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Complete List of Authors:	Berthe-Aucejo, Aurore; Hopital Universitaire Robert Debre, Pharmacy department Nguyen, Phuong Khanh Hoang; Hopital Universitaire Robert Debre, Department of Pharmacy Angoulvant, François; Hopital universitaire Necker-Enfants malades, Emergency unit; INSERM, U1123 Bellettre, Xavier; Hopital Universitaire Robert Debre, Emergency unit Albaret, Patrick; Albaret Pharmacy Weil, Thomas; Hopital Universitaire Robert Debre, Department of Pharmacy Boulkedid, Rym; Hopital Universitaire Robert Debre, Clinical Epidemiology unit; INSERM, U1123 Bourdon, Olivier; Hopital Universitaire Robert Debre, Department of pharmacy; Universite Paris Descartes, Clinical Pharmacy Prot-Labarthe, Sonia; Hopital Universitaire Robert Debre, Department of Pharmacy; INSERM, U1123
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Potentially inappropriate prescriptions and omissions in pediatrics: detection by POPI (Pediatrics: Omission of Prescription and Inappropriate prescription) in the emergency unit and in the ambulatory setting.

A. Berthe-Aucejo[1], H.P.K Nguyen[1], F. Angoulvant[2,3], X. Bellettre[4], P. Albaret[5,6], T. Weil[1], R. Boulkedid[3,7], O. Bourdon[1,6,8,9], S.Prot-Labarthe[1,3,9]

[1] Department of Pharmacy, Robert-Debré Hospital, Paris, France

[2] Emergency unit, Necker Hospital, Paris, France

[3] U1123, INSERM ECEVE, Paris, France

[4] Emergency unit AP-HP, Robert-Debré Hospital, Paris, France

[5] Albaret Pharmacy, Cesson, France

[6] Clinical Pharmacy, Paris Descartes University, Paris, France

[7] Clinical Epidemiology Unit, Robert-Debré Hospital, Paris, France

[8] Laboratoire Educations et Pratiques de Santé, Paris XIII University, Bobigny, France

[9] Groupe Pédiatrie de la Société Française de Pharmacie Clinique, Paris, France

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Corresponding author

Dr Aurore Berthe-Aucejo, Service Pharmacie, AP-HP Hôpital Robert-Debré, 48 Boulevard Sérurier, 75019 Paris, Fax: 01-40-03-24-81, Tel: 01-40-03-57-41, Email: aurore.berthe@aphp.fr

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ABSTRACT

Background and Objective: POPI **(**Pediatrics: Omission of Prescription and Inappropriate prescription) is the first tool of detection for potentially inappropriate medicines (PIM) and potentially prescribing omissions (PPO) in pediatrics. The aim of this study was to evaluate the prevalence of PIM and PPO detected by POPI regarding issuing of prescription in hospital and outpatient car. The second objective is to determine the risk factors related to PIM.

Design: A retrospective and descriptive study was conducted in the emergency department (ED) and community pharmacy (CP) from 1 October 2014 and 31 March 2015. POPI was used to identify inappropriate prescriptions and omissions.

Setting: Robert-Debré Hospital (AP-HP, France) and Albaret community pharmacy (Seine and Marne

Participants: Inclusion criteria included patients who were under 18 years old and who had one medicine prescription between 1st October 2014 and 31st March 2015. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients.

Primary and secondary outcome measures: PIM and PPO rate, PIM risk factors

Results: A total of 18.562 prescriptions for 15.973 patients at the ED and 4.780 prescriptions for 2.225 patients at the CP were analyzed. The PIM rate and PPO rate were respectively 3.3% and 2.6% at the ED and 26.4% and 13.2% at the CP. Respiratory and digestive diseases had the highest rate of PIM in hospital and community pharmacy. Multivariate analysis showed that children aged between 2 and 6 years (OR=2.4; IC 1.9-2.9; p<0,001) and prescriptions issued from outpatient care (OR=5.2, 95% confidence interval (CI) 5.0-6.5, p<0.001) correlated with a higher risk of PIM.

Conclusion: This study is the first to observe the prevalence of PIM and PPO detecting by POPI in a pediatric population. A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice.

Strengths and limitations of this study

- This study is the first to observe the prevalence of PIM and PPO in a pediatric population. The inappropriate prescription rate and omission rate were respectively 3.3% and 2.6% at the emergency unit and 26.4% and 13.2% at the community pharmacy.

- It is a retrospective and monocentric study. Our result in the hospital could be underestimated.

- Ambulatory prescription and the group age between two and six years were associated with a higher risk of inappropriate prescribing.

- Our study showed that there are many criteria which could be detected without access to clinical information and that they are easy to identify.

INTRODUCTION

Inappropriate prescribing is a known preventable cause of adverse drug events (ADE) and has an important impact on public health and cost of care.[1,2] Incidence of hospitalization due to ADE was 42.8% according to a French survey in 2009.[3] The World Health Organization estimated that 50% of medications are prescribed and utilized inappropriately.[4] The most recent definition of inappropriate prescription (IP) encompasses potentially inappropriate medicines (PIM) and prescribing omissions (PPO).[5] In a report from the French National Authority for Health, PIMs are defined as "drugs being used in a situation in which the risks involved in treatment potentially outweigh the benefits, lack of indication demonstrated, high risk of ADE, and an unfavorable cost-effect or risk-benefit ratio exists". PPO or underuse of appropriate medication is defined as the absence of initiation of an effective treatment in subjects with a condition for which one or several drug classes have demonstrated their efficacy [6]. In an elderly population, which presents with age-related physiological changes and high prevalence of polypharmacy, various measures have been developed to detect PIM such as: Beers' criteria, the Inappropriate Prescribing in the Elderly Tool, The Medication Appropriate Index, and STOPP/START (Screening Tool of Older Person's prescriptions/Screening Tool to Alert doctor to Right Treatment).[7–11] Only the STOPP/START enables us to detect under-prescribing.[5] Using these tools, many studies have been carried out which have detected that inappropriate prescriptions are issued to between 35% and 51% of this population.[12–16] Omission prescriptions in geriatric population detected by START tool concerned between 58%-61% of patients.[5,17] Negative outcomes related to an IP such as side effects, hospitalization, mortality and utilization of resources were also demonstrated.[1,11,18–20]

Prescribing in a pediatric population is always a challenge for physician. It is often empirical and primarily based on safety and pharmacology information obtained in adults.[21] This is a worry not only in a hospital or general practitioner setting but also for the community pharmacists. They may only be able to check information and resources or even dispense infrequently for this vulnerable population.[22] Medication errors were identical in adults and children but side effects were three time more common in the pediatric population. This frequency was explained by the vulnerability of young people, pharmacokinetic changes during childhood and pediatric off-label drug used.[23,24] In order to improve the correct drug use and optimize practice, the first tool of detection for PIM and PPO was created by Prot-Labarthe *et al.* in 2013. The tool was named POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions) (Appendix1).[25,26] Presently, the complete tool has not been tested in actual practice and the prevalence of PIM and OP is not known.

Our aim is to evaluate the prevalence of PIM and PPO detected by POPI. This was its first application, regarding issuing of prescriptions in hospital and outpatient care. The second objective is to determine the risk factors related to PIM.

METHODS

Population

A retrospective and descriptive study was conducted in the emergency department (ED) of Robert-Debré hospital (Paris) - the largest French pediatric hospital- and the Albaret community pharmacy (Seine and Marne). Inclusion criteria included patients who were under 18 years old and who had one medicine prescription between 1st October 2014 and 31st March 2015. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients.

Data collection

The prescriptions given while leaving emergency department were extracted from the software Urqual V5® (*) (McKesson Corp, Paris, France). Urqual® is an emergency prescription software which is used in many French hospitals. Patient information including age, sex, weight, medicine prescription and current diagnosis was collected. Medical histories and clinical examinations were consulted individually when necessary. Due to the significant amount of data, clinical files of ED were analyzed, based on primary diagnosis. Assessable criteria in the retrospective study in hospital were identified by the symbol « * » in appendix 1.

Data from the community pharmacy were obtained from the pharmacy management software OPUS® (Computer PG, France). Patient's age and drugs prescribed were collected. Clinical case records and sex were not available in pharmacy as this was a retrospective analysis, so only drugs that did not require assessment of diagnosis (for example Domperidone, Metoclopramide etc.) were analyzed. These criteria were denoted by the symbol « ° » in appendix 1.

Pathologies analyzed by POPI were the same in emergency department and in community.

Statistical analysis

Categorical variables comprised percentages and numbers. Quantitative variables (age, number of prescriptions by patient, number of medications per prescription, comprised the mean, minimum and maximum standard deviation (SD) for parametric variables; the median and interquartile range for non-parametric variables. Influence factors for PIM according to POPI were determined by the model of logistic regression: univariate analysis and then multi-

variate analysis (using adolescents as a reference). We presented the results with their odds ratios (OR) and their 95% confidence intervals (CI). Statistical significance was established at $p<0.05$. SPSS-22® software (SPSS Inc., Chicago, IL, USA) was used for analysis.

This project was approved by the local research ethics committee (n°2015/218).

RESULTS

In the emergency department, 18 562 prescriptions for 15 973 patients consulted were analyzed. Among them, 29% had at least two visits in 6 months. In the community pharmacy, 4 780 prescriptions for 2 225 patients were evaluated (Figure 1). In total, 53% of patients had been issued with one prescription, 21% with two and 26% with more than three prescriptions. The population's characteristics and the frequency of pathologies were presented in table 1 Distribution of number of prescriptions by age category was described in the figure 2.

Table 1. Characteristics of the study population

Population characteristics	Hospital (N=15 973)		Community (N=2 225)
Age* (years)	4.9 ± 4.5 (0-18)		7.9 ± 5.3 (0-18)
Female gender (%)	54.9%		NA
Number of prescriptions/patient*	1.4 ± 0.9 (1-12)		2.2 ± 1.9 (1-16)
Medications/prescriptions*	NA		2.4 ± 1.6 (1-22)
Number of prescriptions by pathology			
Digestive disorders°	2728	(14.7%)	NA
ENT-Pulmonary disorders°	8397	(45.2%)	NA
Dermatological disorders°	604	(3.3%)	NA

Neuropsychiatric disorders°	242	(1.3%)	NA
Various illnesses°,#	6591	(35.5%)	NA

NA: Not available; ENT: ear, nose and throat
** Mean ± standard deviation (Minimum – Maximum)*
° Percentage calculated from 18 562 hospital prescriptions
 # For example, traumatic injury, pain, sickle cell disease

In hospital, POPI tools identified 541 PIM in 2.9% of the prescriptions analyzed. They were detected in 3.3% of the patients (n=530). In the community, PIM represented 12.3% of all prescriptions, affecting 26.4% patients (Table 2).

Table 2. Potentially inappropriate medications (PIMs) identified by POPI

	Hospital N (%)		**Community N (%)**	
No. of PIM identified per prescription *				
1	519	(2.8%)	551	(11.5%)
2	11	(0.1%)	37	(0.8%)
No. of prescriptions with at least one PIM *	530	(2.9%)	588	(12.3%)
No. of patients with at least one PIM °	530	(3.3%)	588	(26.4%)

** Percentage calculated from 18 562 prescriptions at hospital and 4 780 prescriptions in the community.*
° Percentage calculated from 15 793 patients at hospital and 2 225 patients in the community.
No.: Number

Details of PIM detected were presented in Table 3 for ED and in Table 4 for community pharmacy. Respiratory and digestive diseases had the highest rate of PIM in hospital and community pharmacy. For various illnesses, we removed one criterion involving medicines containing codeine because of their new contraindication in children under 12 years old [27]. However, the prescription of codeine was observed in 18 cases. According to our comparison

of PIMs detectable in both settings, out-of-hospital medication always presents with a higher prevalence of PIMs.

Table 3. Most frequently PIMs and PPO identified by POPI in hospital

Criteria		No. of PIMs and PPO	No. of case analyzed	%
Potentially inappropriate medications (PIMs)		**541**	**7 304**	**7.4%**
Various illnesses		**3**	**64**	**4.6%**
AI-6	Opiates to treat migraine attacks	3	64	4.6%
Digestives disorders		**56**	**1 977**	**2.8%**
EI-2	Domperidone	28	1 956	1.4%
FI-3	The use of Diosmectite (Smecta®) in combination with another medication	27	1 956	1.4%
EI-1	Metoclopramide	1	1 956	0.05%
ENT-Pulmonary disorders		**472**	**5 163**	**9.1%**
II-4	Antibiotics to treat acute suppurative otitis media etc.	2	7	28.6%
II-2	Antibiotic treatment for a sore throat, without a positive RDT.	23	160	14.4%
II-9	Ear drops in the event of acute otitis media	86	1 083	7.9%
HI-1	Beta2 agonist, corticosteroids to treat an infant's first case of bronchiolitis	25	386	6.4%
II-5	Corticosteroids to treat acute suppurative otitis media etc.	190	3 616	5.2%
II-1	An antibiotic other than amoxicillin as a first-line treatment.	59	1 259	4.7%
JI-1	H1-antagonist to treat asthma	9	802	1.1%
II-8	Tenoate Etanolamine (Rhinotrophyl®) and other nasal antiseptics	21	2 455	0.8%
II-3	Antibiotics for nasopharyngitis	26	3 444	0.7%
GI-3	Alimemazine (Theralene®), oxomemezine (Toplexil®) etc.	18	2 585	0.7%
JI-2	Cough suppressants to treat asthma	5	802	0.6%
HI-2	H1-antagonists, cough suppressants etc. to treat bronchiolitis	2	386	0.5%
II-7	H1-antagonists with sedative or atropine-like effects.	4	2 585	0.2%
GI-2	Mucolytics drugs, mucokinetics drugs or helicidine before 2 years of age	1	2 585	< 0.1%
II-6	Nasal or oral decongestant etc.	1	2 455	< 0.1%
Dermatological disorders		**10**	**100**	**10%**
OI-1	A combination of locally applied and orally administered antibiotics	9	32	28.1%
PI-2	Topical agents containing acyclovir administered to a	1	68	1.5%

	child under six years of age			
Potentially Prescribing Omissions (PPO)		**425**	**4 508**	**9.4%**
Digestives disorders		**372**	**1 956**	**19.0 %**
EO-1	Oral rehydration solution in the event of vomiting	135	313	43.1%
FO-1	Oral rehydration solution in the event of diarrhea	237	1 643	14.4%
ENT-Pulmonary disorders		**52**	**1 469**	**3.5%**
HO-1	0.9% NaCl to relieve nasal congestion etc.	38	386	9.8%
IO-2	Paracetamol combined with antibiotic treatment for ear infections etc.	14	1 083	1.3%
Dermatological disorders		**1**	**3**	**33.3 %**
NO-2	Griseofulvin taken during a meal containing a moderate amount of fat	1	3	33.3%

ENT: ear, nose and throat; No: Number; RDT: Rapid diagnostic test.
% Percentage calculated by the number of PIMs or PPO detected from the total number of analyzable cases

Table 4. Most frequently occurring PIMs and PPOs identified by POPI in community setting

Criteria		**N**	**%**
Potentially inappropriate medications (PIMs)		**591**	
Various illnesses		**15**	**2.5%**
AI-5	Oral solutions of ibuprofen administered in more than 3 doses etc.	7	1.2%
CI-1	Fluoride supplements prescribed to infants under six months of age	5	0.8%
AI-4	The combined use of two NSAIDs	3	0.5%
Digestives disorders		**201**	**34%**
EI-2	Domperidon	152	25.7%
FI-3	The use of Diosmectite (Smecta®) in combination with another medication	35	5.9%
FI-5	Intestinal antiseptics	9	1.5%
EI-1	Metoclopramide	2	0.3%
EI-6	The use of type H2 antihistamines for long periods of treatment	2	0.3%
FI-1	Loperamide before 3 years of age	1	0.2%
ENT-Pulmonary disorders		**369**	**62.4%**
GI-3	Alimemazine (Theralene®), oxomemezine (Toplexil®)…	202	34,.2%
GI-1	Pholcodine	81	13.7%
II-8	Tenoate etanolamine (Rhinotrophyl®) and other nasal antiseptics	62	10.5%
II-6	Nasal or oral decongestant etc.	20	3.4%
GI-2	Mucolytic drugs, mucokinetic drugs or helicidine prescribed to a child under 2 years of age	3	0.5%
GI-4	Terpene-based suppositories	1	0.2%
Dermatological disorders		**1**	**0.2%**
PI-2	Topical agents containing acyclovir prescribed to	1	0.2%

	a child under six years of age		
Neuropsychiatric disorders		**5**	**0.8%**
RI-3	Levetiracetam in mL or in mg prescribed without systematically indicating XX mg per Y mL	5	0.8%
Potentially Prescribing Omissions (PPO)		**293**	
IO-1	Dose in mg for oral (solution of) amoxicillin etc.	293	100%

NSAIDs: Non-steroidal anti-inflammatory drugs; ENT: ear, nose and throat
% Percentage calculated from the total number of PIMs or PPO detected

Omissions were identified in 425 prescriptions from our hospital (Table 3). The criterion on prescribing amoxicillin in mg (IO-1) was not analyzable due to the fact that this drug is prescribed in great quantity. Nonetheless, one analysis on acute otitis media alone identified a rate of 99.5% (807/811) of prescriptions issued without specification of the doses in mg for oral amoxicillin. In community care, this was observed in 97% prescriptions, in 13.2% of patients (Table 4).

