PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Retrospective study of irrational prescribing in French pediatric hospital: prevalence of inappropriate prescription detected by POPI (Pediatrics: Omission of Prescription and Inappropriate prescription) in the emergency unit and in the ambulatory setting.
AUTHORS	Berthe-Aucejo, Aurore; Nguyen, Phuong Khanh Hoang; Angoulvant, François; Bellettre, Xavier; Albaret, Patrick; Weil, Thomas; Boulkedid, Rym; Bourdon, Olivier; Prot-Labarthe, Sonia

VERSION 1 – REVIEW

REVIEWER	Imti Choonara University of Nottingham,UK I have had one meeting with the investigators to discuss future collaboration on rational prescribing
REVIEW RETURNED	28-Aug-2017

GENERAL COMMENTS	This paper deals with an important clinical issue - rational prescribing in children. The title should be amended, deleting the first five words and replacing with "Retrospective study of irrational prescribing" The main weakness of this study is its retrospective nature and limited clinical information. The authors have only assessed some of the POPI criteria. It is unclear from appendix 1 which ones were fully assessed. The authors have used the symbol (a snowdrop with six limbs) to identify which criteria could be evaluated. However appendix 1 also includes a star with 5 limbs. Is this a typo or does it signify something different?. Were domperidone etc only assessed in the community? Table 3 suggests 7304 cases were analysed for PIMs and 4508 for PPO in hospital. Were these mutually exclusive,ie 11,812 were analysed. The denominator is important but unclear. In the discussion, the authors state that analgesics and antipyretics were not studied, despite these being the most frequently used drugs. This needs to be in both methods & Results. Did the authors have access to any clinical information? Why not? Minor points Introduction should mention rational prescribing and quote recent papers on this topic - see ADC. Also the focus in the INtro should be on reducing drug toxicity not med errors. I would therefore avoid use of the term ADE which includes med errors. Again quote recent papers on drug toxicity in children. The authors state that they could not assess wheter amoxiciliin was prescribed in mg due to the large number of prescriptions. They could however assess 100 prescriptions randomly. If the authors can address these points, then the paper would be an important addition to the literature

REVIEWER	Frank Moriarty Royal College of Surgeons in Ireland, Ireland I was involved in the development of another set of criteria for identifying potentially inappropriate prescribing in children in primary care (the PIPc study: http://bmjopen.bmj.com/content/6/9/e012079)
REVIEW RETURNED	31-Aug-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. It reports on a study of potentially inappropriate prescribing in children in both hospital and ambulatory care settings. This represents a new development in the field of potentially inappropriate prescribing as the first prevalence study in children, using the recently developed POPI criteria. Overall the manuscript is of a very high quality. I have noted some relatively minor comments/queries for the authors below: Introduction 1. Reference 20 is cited in the section on negative outcomes associated with inappropriate prescribing but does not evaluate any negative outcomes. Would suggest amending/removing this reference. Methods 2. More background on the POPI criteria would be of benefit to readers unfamiliar with the tool i.e. how they were developed, how many criteria are contained within the tool, what typical structure to the criteria take e.g. explicit/implicit. 3. Clarification of how the criteria were applied to determine the prevalence (i.e. how the numbers in the "no. of cases analyzed" column in Table 3 were arrived at). Results 4. The Figures referred to in the text do not appear to have been included in the manuscript proof. 5. On page 7, line 24, should this refer to "three or more prescriptions", rather than "more than three"? 6. In table 4, am I correct that the percentages reported are the % of all PIMs/PPOs that each criterion makes up? If so, I would suggest stating this explicitly as these percentages could accidentally be interpreted as the prevalence. 7. In table 5, it is unclear why the multivariate analysis has been omitted for hospital prescribing. Discussion 8. References for the sources of the PIM rate in geriatrics patients could be included on page 12, line 38. 9. Can the authors expand in the text on reasons why the results they present could be an underestimate? (Page 15, line 52-54) 10. It would also be helpful to clarify what is meant by "the effectiveness of the tool" (Page 16, line 26). Does this refer to its effectiveness in identifying PIM/PPO, or in helping clinicians in reducing PIM/PPO? Perhaps the text could be more specific in the design of further studies that are suggested e.g. further observational studies, randomised trials? General comments 11. Outcomes - it would be helpful to summarise in the text both how many of the POPI criteria could be assessed based on the data

	used in this study and broad reasons why some could not be evaluated. 12. In the aims section and elsewhere, the manuscript refers to assessing the prevalence of PIM and PPO, and risk factors relating to PIM. I was initially unsure whether risk factors for PPO were also assessed however from reading the full paper, it appears they were not. However, I do not think this is clearly stated anywhere. It would be helpful to include a statement that risk factors for PPO were not evaluated and the rationale/justification for this. 13. It would be helpful to provide an age range where age groups are referred to in the text e.g. Page 7 line 3 "using adolescents as a reference", Page 11 line 31-33 "showed that children and prescriptions...", Page 15, line 22 "the child group has the highest..."

REVIEWER	Deo Kumar Srivastava St. Jude Children's Research Hospital Department of Biostatistics Memphis, TN 38105 USA
REVIEW RETURNED	25-Sep-2017

GENERAL COMMENTS	In this manuscript the authors propose to evaluate the POPI (Pediatrics: Omission of Prescription and Inappropriate prescription) tool for detecting PIM (potentially inappropriate medicines) and PPO (potentially prescribing omissions in two different settings ED (emergency department) and CP (community pharmacy). The primary objective is to estimate the rates of PIM and PPO and to identify the risk factors associated with PIM. This pretty much is a descriptive study but the design used makes the analysis more complicated and makes the interpretation of the data more difficult. There are several statistical issues, identified below, that need to be addressed. 1. As the authors indicate that the POPI tool was developed by Prot-Labarte et al. in 2013 to improve the correct drug use and optimize practice. They also indicate that this tool has not been tested in actual practice and was applied first time in their study. It is not clear if any validation studies were conducted to better understand the psychometric properties of the tool before implementing in real setting. 2. The unit of analysis is not clear. Sometimes the estimates are based on number of prescriptions and sometimes they are based on number of patients. For example, see the beginning of Results section where the estimates are reported. The authors also talk about Figure 1 and 2, but this reviewer did not have access to them or the submission did not contain the figures. 3. They report that 21% and 26% of the patients were issued with 2 or more than 3 prescription. Now it is not clear if they are talking about the prescription in ED or CP. 4. In Table 5, the authors report the results of the univariate and multivariate regression analyses using logistic regression. However, it is not clear if the outcome was modeled using prescription or patient as the unit of analysis. If prescriptions were used as the unit of analysis then how

	did they account for multiple prescriptions for each patient, as mentioned in comment 3 above? 5. In Discussion section the authors say that incidence of PPO was higher in older people, but no data is shown. It might be in Figure 4, as suggested in the discussion, but this reviewer did not have access to it. In general, this reviewer did not have access to any figures since they were probably not included with the submission. 6. Overall, it seems that the rates of PPO and PIM are significantly lower compared to geriatric hospitals. The authors do suggest that because of several reasons, detailed in the limitations, the reported estimates may have been underestimated. But it is not clear if it is due to these limitations or due to inability of the tool (POPI) to obtain relevant information to estimate PIM and PPO accurately.

