**Author’s response to reviews**

**Title:** Characteristics of Pediatric Adverse Drug Reaction Reports in the Japanese Adverse Drug Event Report Database

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**Author’s response to reviews:**

Geneviève Durrieu (Reviewer 1):

Thank you for your valuable comment of our manuscript. According to your comment, we revised our manuscript as follow. We hope that the manuscript has been sufficiently revised.

Comments:

- Abstract

  - Conclusion: text should be modified according to the comments contained in the conclusion of the manuscript

  &gt; In accordance with your remark, we changed some sentences in the abstract section as follow;

  Page 3 line 44;
“We clarified the characteristics of ADR reports for Japanese children by using the JADER. ADR report databases, especially those for pediatric patients, are valuable pharmacovigilance tools in Japan and other countries. Therefore, a proper understanding of the characteristics of the ADR reports in the JADER is important. Additionally, potential signals for ADRs in pediatric patients should be monitored continuously and carefully.”

- Background

  How did you evaluate the database's utility?

  Certainly, we could not evaluate the database's utility in this study. In accordance with your remark, we removed the sentences in the background section as follow;

  Page 6 line 89,

  “Hence, in this study, we studied ADR reporting for pediatric patients in the JADER with an aim to elucidate the characteristics of the ADR reports therein and the database’s utility for drug safety surveillance in pediatric patients.”

- Methods

  1. Some information on Japanese pharmacovigilance system and JADER would be useful. Who is allowed to extract data from JADER?

  &gt; Anyone is allowed to extract data from the JADER. In accordance with your remark, we added some sentences in the background section as follow;

  Page 6 line 83,

  “This information became available for free download to anyone from the Pharmaceutical and Medical Devices Agency (PMDA) website since 2012 (https://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp).

  • Number of ADR reports from reporters other than companies are very low: how do you explain that?

  &gt; The number of ADR reports from reporters other than companies, especially pharmacists are low. Although most Japanese hospital pharmacists sufficiently understood the spontaneous ADR reporting system, they also had some barriers to report the ADR such as what kind of ADR to be reported [Kobayashi T, Noda A, Obara T, Tsuchiya M, Akasaka K, Yoshida M, Matsuura M, Sato M, Murai Y, Yamaguchi H, Tsuchiya F, Kihira K, Mano N. Knowledge, Attitudes, and Practice of Hospital Pharmacists Regarding Pharmacovigilance and Adverse Drug Reaction Reporting in Japan. Hosp Pharm (in press)]. Additionally, companies are required strictly to
report all ADRs within the reporting deadline, differently from healthcare facilities. Therefore, compared to healthcare facility, the number of ADR reports from company might be relatively high. In accordance with your remark, we added some sentences in the method and Discussion section as follow;

Page12 line 223;

“In this study, the number of ADR reports from reporters other than companies, especially pharmacists are low. Although most Japanese hospital pharmacists sufficiently understood the spontaneous ADR reporting system, they also had some barriers to report the ADR such as what kind of ADR to be reported [Kobayashi T, Noda A, Obara T, Tsuchiya M, Akasaka K, Yoshida M, Matsuura M, Sato M, Murai Y, Yamaguchi H, Tsuchiya F, Kihira K, Mano N. Knowledge, Attitudes, and Practice of Hospital Pharmacists Regarding Pharmacovigilance and Adverse Drug Reaction Reporting in Japan. Hosp Pharm (in press)]. Additionally, companies are required strictly to report all ADRs within the reporting deadline, differently from healthcare facilities. Therefore, compared to healthcare facility, the number of ADR reports from company might be relatively high.”

How a health professional or a patient can declare an ADR to public health authorities (such as a pharmacovigilance center)?

A health professional can declare an ADR to regulatory authority through a system called the Drugs and Medical Devices Safety Information Reporting System. The Direct Patient Reporting System for Adverse Drug Reactions (ADRs), in which patients and consumers can report ADRs directly to the PMDA, was tentatively started from 2012 as a pilot program. In accordance with your remark, we added some sentences in the method section as follow;

Page 7 line 105,

“As for patients, the Direct Patient Reporting System for ADRs, in which patients and consumers can report ADRs directly to the PMDA, was tentatively started from 2012 as a pilot program and a full-scale operation of the system was started on March 26, 2019. However, the JADER have not include the reports from this system yet.”

Is ADR declaration mandatory for some health professionals?