PIMs classed by age were presented in the figure 4. Multivariate analysis showed that children and prescriptions issued from outpatient care correlated with a higher risk of PIM (Table 5).

Table 5. Univariate and multivariate analysis to determine which factors are related to PIM according to POPI criteria

Variable	Univariate analysis		Multivariate analysis	
Model 1 : Hospital	*OR* [CI 95%]*	*p-value*	*OR* [CI 95%]*	*p-value*
Sex				
Male	1			
Female	1.0 [0.9-1.3]	0.3		
Age category				
≤ 28 days	0.000	0.9		
28 days - 2 years	2.5 [1.5-3.8]	< 0.001*		
2 - 6 years	3.9 [2.3-6.0]	< 0.001*		
6 - 12 years	2.2 [1.2-3.4]	0.002*		
12 - 18 years	1			
Model 2 : Community				

Age category				
≤ 28 days	0.000	0.9	0.000	0.9
28 days - 2 years	0.9 [0.6-1.1]	0.4	0.9 [0.6-1.1]	0.4
2 - 6 years	2.1 [1.6-2.6]	< 0.001*	2.0 [1.5-2.5]	< 0.001*
6 - 12 years	1.9 [1.5-2.4]	< 0.001*	2.0 [1.5-2.6]	< 0.001*
12 - 18 years	1		1	
Medications/prescription	1.4 [1.3-1.4]	< 0.001*	1.4 [1.3-1.4]	< 0.001*
Model 3 : Hospital and Community				
Age category				
≤ 28 days	0.000	1.0	0.000	
28 days - 2 years	0.7 [0.5-0.8]	0.004*	1.4 [1.0-1.7]	0.005*
2 - 6 years	1.4 [1.2-1.8]	< 0.001*	2.4 [1.9-2.9]	< 0.001*
6 - 12 years	1.4 [1.1-1.7]	<0.001*	1.9 [1.5-2.2]	< 0.001*
12 - 18 years	1		1	
Service				
Hospital	1			
Community	4.8 [4.2-5.4]	< 0.0001*	5.2 [5.0-6.5]	< 0.0001*

*OR: Odds ratio, CI: Confidence intervals, *: statistically significant p<0.05.*

DISCUSSION

This study is the first to observe the prevalence of PIM and PPO in a pediatric population. 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). Similarly, the incidence of PPO was higher in older people (57.9% and 59.4%) vs (2.6% and 13.2%).[5,12,28] This result could be explained by the comorbidities present in elderly patients. Consequently, polypharmacy is the main factor which leads to PIM (2.4 drugs/prescription observed in our study compared with 6 per prescription).[12,28] The majority of PIM are found in respiratory and digestive pathology, in contrast with a geriatric population. Elderly people are frequently concerned by PIM in cardiovascular and nervous central system indications.[12,28] Respiratory and digestive pathologies are typical in children. These diseases are the most common reasons to be admitted to the ED.[29]

Domperidone, which is considered inappropriate by POPI was prescribed more frequently in the outpatient care. In our hospital, considering its modest effectiveness and adverse events (serious cardiac disorders – QT prolongation and arrythmia), this drug was no longer referenced.[30] Loperamide is not recommended, particularly for infants (contraindicated in France) due to its adverse effects such as ileus or death.[31,32] It is also considered to produce PIM in a geriatric population. One case of prescription of loperamide was detected in a young child (2 years) and we therefore made a phone call to the community pharmacist for intervention. As they hold no recommendation in gastrointestinal disease, metoclopramide and intestinal antiseptic were rarely observed in hospital prescription.[33] This could also be explained by the contraindication of metoclopramide in children < 18 years old, except in the event of nausea or vomiting associated with antimitotic.[33–35] PIM for diosmectite also occurred frequently. It is important to not administer other drugs at the same time as diosmectite leaving a time interval to prevent any ADEs via interaction.[36]

In respiratory tract infections, PIM was most frequently found in cases of a sore throat (14%). Lack of rapid test results is common, although this enables us to avoid excessive prescription of antibiotics and to reduce the emergence of highly resistant bacteria. As we know, the main cause of sore throat in children are viruses, and streptococcal infection only presents in 25-40% of cases.[37] We observed that antibiotics were present for 90% of cases of acute otitis media (AOM). Amoxicillin was not used as the first-line treatment for 145 cases (13%). However, only 59 cases were considered noncompliant according to criterion II-1. Indeed, in the management of conjunctivitis-otitis syndrome caused by *Haemophilus influenza,* giving amoxicillin/clavulanic acid as a first-line treatment is recommended.[38] This antibiotic is also privileged for acute maxillary sinusitis and frontal, ethmoidal and sphenoid sinusitis.[37] Amoxicillin was used in 77% of cases of AOM, at a higher rate than that observed in a national study in 2012 (66%). This result shows that the French recommendation for this

course of action in 2011, in order to reduce the rate of bacteria resistance, has had a strong impact.[37,39] Eardrops are considered inappropriate in cases of AOM without other symptoms. For chronic otitis with otorrhea, perforation of the eardrum or, antibiotic eardrops are recommended.[40,41] This application showed that some of our criteria need to be more detailed, in order to avoid mis-detection of PIM. Prevalence of beta2 agonists or corticosteroids in an infant's first case of bronchiolitis is 6.4% (25/386 cases), lower than that observed in a study of another French area in 2012 (41%).[42–44] A high frequency of prescription of antibiotics, corticosteroids or nasal antiseptic medication was detected in case of nasopharyngitis, although there is no evidence for this.[45] Antiseptics such as tenoate ethanolamine did not receive a favorable opinion from the ANSM (French National Agency for Medicinces and Health Products Safety) because they exposed patients to potential nasal irritation and occasionally to serious allergies.[46] Even so, it was frequently present in prescriptions from outpatient care. Unnecessary exposure to cough suppressants, pholcodine, nasal or oral decongestants was also observed frequently in this sector.[46]

Less PIM were found in dermatological disorders. In the management of scabies, we had removed the criterion on Ascabiol® (Sulfirame and Benzyl Benzoate) as it was out of stock since 2012.

In comparison to PIM, the rate of PPO observed was lower and centred on specific disorders. In the management of diarrhea caused by gastroenteritis, in hospital, our study found that it was common to omit prescription of an oral rehydration solution (ORS): 14% (237/1643 case). Even so, this rate is lower than that found in another national study in 2007 (29%).[47] It could be that the recommendation of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in 2008 has had a positive impact.[31,33] Thus, this criterion serves not only to highlight the importance of ORS for the prescriber but also helps

to increase the frequency of pharmaceutical recommendation of this drug. Another common omission was identified in the prescription of oral liquid formulation. A precise dosage of oral amoxicillin is necessary because many errors occurred when using the dosing spoon.[48] In 62/63 cases, oral acyclovir was not prescribed for herpetic gingivostomatitis. In daily practice, this occurred because a blood test to screen for the primary infection is not realized. However, the oral treatment can prevent recurrences, which cannot be attained by using cream.[49] Once again, the role of the community pharmacist is significant in detecting the omission, intervening or providing education to the patient when necessary.

As estimated, the child group has the highest risk of presenting with a PIM, according to a multivariate analysis. Certainly, this age group is most frequently affected by respiratory diseases and is thus exposed to many unnecessary prescriptions such as cough suppressants or decongestant drugs. As we know, they are also affected by off-label drug prescriptions, which is consistent with reports from other sources.[50,51] Once again, our study highlights the importance of appropriate prescription in this age group. As with geriatrics, an increase in numbers of medications can be associated with PIM.[28] Prescriptions issued from hospitals elicit fewer IP than those issued by the community. The main reason for this is that many drugs are not available in this hospital, such as cough suppressants, Rhinotrophyl® (tenoate ethanolamine), domperidone, etc. This shows that many PIM are preventable in a hospital setting. An efficient method for prevention of PIM could be to focus on the prescribing habits of physicians and thus have an impact on the selection of drugs, thereby reducing the rate of PIM.

Our study has several limitations. Firstly, it is a retrospective and monocentric study. Our result in the hospital could be underestimated. In addition, several criteria could not be analyzed due to the large number of prescriptions (for example, those for fever or pain which

are associated with many diseases) or absence of a specific pathology (mosquitos, lice, hyperactivity etc.). Antibiotic prophylaxis, vitamin supplements, proposition of vaccination etc. can be analyzed in prospective studies. A lack of clinical information is the main limitation in detection in a community setting. This also constitutes a challenge for pharmaceutical care review in elderly patients.[52] However, a certain amount of PIM were identified using POPI. Our study showed that there are many criteria which could be detected without access to clinical information and that they are easy to identify. Moreover, community pharmacists, in their practice, can extrapolate diagnoses from their experience, from common indications or by interviewing their patient.

This is the first study which permits to evaluate prevalence of PIM and PPO in pediatric's prescription Hereafter, in order to prove the effectiveness of this tool, further investigations must be carried out on a larger scale, both in hospital and in community care. It is also necessary to evaluate the impact of this tool on reducing adverse drugs events, both in consultation or upon hospitalization. The impact of pharmacists in providing appropriate prescriptions should be also evaluated. Subsequently, this tool may be proposed to several professional societies such as the French Society for Pediatricians and the French Society of Clinical Pharmacy to make its use more widespread. The tool should be regularly updated to reflect recent events and to specify certain criteria.

To facilitate its use, this tool can be presented as a mobile app, a small handbook or be installed into prescription software. In summary, we hope that POPI could be a practical option used to reduce medication errors and to improve the suitability of prescriptions. It provides rapid detection of PIM and PPO and can also open up a discussion on the relationship between the medicine and the pharmacist to remedy the issue at hand.[53]

CONCLUSION

Our study was carried out in in two sectors, hospital and community, and provides a global view of PIM and PPO in pediatric patients. It highlights the potential role of POPI tools in improving prescription quality in various sectors. POPI should be applied in different services to deepen and reinforce its utilization. A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice.

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ETHICS

This project was approved by the local research ethics committee (n°2015/218).

DISCLOSURE OF INTEREST

None Declared

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AUTHOR'S CONTRIBUTION

Sonia Prot-Labarthe, Aurore Berthe-Aucejo conceptualised and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Rym Boulkedid and HPK Nguyen carried out analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Xavier Bellettre, Thomas Weil, Olivier Bourdon reviewed and revised the manuscript and approved the final manuscript as submitted.

François Angoulvant and Patrick Albaret supplied data from hospital and community pharmacy and reviewed and revised the manuscript and approved the final manuscript as submitted.

DATA SHARING STATEMENT

We have no additional unpublished data

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Appendix 1. POPI - Pediatrics: Omission of Prescriptions & Inappropriate prescriptions

DIVERSE ILLNESSES

A- PAIN AND FEVER

Inappropriate prescriptions	Omissions
AI-1. Prescription of two alternating antipyretics as a first-line treatment. *	**A0-1.** Failure to give sugar solution to new-born babies and infants under four months old two minutes prior to venipuncture.
AI-2. Prescription of a medication other than paracetamol as a first line treatment (except in the case of migraine).	**A0-2.** Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours.
AI-3. Rectal administration of paracetamol as a first-line treatment.	
AI-4. The combined use of two NSAIDs. * °	
AI-5. Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (other than Advil®). °	
AI-6. Opiates to treat migraine attacks. *	

B- URINARY INFECTIONS

Inappropriate prescriptions

BI-1. Nitrofurantoin used as a prophylactic.

BI-2. Nitrofurantoin used as a curative agent in children under six years of age, or indeed any other antibiotic if avoidable.

BI-3. Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy).

BI-4. Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy).

C- VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS

Inappropriate prescriptions	Omissions
CI-1. Fluoride supplements prior to six months of age.	**CO-1.** Insufficient intake of vitamin D. Minimum vitamin D intake: ▪ Breastfed baby = 1 000 to 1 200 IU/day ▪ Infant < 18 months of age (milk enriched in vitamin D) = 600 to 800 IU/day ▪ Child aged between 18 months and five years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80 000 to 100 000 IU/day in winter (adolescents can take this dose in one go). **CO-2.** Antibiotic prophylaxis with phenoxymethylpenicillin (Oracilline) starting from two months of age and lasting until five years of age for children with sickle-cell anemia: 100 000 IU/kg/day (in two doses) for children weighing 10kg or less and 50 000 IU/kg/day for children weighing over 10kg (also in two doses).

D- MOSQUITOS

Inappropriate prescriptions	Omissions
DI-1. The use of skin repellents in infants less than six months old and picardin in children less than 24 months old.	**DO-1. DEET** ‘‘30%’’ (max) before 12 years old ‘‘50%’’ (max) after 12 years old.
DI-2. Citronella (lemon grass) oil (essential oil).	**DO-2. IR3535** ‘‘20%’’ (max) before 24 months old ‘‘35%’’ (max) after 24 months old.
DI-3. Anti-insect bracelets to protect against mosquitos and ticks.	**DO-3.** Mosquito nets and clothes treated with pyrethroids.
DI-4. Ultrasonic pest control devices, vitamin B1, homeopathy, electric bug zappers, sticky tapes without insecticide.	