REVIEWER	M. Shafiqur Rahman ISRT, University of Dhaka Bangladesh
REVIEW RETURNED	29-Sep-2017

GENERAL COMMENTS	The authors presented an interesting topic through this research articles.Although they presented it very clearly, I have some comments and observations given below; solving which may strengthen the paper. Abstract: I am confused with the the way the presented the numbers 18562. Is it 18.562 or 18,562 and similar to others in the abstract. Methods; Statistical analysis: Need to mention what type of multivariate analysis they performed. They defined several models according to Table 5- need to describe how and why they formed several models. Results: It is not clear why the OR is 0.00 for age category <28 days. Need a detail description of the results from multivariable models in table 5. Because these results are important to describe about potential risk factors of PIM.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
“The title should be amended, deleting the first five words and replacing with "Retrospective study of irrational prescribing"
Answer: Done
“The main weakness of this study is its retrospective nature and limited clinical information. The authors have only assessed some of the POPI criteria. It is unclear from appendix 1 which ones were fully assessed. The authors have used the symbol (a snowdrop with six limbs) to identify which criteria could be evaluated. However appendix 1 also includes a star with 5 limbs. Is this a typo or does it signify something different?.”
Answer: It was a mistake. Star with 5 limbs was corrected by snowdrop with six limbs.
“Were domperidone etc only assessed in the community? “
Answer: Domperidone was assessed in the community and in hospital

“Table 3 suggests 7304 cases were analysed for PIMs and 4508 for PPO in hospital. Were these mutually exclusive, i.e. 11,812 were analysed. The denominator is important but unclear.”
Answer: Cases were exclusive.
“In the discussion, the authors state that analgesics and antipyretics were not studied, despite these being the most frequently used drugs. This needs to be in both Methods & Results. Did the authors have access to any clinical information? Why not? “
Answer: Sentence“Criteria included analgesics and antipyretics were not evaluated because of large number of prescriptions and association with many diseases)” was added in Methods.
In hospital, we only had access to the main diagnostic.
Minor points
“Introduction should mention rational prescribing and quote recent papers on this topic - see ADC. Also the focus in the Intro should be on reducing drug toxicity not med errors. I would therefore avoid use of the term ADE which includes med errors.”
Answer: In the literature, ADE is defined by “an injury resulting from medical intervention related to a drug”1,2 This term includes adverse drug reaction, harm from use of the treatment. ADE could be dose error, administration error, adverse drug reaction, use of wrong antibiotic for infection treatment etc…3 POPI enables detection of prescription or omission which can involve toxicity but not only, adverse events like rehospitalization, clinical deterioration …
“Again quote recent papers on drug toxicity in children. “
Answer: recent papers were added about ADR
“The authors state that they could not assess whether amoxicillin was prescribed in mg due to the large number of prescriptions. They could however assess 100 prescriptions randomly.”
Answer: After having randomly assessed 100 hospital prescriptions with amoxicillin, 97 prescriptions were inappropriate. This result is added in the manuscript.
“If the authors can address these points, then the paper would be an important addition to the literature”
Answer: we thank the reviewer for this advice.
Reviewer:2
Thank you for the opportunity to review this manuscript. It reports on a study of potentially inappropriate prescribing in children in both hospital and ambulatory care settings. This represents a new development in the field of potentially inappropriate prescribing as the first prevalence study in children, using the recently developed POPI criteria. Overall the manuscript is of a very high quality. I have noted some relatively minor comments/queries for the authors below:
Introduction
“Reference 20 is cited in the section on negative outcomes associated with inappropriate prescribing but does not evaluate any negative outcomes. Would suggest amending/removing this reference. “
Answer: Reference was removed.
“Methods
2. More background on the POPI criteria would be of benefit to readers unfamiliar with the tool i.e. how they were developed, how many criteria are contained within the tool, what typical structure do the criteria take e.g. explicit/implicit.”
Answer: A paragraph was added in Methods
POPI contains 102 criteria (76 PIMs, 25 PPO). Criteria were validated by 2-round-Delphi consensus technique. A literature review was done to obtain criteria. Criteria were categorized according to the main physiological systems (gastroenterology, respiratory infections, pain, neurology, dermatology and miscellaneous).
“3. Clarification of how the criteria were applied to determine the prevalence (i.e. how the numbers in the "no. of cases analyzed" column in Table 3 were arrived at).”
Answer: Total number of cases corresponds to the clinical contexts. Prevalence is inappropriate prescriptions on the total number of cases. A legend was added to the table 3 " *number of cases analyzed corresponded with clinical situation"
“Results

4. The Figures referred to in the text do not appear to have been included in the manuscript proof. “
Answer: Figures were added
“5. On page 7, line 24, should this refer to "three or more prescriptions", rather than "more than three"?”
Answer: sentence was corrected
“6. In table 4, am I correct that the percentages reported are the % of all PIMs/PPOs that each criterion makes up? If so, I would suggest stating this explicitly as these percentages could accidentally be interpreted as the prevalence.”
Answer: Percentage detail was explained under the table. “% Percentage calculated from the total number of PIMs or PPO detected”
“7. In table 5, it is unclear why the multivariate analysis has been omitted for hospital prescribing.”
Answer: Multivariate analysis has been not omitted for hospital prescription. Indeed, results of univariate analysis showed that only different age categories were associated with risk of PIM in hospital setting. Sex was found not to be significant. We would have performed "multivariate" model using only the different age categories and obtained the same results as for the bivariate model. But to avoid any confusion, we have given a result in multivariate section (same as in univariate section).

Discussion
“8. References for the sources of the PIM rate in geriatrics patients could be included on page 12, line 38”
Answer: References are included after the sentence “As expected, the rate of IP detected is lower than in the geriatric population (pediatric: 3.3% in hospital, 26.4% in community vs geriatric: 35% in hospital and 51.3% in community).”
“9. Can the authors expand in the text on reasons why the results they present could be an underestimate? (Page 15, line 52-54)”
Answer: All criteria could not be analyzed because of retrospective study (missing data, clinical situation not available)
“10. It would also be helpful to clarify what is meant by “the effectiveness of the tool” (Page 16, line 26). Does this refer to its effectiveness in identifying PIM/PPO, or in helping clinicians in reducing PIM/PPO? Perhaps the text could be more specific in the design of further studies that are suggested e.g. further observational studies, randomised trials?”
Answer: “effectiveness of the tool” meant decrease of PIM and PPO. Next study will be a stepped wedge multicenter cluster randomised study. The sentence “In the next few years, a stepped wedge randomized cluster multicenter study will be conducted to prove if POPI decrease number of PIM and PPO.” was added.
General comments
“11. Outcomes - it would be helpful to summarise in the text both how many of the POPI criteria could be assessed based on the data used in this study and broad reasons why some could not be evaluated. “
Answer: Numbers of criteria for hospital and community were added. In retrospective study, all data are not available and certain criteria need clinical context which is not accessible to pharmacist in community
“12. In the Aims section and elsewhere, the manuscript refers to assessing the prevalence of PIM and PPO, and risk factors relating to PIM. I was initially unsure whether risk factors for PPO were also assessed; however from reading the full paper, it appears they were not. However, I do not think this is clearly stated anywhere. It would be helpful to include a statement that risk factors for PPO were not evaluated and the rationale/justification for this.”
Answer: In community, only one PPO is detected (Dose in mg for oral (solution of) amoxicillin etc.). So we cannot compare with hospital. In ED, this criterion can be evaluated because of the large number of prescriptions.
“13. It would be helpful to provide an age range where age groups are referred to in the text e.g. Page

7 line 3 "using adolescents as a reference", Page 11 line 31-33 "showed that children and prescriptions...", Page 15, line 22 "the child group has the highest..."
Answer:
Page 7 line 3 “using adolescents as a reference” was corrected by “using 12-18 years range as a reference”
Page 11 line 31-33, sentence was corrected: “Multivariate analysis showed that children aged between 2 and 12 years and prescriptions issued from outpatient care correlated with a higher risk of PIM”
Page 15 line 22: sentence was modified: “the child aged between 2 and 12 years has the highest risk of presenting with a PIM, according to a multivariate analysis”
Reviewer: 3
In this manuscript the authors propose to evaluate the POPI (Pediatrics: Omission of Prescription and Inappropriate prescription) tool for detecting PIM (potentially inappropriate medicines) and PPO (potential prescribing omissions in two different settings ED (emergency department) and CP (community pharmacy). The primary objective is to estimate the rates of PIM and PPO and to identify the risk factors associated with PIM. This pretty much is a descriptive study but the design used makes the analysis more complicated and makes the interpretation of the data more difficult.
There are several statistical issues, identified below, that need to be addressed.

