Compared with the number (n=2 800) of approved and marketed INN drugs in France in 2016”, page 8, line 3.

- Both the discussion (page 7, line 53) and conclusion (p.9, lines 53-59) contain new information which better fits within the results and discussion section, respectively.

The manuscript was reviewed according to your comments, as followed:

- The sentence “Cephalosporins were the most common antibacterial drug class reported on shortage” was added in the result section, on page 9, line 3 ;

The paragraph: “Reporting of drug shortages has been required to be standardized between all European member States as well as coordination of legal and organizational strategies…” was moved from the conclusion to the discussion on page 10, lines 48 to 50.

- Table 1: data per category do not sum up to 3530, suggesting there is either missing data or a category “other”, e.g. for marketing authorization procedures

All data were checked and corrected according to your remark.

- Figure 4: readability of the legend needs to be improved.

The legend of the figure 4 was detailed according to your request as followed: “Trends in the causes of shortages of pharmaceutical products in 2015-2018”.

In addition, the detailed causes provided by the pharmaceutical companies were added in supplementary materials.

- STROBE statement: study design not mentioned in title, for missing data: see bullet above – this is unclear from the methods section.

We thank you for your focus on this point. Missing data concern a minority of the 2 following variables:

- marketing authorization procedures : 1.81 % of missing data
- duration of marketing authorization grants. : 2.30% of missing data

The following sentence was added in the manuscript in page 6 lines 26 to 27:

“There were no missing data except for marketing authorization procedures and duration of marketing authorization grants.”

A part of the causes of shortages were unknown, which is not similar to “missing data”.

We have completed the title in accordance with your comment. (The study design is also mentioned in the method section: “This observational retrospective study” on page 4 line 15).

VERSION 2 – REVIEW

REVIEWER	Aukje Mantel Utrecht University, the Netherlands
REVIEW RETURNED	06-Dec-2019

GENERAL COMMENTS	I would like to thank the authors for their responses to my questions and comments and the adjustments made to the manuscript. Although most issues have been resolved, I have a few final remarks which I feel need to be addressed before publication is warranted. In their response to my first point on the term MTI, the authors mention that this definition relates to whole ATC classes and thus comprises all drugs from the same therapeutic class. This explanation, however, has not been added to the manuscript. I would like to suggest to add this information for further clarification, also to other readers. It is now clear that the reports include shortages that are reality in practice, but also shortages that are 'predictive', i.e. may never become a shortage in the end. This is a major limitation which in my view needs more attention in the discussion section and also needs to be included in the Article Summary as requested by the Editor. The added line (page 5 of 43 lines 44 to 46) in the manuscript now reads: "the shortage may become effective in a few hours and vice versa". I do not understand what the authors intend to say. The authors indicate that they aimed to provide a quantitative description of drug shortages in France and can therefore not discuss (im)possibilities of preventive measures. In my view, a thorough discussion of a scientific paper also places the results into a broader perspective and provides recommendations for next steps. In this case, a (short) paragraph on potential preventive measures and their (expected) effectiveness based on the wider literature would fit. Maybe the Editor can provide further guidance whether to include such a paragraph or not. In one of their responses, the authors confirm that reporting became mandatory in 2016. Although it was not their aim to assess the effect of this measure, it may affect their results. The modification in the abstract is fine, but I would have expected that the authors would include/discuss this limitation in the discussion section. The increase in shortages in Figure 1, for example, could partly be the result of this mandatory reporting. Finally, I felt that the newly added Strengths & Limitations of the study might need some modifications. The first bullet is not really a strength or limitation of the present study. In the second bullet I would add the calendar years. Bullets 4 and 5 seem to address a similar aspect (?) and could maybe be combined. A limitation that is missing is that shortages are a combination or actual and potential (predictive) shortages – see comment above.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Aukje Mantel

Institution and Country: Utrecht University, the Netherlands

Please state any competing interests or state ‘None declared’: None declared

I would like to thank the authors for their responses to my questions and comments and the adjustments made to the manuscript. Although most issues have been resolved, I have a few final remarks which I feel need to be addressed before publication is warranted.