DIGESTIVE PROBLEMS

E- NAUSEA, VOMITTING, OR GASTROESOPHAGEAL REFLUX

Inappropriate prescriptions	Omissions
EI-1. Metoclopramide.* °	**EO-1.** Oral rehydration solution in the event of vomiting.*
EI-2. Domperidone.* °	
EI-3. Gastric antisecretory drugs to treat gastroesophageal reflux, dyspepsia, the crying of new-born babies (in the absence of any other signs or symptoms), as well as faintness in infants. *	
EI-4. The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors.*	
EI-5. Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube).*	
EI-6. The use of type H2 antihistamines for long periods of treatment.* °	
EI-7. Erythromycin as a prokinetic agent.*	
EI-8. The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting.*	

F- DIARRHEA

Inappropriate prescriptions	Omissions
FI-1. Loperamide before 3 years of age.*°	**FO-1.** Oral rehydration solution in the event of diarrhea.*
FI-2. Loperamide in the case of invasive diarrhea.*	
FI-3. The use of Diosmectite (Smecta®) in combination with another medication.*°	
FI-4. The use of Saccharomyces boulardii (Ultralevure) in powder form, or in a capsule that has to be opened prior to ingestion, to treat patients with a central venous catheter or an immunodeficiency.*	
FI-5. Intestinal antiseptics.*°	

ENT-PULMONARY PROBLEMS

G- COUGH

Inappropriate prescriptions	Omissions
GI-1. Pholcodine.* °	**GO-1.** Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family and entourage of expectant parents (parents, grand-parents, nannies/child minders).
GI-2. Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age.* °	
GI-3. Alimemazine (Theralene®), oxomemazine (Toplexil®), promethazine (Phenergan®), and other types.* °	
GI-4. Terpene-based suppositories.* °	

H- BRONCHIOLITIS IN INFANTS

Inappropriate prescriptions	Omissions
HI-1. Beta2 agonists, corticosteroids to treat an infant's first case of bronchiolitis.*	**HO-1.** 0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer).*
HI-2. H1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis.*	**HO-2.** Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities.
HI-3. Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.).*	

DERMATOLOGICAL PROBLEMS

I- ENT INFECTIONS

Inappropriate prescriptions	Omissions
II-1. An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for an pneumoncoccal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day.*	**IO-1.** Doses in mg for drinkable (solutions of) amoxicillin or josamycin.*
II-2. Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children more than three years old.*	**IO-2.** Paracetamol combined with antibiotic treatment for ear infections to relieve pain.*
II-3. Antibiotics for nasopharyngitis, congestive otitis, sore throat before three years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, after two years of age.*	
II-4. Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months.*	
II-5. Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat.*	
II-6. Nasal or oral decongestant (oxymetazoline (Aturgyl®), pseudoephedrine (Sudafed®), naphazoline (Derinox®), ephedrine (Rhinamide®), tuaminoheptane (Rhinofluimicil®), phenylephrine (Humoxal®)).*	
II-7. H1-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor; inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age.*	
II-8. Ethanolamine tenoate (Rhinotrophyl®) and other nasal antiseptics.* °	
II-9. Ear drops in the case of acute otitis media.*	

J- ASTHMA

Inappropriate prescriptions	Omissions
JI-1. Ketotifen and other H1-antagonists, sodium cromoglycate.*	**JO-1.** Asthma inhaler appropriate for the child's age.
JI-2. Cough suppressants.*	**JO-2.** Preventative treatment (inhaled corticosteroids) in the case of persistent asthma.*

K-ACNE VULGARIS

Inappropriate prescriptions	Omissions
KI-1. Minocycline.* °	**KO-1.** Contraception (provided with a logbook/diary) for menstruating girls taking isotretinoin.
KI-2. Isotretinoin in combination with a member of the tetracycline family of antibiotics.* °	**KO-2.** Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy.*
KI-3. The combined use of an oral and a local antibiotic.*	
KI-4. Oral or local antibiotics as a monotherapy (not in combination with another drug).*	
KI-5. Cyproterone+ethinylestradiol (Diane 35®) as a contraceptive to allow isotretinoin per os.* °	
KI-6. Androgenic progestins (levonorgestrel, norgestrel, norethisterone, lynestrenol, dienogest, contraceptive implants or vaginal rings).*	

L- SCABIES

Omissions

LO-1. A second dose of ivermectin two weeks after the first.*

LO-2. Decontamination of household linen and clothes and treatment for other family members.

M- LICE

Inappropriate prescriptions

MI-1. The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnea.

N- RINGWORM

Inappropriate prescriptions

NI-1. Treatment other than griseofulvin for Microsporum.*

Omissions

NO-1. Topical treatment combined with an orally-administered treatment.*

NO-2. Griseofulvin taken during a meal containing a moderate amount of fat.* °

O-IMPETIGO

Inappropriate prescriptions

OI-1. The combination of locally applied and orally administered antibiotic.*

OI-2. Fewer than two applications per day for topical antibiotics.*

OI-3. Any antibiotic other than mupirocin as a first-line treatment (except in cases of hypersensitivity to mupirocin).*

P- HERPES SIMPLEX

Inappropriate prescriptions

PI-1. Topical agents containing corticosteroids.*

PI-2. Topical agents containing acyclovir before six years of age.* °

Omissions

PO-1. Paracetamol during an outbreak of herpes.*

PO-2. Orally administered acyclovir to treat primary herpetic gingivostomatitis.*

Q-DERMATITE ATOPIQUE

Inappropriate prescriptions

QI-1. A strong dermocorticoid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate Diprosone) applied to the face, the armpits or groin, and the backside of babies or young children.*

More than one application per day of a dermocorticoid, except in cases of severe lichenification. *

QI-2. Local or systemic antihistamine during the treatment of outbreaks.*

QI-3. Topically applied 0.03% tacrolimus before two years of age.*

Topically applied 0.1% tacrolimus before 16 years of age.

QI-4. Oral corticosteroids to treat outbreaks.*

NEUROPSYCHIATRIC DISORDERS

R- EPILEPSY

Inappropriate prescriptions

RI-1. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy.*

RI-2. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabaline, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy).*

RI-3. Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL.* °

S-DEPRESSION

Inappropriate prescriptions

SI-1. An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy).*

SI-2. Tricyclic antidepressants to treat depression.*

T- NOCTURNAL ENURESIS

Inappropriate prescriptions

TI-1. Desmopressin administered by a nasal spray.*

	Desmopressin in the case of daytime symptoms.
TI-2.	An anticholinergic agent used as a monotherapy in the absence of daytime symptoms.*
TI-3.	Tricyclic agents in combination with anticholinergic agents.* °
TI-4.	Tricyclic agents as a first-line treatment.*
U- ANOREXIA	
Inappropriate prescriptions	
UI-1.	Cyproheptadine (Periactin®), clonidine * °
V- ATTENTION DEFICIT DISORDER WITH OR WITHOUT HYPERACTIVITY	
Inappropriate prescriptions	**Omissions**
VI-1. Pharmacological treatment before age six (before school), except in severe cases.*	**VO-1.** Recording a growth chart (height and weight) if the patient is taking methylphenidate.*
VI-2. Antipsychotic drugs to treat attention deficit disorder without hyperactivity.*	
VI-3. Slow release methylphenidate as two doses per day, rather than only one dose.*°	

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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.

A. Berthe-Aucejo[1], H.P.K Nguyen[1], F. Angoulvant[2,3], X. Bellettre[4], P. Albaret[5,6], T. Weil[1], R. Boulkedid[3,7,8], O. Bourdon[1,6,9,10], S.Prot-Labarthe[1,3,10]

[1] Department of Pharmacy, Robert-Debré Hospital, Paris, France

[2] Emergency unit, Necker Hospital, Paris, France

[3] UMR-S1123, ECEVE; Inserm U1123, Paris, France

[4] Emergency unit AP-HP, Robert-Debré Hospital, Paris, France

[5] Albaret Pharmacy, Cesson, France

[6] Clinical Pharmacy, Paris Descartes University, Paris, France

[7] Assistance publique-Hôpitaux de Paris, Hôpital Robert Debré, Clinical Epidemiology Unit, 75 019 Paris, France

[8] CIC-EC 1426, 75019 Paris, France

[9] Laboratoire Educations et Pratiques de Santé, Paris XIII University, Bobigny, France

[10] Groupe Pédiatrie de la Société Française de Pharmacie Clinique, Paris, France

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Corresponding author

Dr Aurore Berthe-Aucejo, Service Pharmacie, AP-HP Hôpital Robert-Debré, 48 Boulevard Sérurier, 75019 Paris, Fax: 01-40-03-24-81, Tel: 01-40-03-57-41, Email: aurore.berthe@aphp.fr

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Inappropriate prescription, omission, tool, detection

ABSTRACT

Background and Objective: POPI **(**Pediatrics: Omission of Prescription and Inappropriate prescription) is the first tool of detection for potentially inappropriate medicines (PIM) and potentially prescribing omissions (PPO) in pediatrics. The aim of this study was to evaluate the prevalence of PIM and PPO detected by POPI regarding issuing of prescription in hospital and outpatient care. The second objective is to determine the risk factors related to PIM.

Design: A retrospective and descriptive study was conducted in the emergency department (ED) and community pharmacy (CP) during 6 months. POPI was used to identify PIM and PPO.

Setting: Robert-Debré Hospital (AP-HP, France) and Albaret community pharmacy (Seine and Marne).

Participants: Inclusion criteria included patients who were under 18 years old and who had one medicine prescription. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients.

Primary and secondary outcome measures: PIM and PPO rate, PIM risk factors

Results: At ED, 18,562 prescriptions for 15,973 patients and 4,780 prescriptions for 2,225 patients at the CP were analyzed. The PIM rate and PPO rate were respectively 3.3% and 2.6% at the ED and 26.4% and 13.2% at the CP. Respiratory and digestive diseases had the highest rate of PIM. Multivariate logistic regression model showed that children aged between 0 and 12 years (OR=1.3 $CI_{95\%}$ [1.0-1.6] p=0.03 for 0-2 years, OR=2.4 $CI_{95\%}$ [1.9-2.9] p<0.001 for 2-6 years, OR=1.9 $CI_{95\%}$ [1.5-2.3] p<0.001 for 6-12 years) and prescriptions issued from outpatient care (OR= 5.7 $CI_{95\%}$ [5.0-6.4] p<0.001)) were significantly associated with a higher risk of PIM.

Conclusion: This study is the first that assesses the prevalence of PIM and PPO detecting by POPI in a pediatric population. A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice.

Strengths and limitations of this study

- This study is the first to observe the prevalence of PIM and PPO in a pediatric population.

- It is a retrospective and monocentric study. The prevalence of PIM and PPO may be underestimated (large number of prescriptions, absence of specific pathology). Some criteria could be analyzed only in a prospective study. A lack of clinical information is the main limitation in detection in a community setting.

- Many omissions and inappropriate prescriptions can be easily detected with POPI despite limited clinical information.

INTRODUCTION

Inappropriate prescribing is a known preventable cause of adverse drug events (ADE) and has an important impact on public health and cost of care.[1,2] ADE included adverse drug reaction, harm from use of the treatment. Incidence of hospitalization due to ADE was 42.8% according to a French survey in 2009.[3] In the paediatric population, incidence of adverse drug reaction responsible for hospital admission was estimated from 0.4% to 10.3%.[4] Many drugs were concerned in commonly used medication.[5–7] The World Health Organization estimated that 50% of medications are prescribed and utilized inappropriately.[8] The most recent definition of inappropriate prescription (IP) encompasses potentially inappropriate medicines (PIM) and prescribing omissions (PPO).[9] In a report from the French National Authority for Health, PIMs are defined as "drugs being used in a situation in which the risks involved in treatment potentially outweigh the benefits, lack of demonstrated indication, high risk of ADE, and an unfavorable cost-effect or risk-benefit ratio exists". PPO or underuse of appropriate medication is defined as the absence of initiation of an effective treatment in subjects with a condition for which one or several drug classes have demonstrated their efficacy. In an elderly population, which presents with age-related physiological changes and high prevalence of polypharmacy, various measures have been developed to detect PIM such as: Beers' criteria, the Inappropriate Prescribing in the Elderly Tool, The Medication Appropriate Index, and STOPP/START (Screening Tool of Older Person's prescriptions/Screening Tool to Alert doctor to Right Treatment).[10–15]

Only the STOPP/START enables us to detect under-prescribing.[9] Using these tools, many studies have been carried out which have detected that inappropriate prescriptions are issued to between 35% and 51% of this population.[16–20]

Omission prescriptions in geriatric population detected by START tool concerned between 58%-61% of patients.[9,21] Negative outcomes related to an IP such as side effects, hospitalization, mortality and utilization of resources were also demonstrated.[1,15,22,23]

Prescribing in a pediatric population is always a challenge for physician. It is often empirical and primarily based on safety and pharmacology information obtained in adults.[24] This is a worry not only in a hospital or general practitioner setting but also for the community pharmacists. They may only be able to check information and resources or even dispense infrequently for this vulnerable population.[25] Medication errors were identical in adults and children but side effects were three time more common in the pediatric population. This frequency was explained by the vulnerability of young people, pharmacokinetic changes during childhood and pediatric off-label drug used.[26–28]

Large differences relating to treatment were seen within and between the countries.[28,29] Question about rational of prescription could be asked.[30] Optimizing children's care is based on rational prescribing and allowing a decrease in side effects.[29,30] In order to improve the correct drug use and optimize practice, the first tool of detection for PIM and PPO was created by Prot-Labarthe *et al.* in 2013. The tool was named POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions) (Appendix1).[31,32] Presently, the complete tool has not been tested in actual practice and the prevalence of PIM and OP is not known.

Our aim is to evaluate the prevalence of PIM and PPO detected by POPI. This was its first application, regarding issuing of prescriptions in hospital and outpatient care. The second objective is to determine the risk factors related to PIM.

METHODS

Population

A retrospective and descriptive study was conducted in the emergency department (ED) of AP-HP Robert-Debré hospital (Paris) - the largest French pediatric hospital - and the Albaret community pharmacy (Seine and Marne). Inclusion criteria included patients who were under 18 years old and who had one medicine prescription between 1st October 2014 and 31st March 2015. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients. POPI contains 102 criteria (76 PIMs, 25 PPO). 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). Criteria were validated by 2-round-Delphi consensus technique.[32]

Data collection

The prescriptions given on leaving the emergency department were extracted from the software Urqual V5® (*) (McKesson Corp, Paris, France). Urqual® is an emergency prescription software which is used in many French hospitals. Patient information including age, sex, weight, medicine prescription and current diagnosis was collected. Medical histories and clinical examinations were consulted individually when necessary. Due to the significant amount of data, clinical files of ED were analyzed, based on primary diagnosis. Assessable criteria in the retrospective study in hospital were identified by the symbol "*" in appendix 1 (82 criteria).

Data from the community pharmacy were obtained from the pharmacy management software OPUS® (Computer PG, France). Patient's age and drugs prescribed were collected. Clinical

case records and sex were not available in pharmacy as this was a retrospective analysis, so only drugs that did not require assessment of diagnosis (for example domperidone, metoclopramide etc.) were analyzed. These criteria were denoted by the symbol "°" in appendix 1 (28 criteria).

Criteria including analgesics and antipyretics were not evaluated because of the large number of prescriptions and association with many diseases.

Pathologies analyzed by POPI were the same in emergency department and in community.

Statistical analysis

Data were presented as continuous variables (age, number of prescriptions by patient, number of medications per prescription) and were presented as median and interquartile range (25th-75th percentiles) or mean (standard deviation), minimum and maximum depending on normal distribution.

Logistic regression models were used to identify factors associated with risk of PIM (yes/no) in hospital, community setting and in hospital and community grouped.

Univariate models were performed using different candidate factors as:

- For model performed with hospital data: sex and age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years);
- For model performed with community data: age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years) and number of medications per prescription;
- For model performed with hospital and community data: age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years) and setting of prescription (hospital or community setting).

The multivariate logistic regression model was constructed using the parameters of the univariate analysis, which showed at least a trend toward significance, with a cut-off of p=0.2. Backward elimination will start with all candidates in the model and run a sequence of statistical tests to remove them from or keep them in the model based on a nominal p-value <0.05. Odds ratios (OR) with 95% confidence intervals (CI) were estimated. Statistical significance was established at p<0.05. SPSS-22® software (SPSS Inc., Chicago, IL, USA) was used for analysis.

This project was approved by the local research ethics committee (n°2015/218).

RESULTS

In the emergency department, 18,562 prescriptions for 15,973 patients consulted were analyzed. Among them, 29% had at least two visits in 6 months. In the community pharmacy, 4,780 prescriptions for 2,225 patients were evaluated (Figure 1). In ED and CP, 53% of patients had been issued with one prescription, 21% with two and 26% with three or more prescriptions. The population's characteristics and the frequency of pathologies were presented in table 1. Distribution of number of prescriptions by age category was described in the figure 2.

Table 1. Characteristics of the study population

Population characteristics	Hospital (N=15,973)	Community (N=2,225)
Age (years) mean (SD) Min, Max	4.9 (4.5) 0-18	7.9 (5.3) 0-18
Female gender N(%)	8,769 (54.9)	NA

Number of prescriptions/patient mean (SD) Min, Max	1.4 (0.9) 1-12	2.2 (1.9) 1-16
Number of medications per prescription mean (SD) Min, Max	NA	2.4 (1.6) 1-22
Number of prescriptions by pathology N(%)		
Digestive disorders	2,728 (14.7)	NA
ENT-Pulmonary disorders	8,397 (45.2)	NA
Dermatological disorders	604 (3.3)	NA
Neuropsychiatric disorders	242 (1.3)	NA
Other illnesses[#]	6,591 (35.5)	NA

NA: Not available; ENT: ear, nose and throat
[#] *For example, traumatic injury, pain, sickle cell disease*

In hospital, POPI tools identified 541 PIM in 2.9% of the prescriptions analyzed. They were detected in 3.3% of the patients (n=530). In the community, PIM represented 12.3% of all prescriptions, affecting 26.4% patients (Table 2).