“1. As the authors indicate that the POPI tool was developed by Prot-Labarte et al. in 2013 to improve the correct drug use and optimize practice. They also indicate that this tool has not been tested in actual practice and was applied first time in their study. It is not clear if any validation studies were conducted to better understand the psychometric properties of the tool before implementing in real setting.”

Answer: This tool has not been tested in practice. A stepped wedge multicenter cluster randomised study will be conducted in the next few years. The sentence “In the new few years, a stepped wedge randomized cluster multicenter study will be conducted to prove if POPI decrease number of PIM and PPO.” was added.

“2. The unit of analysis is not clear. Sometimes the estimates are based on number of prescriptions and sometimes they are based on number of patients. For example, see the beginning of Results section where the estimates are reported.
Answer: We have to present both prescriptions and patients results. For example in the text, we showed that 541 PIM were identified, but the table 2 explains that sometimes patients have 1 or two PIM (519 + 2*11=541). We always try to develop and illustrate our results and examples.

The authors also talk about Figure 1 and 2, but this reviewer did not have access to them or the submission did not contain the figures.”
Answer: Figures were added

2-They report that 21% and 26% of the patients were issued with 2 or more than 3 prescription. Now it is not clear if they are talking about the prescription in ED or CP. 4.
Answer: sentence was corrected “In ED and CP, 53% of patients had been issued with one prescription, 21% with two and 26% with three or more prescriptions”

In Table 5, the authors report the results of the univariate and multivariate regression analyses using logistic regression. However, it is not clear if the outcome was modeled using prescription or patient as the unit of analysis. If prescriptions were used as the unit of analysis then how did they account for multiple prescriptions for each patient, as mentioned in comment 3 above?”

Answer:
Line of prescription was used as a unit of analysis, for example, if a patient has 1 prescription with 5 drugs, we include 5 lines of prescription. So because each drug represents one line, inappropriate prescription is different between each line of prescription.

“5. In Discussion section the authors say that incidence of PPO was higher in older people, but no data is shown.
Answer: we note in discussion that the incidence of PPO was higher in older people (ED: 57.9% and CP: 59.4%) vs (ED: 2.6% and CP: 13.2%)

It might be in Figure 4, as suggested in the discussion, but this reviewer did not have access to it. In general, this reviewer did not have access to any figures since they were probably not included with the submission.”
Answer: Figure is added

6. Overall, it seems that the rates of PPO and PIM are significantly lower compared to geriatric hospitals. The authors do suggest that because of several reasons, detailed in the limitations, the reported estimates may have been underestimated. But it is not clear if it is due to these limitations or due to inability of the tool (POPI) to obtain relevant information to estimate PIM and PPO accurately.”

Answer: The underestimation is due to limitations of the study. It is a retrospective study so there are missing data, absence of clinical situation). This study showed that the tool needs certain criteria, clinical data which is not always available to the pharmacist in the community. However we still think that inappropriate prescriptions in children is less frequent than for elderly people.

Reviewer: 4
The authors presented an interesting topic through this research article. Although they presented it very clearly, I have some comments and observations given below; solving which may strengthen the paper. Abstract:
“I am confused with the way they presented the numbers 18562. Is it 18.562 or 18,562 and similar to others in the abstract. “
Answer: Numbers were corrected to 18,562. This issue has been taken to account in the revised of the manuscript.
“Methods:
Statistical analysis: Need to mention what type of multivariate analysis they performed. They defined several models according to Table 5- they need to describe how and why they formed several models”.
Answer: Statistical sections were rewritten and indicate type of multivariate analysis performed.
“Results: it is not clear why the OR is 0.00 for age category <28 days.
Need a detailed description of the results from multivariable models in table 5. Because these results are important to describe about potential risk factors of PIM.”
Answer: Response: OR is 0.00 for age category <28 days because there was no inappropriate prescription in patients younger than 28 days. For a better interpretation of the results, we grouped patients younger than 28 days with those aged 28 days to 2 years.

References
1 Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA 1995 274 29 34
2 Kohn LT, Corrigan JM, Donaldson MS. To Err Is Human: Building a Safer Health System.

Washington, DC National Academy Pr 1999
3 Rainu Kaushal, David W. Bates, Christopher Landrigan, et al Medication Errors and Adverse Drug Events in Pediatric Inpatients JAMA. 2001;285(16):2114-2120. doi:10.1001/jama.285.16.2114

VERSION 2 – REVIEW

REVIEWER	Imti Choonara Univ of Nottingham, UK I have met some of the authors to discuss POPI
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	This paper has improved. However, there are still major issues. Introduction still mentions med errors, whereas POPI is a tool to assess prescribing. I would avoid use of term ADE and focus on ADRs. Methods implies analgesics and antipyretics were not evaluated and yet A1-1,A1-4,5&5 were all tested. Appendix needs to be in the actual paper. I am concerned that mean number of meds/ prescriptions(hospital) in Table 1 is not given. How can one evaluate if prescribing is rational if one does not know the number of meds? This is important. Table 3 highlights the important findings for hospital :steroids for bronchiolitis and OM; inappropriate antibiotic,domperidone and omissions (ORS). Only ORS is discussed. Why not discuss the others as these are your main findings? There is overemphasis of statistical anlysis - Table 5 should be supplementry table. Also the stats analysis is not needed in the abstract, which should focus on clinicalrelevance see comments on Table 3. Discussion needs a major rewrite - why compare to elderly when you have not assessed all criteria. Better to focus on clinical relevance. At present discussion is too long. Despite all these concerns the paper is important

REVIEWER	Frank Moriarty Royal College of Surgeons in Ireland, Ireland Involved in development of a set of criteria for potentially inappropriate prescribing in children in primary care: http://bmjopen.bmj.com/content/6/9/e012079
REVIEW RETURNED	01-Dec-2017

GENERAL COMMENTS	- It's still somewhat unclear what the no. of cases analyzed column in table 3 refers to; are these the number of prescriptions/individuals who were at risk of having each PIM/PPO? e.g. for JI-2 Cough suppressants to treat asthma, does 802 refer to number of individuals with asthma? This could be clarified more effectively in either the table footnote or methods. - I am also still unclear on table 4 and how these percentages were calculated. In table 3, I can see the % is the proportion of cases analysed for each criterion where there is a PIM/PPO. Table 4 does not have a cases analyzed column, so it is not clear what the % column refers to. Is N=591 the total number of PIMs detected in community, and does each % refer to the proportion of all PIMs made up by each criterion? This appears to be different from what

	the percentages represent in table 3 and this should be made clearer. - I would suggest adding to the manuscript the explanation/rationale as to why risk factors for PPO were not assessed, as per your response to my previous comment. - From a response to another reviewer's comment, am I correct that for the regression analyses that the unit of analysis is each prescription line i.e. the n included in these analyses were the total number of prescribed items? Two points relating to this. (i) How does this work given some criteria relate to a combination of medications (i.e. A combination of locally applied and orally administered antibiotics)? (ii) One of the assumptions of logistic regression is that observations/data points are independent or have independent error terms, which is not the case for lines of a prescription. If this was the unit of analysis, the clustering of lines within prescriptions, and potentially multiple prescriptions within patients needs to be accounted for. If this was already done, this should be reported in the methods, and that prescription line is the unit of analysis.