ADR declaration is mandatory for health professionals. In accordance with your remark, we added some sentences in the method section as follow;

Page 6 line 102,

“The PMDA recommend companies and healthcare professionals to report ADRs through a system called the Drugs and Medical Devices Safety Information Reporting System, even if the causal relationship between medication use and ADR was unclear.”

- Are the ADR reports checked and analyzed before being registered in the PV database?
The ADR reports are checked and analyzed before being registered in the PV database (JADER) by pharmaceutical companies and the PMDA. In accordance with your remark, we added some sentences in the method section as follow;

Page 6 line 97;

“The ADR reports are checked and evaluated whether the ADR report is serious or not before being registered in the JADER by the PMDA, and the JADER in principle comprises serious ADR reports selected by the PMDA.”

2. Line 95: what does this sentence mean?

In accordance with your remark, we changed the sentences “Information was extracted from the JADER downloaded in April 2018.” in the abstract and method section as follow;

Page 3 line 33, Page 6 line 95;

“We used spontaneous ADR reports included in the JADER since April 1, 2004 to December 31, 2017, which was downloaded in April 2018.”

3. For ADR, why did you choose to present only PTs?

We used PTs for ADR because ADRs in the JADER were described by using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT). In accordance with your remark, we changed some sentences in the method section as follow;

Page 7 line 118;

“The adverse reaction and primary disease fields in the JADER are described by using the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA®/J) and were coded as preferred terms (PTs). Therefore, we used MedDRA®/J Version 21.0 in the present study.”

4. In the collected data, it was not listed "suspected drugs". Which drug classification is used for drugs? Only INN?

We collected both INNs and brand names for suspected drugs and used INN only to treat drugs with the same ingredients as the same drugs. In accordance with your remark, we added some sentences in the method section as follow;

Page 8 line 128;

“As for suspected drugs, we collected both International Nonproprietary Name (INN) and brand name and used INN to treat drugs with the same ingredients as the same drugs for analysis.”
5. What about ADR seriousness? We read further that JADER only contains "serious ADR reports. This should be added here.

ADR seriousness was defined as follow; [1]Fatal, [2]Disabilities, [3]Cases that may be fatal, [4]Cases that may lead to disabilities, [5]Cases requiring hospitalization or prolonging duration of hospitalization for treatment at the hospital or clinic (excluding cases noted in [3] and [4]), [6]Serious cases in accordance with cases noted in [1] to [5], [7]Congenital disorders or abnormalities in later generations, [8]Occurrence of infectious disease cases suspected to occur due to the use of relevant drugs, medical devices, etc., [9]Of the malfunctions that occur due to the use of relevant medical devices, etc., those with the risk of occurrence of cases, etc. noted in [1] to [7], [10]Besides the cases noted in [1] to [8], occurrence of cases which are not mild and could not be predicted based on the package insert, etc., [11]Of the malfunctions that occur due to the use of relevant medical devices, regenerative medicines, etc., those with the risk of occurrence of cases noted in [10]. In accordance with your remark, we added some sentences in the method section as follow:

Page 8 line 136;

“ADR seriousness was defined as follow; (1)Fatal, (2)Disabilities, (3)Cases that may be fatal, (4)Cases that may lead to disabilities, (5)Cases requiring hospitalization or prolonging duration of hospitalization for treatment at the hospital or clinic (excluding cases noted in (3) and (4)), (6)Serious cases in accordance with cases noted in (1) to (5), (7)Congenital disorders or abnormalities in later generations, (8)Occurrence of infectious disease cases suspected to occur due to the use of relevant drugs, medical devices, etc., (9)Of the malfunctions that occur due to the use of relevant medical devices, etc., those with the risk of occurrence of cases, etc. noted in (1) to (7), (10)Besides the cases noted in (1) to (8), occurrence of cases which are not mild and could not be predicted based on the package insert, etc., (11)Of the malfunctions that occur due to the use of relevant medical devices, regenerative medicines, etc., those with the risk of occurrence of cases noted in (10).”

6. What is your definition of a serious ADR?

Our definition of a serious ADR was same as above. However, a single ADR report often include multiple ADRs, which can include non-critical events such as pyrexia and rash. In accordance with your remark, we added some sentences in the method section as follow:

Page 6 line 100;

“A single ADR report often include multiple ADRs, which can include non-serious events such as pyrexia and rash.”