Table 2. Potentially inappropriate medications (PIMs) identified by POPI

	Hospital N (%)	**Community N (%)**
PIM identified per prescription *		
1	519 (2.8%)	551 (11.5%)
2	11 (0.1%)	37 (0.8%)

Prescriptions with at least one PIM *	530 (2.9%)	588 (12.3%)
Patients with at least one PIM °	530 (3.3%)	588 (26.4%)

** Percentage calculated from 18,562 prescriptions at hospital and 4,780 prescriptions in the community.*

° Percentage calculated from 15,793 patients at hospital and 2,225 patients in the community.

Details of PIM detected were presented in Table 3 for ED and in Table 4 for community pharmacy. Respiratory and digestive diseases had the highest rate of PIM in hospital and community pharmacy. For various illnesses, we removed one criterion involving medicines containing codeine because of their new contraindication in children under 12 years old.[33] However, the prescription of codeine was observed in 18 cases. According to our comparison of PIMs detectable in both settings, out-of-hospital medication always presents with a higher prevalence of PIMs (Figure 3).

Table 3. Prevalence of PIMs and PPO identified by POPI in hospital

Criteria		**No. of PIMs and PPO**	**No. of case analyzed***	**%**
Potentially inappropriate medications (PIMs)		**541**	**7,304**	**7.4%**
Various illnesses		**3**	**64**	**4.6%**
AI-6	Opiates to treat migraine attacks	3	64	4.6%
Digestive disorders		**56**	**1,977**	**2.8%**
EI-2	Domperidone	28	1,956	1.4%
FI-3	The use of Diosmectite (Smecta®) in combination with another medication	27	1,956	1.4%
EI-1	Metoclopramide	1	1,956	0.05%
ENT-Pulmonary disorders		**472**	**5,163**	**9.1%**
II-4	Antibiotics to treat acute suppurative otitis media etc.	2	7	28.6%
II-2	Antibiotic treatment for a sore throat, without a positive RDT.	23	160	14.4%
II-9	Ear drops in the event of acute otitis media	86	1,083	7.9%
HI-1	Beta2 agonist, corticosteroids to treat an infant's first case of bronchiolitis	25	386	6.4%
II-5	Corticosteroids to treat acute suppurative otitis media etc.	190	3,616	5.2%
II-1	An antibiotic other than amoxicillin as a first-line treatment.	59	1,259	4.7%
JI-1	H1-antagonist to treat asthma	9	802	1.1%

II-8	Tenoate Etanolamine (Rhinotrophyl®) and other nasal antiseptics	21	2,455	0.8%
II-3	Antibiotics for nasopharyngitis	26	3,444	0.7%
GI-3	Alimemazine (Theralene®), oxomemezine (Toplexil®) etc.	18	2,585	0.7%
JI-2	Cough suppressants to treat asthma	5	802	0.6%
HI-2	H1-antagonists, cough suppressants etc. to treat bronchiolitis	2	386	0.5%
II-7	H1-antagonists with sedative or atropine-like effects.	4	2,585	0.2%
GI-2	Mucolytics drugs, mucokinetics drugs or helicidine before 2 years of age	1	2,585	< 0.1%
II-6	Nasal or oral decongestant etc.	1	2,455	< 0.1%
Dermatological disorders		**10**	**100**	**10%**
OI-1	A combination of locally applied and orally administered antibiotics	9	32	28.1%
PI-2	Topical agents containing acyclovir administered to a child under six years of age	1	68	1.5%
Potentially Prescribing Omissions (PPO)		**425**	**4,508**	**9.4%**
Digestive disorders		**372**	**1,956**	**19.0 %**
EO-1	Oral rehydration solution in the event of vomiting	135	313	43.1%
FO-1	Oral rehydration solution in the event of diarrhea	237	1,643	14.4%
ENT-Pulmonary disorders		**52**	**1,469**	**3.5%**
HO-1	0.9% NaCl to relieve nasal congestion etc.	38	386	9.8%
IO-2	Paracetamol combined with antibiotic treatment for ear infections etc.	14	1,083	1.3%
Dermatological disorders		**1**	**3**	**33.3 %**
NO-2	Griseofulvin taken during a meal containing a moderate amount of fat	1	3	33.3%

ENT: ear, nose and throat; No: Number; RDT: Rapid diagnostic test.
% Percentage calculated by the number of PIMs or PPO detected from the total number of analyzable cases
**number of cases analyzed corresponded with situation of inappropriate prescription or omission*

Table 4. Most frequently occurring PIMs and PPOs identified by POPI in community setting

Criteria		**N**	**%**
Potentially inappropriate medications (PIMs) N= 591			
Various illnesses		**15**	**2.5%**
AI-5	Oral solutions of ibuprofen administered in more than 3 doses etc.	7	1.2%
CI-1	Fluoride supplements prescribed to infants under six months of age	5	0.8%
AI-4	The combined use of two NSAIDs	3	0.5%
Digestive disorders		**201**	**34%**

EI-2	Domperidone	152	25.7%
FI-3	The use of Diosmectite (Smecta®) in combination with another medication	35	5.9%
FI-5	Intestinal antiseptics	9	1.5%
EI-1	Metoclopramide	2	0.3%
EI-6	The use of type H2 antihistamines for long periods of treatment	2	0.3%
FI-1	Loperamide before 3 years of age	1	0.2%
ENT-Pulmonary disorders		**369**	**62.4%**
GI-3	Alimemazine (Theralene®), oxomemazine (Toplexil®)…	202	34,.2%
GI-1	Pholcodine	81	13.7%
II-8	Tenoate etanolamine (Rhinotrophyl®) and other nasal antiseptics	62	10.5%
II-6	Nasal or oral decongestant etc.	20	3.4%
GI-2	Mucolytic drugs, mucokinetic drugs or helicidine prescribed to a child under 2 years of age	3	0.5%
GI-4	Terpene-based suppositories	1	0.2%
Dermatological disorders		**1**	**0.2%**
PI-2	Topical agents containing acyclovir prescribed to a child under six years of age	1	0.2%
Neuropsychiatric disorders		**5**	**0.8%**
RI-3	Levetiracetam in mL or in mg prescribed without systematically indicating XX mg per Y mL	5	0.8%
Potentially Prescribing Omissions (PPO)		**293**	
IO-1	Dose in mg for oral (solution of) amoxicillin etc.	293	100%

NSAIDs: Non-steroidal anti-inflammatory drugs; ENT: ear, nose and throat
% Percentage calculated from the total number of PIMs or PPO detected

Omissions were identified in 425 prescriptions from our hospital (Table 3). The criterion on prescribing amoxicillin in mg (IO-1) was not analyzable due to the fact that this drug is prescribed in great quantity. Among 100 prescriptions randomly assessed in hospital extractions, 97 prescriptions were inappropriate. Nonetheless, one analysis on acute otitis media alone identified a rate of 99.5% (807/811) of prescriptions issued without specification of the doses in mg for oral amoxicillin. In community care, this was observed in 97% of prescriptions, in 13.2% of patients (Table 4).

PIMs classed by age were presented in the figure 4. Potential factors associated with PIM are presented in Table 5. On univariate analysis, only different age categories were associated with risk of PIM in hospital setting. In community setting, the number of medications per prescription and different age categories were found to be significantly associated with risk of PIM on univariate analysis. In the multivariable logistic regression model, the same results were obtained. When data from hospital and community were grouped, univariate analysis showed that different age categories and prescription setting were associated with risk of PIM. In the multivariable logistic regression model, prescription issued from outpatient care was significantly associated with a higher risk of PIM (OR: 5.7 [5.0; 6.4] 95%CI, p<0.001). In addition, patients aged 0-12 years are more at risk of having a PIM than patients aged between 12-18 years (OR: 1.3 [1.0-1.6] 95%CI, p=0.03 for 0-2 years; OR 2.4 [1.9-2.9] p< 0.001 for 2-6 years; OR 1.9 [1.5-2.3] p< 0.001).

Table 5. Univariate and multivariate analysis to determine factors associated with PIM according to POPI criteria

Variable	Univariate analysis		Multivariate analysis	
Model 1: Hospital prescription	*OR* [CI 95%]*	*p-value*	*OR* [CI 95%]*	*p-value*
Sex				
Male	1			
Female	1.0 [0.9-1.3]	0.3		
Age category				
0 - 2 years	2.4 [1.5-3.8]	< 0.001	2.4 [1.5-3.8]	< 0.001
2 - 6 years	3.8 [2.3-6.0]	< 0.001	3.8 [2.3-6.0]	< 0.001
6 - 12 years	2.1 [1.2-3.4]	0.005	2.1 [1.2-3.4]	0.005
12 - 18 years	1		1	
Model 2: Community prescription				
Age category				

0 - 2 years	0.8 [0.6-1.1]	0.2	0.8 [0.6-1.1]	0.1
2 - 6 years	2.1 [1.6-2.6]	< 0.001	2.0 [1.5-2.5]	< 0.001
6 - 12 years	1.9 [1.5-2.5]	< 0.001	2.0 [1.6-2.6]	< 0.001
12 - 18 years	1		1	
Number of medications per prescription	1.4 [1.3-1.4]	< 0.001	1.4 [1.3-1.4]	< 0.001
Model 3: Hospital and Community prescription				
Age category				
0 - 2 years	0.7 [0.6-0.8]	<0.001	1.3 [1.0-1.6]	0.03
2 - 6 years	1.4 [1.1-1.7]	0.002	2.4 [1.9-2.9]	< 0.001
6 - 12 years	1.4 [1.1-1.7]	0.002	1.9 [1.5-2.3]	< 0.001
12 - 18 years	1		1	
Service				
Hospital	1			
Community	5.3 [4.7-6.0]	< 0.001	5.7 [5.0-6.4]	< 0.001

OR: Odds ratio, CI: Confidence intervals.

DISCUSSION

This study is the first to observe the prevalence of PIM and PPO in a pediatric population. 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).[9,16,34] Similarly, the incidence of PPO was higher in older people (57.9% and 59.4%) vs (2.6% and 13.2%). This result could be explained by the comorbidities present in elderly patients. Consequently, polypharmacy is the main factor which leads to PIM (2.4 drugs/prescription observed in our study compared with 6 per prescription).[16,34] The majority of PIM are found in respiratory and digestive pathology, in contrast with a geriatric population. Elderly people are frequently concerned by PIM in cardiovascular and nervous

central system indications.[16,34] Respiratory and digestive pathologies are typical in children. These diseases are the most common reasons to be admitted to the ED.[35]

Domperidone, which is considered inappropriate by POPI was prescribed more frequently in outpatient care. In our hospital, considering its modest effectiveness and adverse events (serious cardiac disorders – QT prolongation and arrythmia), this drug was no longer referenced.[36] Loperamide is not recommended, particularly for infants (contraindicated in France) due to its adverse effects such as ileus or death.[37,38] It is also considered to produce PIM in a geriatric population. One case of prescription of loperamide was detected in a young child (2 years) and we therefore made a phone call to the community pharmacist for intervention. As they hold no recommendation in gastrointestinal disease, metoclopramide and intestinal antiseptic were rarely observed in hospital prescription.[39] This could also be explained by the contraindication of metoclopramide in children < 18 years old, except in the event of nausea or vomiting associated with antimitotic.[39–41]

PIM for diosmectite also occurred frequently. It is important to not administer other drugs at the same time as diosmectite leaving a time interval to prevent any ADEs via interaction.[42]

In respiratory tract infections, PIM was most frequently found in cases of a sore throat (14%). Lack of rapid test results is common, although this enables us to avoid excessive prescription of antibiotics and to reduce the emergence of highly resistant bacteria. As we know, the main cause of sore throat in children is viruses, and streptococcal infection only presents in 25-40% of cases.[43] We observed that antibiotics were present for 90% of cases of acute otitis media (AOM). Amoxicillin was not used as the first-line treatment for 145 cases (13%). However, only 59 cases were considered noncompliant according to criterion II-1. Indeed, in the management of conjunctivitis-otitis syndrome caused by *Haemophilus influenza,* giving amoxicillin/clavulanic acid as a first-line treatment is recommended.[44] This antibiotic is

also privileged for acute maxillary sinusitis and frontal, ethmoidal and sphenoid sinusitis.[43] Amoxicillin was used in 77% of cases of AOM, at a higher rate than that observed in a national study in 2012 (66%). This result shows that the French recommendation for this course of action in 2011, in order to reduce the rate of bacteria resistance, has had a strong impact.[43,45] Eardrops are considered inappropriate in cases of AOM without other symptoms. For chronic otitis with otorrhea, perforation of the eardrum or, antibiotic eardrops are recommended.[46,47] This application showed that some of our criteria need to be more detailed, in order to avoid mis-detection of PIM. Prevalence of beta2 agonists or corticosteroids in an infant's first case of bronchiolitis is 6.4% (25/386 cases), lower than that observed in a study of another French area in 2012 (41%).[48–50]

A high frequency of prescription of antibiotics, corticosteroids or nasal antiseptic medication was detected in case of nasopharyngitis, although there is no evidence for this.[51] Antiseptics such as tenoate ethanolamine did not receive a favorable opinion from the ANSM (French National Agency for Medicines and Health Products Safety) because they exposed patients to potential nasal irritation and occasionally to serious allergies.[52] Even so, it was frequently present in prescriptions from outpatient care. Unnecessary exposure to cough suppressants, pholcodine, nasal or oral decongestants was also observed frequently in this sector.[52]

Less PIM were found in dermatological disorders. In the management of scabies, we had removed the criterion on Ascabiol® (Sulfirame and Benzyl Benzoate) as it was out of stock since 2012.

In comparison to PIM, the rate of PPO observed was lower and centred on specific disorders. In the management of diarrhea caused by gastroenteritis, in hospital, our study found that it was common to omit prescription of an oral rehydration solution (ORS): 14% (237/1643 case). Even so, this rate is lower than that found in another national study in 2007 (29%).[53]

It could be that the recommendation of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in 2008 has had a positive impact.[37,39] Thus, this criterion serves not only to highlight the importance of ORS for the prescriber but also helps to increase the frequency of pharmaceutical recommendation of this drug. Another common omission was identified in the prescription of oral liquid formulation. A precise dosage of oral amoxicillin is necessary because many errors occurred when using the dosing spoon.[54] In 62/63 cases, oral acyclovir was not prescribed for herpetic gingivostomatitis. In daily practice, this occurred because a blood test to screen for the primary infection is not performed . However, the oral treatment can prevent recurrences, which cannot be attained by using cream.[55] Once again, the role of the community pharmacist is significant in detecting the omission, intervening or providing education to the patient when necessary.

As estimated, the child aged between 0 and 12 years has the highest risk of presenting with a PIM, according to a multivariate analysis. No inappropriate prescription or omission were detected for patient aged less 28 days. Certainly, this age group is most frequently affected by respiratory diseases and is thus exposed to many unnecessary prescriptions such as cough suppressants or decongestant drugs. As we know, they are also affected by off-label drug prescriptions, which is consistent with reports from other sources.[56,57] Once again, our study highlights the importance of appropriate prescription in this age group. As with geriatrics, an increase in numbers of medications can be associated with PIM.[34] Prescriptions issued from hospitals elicit fewer IP than those issued by the community. The main reason for this is that many drugs are not available in this hospital, such as cough suppressants, Rhinotrophyl® (tenoate ethanolamine), domperidone, etc. This shows that many PIM are preventable in a hospital setting. An efficient method for prevention of PIM could be to focus on the prescribing habits of physicians and thus have an impact on the selection of drugs, thereby reducing the rate of PIM.

Our study has several limitations. Firstly, it is a retrospective and monocentric study. Our result in the hospital could be underestimated. In addition, several criteria could not be analyzed due to the large number of prescriptions (for example, those for fever or pain which are associated with many diseases) or absence of a specific pathology (mosquitos, lice, hyperactivity etc.). Antibiotic prophylaxis, vitamin supplements, proposition of vaccination etc. can be analyzed in prospective studies. A lack of clinical information is the main limitation in detection in a community setting. This also constitutes a challenge for pharmaceutical care review in elderly patients.[58] However, a certain amount of PIM were identified using POPI. Our study showed that there are many criteria which could be detected without access to clinical information and are easy to identify. Moreover, community pharmacists, in their practice, can extrapolate diagnoses from their experience, from common indications or by interviewing their patient.