REVIEWER	Deo Kumar Srivastava, Ph.D. Member, Interim Chair Department of Biostatistics St. Jude Children's Research Hospital 262 Danny Thomas Place Memphis, TN 38105 USA
REVIEW RETURNED	03-Dec-2017

GENERAL COMMENTS	In this revised manuscript the authors have addressed most of the issues raised in my previous review. However, there are just still some issues that need to be addressed that are listed below: 1. On page 6, line 3, the authors say that the, “Inclusion criteria included patient who were under 18 years old and who had one medicine prescription..” and then on page 8 in Results section they say that, “In ED and CP, 53% of patients had been issued with one prescription, …prescriptions.” Then in Table 1 in number of medication per prescription the Hospital column says NA and the community column says mean of 2.4(1.6). This suggests that the inclusion criteria were different for Hospital and Community patients this needs to be clearly articulated in the manuscript. 2. If light of comment # 1 and also, in general, the rationale for conducting multiple logistic modeling for the combined groups is not clear. It is very clear that community pharmacies had a much higher rate of PIM and that could be highly related to the number medicines per prescription 3. Also, in Tables 3 and 4 the authors provide details of PIMs and PPO by criteria for the patients in Hospital and in Community. But in Table 5 they only focus on PIM but there is no explanation provided as to why PPO was dropped the evaluation in Table 5. 4. For Table 5, the authors have clarified that the unit of analysis

	was each drug and if there were 5 drugs in one prescription then 5 lines of prescription were included in the multiple regression model. In doing so the authors have implicitly assumed that the chance of PIM for each drug within each prescription is independent and this needs to be included in the statistical section.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Imti Choonara
Institution and Country: Univ of Nottingham, UK
Please state any competing interests: I have met some of the authors to discuss POPI.

This paper has improved. However, there are still major issues.
Introduction still mentions med errors, whereas POPI is a tool to assess prescribing.
Response: Sentence was modified.
I would avoid use of term ADE and focus on ADRs.
Response: Done, as suggested. We only kept ADE to introduce ADRs and for one reference presented in the introduction. Otherwise we have focused on ADRs;

The method implies that analgesics and antipyretics were not evaluated and yet A1-1, A1-4.5 & 5 were all tested.
Response: Of 5 criteria, including analgesics and antipyretics, only three of them were evaluated due to a large number of prescriptions and their association with many diseases.

Appendix needs to be in the actual paper.
Response: Done (Table 1)

I am concerned that the mean number of meds/prescriptions (hospital) in Table 1 is not given. How can one evaluate if prescribing is rational if one does not know the number of meds? This is important.
Response: The prescriptions given in the hospital's emergency department were extracted from the Urqual software. Unfortunately, the data extraction only allowed us to extract one line per patient with one diagnosis and the first drug prescribed. Once extracted, the prescription was then analyzed as a whole. But the data extraction cannot give us the real number of meds per patient. That is why the number of medications per prescription was missing for the hospital. However, all prescriptions have been manually reviewed and Potentially Inappropriate Medicines (PIM) and Potential Prescribing Omissions (PPO) were assessed.
This was specified in the method section (page 7, lines 5.)

Table 3 highlights the important findings for the hospital: steroids for bronchiolitis and OM; inappropriate antibiotics, domperidone and omissions (ORS). Only ORS is discussed. Why not discuss the others as these are your main findings? There is overemphasis of statistical analysis - Table 5 should be a supplementary table. Also, the stats analysis is not needed in the abstract, which should focus on clinical relevance; see comments on Table 3. Discussion needs a major rewrite - why compare to elderly when you have not assessed all criteria? Better to focus on clinical relevance. At present discussion is too long.
Response: Done. As suggested by reviewer no.1, we have revised in depth the discussion focusing on clinical relevance.

Reviewer: 2
Reviewer Name: Frank Moriarty
Institution and Country: Royal College of Surgeons in Ireland, Ireland

Please state any competing interests: Involved in development of a set of criteria for potentially inappropriate prescribing in children in primary care: http://bmjopen.bmj.com/content/6/9/e012079

- It's still somewhat unclear what the no. of cases analyzed column in table 3 refers to; are these the number of prescriptions/individuals who were at risk of having each PIM/PPO? e.g. for JI-2 Cough suppressants to treat asthma, does 802 refer to number of individuals with asthma? This could be clarified more effectively in either the table footnote or methods.
Response: As observed by reviewer no. 2, the no. of cases analyzed refers to the number of patients with the targeted disorders, i.e. individuals who were at a risk of having PIM/PPO. For cough suppressants for asthma, we had 802 cases of patients with asthma.
This was specified in Table 4 and in the results section (page 18 lines 21-22).

- I am also still unclear on table 4 and how these percentages were calculated. In Table 3, I can see the % is the proportion of cases analysed for each criterion where there is a PIM/PPO. Table 4 does not have a "cases analyzed" column, so it is not clear what the % column refers to. Is N=591 the total number of PIMs detected in community, and does each % refer to the proportion of all PIMs made up by each criterion? This appears to be different from what the percentages represent in table 3 and this should be made clearer.

Response:
As observed by reviewer no. 2, the percentages in Table 4 (ex-Table 3) and Table 5 (ex-Table 4) were not the same. For the hospital, we know the total number of patients with the diagnosis, so we are able to evaluate the prevalence. For the community pharmacy, as we do not know the total number of patients per diagnosis, the prevalence is not presented: the percentage corresponds to the proportion of PIM/PPO among all PIM/PPO. The denominator was either the total number of Potentially Inappropriate Medications (PIMs) (N=591) or the total number of Potential Prescribing Omissions (PPO) (N=293).
As suggested, the presentation of Table 5 has been modified. Similarly, an indication was added in the results section (page 18 lines 20-26).
Table 4presents the proportion of cases analyzed for each criterion with a risk of PIM or PPO in hospital.
Table 5 presents the proportion of PIM or PPO among the total PIM or PPO in the community. In CP, we could only analyze criteria without a clinical situation such as a prescription of less than 2 years for domperidone or mucolytic drugs. The definition of each percentage was modified in the footnotes and Table 5 was modified.

- I would suggest adding to the manuscript the explanation/rationale as to why risk factors for PPO were not assessed, as per your response to my previous comment.
Response: As suggested by reviewer no. 2, an explanation for the absence of a PPO analysis was added in the manuscript. (page 22, lines 11).