7. Same comment for age groups: explain that you are not able to use WHO age group classification
We were not able to use WHO age group classification such as children aged 5–17 years, since the JADER only included age information as a categorical variable such as children aged <10 and 10–19 years because of privacy considerations. In accordance with your remark, we added some sentences in the method section as follow:

Page 8 line 130;

“Since the JADER only included age information as a categorical variable, we extracted ADR reports for children aged <10 and 10–19 years.”

8. What about causality?

Causality is defined as the causal relationship between medication use and ADR. The PMDA recommend companies and healthcare professionals to report ADRs, even if the causality was unclear. In accordance with your remark, we added some sentences in the method section as follow;

Page 6 line 102,

“The PMDA recommend companies and healthcare professionals to report ADRs through a system called the Drugs and Medical Devices Safety Information Reporting System, even if the causal relationship between medication use and ADR was unclear.”

- Results

1. Percent of unknown age should be added in the text.

In accordance with your remark, we added percent of unknown age in the abstract and result section as follow;

Page 3 line 35, Page 9 line 154,

“Of these, the number of spontaneous reports was 386400 (76.6%), in which 37534 (7.4%) were unknown age reports. After extraction of 27800 ADR reports for children aged <10 and 10–19 years, we excepted for ADR reports associated with vaccine (n=6355) and no-suspected drug reports (n=86). A total of 21359 (4.2%) reports were finally included in this analysis.”

2. What are the characteristics of fatal ADR reports?: suspected drugs? ADR? Poisoning? Suicide?

Please see the uploaded file, "200303_Response to Reviewer's comments". The most frequently reported drugs, reaction, and drug-reaction pairs in fatal ADR reports for patients aged <10 were etoposide (3.6%), sepsis (2.6%), and “etoposide and acute respiratory distress
syndrome” (0.3%), respectively. The most frequently reported drugs, reaction, and drug-reaction pairs in fatal ADR reports for patients aged 10–19 years were tacrolimus (5.1%), sepsis (3.4%), and “bortezomib and neutropenia” (0.4%), respectively. In accordance with your remark, we added some sentences in the result section as follow;

Page 10 line 193;

“Among 1128 and 764 reported drugs of 552 and 369 fatal ADR reports for patients aged <10 and 10–19 years, the most frequently reported drugs were etoposide (3.6%) and tacrolimus (5.1%), respectively.”

Page 11 line 203;

“Among 1095 and 768 reported reactions of 552 and 369 fatal ADR reports for patients aged <10 and 10–19 years, the most frequently reported reactions were "death" (3.0%) and sepsis (3.4%), respectively.

Page 11 line 215;

“Among 2363 and 1852 reported drug-reaction pairs of 552 and 369 fatal ADR reports for patients aged <10 and 10–19 years, the most frequently reported drug-reaction pairs were “etoposide and acute respiratory distress syndrome” (0.3%) and “bortezomib and neutropenia” (0.4%), respectively.”

- Discussion

1. A qualitative description of fatal ADR reports should be added.

Page 12 line 240;

“Fatal ADR reports are the cases where outcomes are described as death and tend to be reported more positively because of their importance and difficulty in understanding.”

2. Have you checked that oseltamivir and zanamivir did not influence on detecting other signals? Did you perform an analysis excluding these 2 drugs? Or did you compare data before 2010 and after 2010?

Thank you for your valuable comments of our manuscript. Indeed, it is very important to perform an analysis excluding these 2 drugs and compare data before 2010 and after 2010 in considering the utility of the JADER as a database for signal detection. I think it is necessary to
evaluate the ability of the JADER for signal detection. In accordance with your remark, we added some sentences in the discussion section as follow;

Page 16 line 340;

“In future studies, we will evaluate the ability of the JADER for signal detection based on the characteristics of the JADER clarified in this study.”

- Conclusion

This study described several weakness (age groups, duplicate…). The conclusion should include the areas that need to be improved in order to obtain reliable data.

We described several limitations according to your remark, and we added some sentences in the conclusion section as follow;

Page 17 line 346;

“Therefore, a proper understanding of the characteristics of the ADR reports in the JADER is important and several limitations such as age group and duplicated reports need to be improved. Additionally, potential signals for ADRs in pediatric patients should be monitored continuously and carefully.”

Ugo Moretti (Reviewer 2):

Thank you for your valuable comment for our manuscript. We divided your comment into several parts and revised our manuscript as follow. We hope that the manuscript has been sufficiently revised.