This is the first study which permits to evaluate prevalence of PIM and PPO in pediatrics prescription. Hereafter, in order to prove the effectiveness of this tool (decrease of PIM and PPO), further investigations must be carried out on a larger scale, both in hospital and in community care. In the next few years, a stepped wedge randomized cluster multicenter study will be conducted to prove if POPI decreases number of PIM and PPO. It is also necessary to evaluate the impact of this tool on reducing adverse drugs events, both in consultation or upon hospitalization. The impact of pharmacists in providing appropriate prescriptions should be also evaluated. Subsequently, this tool may be proposed to several professional societies such as the French Society for Pediatricians and the French Society of Clinical Pharmacy to make its use more widespread. The tool should be regularly updated to reflect recent events and to specify certain criteria.

To facilitate its use, this tool can be presented as a mobile app, a small handbook or be installed into prescription software. In summary, we hope that POPI could be a practical option used to reduce medication errors and to improve the suitability of prescriptions. It provides rapid detection of PIM and PPO and can also open up a discussion on the relationship between the doctor and the pharmacist to remedy the issue at hand.[59]

CONCLUSION

Our study was carried out in in two sectors, hospital and community, and provides a global view of PIM and PPO in pediatric patients. It highlights the potential role of POPI tools in improving prescription quality in various sectors. POPI should be applied in different services to deepen and reinforce its utilization. A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice.

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ETHICS

This project was approved by the local research ethics committee (n°2015/218).

DISCLOSURE OF INTEREST

None Declared

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AUTHOR'S CONTRIBUTION

Sonia Prot-Labarthe, Aurore Berthe-Aucejo conceptualised and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Rym Boulkedid and HPK Nguyen carried out analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Xavier Bellettre, Thomas Weil, Olivier Bourdon reviewed and revised the manuscript and approved the final manuscript as submitted.

François Angoulvant and Patrick Albaret supplied data from hospital and community pharmacy and reviewed and revised the manuscript and approved the final manuscript as submitted.

DATA SHARING STATEMENT

We have no additional unpublished data

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Figure 1. Flow chart indicating the course of the study

* Prescriptions with only one medical device, dietary supplement or hygiene product, ED: Emergency department

Figure 2. Distribution of number of prescriptions according to age category in hospital and community settings

Figure 3. Comparison of PIMs detected in hospital and in outpatient care

Figure 4. Total prescription and PIMs in both hospital and outpatient care: Percentage distribution by age group

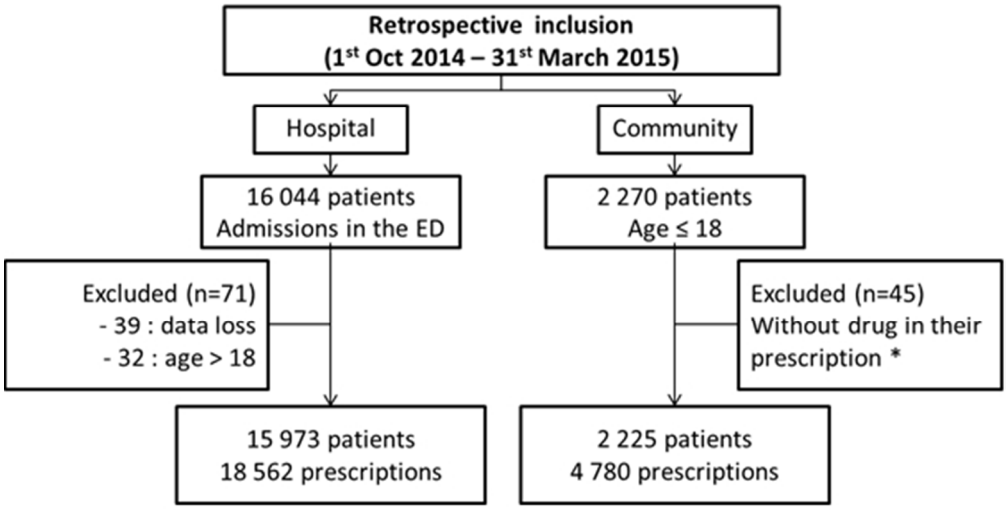

Figure 1. Flow chart indicating the course of the study† * Prescriptions with only one medical device, dietary supplement or hygiene product, ED: Emergency department

51x27mm (300 x 300 DPI)

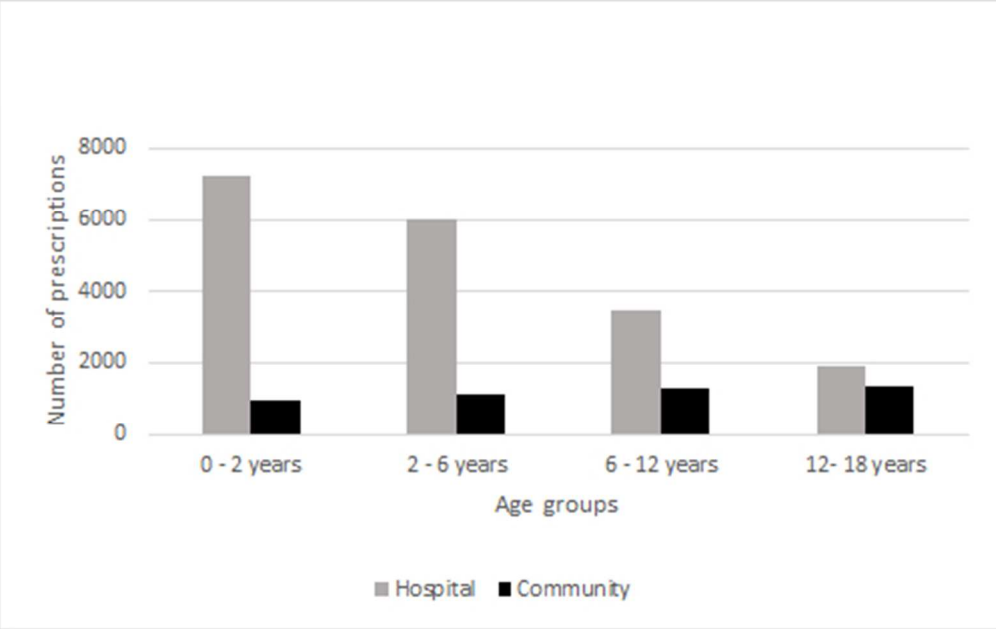

Figure 2. Distribution of number of prescriptions according to age category in hospital and community settings

42x26mm (300 x 300 DPI)

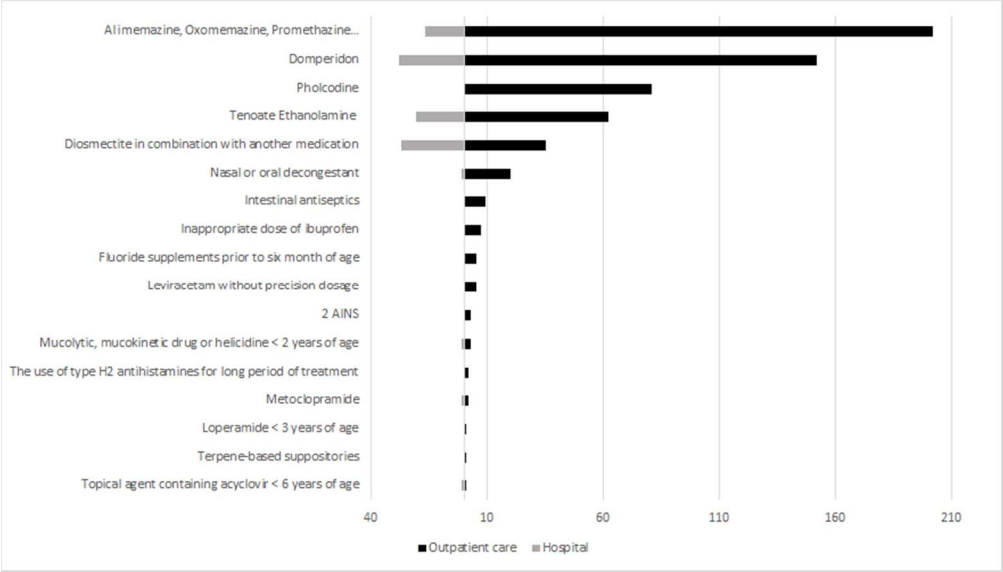

Figure 3. Comparison of PIMs detected in hospital and in outpatient care

74x42mm (300 x 300 DPI)

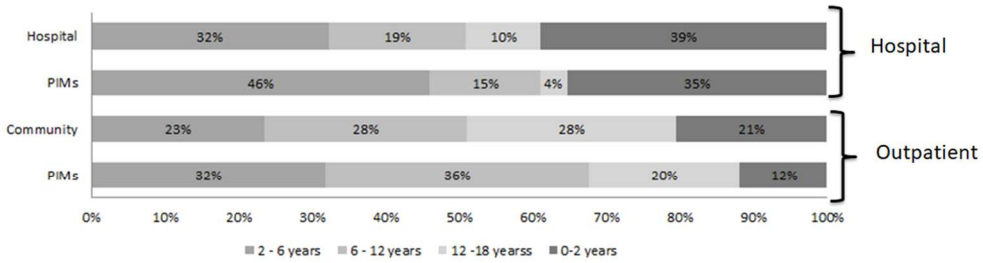

Figure 4. Total prescription and PIMs in both hospital and outpatient care: Percentage distribution by age group

90x23mm (300 x 300 DPI)

Appendix 1. POPI - Pediatrics: Omission of Prescriptions & Inappropriate prescriptions

DIVERSE ILLNESSES

A- PAIN AND FEVER

Inappropriate prescriptions	Omissions
AI-1. Prescription of two alternating antipyretics as a first-line treatment. *	**A0-1.** Failure to give sugar solution to new-born babies and infants under four months old two minutes prior to venipuncture.
AI-2. Prescription of a medication other than paracetamol as a first line treatment (except in the case of migraine).	**A0-2.** Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours.
AI-3. Rectal administration of paracetamol as a first-line treatment.	
AI-4. The combined use of two NSAIDs. * ◦	
AI-5. Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (other than Advil ®). ◦	
AI-6. Opiates to treat migraine attacks. *	

B- URINARY INFECTIONS

Inappropriate prescriptions

BI-1. Nitrofurantoin used as a prophylactic. *

BI-2. Nitrofurantoin used as a curative agent in children under six years of age, or indeed any other antibiotic if avoidable. *

BI-3. Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy). *

BI-4. Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy). *

C- VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS

Inappropriate prescriptions	Omissions
CI-1. Fluoride supplements prior to six months of age. ◦*	**CO-1.** Insufficient intake of vitamin D. Minimum vitamin D intake: ▪ Breastfed baby = 1 000 to 1 200 IU/day ▪ Infant < 18 months of age (milk enriched in vitamin D) = 600 to 800 IU/day ▪ Child aged between 18 months and five years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80 000 to 100 000 IU/day in winter (adolescents can take this dose in one go). **CO-2.** Antibiotic prophylaxis with phenoxymethylpenicillin (Oracilline) starting from two months of age and lasting until five years of age for children with sickle-cell anemia: 100 000 IU/kg/day (in two doses) for children weighing 10kg or less and 50 000 IU/kg/day for children weighing over 10kg (also in two doses). *

D- MOSQUITOS

Inappropriate prescriptions	Omissions
DI-1. The use of skin repellents in infants less than six months old and picardin in children less than 24 months old.	**DO-1. DEET** ‘‘30%’’ (max) before 12 years old ‘‘50%’’ (max) after 12 years old.
DI-2. Citronella (lemon grass) oil (essential oil).	**DO-2. IR3535** ‘‘20%’’ (max) before 24 months old ‘‘35%’’ (max) after 24 months old.
DI-3. Anti-insect bracelets to protect against mosquitos and ticks.	**DO-3.** Mosquito nets and clothes treated with pyrethroids.
DI-4. Ultrasonic pest control devices, vitamin B1, homeopathy, electric bug zappers, sticky tapes without insecticide.	

DIGESTIVE PROBLEMS

E- NAUSEA, VOMITTING, OR GASTROESOPHAGEAL REFLUX

Inappropriate prescriptions	Omissions
EI-1. Metoclopramide. * °	**EO-1.** Oral rehydration solution in the event of vomiting.*
EI-2. Domperidone. * °	
EI-3. Gastric antisecretory drugs to treat gastroesophageal reflux, dyspepsia, the crying of new-born babies (in the absence of any other signs or symptoms), as well as faintness in infants. *	
EI-4. The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors. *	
EI-5. Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube). *	
EI-6. The use of type H2 antihistamines for long periods of treatment. * °	
EI-7. Erythromycin as a prokinetic agent. *	
EI-8. The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting. *	

F- DIARRHEA

Inappropriate prescriptions	Omissions
FI-1. Loperamide before 3 years of age.*°	**FO-1.** Oral rehydration solution in the event of diarrhea.*
FI-2. Loperamide in the case of invasive diarrhea.*	
FI-3. The use of Diosmectite (Smecta®) in combination with another medication.*°	
FI-4. The use of Saccharomyces boulardii (Ultralevure) in powder form, or in a capsule that has to be opened prior to ingestion, to treat patients with a central venous catheter or an immunodeficiency.*	
FI-5. Intestinal antiseptics.*°	

ENT-PULMONARY PROBLEMS

G- COUGH

Inappropriate prescriptions	Omissions
GI-1. Pholcodine. * °	**GO-1.** Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family and entourage of expectant parents (parents, grand-parents, nannies/child minders).
GI-2. Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age. * °	
GI-3. Alimemazine (Theralene®), oxomemazine (Toplexil®), promethazine (Phenergan®), and other types. * °	
GI-4. Terpene-based suppositories. * °	

H- BRONCHIOLITIS IN INFANTS

Inappropriate prescriptions	Omissions
HI-1. Beta2 agonists, corticosteroids to treat an infant's first case of bronchiolitis. *	**HO-1.** 0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer). *
HI-2. H1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis. *	**HO-2.** Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities.
HI-3. Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.). *	

DERMATOLOGICAL PROBLEMS

I- ENT INFECTIONS

Inappropriate prescriptions	Omissions
II-1. An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for an pneumoncoccal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day.*	**IO-1.** Doses in mg for drinkable (solutions of) amoxicillin or josamycin. *◦
II-2. Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children more than three years old.*	**IO-2.** Paracetamol combined with antibiotic treatment for ear infections to relieve pain. *
II-3. Antibiotics for nasopharyngitis, congestive otitis, sore throat before three years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, after two years of age.*	
II-4. Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months.*	
II-5. Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat.*	
II-6. Nasal or oral decongestant (oxymetazoline (Aturgyl®), pseudoephedrine (Sudafed®), naphazoline (Derinox®), ephedrine (Rhinamide®), tuaminoheptane (Rhinofluimicil®), phenylephrine (Humoxal®)).*◦	
II-7. H1-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor; inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age.* ◦	
II-8. Ethanolamine tenoate (Rhinotrophyl®) and other nasal antiseptics.* ◦	
II-9. Ear drops in the case of acute otitis media.*	

J- ASTHMA

Inappropriate prescriptions	Omissions
JI-1. Ketotifen and other H1-antagonists, sodium cromoglycate. *	**JO-1.** Asthma inhaler appropriate for the child's age.
JI-2. Cough suppressants. *	**JO-2.** Preventative treatment (inhaled corticosteroids) in the case of persistent asthma. *

K-ACNE VULGARIS

Inappropriate prescriptions	Omissions
KI-1. Minocycline.* ◦	**KO-1.** Contraception (provided with a logbook/diary) for menstruating girls taking isotretinoin.
KI-2. Isotretinoin in combination with a member of the tetracycline family of antibiotics.* ◦	**KO-2.** Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy. *
KI-3. The combined use of an oral and a local antibiotic.*	
KI-4. Oral or local antibiotics as a monotherapy (not in combination with another drug).*	
KI-5. Cyproterone+ethinylestradiol (Diane 35®) as a contraceptive to allow isotretinoin per os.* ◦	
KI-6. Androgenic progestins (levonorgestrel, norgestrel, norethisterone, lynestrenol, dienogest, contraceptive implants or vaginal rings).*	

L- SCABIES

Omissions

LO-1. A second dose of ivermectin two weeks after the first. *

LO-2. Decontamination of household linen and clothes and treatment for other family members.