- From a response to another reviewer's comment, am I correct that for the regression analyses the unit of analysis is each prescription line i.e. the n included in these analyses were the total number of prescribed items? Two points relating to this.
(i) How does this work given some criteria relate to a combination of medications (i.e. a combination of locally applied and orally administered antibiotics)?
Response: For each criterion, we filtered the data by diagnosis in order to obtain the patients' drug lists. Medical records with treatments were analyzed and we were able to view a combination of medications.
(ii) One of the assumptions of logistic regression is that observations/data points are independent or have independent error terms, which is not the case for lines of a prescription. If this was the unit of analysis, the clustering of lines within prescriptions, and potentially multiple prescriptions within patient needs to be accounted for. If this was already done, this should be reported in the methods, and that prescription line is the unit of analysis.
Response: We agree with the reviewer. Indeed, in our database, there were one or multiple prescriptions per patient. A prescription may contain several drugs (medications), but these were not presented in our data base. PIM was identified by prescription, even if a prescription contained

several medications. Therefore we performed mixed effects logistic regression modelling for repeated measurements, since observations from the same subject are likely to be correlated.

Reviewer: 3
Reviewer Name: Deo Kumar Srivastava, Ph.D.
Institution and Country: Member, Interim Chair, Department of Biostatistics, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA
Please state any competing interests: None

In this revised manuscript the authors have addressed most of the issues raised in my previous review. However, there are just still some issues that need to be addressed that are listed below:
1. On page 6, line 3, the authors say that the, "Inclusion criteria included patient who were under 18 years old and who had one medicine prescription.." and then on page 8 in Results section they say that, "In ED and CP, 53% of patients had been issued with one prescription, …prescriptions." Then in Table 1 in number of medication per prescription the Hospital column says NA and the community column says mean of 2.4(1.6). This suggests that the inclusion criteria were different for Hospital and Community patients this needs to be clearly articulated in the manuscript.
Response:
We agree with the reviewer. We corrected the inclusion criteria and added "one or more prescription"; see method section page 6 line 18).
2. In light of comment # 1 and also, in general, the rationale for conducting multiple logistic modeling for the combined groups is not clear. It is very clear that community pharmacies had a much higher rate of PIM and that could be highly related to the number medicines per prescription.
Response:
We agree with the reviewer. Indeed, in our database, there were one or multiple prescriptions per patient. A prescription may contain several drugs (medications), but these were not presented in our data base. PIM was identified by prescription, even if a prescription contained several medications. Therefore, we performed mixed effects logistic regression modelling for repeated measurements since observations from the same subject is likely to be correlated.

3. Also, in Tables 3 and 4 the authors provide details of PIMs and PPO by criteria for the patients in Hospital and in Community. But in Table 5 they only focus on PIM but there is no explanation provided as to why PPO was dropped the evaluation in Table 5.
Response: an explanation for the absence of a PPO analysis was added in the manuscript. (page22, lines 11)

4. For Table 5, the authors have clarified that the unit of analysis was each drug and if there were 5 drugs in one prescription then 5 lines of prescription were included in the multiple regression model. In doing so the authors have implicitly assumed that the chance of PIM for each drug within each prescription is independent and this needs to be included in the statistical section.
Response:
We apologize to the reviewers. After checking the data base, the unit of analysis was not each drug, but each prescription (one prescription may contains several drugs). Therefore only prescriptions (one or more per patient) were included in the model (one patient can have one or more prescription) We therefore performed a mixed effects logistic regression modelling for repeated measurements.

VERSION 3 – REVIEW

REVIEWER	Imti Choonara Univ of Nottingham,UK I have collaborated with the authors
REVIEW RETURNED	17-Feb-2018

GENERAL COMMENTS	The paper has improved, but the authors have inadequately explained hospital data collection. I understand that the only the first drug prescribed was identified and analysed. If so, how can there be more than one PIM? (table 3). The authors state that all prescriptions were manually reviewed. What does this mean?

	Please expand and explain fully data collected and what could not be collected. One cannot determine prevalence of PIM or PPO in hospital pts if only one medicine was analysed, This is a major limitation and needs to be emphasised. Discussion is much better. A more recent reference re bronchiolitis treatment in France is Retrospective audit of guidelines for investigation and treatment of bronchiolitis: a French perspective BMJ Paediatrics Open Oct 2017, 1 (1) e000089; DOI: 10.1136/bmjpo-2017-000089 . The authors may wish to refer to this paper which also highlights irrational prescribing

REVIEWER	Frank Moriarty Royal College of Surgeons in Ireland, Ireland Involvement in the development of a set of criteria for potentially inappropriate prescribing in children in primary care: http://bmjopen.bmj.com/content/6/9/e012079
REVIEW RETURNED	28-Feb-2018

GENERAL COMMENTS	1. On page 18, line 24-26, the authors have clarified what the percentages in Table 5 (community pharmacy) refer to, however I feel this is still somewhat ambiguous, and could be rephrased to "Table 5, however, presents the PIMs (or PPOs) as a proportion of the total number of PIMs (or PPOs) in the community pharmacy." 2. Despite the added clarification on page 22, line 11, it is still not clear to me why risk factors/predictors of PPOs were not analysed. The authors make a case for why these factors could not be compared between hospital and community pharmacy, but this does not justify assessing age/sex in the hospital and age/number of medications in the CP as predictors. 3. Based on the response to another reviewer's comment, I am also unsure whether it is appropriate to combine the hospital and CP groups for the regression analysis of risk factors, particularly when the only difference between settings controlled for is age group. I feel the authors should offer a stronger rationale for why this combined analysis is appropriate, and whether at the very least, an interaction term for age group and setting/service be considered as age group may have a different magnitude of association with PIMs in the two settings (based on the results of the separate hospital and CP regression models). 4. Related to this, the explanation of why number of medications is absent for the hospital group is still unclear (page 6 line 54 to page 7 line 8). Could the authors please clarify this, as it begs the question whether a "prescription" is defined in the same way in both settings (i.e. in hospital, can a prescription contain multiple medications, or did each "prescription" extracted correspond to one prescribed medication). 5. For figure 3, it is unclear what the numbers refer to as the X-axis is unlabelled. Page 18, line 35 refers to this as "prevalence of PIM", but it is unclear whether this is as a proportion of patients, prescriptions, or PIMs. 6. I feel the list of all POPI indicators (now Table 1) is not fully necessary in the main part of the paper given Table 4/5 list those that were applied with their prevalences.

	7. In Appendix 1, for hospital, the univariate and multivariate models (both of which only contain age as the only covariate as I understand it) have some slight differences in numbers which should be addressed. 8. The final two sentences of the Results of the Abstract are not really presenting results and should either be moved to the Conclusion or removed in favour of adding results from the regression analysis. In the Abstract Conclusion, the sentence "A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice" to clarify what is being referred to as "its" e.g. "to evaluate the impact and benefit of implementing POPI/the POPI tool in clinical practice".