1. The study aims to evaluate the adverse drug reactions in the Japanese spontaneous reporting database. The study has important critical issues. The most important one is related to the type of data used in the analysis, obtained through the public version of the Japanese database. In this database, the age of the patient is reported only as categorical value expressed in decades. The Authors analyze two decades, including patients not related to the pediatric age (age higher than 16 or 17 years). Moreover it is not possible to analyze the situation for age groups that are very different (eg neonatal or infant vs adolescent).

As stated by the Authors "information on age is essential in discussion about SDRs, especially in pediatric patients". This is an important limitation of the relevance of the study. With these age categories it could at least presented and discussed the comparison between children and adults with respect to the reported drugs and reactions.
In accordance with your remark, we added some sentences to emphasize that it is not possible to analyze the situation for age groups in the discussion section as follow;

Page 16 line 325;

“Second, it was not possible to analyze the situation according to WHO age group classification such as children aged 5–17 years because the JADER only included age information as a categorical variable such as children aged <10 and 10–19 years.”

2. Since almost all reports come from drug companies it could be more interesting to analyze Japanese reports through the analyses of the FDA spontaneous reporting database (FAERS), publicly available for download. FAERS include non-US data received by drug companies worldwide and it is possible to select Japanese reports with detailed information for age.

Thank you for your valuable comment for our manuscript. Nomura et al. have already compared Japanese ADR reports between the FAERS and the JADER [Nomura K, Takahashi K, Hinomura Y, Kawaguchi G, Matsushita Y, Marui H, Anzai T, Hashiguchi M, Mochizuki M. Effect of database profile variation on drug safety assessment: an analysis of spontaneous adverse event reports of Japanese cases. Drug Des Devel Ther. 2015;9:3031–3041.]. Although the FAERS included non-US data received by drug companies worldwide and it was possible to select Japanese reports with detailed information for age, they clarified that the FAERS and the JADER had different properties. Therefore, in our study, we clarified the characteristics of ADR reports for Japanese children by using the JADER. In accordance with your remark, we added some sentences in the discussion section as follow;

Page 16 line 328;

“Nomura et al. have already compared Japanese ADR reports between the FAERS and the JADER [Nomura K, Takahashi K, Hinomura Y, Kawaguchi G, Matsushita Y, Marui H, Anzai T, Hashiguchi M, Mochizuki M. Effect of database profile variation on drug safety assessment: an analysis of spontaneous adverse event reports of Japanese cases. Drug Des Devel Ther. 2015;9:3031–3041.]. Although the FAERS included non-US data received by drug companies worldwide and it was possible to select Japanese reports with detailed information for age, they clarified that the FAERS and the JADER had different properties. Therefore, in our study, we clarified the characteristics of ADR reports for Japanese children by using the JADER.”

3. Another important issue is related to serious events. The Authors stated that JADER database includes only serious ADRs. It is not clear how seriousness has been defined, generally serious reports include deaths, life-threatening events, hospitalization, persistent or significant disabilities and congenital abnormalities but it could be possible to define seriousness according to the clinical judgment of the reporter. Table 3 lists among the most frequently reported reactions non-serious events like pyrexia and rash, it is not clear why these reports have been defined serious.
Although the definition of ADR seriousness was not exactly known because PMDA has selected serious ADRs, ADR seriousness should be assessed by the items in the reports based on “ADR seriousness judgment criteria” as follow; deaths, life-threatening events, hospitalization or extension of hospital stay for treatment, persistent or significant disabilities and congenital abnormalities. The reason why Table 3 included non-serious events like pyrexia and rash was that a single ADR report often included multiple ADRs, which could include non-serious events. In accordance with your remark, we added some sentences in the method section as follow;

Page 6 line 100;

“A single ADR report often include multiple ADRs, which can include non-serious events such as pyrexia and rash.”

Page 8 line 136;

“ADR seriousness was defined as follow; (1) Fatal, (2) Disabilities, (3) Cases that may be fatal, (4) Cases that may lead to disabilities, (5) Cases requiring hospitalization or prolonging duration of hospitalization for treatment at the hospital or clinic (excluding cases noted in (3) and (4)), (6) Serious cases in accordance with cases noted in (1) to (5), (7) Congenital disorders or abnormalities in later generations, (8) Occurrence of infectious disease cases suspected to occur due to the use of relevant drugs, medical devices, etc., (9) Of the malfunctions that occur due to the use of relevant medical devices, etc., those with the risk of occurrence of cases, etc. noted in (1) to (7), (10) Besides the cases noted in (1) to (8), occurrence of cases which are not mild and could not be predicted based on the package insert, etc., (11) Of the malfunctions that occur due to the use of relevant medical devices, regenerative medicines, etc., those with the risk of occurrence of cases noted in (10).”