M- LICE

Inappropriate prescriptions

MI-1. The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnea.

N- RINGWORM

Inappropriate prescriptions

NI-1. Treatment other than griseofulvin for Microsporum. *

Omissions

NO-1. Topical treatment combined with an orally-administered treatment. *

NO-2. Griseofulvin taken during a meal containing a moderate amount of fat. * ◦

O-IMPETIGO

Inappropriate prescriptions

OI-1. The combination of locally applied and orally administered antibiotic.*

OI-2. Fewer than two applications per day for topical antibiotics.*

OI-3. Any antibiotic other than mupirocin as a first-line treatment (except in cases of hypersensitivity to mupirocin).*

P- HERPES SIMPLEX

Inappropriate prescriptions

PI-1. Topical agents containing corticosteroids. *

PI-2. Topical agents containing acyclovir before six years of age. * ◦

Omissions

PO-1. Paracetamol during an outbreak of herpes. *

PO-2. Orally administered acyclovir to treat primary herpetic gingivostomatitis. *

Q-DERMATITE ATOPIQUE

Inappropriate prescriptions

QI-1. A strong dermocorticoid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate Diprosone) applied to the face, the armpits or groin, and the backside of babies or young children. *

More than one application per day of a dermocorticoid, except in cases of severe lichenification. *

QI-2. Local or systemic antihistamine during the treatment of outbreaks. *

QI-3. Topically applied 0.03% tacrolimus before two years of age. *◦

Topically applied 0.1% tacrolimus before 16 years of age.

QI-4. Oral corticosteroids to treat outbreaks. *

NEUROPSYCHIATRIC DISORDERS

R- EPILEPSY

Inappropriate prescriptions

RI-1. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy. *

RI-2. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabaline, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy). *

RI-3. Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL. * ◦

S-DEPRESSION

Inappropriate prescriptions

SI-1. An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy). *

SI-2. Tricyclic antidepressants to treat depression. *

T- NOCTURNAL ENURESIS

Inappropriate prescriptions

TI-1.	Desmopressin administered by a nasal spray. * ◦ Desmopressin in the case of daytime symptoms.
TI-2.	An anticholinergic agent used as a monotherapy in the absence of daytime symptoms. *
TI-3.	Tricyclic agents in combination with anticholinergic agents. * ◦
TI-4.	Tricyclic agents as a first-line treatment. *
U- ANOREXIA	
Inappropriate prescriptions	
UI-1.	Cyproheptadine (Periactin®), clonidine * ◦
V- ATTENTION DEFICIT DISORDER WITH OR WITHOUT HYPERACTIVITY	
Inappropriate prescriptions	**Omissions**
VI-1. Pharmacological treatment before age six (before school), except in severe cases. *	VO-1. Recording a growth chart (height and weight) if the patient is taking methylphenidate. *
VI-2. Antipsychotic drugs to treat attention deficit disorder without hyperactivity. *	
VI-3. Slow release methylphenidate as two doses per day, rather than only one dose. *◦	

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Done
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Done
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Done
Objectives	3	State specific objectives, including any prespecified hypotheses	Done
Methods			
Study design	4	Present key elements of study design early in the paper	Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Done NA
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Done
Bias	9	Describe any efforts to address potential sources of bias	Done
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Done
		(*b*) Describe any methods used to examine subgroups and interactions	Done
		(*c*) Explain how missing data were addressed	Done
		(*d*) If applicable, explain how loss to follow-up was addressed	Done
		(*e*) Describe any sensitivity analyses	Done
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Done
		(b) Give reasons for non-participation at each stage	Done
		(c) Consider use of a flow diagram	Done
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Done
		(b) Indicate number of participants with missing data for each variable of interest	Done
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	NA

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	Done
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Done

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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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.

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	General practice / Family practice
Keywords:	inappropriate prescription, omission, tool, detection

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.

A. Berthe-Aucejo[1,2], H.P.K Nguyen[1], F. Angoulvant[2,3], X. Bellettre[4], P. Albaret[5,6], T. Weil[1], R. Boulkedid[2,7,8], O. Bourdon[1,6,9,10], S.Prot-Labarthe[1,2,10]

[1] Department of Pharmacy, Robert-Debré Hospital, Paris, France

[2] UMR-S1123, ECEVE; Inserm U1123, Paris, France

[3] Emergency unit, Necker Hospital, Paris, France

[4] Emergency unit AP-HP, Robert-Debré Hospital, Paris, France

[5] Albaret Pharmacy, Cesson, France

[6] Clinical Pharmacy, Paris Descartes University, Paris, France

[7] Assistance publique-Hôpitaux de Paris, Hôpital Robert Debré, Clinical Epidemiology Unit, 75 019 Paris, France

[8] CIC-EC 1426, 75019 Paris, France

[9] Laboratoire Educations et Pratiques de Santé, Paris XIII University, Bobigny, France

[10] Groupe Pédiatrie de la Société Française de Pharmacie Clinique, Paris, France

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Corresponding author

Dr Aurore Berthe-Aucejo, Service Pharmacie, AP-HP Hôpital Robert-Debré, 48 Boulevard Sérurier, 75019 Paris, Fax: 01-40-03-24-81, Tel: 01-40-03-57-41, Email: aurore.berthe@aphp.fr

Keywords

Inappropriate prescription, omission, tool, detection

ABSTRACT

Background and Objective: POPI **(**Pediatrics: Omission of Prescription and Inappropriate prescription) is the first tool of detection for potentially inappropriate medicines (PIM) and potentially prescribing omissions (PPO) in pediatrics. The aim of this study was to evaluate the prevalence of PIM and PPO detected by POPI regarding issuing of prescription in hospital and outpatient care. The second objective is to determine the risk factors related to PIM.

Design: A retrospective and descriptive study was conducted in the emergency department (ED) and community pharmacy (CP) during 6 months. POPI was used to identify PIM and PPO.

Setting: Robert-Debré Hospital (AP-HP, France) and Albaret community pharmacy (Seine and Marne).

Participants: Inclusion criteria included patients who were under 18 years old and who had one medicine prescription. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients.

Primary and secondary outcome measures: PIM and PPO rate, PIM risk factors

Results: At ED, 18,562 prescriptions for 15,973 patients and 4,780 prescriptions for 2,225 patients at the CP were analyzed. The PIM rate and PPO rate were respectively 3.3% and 2.6% at the ED and 26.4% and 13.2% at the CP. Respiratory and digestive diseases had the highest rate of PIM. Multivariate logistic regression model showed that prescriptions from community pharmacy were significantly associated with a higher risk of PIM. This study has enable us to describe PIMs or PPOs within a hospital and a community pharmacy. POPI could be used to improve medication use and patient care and to limit hospitalization and adverse drug reaction.

Conclusion: This is the first study to assess the prevalence of PIM and PPO detecting by POPI in a pediatric population. A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice.

Strengths and limitations of this study

- This study is the first to observe the prevalence of PIM and PPO in a pediatric population.

- It is a retrospective and monocentric study. The prevalence of PIM and PPO may be underestimated (large number of prescriptions, absence of specific pathology). Some criteria could be analyzed only in a prospective study. A lack of clinical information is the main limitation in detection in a community setting.

- Many omissions and inappropriate prescriptions can be easily detected with POPI despite limited clinical information.

INTRODUCTION

Inappropriate prescribing is a known preventable cause of adverse drug events (ADE) and has an important impact on public health and cost of care. [1,2] In the literature, ADE is defined by "an injury resulting from medical intervention related to a drug" (dose error, adverse drug reaction (ADR), misuse of medication such as antibiotics).[3–5] In the pediatric population, ADR during hospitalization was estimated between 0.6% and 33.7% and between 1% and 1.5% for outpatients.[6–9] Incidence of ADR leading to admission was evaluated between 1.8% and 17.7%.[6,7,10] Many drugs were concerned in commonly used medication.[11–13]

The World Health Organization estimated that 50% of medications are prescribed and used inappropriately.[14] The most recent definition of inappropriate prescription (IP) encompasses potentially inappropriate medicines (PIM) and prescribing omissions (PPO).[15] In a report from the French National Authority for Health, PIMs are defined as "drugs being used in a situation in which the risks involved in treatment potentially outweigh the benefits, lack of demonstrated indication, high risk of ADE, and an unfavorable cost-effect or risk-benefit ratio exists". PPO or underuse of appropriate medication is defined as the absence of initiation of an effective treatment in subjects with a condition for which one or several drug classes have demonstrated their efficacy. In an elderly population, which presents with age-related physiological changes and high prevalence of polypharmacy, various measures have been developed to detect PIM such as: Beers' criteria, the Inappropriate Prescribing in the Elderly Tool, The Medication Appropriate Index, and STOPP/START (Screening Tool of Older Person's prescriptions/Screening Tool to Alert doctor to Right Treatment).[16–21]

Only the STOPP/START enables us to detect under-prescribing.[15] Using these tools, many studies have been carried out which have detected that inappropriate prescriptions are issued to between 35% and 51% of this population.[22–26]

Omission prescriptions in geriatric population detected by START tool concerned between 58%-61% of patients.[27,28] Negative outcomes related to an IP such as side effects, hospitalization, mortality and utilization of resources were also demonstrated.[21,29–31]

Prescribing in a pediatric population is always a challenge for physician. It is often empirical and primarily based on safety and pharmacology information obtained in adults.[32] This is a worry not only in a hospital or general practitioner setting but also for the community pharmacists. They may only be able to check information and resources or even dispense infrequently for this vulnerable population.[33] ADRs were three time higher in the pediatric population. This frequency was explained by the vulnerability of young people, pharmacokinetic changes during childhood and pediatric off-label drug used.[4,34] Large differences relating to treatment were seen within and between the countries.[6,35] Question about rational of prescription could be asked.[36] Optimizing children's care is based on rational prescribing and allowing a decrease in side effects.[35,36] In order to improve the correct drug use and optimize practice, the first tool of detection for PIM and PPO was created by Prot-Labarthe *et al.* in 2013. The tool was named POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions) (Appendix1).[37,38] Presently, the complete tool has not been tested in actual practice and the prevalence of PIM and OP is not known.

Our aim is to assess the prevalence of PIM and PPO detected using POPI in hospital and outpatient care. This was its first application, regarding issuing of prescriptions in the emergency department and the community pharmacy. The second objective is to determine the risk factors related to PIM.

METHODS

Population

A retrospective and descriptive study was conducted in the emergency department (ED) of AP-HP Robert-Debré hospital (Paris) - the largest French pediatric hospital - and the Albaret community pharmacy (CP) (Seine and Marne). Inclusion criteria included patients who were under 18 years old and who had one or more medicine prescriptions between 1st October 2014 and 31st March 2015. Prescription was defined as one or more lines of drugs prescribed by a physician. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients. POPI contains 102 criteria (76 PIMs, 25 PPO). 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). Criteria were validated by 2-round-Delphi consensus technique.[38]

Data collection

The prescriptions given on leaving the hospital emergency department were extracted from the Urqual software V5® (*) (McKesson Corp, Paris, France). Urqual® is an emergency prescription software which is used in many French hospitals. Patient information including age, sex, weight, medicine prescription and current diagnosis was collected. Medical histories and clinical examinations were consulted individually when necessary. Due to the significant amount of data, clinical files of ED were analyzed, based on primary diagnosis. For this study, 82/102 criteria were analyzed (Table 1). Some criteria could not be used for a hospital setting.

The data extracted from Urqual software give only one line per patient with one diagnosis and the first drug prescribed. Once extracted, the prescription was then analyzed as a whole.

Consequently, the number of medications per prescription was not included. However, all prescriptions have been manually reviewed. For each targeted disorder, the prescription was analyzed to detect PIMs or PPOs.

Table 1. POPI - Pediatrics: Omission of Prescriptions & Inappropriate prescriptions

DIVERSE ILLNESSES	**A- PAIN AND FEVER**	
	Inappropriate prescriptions	**Omissions**
	AI-1. Prescription of two alternating antipyretics as a first-line treatment. **AI-2.** Prescription of a medication other than paracetamol as a first line treatment (except in the case of migraine). **AI-3.** Rectal administration of paracetamol as a first-line treatment. **AI-4.** The combined use of two NSAIDs. * ◦ **AI-5.** Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (other than Advil ®). ◦ **AI-6.** Opiates to treat migraine attacks. *	**A0-1.** Failure to give sugar solution to new-born babies and infants under four months old two minutes prior to venipuncture. **A0-2.** Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours.
	B- URINARY INFECTIONS	
	Inappropriate prescriptions	
	BI-1. Nitrofurantoin used as a prophylactic. * **BI-2.** Nitrofurantoin used as a curative agent in children under six years of age, or indeed any other antibiotic if avoidable. * **BI-3.** Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy). * **BI-4.** Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy). *	
	C- VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS	

	Inappropriate prescriptions	Omissions
	CI-1. Fluoride supplements prior to six months of age. ◦*	CO-1. Insufficient intake of vitamin D. Minimum vitamin D intake: ▪ Breastfed baby = 1,000 to 1,200 IU/day ▪ Infant < 18 months of age (milk enriched with vitamin D) = 600 to 800 IU/day ▪ Child aged between 18 months and five years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80,000 to 100,000 IU/day in winter (adolescents can take this as one dose). CO-2. Antibiotic prophylaxis with phenoxymethylpenicillin (Oracilline) starting from two months of age and lasting until five years of age for children with sickle-cell anemia: 100,000 IU/kg/day (in two doses) for children weighing 10kg or less and 50,000 IU/kg/day for children weighing over 10kg (also in two doses). *
	D- MOSQUITOS	
	Inappropriate prescriptions	**Omissions**
	DI-1. The use of skin repellents in infants less than six months old and picardin in children less than 24 months old. DI-2. Citronella (lemon grass) oil (essential oil). DI-3. Anti-insect bracelets to protect against mosquitos and ticks. DI-4. Ultrasonic pest control devices, vitamin B1, homeopathy, electric bug zappers, sticky tapes without insecticide.	DO-1. **DEET** ‘‘30%’’ (max) before 12 years old ‘‘50%’’ (max) after 12 years old. DO-2. **IR3535** ‘‘20%’’ (max) before 24 months old ‘‘35%’’ (max) after 24 months old. DO-3. Mosquito nets and clothes treated with pyrethroids.
PROBLEMS	**E- NAUSEA, VOMITTING, OR GASTROESOPHAGEAL REFLUX**	
	Inappropriate prescriptions	**Omissions**
	EI-1. Metoclopramide. * ◦ EI-2. Domperidone. * ◦ EI-3. Gastric antisecretory drugs to treat gastroesophageal reflux, dyspepsia, the crying of new-born babies (in the absence of	EO-1. Oral rehydration solution in the event of vomiting.*

	any other signs or symptoms), as well as faintness in infants. *	
	EI-4. The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors. *	
	EI-5. Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube). *	
	EI-6. The use of type H2 antihistamines for long periods of treatment. * ◦	
	EI-7. Erythromycin as a prokinetic agent. *	
	EI-8. The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting. *	
	F- DIARRHEA	
	Inappropriate prescriptions	**Omissions**
	FI-1. Loperamide before 3 years of age.*°	**FO-1.** Oral rehydration solution in the event of diarrhea.*
	FI-2. Loperamide in the case of invasive diarrhea.*	
	FI-3. The use of Diosmectite (Smecta®) in combination with another medication.*°	
	FI-4. The use of Saccharomyces boulardii (Ultralevure) in powder form, or in a capsule that has to be opened prior to ingestion, to treat patients with a central venous catheter or an immunodeficiency.*	
	FI-5. Intestinal antiseptics.*°	
ENT-PULMONARY PROBLEMS	**G- COUGH**	
	Inappropriate prescriptions	**Omissions**
	GI-1. Pholcodine. * ◦	**GO-1.** Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family of expectant parents and those in contact with them (parents, grand-parents, nannies/child minders).
	GI-2. Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age. * ◦	
	GI-3. Alimemazine (Theralene®), oxomemazine (Toplexil®), promethazine (Phenergan®), and other types. * ◦	
	GI-4. Terpene-based suppositories. * ◦	
	H- BRONCHIOLITIS IN INFANTS	