REVIEWER	Deo Kumar Srivastava, Ph.D. St. Jude Children's Research Hospital, USA
REVIEW RETURNED	25-Feb-2018

GENERAL COMMENTS	In this revised manuscript the authors have addressed some of the concerns raised in my previous review. However, this reviewer feels that some of the issues have not been addressed in a satisfactory manner and some additional issues are listed below: 1. In general the manuscript has merit in identifying the prevalence of PIM and PPO in ED and CP. This reviewer feels that authors should report the analysis separately for the two cohorts, ED and CP, by clearly stating the inclusion criteria, the unit of analysis, the criteria for classifying it as a PIM or PPO and the appropriate modeling approach used for identifying the risk factors associated with PIM in the two cohorts. 2. On page 2, in Participants section, the authors say that the, “Inclusion criteria included patient who were under 18 years old and who had one medicine prescription..” and then on page 8 in Results section they say that, “In ED and CP, 53% of patients had been issued with one prescription, …prescriptions.” Then in Table 2 in number of medication per prescription the Hospital column says NA and the community column says mean of 2.4(1.6). The inclusion criteria seems to be different for Hospital and Community patients this has not been clearly articulated in the manuscript. 3. If light of comment # 1 and also, in general, the rationale for conducting multiple logistic modeling for the combined groups is not clear. The meaning of the last sentence on page 6, “Once extracted, the …as a whole,” is not clear. Does it mean that if there were multiple medications then PIM or PPO was counted as yes if it was true for any medication? Also, on page 14, last sentence states that, “Only drugs … were analyzed (Table 1) (28 criteria/102).” Thus, it is very clear that community pharmacies had a very different inclusion criteria and it is possible that much higher rate of PIM in CP could be highly

	related to the number medicines per prescription. Based on the comments above it is not clear if a comparison of ED and CP makes any sense. Yes, identifying the factors affecting PIM within each group, ED and CP, makes sense as some interventions for mitigating PIM could be proposed. 4. For Table 5, the authors have clarified that the unit of analysis was each drug and if there were 5 drugs in one prescription then 5 lines of prescription were included in the multiple regression model. In doing so the authors have implicitly assumed that the chance of PIM for each drug within each prescription is independent and this needs to be included in the statistical section. For the results reported in Appendix 1 corresponding to identifying risk factors associated with PIM it is once again not clear what is the unit of analysis, patients or prescription or medications? Also, if a patients had 5 medications or 5 prescriptions then was that patient included 5 times with approximately the same age in the model? 2 5. In Statistical Analysis section the authors say that, “Mixed effects logistic regression … community settings,” but it is not clear why a repeated measure analysis was undertaken. Please clearly state the unit of analysis was and what was repeatedly measured? 6. The idea of single medicine per prescription vs. multiple medicines per prescription is quite confusing throughout the manuscript. It has to be clearly stated that for ED only one medicine per prescription was used for analysis but for CP multiple medicines per prescription were used and this needs to stay consistent throughout the manuscript.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Imti Choonara
Institution and Country: Univ of Nottingham, UK
Please state any competing interests: I have collaborated with the authors

1- ***The paper has improved, but the authors have inadequately explained hospital data collection. I understand that the only the first drug prescribed was identified and analysed. If so, how can there be more than one PIM? (table 3). The authors state that all prescriptions were manually reviewed. What does this mean? Please expand and explain fully data collected and what could not be collected. One cannot determine prevalence of PIM or PPO in hospital pts if only one medicine was analysed, This is a major limitation and needs to be emphasised.***

Response: From extracted data, we couldn’t have number of medicine by patient. To determine PIM/PPO, each medical file for each patient was analyzed diagnosis. But, number of medication was not collected. We have clarified this point in method section.

"The data extracted from Urqual software give only the first drug per prescription for each diagnosis (no possibility to extract all drugs for all prescriptions). Once extracted, the prescription was then manually analyzed for each diagnosis. Consequently, the number of medications per prescription was not included. However, all prescriptions have been manually reviewed directly from medical file by two authors. For each targeted disorder, the prescription was analyzed to detect PIMs or PPOs"

2- ***Discussion is much better. A more recent reference re bronchiolitis treatment in France is Retrospective audit of guidelines for investigation and treatment of bronchiolitis: a French perspective BMJ Paediatrics Open Oct 2017, 1 (1) e000089; DOI: 10.1136/bmjpo-2017-000089 . The authors may wish to refer to this paper which also highlights irrational prescribing***

Response: Done

Reviewer: 2
Reviewer Name: Frank Moriarty
Institution and Country: Royal College of Surgeons in Ireland, Ireland
Please state any competing interests: Involvement in the development of a set of criteria for potentially inappropriate prescribing in children in primary care:
http://bmjopen.bmj.com/content/6/9/e012079

Thank you to the authors for their responses to the previous comments. I feel some points still require clarification:

1- ***On page 18, line 24-26, the authors have clarified what the percentages in Table 5 (community pharmacy) refer to, however I feel this is still somewhat ambiguous, and could be rephrased to "Table 5, however, presents the PIMs (or PPOs) as a proportion of the total number of PIMs (or PPOs) in the community pharmacy."***

Response: Done

2- ***Despite the added clarification on page 22, line 11, it is still not clear to me why risk factors/predictors of PPOs were not analyzed. The authors make a case for why these factors could not be compared between hospital and community pharmacy, but this does not justify assessing age/sex in the hospital and age/number of medications in the CP as predictors.***

Response: We added analyze of risk factors associated with PPO in Appendix 2a.

3- ***Based on the response to another reviewer's comment, I am also unsure whether it is appropriate to combine the hospital and CP groups for the regression analysis of risk factors, particularly when the only difference between settings controlled for is age group. I feel the authors should offer a stronger rationale for why this combined analysis is appropriate, and whether at the very least, an interaction term for age group and setting/service be considered as age group may have a different magnitude of association with PIMs in the two settings (based on the results of the separate hospital and CP regression models).***

Response: We agree with the reviewers and the multiple logistic modeling for the combined groups was removed (In Appendix 2, model 3 was removed).

4- ***Related to this, the explanation of why number of medications is absent for the hospital group is still unclear (page 6 line 54 to page 7 line 8). Could the authors please clarify this, as it begs the question whether a "prescription" is defined in the same way in both settings (i.e. in hospital, can a prescription contain multiple***

medications, or did each "prescription" extracted correspond to one prescribed medication).

Response: In the manuscript, prescription is defined in the method "*as one or more lines of drugs prescribed by a physician*". From extracted data in hospital setting, we couldn't have number of drugs by patient as explained and modified for reviewer 1. To determine PIM/PPO, each medical file for each patient was analyzed among diagnosis. But, number of medication was not collected.

We have clarified this point in data collection method section.
"The data extracted from Urqual software give only the first drug per prescription for each diagnosis (no possibility to extract all drugs for all prescriptions). Once extracted, the prescription was then manually analyzed among diagnosis. Consequently, the number of medications per prescription was not included. However, all prescriptions have been manually reviewed directly from medical file by two authors. For each targeted disorder, the prescription was analyzed to detect PIMs or PPOs"

5- ***For figure 3, it is unclear what the numbers refer to as the X-axis is unlabelled. Page 18, line 35 refers to this as "prevalence of PIM", but it is unclear whether this is as a proportion of patients, prescriptions, or PIMs.***

Response: X-axis label was added. It corresponds to number of PIMs.

6- ***I feel the list of all POPI indicators (now Table 1) is not fully necessary in the main part of the paper given Table 4/5 list those that were applied with their prevalences.***

Response: Table 1 was added at another's reviewer request. Let us know if the editor decides to keep it, remove it or keep as an appendix.

7- ***In Appendix 1, for hospital, the univariate and multivariate models (both of which only contain age as the only covariate as I understand it) have some slight differences in numbers which should be addressed.***

Response: It was a tipping error. Data were modified in appendix 2 (Appendix 1 became Appendix 2).

8- ***The final two sentences of the Results of the Abstract are not really presenting results and should either be moved to the Conclusion or removed in favour of adding results from the regression analysis.***

Response: Done

9- ***In the Abstract Conclusion, the sentence "A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice" to clarify what is being referred to as "its" e.g. "to evaluate the impact and benefit of implementing POPI/the POPI tool in clinical practice".***

Response: Done

Reviewer: 3

Reviewer Name: Deo Kumar Srivastava, Ph.D.
Institution and Country: St. Jude Children's Research Hospital, USA Please state any competing interests: None

Please leave your comments for the authors below Please see the attached file.