4. Spontaneous reporting databases include literature reports, cases selected by drug companies in the literature and sent as individual case safety reports. Literature reports include many duplicates since the same case is reported by different drug companies. It should be specified if JADER database include literature data and, if the answer is yes, if duplicates have been deleted.

Spontaneous reports were defined as ADR reports derived from unsolicited sources in the ICH E2B, which included direct reports from medical institutions or pharmaceutical companies, ADR reports from abstracts, literature, Internet, etc. However, in the JADER, detailed information on the source of spontaneous ADR reports was not revealed. Therefore, we added some sentences in the method and discussion section as follow;

Page 7 line 112;

“Spontaneous reports were defined as ADR reports derived from unsolicited sources in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E2B, which included direct reports from healthcare facilities or companies, ADR reports from abstracts, literature, Internet, etc.”
“Third, in the JADER, detailed information on the source of spontaneous ADR reports was not revealed. Therefore, there remains the possibility of duplicated reports, whereby one case might be reported multiple times.”

5. The list of the most frequently reported drugs seems not related to the drug use. This result should be discussed, specifying if stimulated reporting or other form of active reporting was present for some drugs (like oseltamivir and zanamivir).

Stimulated reporting might be present for oseltamivir as described in the text. As for the drugs in the list, safety information regarding the revision of the precautions of package inserts of drugs have been provided in Pharmaceuticals and Medical Devices Safety Information published by Ministry of Health, Labour and Welfare or Drug Safety Update published by the Federation of Pharmaceutical Manufacturers' Associations of Japan. This information might have boosted the number of ADR reports. Therefore, the list of drugs in Table 2 seemed not to be related to the drug use. In accordance with your remark, we added some sentences in the discussion section as follow;

Page 13 line 258;

“As for the most frequently reported drugs in Table 2, the number of ADR reports regarding to oseltamivir might be increased by the Dear Healthcare Professional Letters. All drugs in the list, safety information regarding the revision of the precautions of package inserts of drugs have been provided in Pharmaceuticals and Medical Devices Safety Information published by Ministry of Health, Labour and Welfare or Drug Safety Update published by the Federation of Pharmaceutical Manufacturers' Associations of Japan. This information might have boosted the number of ADR reports. Therefore, the list of drugs in Table 2 seemed not to be related to the drug use.”

6. Moreover among reported reactions the number of reports of toxic epidermal necrolysis and Stevens-Johnson syndrome associated to paracetamol is very high. This finding should be highlighted and discussed

As you pointed out, the number of reports of toxic epidermal necrolysis and Stevens-Johnson syndrome (SJS) associated to acetaminophen was very high. This result may be explained by the potential inclusion of viral infection-induced SJS in data from the JADER. SJS can be induced by mycoplasma infection, which is commonly observed in patients aged &lt;10 years, and the treatment strategy for this condition would include antibiotics and/or acetaminophen. [Abe J, Umetsu R, Mataka K, Kato Y, Ueda N, Nakayama Y, Hane Y, Matsui T, Hatahira H, Sasoaka S, Motooka Y, Hara H, Kato Z, Kinosada Y, Inagaki N, Nakamura M. Analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis using the Japanese Adverse Drug Event Report database. J Pharm Health Care Sci. 2016;2:14.] Therefore, it might
be reverse causality. In accordance with your remark, we added some sentences in the discussion section as follow;

Page 15 line 304;

“The number of reports of toxic epidermal necrolysis and Stevens-Johnson syndrome (SJS) associated to acetaminophen was also very high. This result may be explained by the potential inclusion of viral infection-induced SJS in data from the JADER. SJS can be induced by mycoplasma infection, which is commonly observed in patients aged &lt;10 years, and the treatment strategy for this condition would include antibiotics and/or acetaminophen [Abe J, Umetsu R, Mataka K, Kato Y, Ueda N, Nakayama Y, Hane Y, Matsui T, Hatahira H, Sasaoka S, Motooka Y, Hara H, Kato Z, Kinosada Y, Inagaki N, Nakamura M. Analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis using the Japanese Adverse Drug Event Report database. J Pharm Health Care Sci. 2016;2:14.]. Therefore, it might be a reverse causality.”