Inappropriate prescriptions	Omissions
HI-1. Beta2 agonists, corticosteroids to treat an infant's first case of bronchiolitis. *	**HO-1.** 0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer). *
HI-2. H1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis. *	**HO-2.** Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities.
HI-3. Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.). *	

I- ENT INFECTIONS

Inappropriate prescriptions	Omissions
II-1. An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for an pneumococcal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day.*	**IO-1.** Doses in mg for drinkable (solutions of) amoxicillin or josamycin. *◦
II-2. Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children more than three years old.*	**IO-2.** Paracetamol combined with antibiotic treatment for ear infections to relieve pain. *
II-3. Antibiotics for nasopharyngitis, congestive otitis, sore throat before three years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, after two years of age.*	
II-4. Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months.*	
II-5. Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat.*	
II-6. Nasal or oral decongestant (oxymetazoline	

(Aturgyl®), pseudoephedrine (Sudafed®), naphazoline (Derinox®), ephedrine (Rhinamide®), tuaminoheptane (Rhinofluimicil®), phenylephrine (Humoxal®)).*◦

II-7. H1-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor; inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age.* ◦

II-8. Ethanolamine tenoate (Rhinotrophyl®) and other nasal antiseptics.* °

II-9. Ear drops in the case of acute otitis media.*

J- ASTHMA

Inappropriate prescriptions	Omissions
JI-1. Ketotifen and other H1-antagonists, sodium cromoglycate. *	**JO-1.** Asthma inhaler appropriate for the child's age.
JI-2. Cough suppressants. *	**JO-2.** Preventative treatment (inhaled corticosteroids) in the case of persistent asthma. *

DERMATOLOGICAL PROBLEMS

K-ACNE VULGARIS

Inappropriate prescriptions	Omissions
KI-1. Minocycline.* °	**KO-1.** Contraception (provided with a logbook/diary) for menstruating girls taking isotretinoin.
KI-2. Isotretinoin in combination with a member of the tetracycline family of antibiotics.* °	**KO-2.** Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy. *
KI-3. The combined use of an oral and a local antibiotic.*	
KI-4. Oral or local antibiotics as a monotherapy (not in combination with another drug).*	
KI-5. Cyproterone+ethinylestradiol (Diane 35®) as a contraceptive to allow isotretinoin per os.* °	
KI-6. Androgenic progestins (levonorgestrel, norgestrel, norethisterone, lynestrenol, dienogest, contraceptive implants or vaginal rings).*	

L- SCABIES

Omissions

LO-1. A second dose of ivermectin two weeks after the first. *
LO-2. Decontamination of household linen and clothes and treatment for other family members.

M- LICE

Inappropriate prescriptions

MI-1. The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnea.

N- RINGWORM

Inappropriate prescriptions

NI-1. Treatment other than griseofulvin for Microsporum. *

Omissions

NO-1. Topical treatment combined with an orally-administered treatment. *
NO-2. Griseofulvin taken during a meal containing a moderate amount of fat. * ◦

O-IMPETIGO

Inappropriate prescriptions

OI-1. The combination of locally applied and orally administered antibiotics.*
OI-2. Fewer than two applications per day for topical antibiotics.*
OI-3. Any antibiotic other than mupirocin as a first-line treatment (except in cases of hypersensitivity to mupirocin).*

P- HERPES SIMPLEX

Inappropriate prescriptions

PI-1. Topical agents containing corticosteroids. *
PI-2. Topical agents containing acyclovir before six years of age. * ◦

Omissions

PO-1. Paracetamol during an outbreak of herpes. *
PO-2. Orally administered acyclovir to treat primary herpetic gingivostomatitis. *

NEUROPSYCHIATRIC DISORDERS

Q-ATOPIC DERMATITIS

Inappropriate prescriptions

QI-1. A strong topic steroid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate Diprosone) applied to the face, armpits or groin, and to the backside of babies or young children. *
More than one application per day of a topical steroid, except in cases of severe lichenification. *
QI-2. Local or systemic antihistamine during the treatment of outbreaks. *
QI-3. Topically applied 0.03% tacrolimus before two years of age. *◦
Topically applied 0.1% tacrolimus before 16 years of age.
QI-4. Oral corticosteroids to treat outbreaks. *

R- EPILEPSY

Inappropriate prescriptions

RI-1. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy. *
RI-2. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabaline, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy). *
RI-3. Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL. * ◦

S-DEPRESSION

Inappropriate prescriptions

SI-1. An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy). *
SI-2. Tricyclic antidepressants to treat depression. *

T- NOCTURNAL ENURESIS

Inappropriate prescriptions

TI-1. Desmopressin administered by a nasal spray. * ◦

	Desmopressin in the case of daytime symptoms.
TI-2.	An anticholinergic agent used as a monotherapy in the absence of daytime symptoms. *
TI-3.	Tricyclic agents in combination with anticholinergic agents. * ◦
TI-4.	Tricyclic agents as a first-line treatment. *
U- ANOREXIA	
Inappropriate prescriptions	
UI-1.	Cyproheptadine (Periactin®), clonidine * ◦
V- ATTENTION DEFICIT DISORDER WITH OR WITHOUT HYPERACTIVITY	
Inappropriate prescriptions	**Omissions**
VI-1. Pharmacological treatment before age six (before school), except in severe cases. *	**VO-1.** Recording a growth chart (height and weight) if the patient is taking methylphenidate. *
VI-2. Antipsychotic drugs to treat attention deficit disorder without hyperactivity. *	
VI-3. Slow release methylphenidate as two doses per day, rather than only one dose. *◦	

* Criteria analyzed in emergency department

◦ Criteria analyzed in community pharmacy

Data from the community pharmacy were obtained from the pharmacy management software OPUS® (Computer PG, France). Patient's age and drugs prescribed were collected. Current diagnosis and sex were not available, in the OPUS software, so the number of patients per pathology and the number of prescriptions per pathology were missed. Only drugs that did not require assessment of diagnosis (for example domperidone, metoclopramide etc.) were analyzed (Table 1) (28 criteria/102).

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.

Pathologies analyzed by POPI were the same in emergency department and in community.

Statistical analysis

Data were presented as continuous variables (age, number of prescriptions by patient, number of medications per prescription) and were presented as median and interquartile range (25th-75th percentiles) or mean (standard deviation), minimum and maximum depending on normal distribution.

Mixed effects logistic regression modelling for repeated measurements was applied to identify factors associated with PIM (yes/no) in the hospital and community settings. PIM was identified by prescription, even if the prescription contained several medications.

Univariate models were performed using different candidate factors as:

- For model performed with hospital data: sex and age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years);
- For model performed with community data: age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years) and number of medications per prescription;
- For model performed with hospital and community data: Age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years) and setting of prescription (hospital or community setting)

The model was constructed using the parameters of the univariate analysis, which showed at least a trend toward significance, with a cut-off of p=0.2.. Odds ratios (OR) with 95%

confidence intervals (CI) were estimated. Statistical significance was established at $p<0.05$. SPSS-22® software (SPSS Inc., Chicago, IL, USA) and SAS 9.4 were used for analysis.

This project was approved by the local research ethics committee (n°2015/218).

RESULTS

In the emergency department, 18,562 prescriptions for 15,973 patients consulted were analyzed. Among them, 29% had at least two visits in 6 months. In the community pharmacy, 4,780 prescriptions for 2,225 patients were evaluated (Figure 1). In ED and CP, 53% of patients had been issued with one prescription, 21% with two and 26% with three or more prescriptions. The population's characteristics and the frequency of pathologies were presented in Table2. Distribution of number of prescriptions by age category was described in the figure 2.

Table 2. Characteristics of the study population

Population characteristics	Hospital (N=15,973)	Community (N=2,225)
Age (years) mean (SD) Min, Max	4.9 (4.5) 0-18	7.9 (5.3) 0-18
Female gender N(%)	8,769 (54.9)	NA
Number of prescriptions/patient mean (SD) Min, Max	1.4 (0.9) 1-12	2.2 (1.9) 1-16
Number of medications per prescription mean (SD) Min, Max	NA	2.4 (1.6) 1-22

Number of prescriptions by pathology N(%)		
Digestive disorders	2,728 (14.7)	NA
ENT-Pulmonary disorders	8,397 (45.2)	NA
Dermatological disorders	604 (3.3)	NA
Neuropsychiatric disorders	242 (1.3)	NA
Other illnesses[#]	6,591 (35.5)	NA

NA: Not available; ENT: ear, nose and throat
[#] For example, traumatic injury, pain, sickle cell disease

In hospital, POPI tools identified 541 PIMs in 2.9% of the prescriptions analyzed. They were detected in 3.3% of the patients (n=530). PPOs were detected in 0.1% of prescriptions for 0.1% of patients. In the community, PIMs and PPOs represented 12.3% and 0.9% of all prescriptions, affecting 26.4% and 1.9% patients respectively (Table 3).

Table 3. Potentially Inappropriate Medications (PIMs) and Potential Prescription Omission (PPOs) identified by POPI

	Hospital N (%)	**Community N (%)**
Number of prescriptions (N)	**18,562**	**4,780**
PIMs identified per prescription		
1	519 (2.8%)	551 (11.5%)
2	11 (0.1%)	37 (0.8%)
Prescriptions with at least one PIM	530 (2.9%)	588 (12.3%)
PPOs identified per prescription		
1	0 (0%)	0 (0%)

2	20 (0.1%)	44 (0.9%)
3	1 (0.01%)	1 (0.02%)
Prescriptions with at least one PPO	21 (0.1%)	45 (0.9%)
Number of patients (N)	**15,793**	**2,225**
Patients with at least one PIM °	530 (3.3%)	588 (26.4%)
Patients with at least one PPO	21 (0.1%)	43 (1.9%)

Table 4 presents the prevalence of PIMs (or PPOs) in the ED in patients with the targeted disorders. Patients with the targeted disorders represent the individuals who were at risk of each PIM/PPO. Table 5, however, presents the proportion of PIMs per disorder (or PPO) according to the total number of PIMs (or PPOs) in the community pharmacy. Respiratory and digestive diseases had the highest rate of PIM in hospital and community pharmacy. For various illnesses, we removed one criterion involving medicines containing codeine because of their new contraindication in children under 12 years old.[39] However, the prescription of codeine was observed in 18 cases. According to our comparison of PIMs detectable in both settings, out-of-hospital medication always presents with a higher prevalence of PIMs (Figure 3).

Table 4. Prevalence of PIMs and PPOs identified by POPI in hospital

Criteria		No. of PIMs	No. of patients with the targeted disorders	% of PIMs in patients with the targeted disorders
Potentially inappropriate medications (PIMs)		**541**	**7,304**	**7.4%**
Various illnesses		**3**	**64**	**4.6%**
AI-6	Opiates to treat migraine attacks	3	64	4.6%
Digestive disorders		**56**	**1,956**	**2.8%**

EI-2	Domperidone	28	1,956	1.4%
FI-3	The use of Diosmectite (Smecta®) in combination with another medication	27	1,956	1.4%
EI-1	Metoclopramide	1	1,956	0.05%
ENT-Pulmonary disorders		**472**	**5,163**	**9.1%**
II-4	Antibiotics to treat acute suppurative otitis media etc.	2	7	28.6%
II-2	Antibiotic treatment for a sore throat, without a positive RDT.	23	160	14.4%
II-9	Ear drops in the event of acute otitis media	86	1,083	7.9%
HI-1	Beta2 agonist, corticosteroids to treat an infant's first case of bronchiolitis	25	386	6.4%
II-5	Corticosteroids to treat acute suppurative otitis media etc.	190	3,616	5.2%
II-1	An antibiotic other than amoxicillin as a first-line treatment.	59	1,259	4.7%
JI-1	H1-antagonist to treat asthma	9	802	1.1%
II-8	Tenoate Etanolamine (Rhinotrophyl®) and other nasal antiseptics	21	2,455	0.8%
II-3	Antibiotics for nasopharyngitis	26	3,444	0.7%
GI-3	Alimemazine (Theralene®), oxomemezine (Toplexil®) etc.	18	2,585	0.7%
JI-2	Cough suppressants to treat asthma	5	802	0.6%
HI-2	H1-antagonists, cough suppressants etc. to treat bronchiolitis	2	386	0.5%
II-7	H1-antagonists with sedative or atropine-like effects.	4	2,585	0.2%
GI-2	Mucolytics drugs, mucokinetics drugs or helicidine before 2 years of age	1	2,585	< 0.1%
II-6	Nasal or oral decongestant etc.	1	2,455	< 0.1%
Dermatological disorders		**10**	**100**	**10%**
OI-1	A combination of locally applied and orally administered antibiotics	9	32	28.1%
PI-2	Topical agents containing acyclovir administered to a child under six years of age	1	68	1.5%
		No. of PPO	**No. of patients with the targeted disorders**	**% of PIMs in patients with the targeted disorders**
Potentially Prescribing Omissions (PPO)		**425**	**4,508**	**9.4%**
Digestive disorders		**372**	**1,956**	**19.0%**
EO-1	Oral rehydration solution in the event of vomiting	135	313	43.1%
FO-1	Oral rehydration solution in the event of diarrhea	237	1,643	14.4%
ENT-Pulmonary disorders		**52**	**1,469**	**3.5%**

HO-1	0.9% NaCl to relieve nasal congestion etc.	38	386	9.8%
IO-2	Acetaminophen combined with antibiotic treatment for ear infections etc.	14	1,083	1.3%
Dermatological disorders		**1**	**3**	**33.3%**
NO-2	Griseofulvin taken during a meal containing a moderate amount of fat	1	3	33.3%

ENT: ear, nose and throat; No: Number; RDT: Rapid diagnostic test.
% Percentage calculated by the number of PIMs or PPO detected from the total number of analyzable cases
**the number of patients with the targeted disorder corresponds to patients with clinical situations at risk of PIM or PPO*

Table 5. Most frequently occurring PIMs and PPOs identified by POPI in community setting

Criteria	Proportion of PIMs per disorder according to total number of PIMs N(%)
Total number of Potentially Inappropriate Medications (PIMs) N= 591	
Various illnesses	**15 (2.5)**
AI-5 Oral solutions of ibuprofen administered in more than 3 doses etc.	7 (1.2)
CI-1 Fluoride supplements prescribed to infants under six months of age	5 (0.8)
AI-4 The combined use of two NSAIDs	3 (0.5)
Digestive disorders	**201 (34)**
EI-2 Domperidone	152 (25.7)
FI-3 The use of Diosmectite (Smecta®) in combination with another medication	35 (5.9)
FI-5 Intestinal antiseptics	9 (1.5)
EI-1 Metoclopramide	2 (0.3)
EI-6 The use of type H2 antihistamines for long periods of treatment	2 (0.3)
FI-1 Loperamide before 3 years of age	1 (0.2)
ENT-Pulmonary disorders	**369 (62.4)**
GI-3 Alimemazine (Theralene®), oxomemazine (Toplexil®), etc.	202 (34.2)
GI-1 Pholcodine	81 (13.7)
II-8 Etanolamine tenoate (Rhinotrophyl®) and other nasal antiseptics	62(10.5)
II-6 Nasal or oral decongestant etc.	20 (3.4)
GI-2 Mucolytic drugs, mucokinetic drugs or helicidine prescribed to a child under 2 years of age	3(0.5)

GI-4 Terpene-based suppositories	1(0.2)
Dermatological disorders	**1(0.2)**
PI-2 Topical agents containing acyclovir prescribed to a child under six years of age	1(0.2)
Neuropsychiatric disorders	**5 (0.8)**
RI-3 Levetiracetam in mL or in mg prescribed without systematically indicating XX mg per Y mL	5(0.8)
	Proportion of PIM per disorder according to total number of PIM N(%)
Potential Prescribing Omissions (PPOs) N= 293	
IO-1 Dose in mg for oral (solution of) amoxicillin etc. N (%)	293 (100%)

NSAIDs: Non-steroidal anti-inflammatory drugs; ENT: ear, nose and throat
% Percentage of PIMs or PPOs calculated from the total number of PIMs or PPO detected

The criterion on prescribing amoxicillin in mg (IO-1) was not analyzable due to the fact that this drug is prescribed in great quantity. Among 100 prescriptions randomly assessed in hospital extractions, 97 prescriptions were inappropriate. Nonetheless, one analysis on acute otitis media alone identified a rate of 99.5% (807/811) of prescriptions issued without specification of the doses in mg for oral amoxicillin. In community care, this was observed in 97% of prescriptions, in 13.2% of patients (Table 5).