In this revised manuscript the authors have addressed some of the concerns raised in my previous review. However, this reviewer feels that some of the issues have not been addressed in a satisfactory manner and some additional issues are listed below:

1- ***In general the manuscript has merit in identifying the prevalence of PIM and PPO in ED and CP. This reviewer feels that authors should report the analysis separately for the two cohorts, ED and CP, by clearly stating the inclusion criteria, the unit of analysis, the criteria for classifying it as a PIM or PPO and the appropriate modeling approach used for identifying the risk factors associated with PIM in the two cohorts.***

Response: The comments of the reviewer have been taken into account. We analyzed independently the two cohorts (ED and CP) especially to identify factors associated with PIM (and PPO). The inclusion criteria have been modified in the previous revised version. The inclusion criteria were: patients who were under 18 years old and who had one or more medicine prescriptions between 1st October 2014 and 31st March 2015. Indeed, this notion has not been updated in the abstract section, which has created some confusion. We have so updated the abstract as consequently.
Regarding modeling approach used for identifying the risk factors associated with PIM in the two cohorts, details of analysis are presented below.

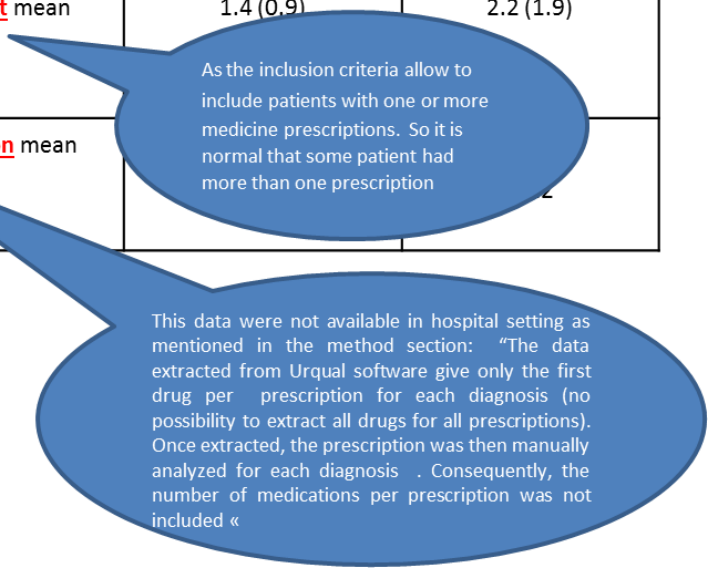
2- ***On page 2, in Participants section, the authors say that the, "Inclusion criteria included patient who were under 18 years old and who had one medicine prescription.." and then on page 8 in Results section they say that, "In ED and CP, 53% of patients had been issued with one prescription, …prescriptions." Then in Table 2 in number of medication per prescription the Hospital column says NA and the community column says mean of 2.4(1.6). The inclusion criteria seem to be different for Hospital and Community patients this has not been clearly articulated in the manuscript.***

Response: We apologize. The inclusion criteria in the abstract have not been updated as in the text. The inclusion criteria were: patients who were under 18 years old and who **had one or more medicine prescriptions** between 1st October 2014 and 31st March 2015. Inclusion criteria are not different between ED and CP.

Regarding table 2, there seems to be some confusion between the variable "Number of prescriptions / patient" and the variable "Number of medications per prescription". You will find additional explanations in the bubbles.

Number of **medications per prescription** was replaced by Number of **drugs per prescription**

Population characteristics	Hospital (N=15,973)	Community (N=2,225)
Number of prescriptions/patient mean (SD) Min, Max	1.4 (0.9)	2.2 (1.9)
Number of drugs per prescription mean (SD) Min, Max		



3- If light of comment # 1 and also, in general, the rationale for conducting multiple logistic modeling for the combined groups is not clear. The meaning of the last sentence on page 6, "Once extracted, the …as a whole," is not clear. Does it mean that if there were multiple medications then PIM or PPO was counted as yes if it was true for any medication? Also, on page 14, last sentence states that, "Only drugs … were analyzed (Table 1) (28 criteria/102)." Thus, it is very clear that community pharmacies had a very different inclusion criteria and it is possible that much higher rate of PIM in CP could be highly related to the number medicines per prescription. Based on the comments above it is not clear if a comparison of ED and CP makes any sense. Yes, identifying the factors affecting PIM within each group, ED and CP, makes sense as some interventions for mitigating PIM could be proposed.

Response: We agree with the reviewers and the multiple logistic modeling for the combined groups was removed. The sentence: "Once extracted, the …as a whole" was rephrase to make it more comprehensible:
"The data extracted from Urqual software give only the first drug per prescription for each diagnosis (no possibility to extract all drugs for all prescriptions). Once extracted, the prescription was then manually analyzed among diagnosis. Consequently, the number of medications per prescription was not included. However, all prescriptions have been manually reviewed directly from medical file by two authors. For each targeted disorder, the prescription was analyzed to detect PIMs or PPOs"

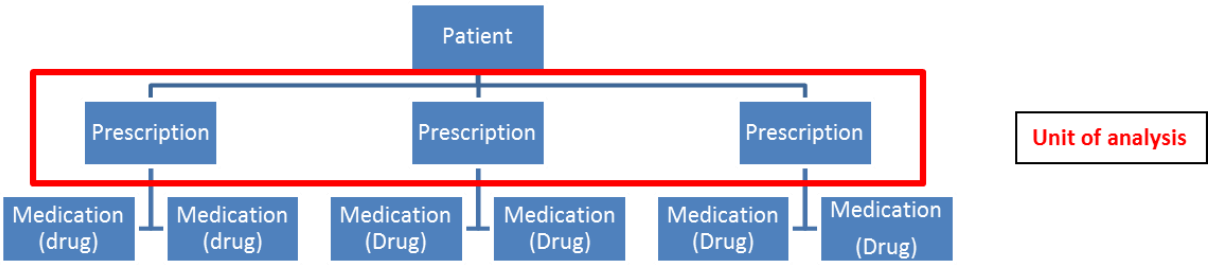
4- For Table 5, the authors have clarified that the unit of analysis was each drug and if there were 5 drugs in one prescription then 5 lines of prescription were included in the multiple regression model. In doing so the authors have implicitly assumed that the chance of PIM for each drug within each prescription is independent and this needs to be included in the statistical section. For the results reported in Appendix 1 corresponding to identifying risk factors associated with PIM it is once again not clear what is the unit of analysis, patients or prescription or medications? Also, if a patient had 5 medications or 5 prescriptions then was that patient included 5 times with approximately the same age in the model?

Response: There seems to be some confusion in the understanding of the multiple logistic regression analysis conducted in the revised version (revision 2).
We have specified that the unit of analysis was prescription,
And an answer was given to the reviewer to specify the unit of analysis.

Cf response to the reviewers send on revision 2:

"We agree with the reviewer. Indeed, in our database, there were one or multiple prescriptions per patient. A prescription may contain several drugs (medications), but these were not presented in our data base. PIM was identified by prescription, even if a prescription contained several medications. Therefore we performed mixed effects logistic regression modelling for repeated measurements since observations from the same subject are likely to be correlated."