We are also grateful for the time you took to improve our manuscript and for your interesting comments.

In their response to my first point on the term MTI, the authors mention that this definition relates to whole ATC classes and thus comprises all drugs from the same therapeutic class. This explanation, however, has not been added to the manuscript. I would like to suggest to add this information for further clarification, also to other readers.

We thank you for mentioning this point. We added the following sentence in the introduction section of the manuscript in page 5 of 45 lines 41-42: “This definition relates to some ATC classes and thus comprises all drugs from the same therapeutic class, whether they are generics or brand names.”

It is now clear that the reports include shortages that are reality in practice, but also shortages that are ‘predictive’, i.e. may never become a shortage in the end. This is a major limitation which in my view needs more attention in the discussion section and also needs to be included in the Article Summary as requested by the Editor. The added line (page 5 of 43 lines 44 to 46) in the manuscript now reads: “the shortage may become effective in a few hours and vice versa”. I do not understand what the authors intend to say.

We apologize if this point was not clear enough.

The present study aimed to analyze the reports of drug shortages and not short supplies. MAH shall follow the manufacturing circuit of its drugs, as well as the dysfunctions of this manufacturing circuit, and reporting to the ANSM is required for each dysfunction. This is why MAH report effective or predictive shortages. There will indeed be cases where the risk of shortage will not become a short supply, but these two situations both reflect a production problem and may lead to short supplies.

Otherwise, in the chronology of events, drug shortage occurs before short supply. The ANSM is responsible for taking preventive measures and taking an interest in short supply will not allow them to be placed, because when a short supply occurs, it is already too late to implement preventive measures.

The method, summary and discussion sections have been modified accordingly.

The authors indicate that they aimed to provide a quantitative description of drug shortages in France and can therefore not discuss (im)possibilities of preventive measures. In my view, a thorough discussion of a scientific paper also places the results into a broader perspective and provides

recommendations for next steps. In this case, a (short) paragraph on potential preventive measures and their (expected) effectiveness based on the wider literature would fit. Maybe the Editor can provide further guidance whether to include such a paragraph or not.

We do understand your point of view, and we suggest to add the following guideline to the conclusion paragraph page 12 of 45 lines 10-15: “According to Woodcock &al,33 it would be useful to stimulate investments to increase industrial production capacities, in particular for injectable drugs. Moreover, data of the financial impact of drug shortages are lacking. A calculation of the opportunity cost would be an argument to stimulate these investments.”

In one of their responses, the authors confirm that reporting became mandatory in 2016. Although it was not their aim to assess the effect of this measure, it may affect their results. The modification in the abstract is fine, but I would have expected that the authors would include/discuss this limitation in the discussion section. The increase in shortages in Figure 1, for example, could partly be the result of this mandatory reporting.

We thank you for your comment. We have mentioned in the methods section that the MAH were mandated to report drug shortages since 2012. We have also added in the discussion section the following sentence page 11 of 45 lines 8-9: “Regulatory changes may impact the reporting of drug shortage.”

Finally, I felt that the newly added Strengths & Limitations of the study might need some modifications.

The first bullet is not really a strength or limitation of the present study. This has been modified.

In the second bullet I would add the calendar years. This has been modified.

Bullets 4 and 5 seem to address a similar aspect (?) and could maybe be combined.

The bullet 4 states that only the MTI drugs and not all drugs, are on shortage, whereas the bullet 5 explains the difference between drug shortage and short supply: drug shortage defines the lack of drug at the pharmaceutical company whereas the short supply defines the lack of drug in pharmacies. The present study analyzes drug shortages according to the pharmaceutical company’s perspective; this is why we believe that bullet 4 and 5 are different issues.

A limitation that is missing is that shortages are a combination or actual and potential (predictive) shortages – see comment above. The manuscript has been modified accordingly.

VERSION 3 - REVIEW

REVIEWER	Aukje Mantel-Teeuwisse Utrecht University, the Netherlands
REVIEW RETURNED	04-Jan-2020

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.