To better understand the structuring of the data, we propose the following figure:



One patient may have one or more prescriptions and, one prescription may contain one or more medication (drug).
The unit of analysis (in the mixed effect model) is **the prescription**. In the database, there is one line per prescription and as a patient can have several prescriptions, there can be several lines for one patient. The most appropriate way to analyze this data is a mixed effects logistic regression modelling.
This justification has already been given in the previous response to the reviewer. Cf response to the reviewers send on revision 2.

For removing any doubt about this point, we added in the statistical analysis section the following sentence:
"Unit of analysis was "the prescription"."

5- In Statistical Analysis section the authors say that, "Mixed effects logistic regression … community settings," but it is not clear why a repeated measure analysis was undertaken. Please clearly state the unit of analysis was and what was repeatedly measured?

Response: Cf response to question 4

6- The idea of single medicine per prescription vs. multiple medicines per prescription is quite confusing throughout the manuscript. It has to be clearly stated that for ED only

one medicine per prescription was used for analysis but for CP multiple medicines per prescription were used and this needs to stay consistent throughout the manuscript

Response: To clarify differences between the two cohorts, we propose a summary in appendix 1.

VERSION 4 – REVIEW

REVIEWER	Imti Choonara University of Nottingham I have been in discussions with the authors re POPI and evaluating its use in other countries
REVIEW RETURNED	28-Mar-2018

GENERAL COMMENTS	The paper has improved. Two minor suggestions: state the number of prescriptions reviewed manually. Add a sentence in the discussion re limitation of their study in that they were unable to evaluate all medicines prescribed

REVIEWER	Frank Moriarty Royal College of Surgeons in Ireland, Ireland Involvement in the development of a set of criteria for potentially inappropriate prescribing in children in primary care: http://bmjopen.bmj.com/content/6/9/e012079
REVIEW RETURNED	10-Apr-2018

GENERAL COMMENTS	Thank you to the authors for taking on the previous comments and making extensive revisions to address these. There are still a couple of minor points that I feel should be addressed. (1) I would suggest the authors check the figures in Table 3 and those in Tables 4 and 5 as there seem to be a few inconsistencies. These should also be checked against those quoted in the abstract which for PPOs do not match Table 3. -Table 3 suggests there are 43 PPOs in hospital (20 prescriptions with two PPOs, and 1 prescription with three PPOs) and Table 4 states there are 425 PPOs. - Table 3 has 91 PPOs in community pharmacy, and Table 5 states there are 293. - Table 3 has 625 PIMs in community pharmacy, and Table 5 states there are 591. (2) I appreciate the authors have made efforts to clarify what and how data was extracted in hospitals and address queries raised by myself and other reviewers. The two paragraphs under "Data collection" on page 6 outline this. Some of the points included are still somewhat unclear e.g. "clinical files of ED were analyzed, based on primary diagnosis". I think it would be helpful to provide slightly more information here to aid readers' understanding. Am I correct in the following - -At emergency department discharge, are prescriptions entered into the Urqual system for patients classified by diagnosis? e.g. Patient A > Diagnosis A > Medication A, Medication B, Medication C

	> Diagnosis B > Medication D. -So extracting data from the software only gives Diagnosis A > Medication A and Diagnosis B > Medication D, but the authors manually extracted and reviewed Medications B and C? -If this is correct, can the authors clarify whether the above scenario represents one prescription (i.e. all the medications prescribed on one occasion) or two prescriptions (one each for Diagnoses A and B)? -In light of this, could the authors clarify what is meant by "clinical files of ED were analyzed, based on primary diagnosis."

REVIEWER	Deo Kumar Srivastava, Ph.D. St. Jude Children's Research Hospital, USA
REVIEW RETURNED	05-Apr-2018

GENERAL COMMENTS	The authors have adequately addressed all the concerns that were raised in my previous reviews and the revised manuscript can be accepted for publication.

VERSION 4 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Imti Choonara
Institution and Country: University of Nottingham Please state any competing interests: I have been in discussions with the authors re POPI and evaluating its use in other countries

Please leave your comments for the authors below. The paper has improved. Two minor suggestions: state the number of prescriptions reviewed manually.
Response: Done

Add a sentence in the discussion re limitation of their study in that they were unable to evaluate all medicines prescribed
Response: Done

Reviewer: 2
Reviewer Name: Frank Moriarty
Institution and Country: Royal College of Surgeons in Ireland, Ireland Please state any competing interests: Involvement in the development of a set of criteria for potentially inappropriate prescribing in children in primary care: http://bmjopen.bmj.com/content/6/9/e012079

Please leave your comments for the authors below Thank you to the authors for taking on the previous comments and making extensive revisions to address these. There are still a couple of minor points that I feel should be addressed.

(1) I would suggest the authors check the figures in Table 3 and those in Tables 4 and 5 as there seem to be a few inconsistencies. These should also be checked against those quoted in the abstract which for PPOs do not match Table 3.
- Table 3 suggests there are 43 PPOs in hospital (20 prescriptions with two PPOs, and 1 prescription with three PPOs) and Table 4 states there are 425 PPOs.
- Table 3 has 91 PPOs in community pharmacy, and Table 5 states there are 293.
- Table 3 has 625 PIMs in community pharmacy, and Table 5 states there are 591.
Response: It was a mistake. Corrections were done.

(2) I appreciate the authors have made efforts to clarify what and how data was extracted in hospitals and address queries raised by myself and other reviewers. The two paragraphs under "Data collection" on page 6 outline this. Some of the points included are still somewhat unclear e.g. "clinical files of ED were analyzed, based on primary diagnosis". I think it would be helpful to provide slightly more information here to aid readers' understanding. Am I correct in the following -

-At emergency department discharge, are prescriptions entered into the Urqual system for patients classified by diagnosis?
e.g. Patient A > Diagnosis A > Medication A, Medication B, Medication C
> Diagnosis B > Medication D.
-So extracting data from the software only gives Diagnosis A > Medication A and Diagnosis B > Medication D, but the authors manually extracted and reviewed Medications B and C?
-If this is correct, can the authors clarify whether the above scenario represents one prescription (i.e. all the medications prescribed on one occasion) or two prescriptions (one each for Diagnoses A and B)?
Response: We have only analyzed prescription for primary diagnosis (Diagnosis A). If diagnosis A were concerned by POPI tool, clinical file was analyzed to detect a PIM/PPO or not (medication A, B, C).

-In light of this, could the authors clarify what is meant by "clinical files of ED were analyzed, based on primary diagnosis?"
Response: Done

Reviewer: 3
Reviewer Name: Deo Kumar Srivastava, Ph.D.
Institution and Country: St. Jude Children's Research Hospital, USA Please state any competing interests: None

Please leave your comments for the authors below The authors have adequately addressed all the concerns that were raised in my previous reviews and the revised manuscript can be accepted for publication. Please let me know if you have any questions. Thanks.
Response: We thank the reviewer

VERSION 5 – REVIEW

REVIEWER	Frank Moriarty Royal College of Surgeons in Ireland, Ireland Involvement in the development of a set of criteria for potentially inappropriate prescribing in children in primary care: http://bmjopen.bmj.com/content/6/9/e012079
REVIEW RETURNED	01-Jun-2018

GENERAL COMMENTS	The following sentences had been added to the results section, however, they relate to the methods and so should be moved here: "We consulted the software used by the emergency department by searching either: 1/ per drug and by therapeutic class extension; 2 / by main diagnosis for which a POPI item could matched. In each case, if there was a PMI / PPO, the data was collected." Also, could the authors clarify the last sentence as I assume data were collected regardless of whether there was a PIM/PPO.