PIMs classed by age were presented in the figure 4. Potential factors associated with PIM are presented in Appendix 1. On univariate analysis, only different age categories were associated with risk of PIM in hospital setting. In community setting, the number of medications per prescription and different age categories were found to be significantly associated with risk of PIM on univariate analysis. In the multivariable logistic regression model, the same results were obtained. When data from hospital and community were grouped, univariate analysis showed that different age categories and prescription setting were associated with risk of PIM. In the multivariable logistic regression model, prescription issued from outpatient care was significantly associated with a higher risk of PIM (OR: 5.4 [4.8; 6.2] 95%CI, p<0.0001). In

addition, patients aged 0-12 years are more at risk of having a PIM than patients aged between 12-18 years (OR: 1.3 [1.0-1.6] 95%CI, p=0.01 for 0-2 years; OR 2.4 [1.9-2.9] p< 0.0001 for 2-6 years; OR 1.8 [1.5-2.3] p< 0.0001). In the community pharmacy, only one PPO was detected (dose in mg for oral solution of amoxicillin etc.). So we cannot compare this with the hospital setting. In the ED, this criterion can be evaluated due to a larger number of prescriptions.

DISCUSSION

This is the first study to observe the prevalence of PIMs and PPOs in a pediatric population. In the literature, the tool detected PIMs/PPOs in a geriatric population. [22,40–42] The two populations are not comparable. Respiratory and digestive pathologies are typical in children and not so in a geriatric population, which is concerned by cardiovascular and nervous central system diseases.[22,40,43].

Domperidone was frequently prescribed in a community setting, yet this drug is responsible for cardiac adverse effects such as QT prolongation. This side effect is described in the literature in adult populations and pediatric populations. Detecting of this prescription will enable us to avoid cardiac risks. [44–49]

Prevalence of beta2 agonists or corticosteroids in an infant's first case of bronchiolitis is 6.4% (25/386 cases), lower than that observed in a study of another French area in 2012 (41%).[50–52] Use of beta2 agonists in a first case of bronchiolitis has no impact on oxygen saturation, length of hospitalization or length of illness. They concurrently cause side effects as tachycardia, oxygen saturation, and tremors. [53]

Unnecessary exposure to cough suppressants, pholcodine, nasal or oral decongestants was also observed frequently in this sector.[54] In Norway, all drugs containing pholcodine have

been refused marketing authorization for March 2007. As of this date, a decrease in sensitization to suxamethonium used in anesthesia and a decrease of 30-40% cases of anaphylaxis were identified. [55]

Our tool enabled us to detect rare PIMs but with a major impact, such as opioid use for migraines. The use of opioids for this disease induces a transition from episodic to chronic headaches and an increase of sensitivity to pain.[56–58] Overuse of medication overuse, in particular opioids, could contribute to the chronicity of headaches in 20–30% of children and adolescents with chronic daily headaches.[59]

In the management of diarrhea caused by gastroenteritis, in hospital, our study found that it was common to omit prescription of an oral rehydration solution (ORS): 14% (237/1643 case). Even so, this rate is lower than that found in another national study in 2007 (29%).[60] However, ORSs prevent hospitalization in cases of acute gastroenteritis. In the United Kingdom, the use of ORSs has enabled a decrease from 300 deaths/year in 1970s to 25 deaths/year in 1980s. [61,62]. The need for ORS prescriptions was confirmed by the recommendation of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in 2014.[63]

As estimated, the child aged between 0 and 12 years has the highest risk of presenting with a PIM, according to a multivariate analysis. No inappropriate prescriptions or omissions were detected for patients aged less than 28 days. As we know, they are also affected by off-label drug prescriptions, which is consistent with reports from other sources.[64,65] As with geriatrics, an increase in numbers of medications can be associated with PIM.[40] Prescriptions issued from hospitals elicit fewer PIMs than those issued by the community. The main reason for this is that many drugs are not available in this hospital, such as cough suppressants, Rhinotrophyl® (tenoate ethanolamine), domperidone, etc. This shows that many

PIM are preventable in a hospital setting. An efficient method for prevention of PIM could be to focus on the prescribing habits of physicians and thus have an impact on the selection of drugs, thereby reducing the rate of PIM.

Our study has several limitations. Firstly, it is a retrospective and monocentric study. Our result in the hospital could be underestimated. In addition, several criteria could not be analyzed due to the large number of prescriptions (for example, those for fever or pain which are associated with many diseases) or absence of a specific pathology (mosquitos, lice, hyperactivity etc.). Antibiotic prophylaxis, vitamin supplements, proposition of vaccination etc. can be analyzed in prospective studies. A lack of clinical information is the main limitation in detection in a community setting. This also constitutes a challenge for pharmaceutical care review in elderly patients.[66] However, a certain amount of PIM was identified using POPI. Our study showed that there are many criteria which could be detected without access to clinical information and are easy to identify. Moreover, community pharmacists, in their practice, can extrapolate diagnoses from their experience, from common indications or by interviewing their patient. The study presents a limitation regarding the URQUAL software, from which the number of medications per prescription could not be extracted.

This is the first study which permits to evaluate prevalence of PIM and PPO in pediatrics prescription. Detecting of PIMs/PPOs would improve patient care, and prevent hospitalization and adverse drug reactions. A stepped wedge randomized cluster multicenter study will be conducted to prove if POPI decreases number of PIM and PPO. It is also necessary to evaluate the impact of this tool on reducing adverse drugs events, both in consultation or upon hospitalization. The impact of pharmacists in providing appropriate prescriptions should be also evaluated. Subsequently, this tool may be proposed to several professional societies such

as the French Society for Pediatricians and the French Society of Clinical Pharmacy to make its use more widespread. The tool should be regularly updated to reflect recent events and to specify certain criteria.

To facilitate its use, this tool can be presented as a mobile app, a small handbook or be installed into prescription software. In summary, we hope that POPI could be a practical option used to reduce medication errors and to improve the suitability of prescriptions. It provides rapid detection of PIM and PPO and can also open up a discussion on the relationship between the doctor and the pharmacist to remedy the issue at hand.[67]

CONCLUSION

Our study was carried out in in two sectors, hospital and community, and provides a global view of PIM and PPO in pediatric patients. POPI has a clinical impact and plays a role in improving prescription quality in various sectors and patient care. POPI should be applied in different services to deepen and reinforce its utilization. A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice.

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ETHICS

This project was approved by the local research ethics committee (n°2015/218).

DISCLOSURE OF INTEREST

None Declared

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AUTHOR'S CONTRIBUTION

Sonia Prot-Labarthe, Aurore Berthe-Aucejo conceptualised and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Rym Boulkedid and HPK Nguyen carried out analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Xavier Bellettre, Thomas Weil, Olivier Bourdon reviewed and revised the manuscript and approved the final manuscript as submitted.

François Angoulvant and Patrick Albaret supplied data from hospital and community pharmacy and reviewed and revised the manuscript and approved the final manuscript as submitted.

DATA SHARING STATEMENT

We have no additional unpublished data

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Figure 1. Flow chart indicating the course of the study

* Prescriptions with only one medical device, dietary supplement or hygiene product, ED: Emergency department

Figure 2. Distribution of number of prescriptions according to age category in hospital and community settings

Figure 3. Comparison of PIMs detected in hospital and in outpatient care

Figure 4. Total prescription and PIMs in both hospital and outpatient care: Percentage distribution by age group

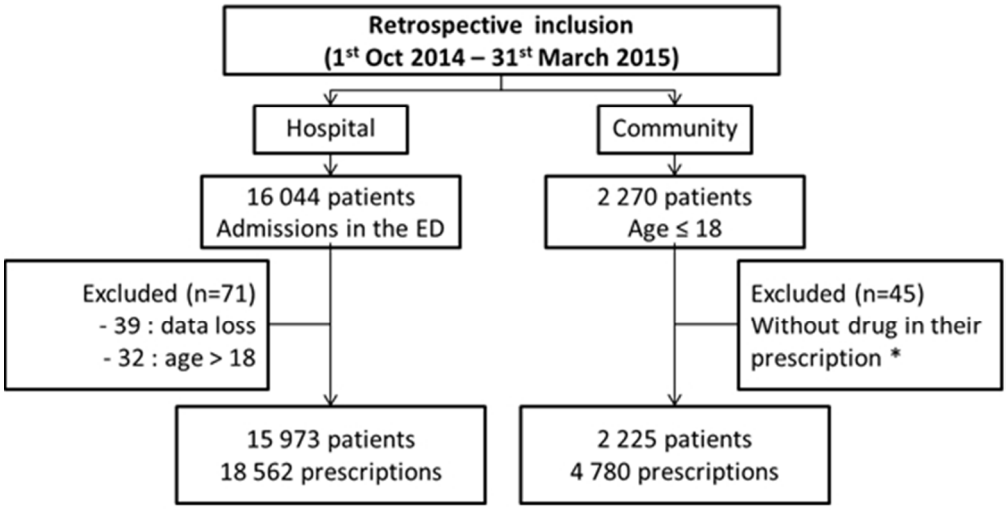

Figure 1. Flow chart indicating the course of the study† * Prescriptions with only one medical device, dietary supplement or hygiene product, ED: Emergency department

51x27mm (300 x 300 DPI)

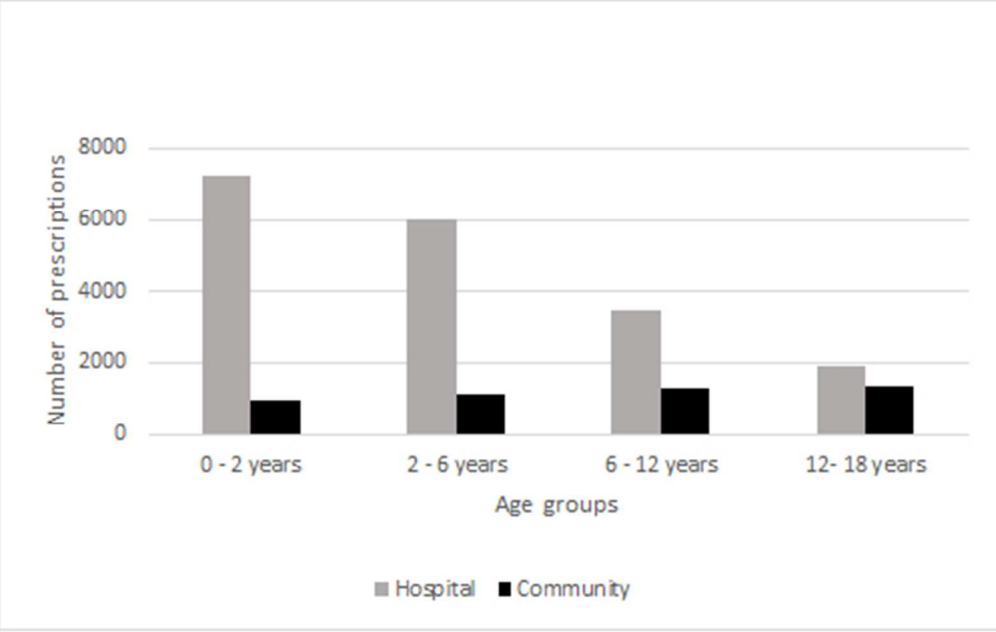

Figure 2. Distribution of number of prescriptions according to age category in hospital and community settings

42x26mm (300 x 300 DPI)

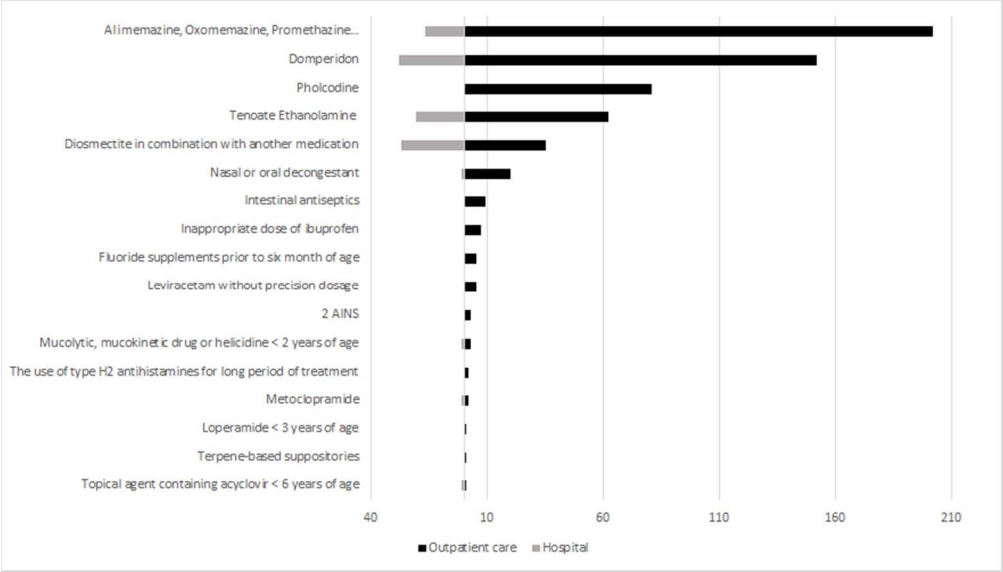

Figure 3. Comparison of PIMs detected in hospital and in outpatient care

74x42mm (300 x 300 DPI)

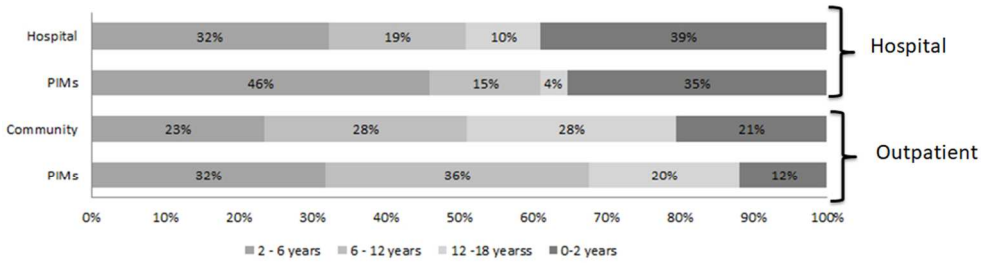

Figure 4. Total prescription and PIMs in both hospital and outpatient care: Percentage distribution by age group

90x23mm (300 x 300 DPI)

Appendix 1. Univariate and multivariate analysis to determine factors associated with PIM according to POPI criteria

Variable	Univariate analysis		Multivariate analysis	
Model 1: Hospital prescription	*OR* [CI 95%]*	*p-value*	*OR* [CI 95%]*	*p-value*
Sex				
Male	1			
Female	1.1 [0.9-1.3]	0.3		
Age category				
0 - 2 years	2.5 [1.6-3.9]	0.0001	2.4 [1.6-3.8]	< 0.001
2 - 6 years	4.0 [2.5-6.3]	< 0.0001	4.0 [2.5-6.3]	< 0.0001
6 - 12 years	2.2 [1.4-3.6]	0.0016	2.2 [1.4-3.6]	0.0016
12 - 18 years	1		1	
Model 2: Community prescription				
Age category				
0 - 2 years	0.8 [0.6-1.1]	0.1	0.7 [0.5-1.0]	0.06
2 - 6 years	2.0 [1.5-2.6]	< 0.0001	1.85 [1.4-2.4]	< 0.0001
6 - 12 years	1.9 [1.5-2.4]	< 0.0001	1.9 [1.5-2.5]	< 0.0001
12 - 18 years	1		1	
Number of medications per prescription	1.4 [1.3-1.6]	< 0.001	1.4 [1.3-1.6]	< 0.0001
Model 3: Hospital and Community prescription				
Age category				
0 - 2 years	0.7 [0.6- 0.9]	0.002	1.3 [1.0-1.6]	0.01
2 - 6 years	1.4 [1.1-1.7]	0.0006	2.4 [1.9-2.9]	< 0.0001
6 - 12 years	1.4 [1.1-1.7]	0.002	1.8 [1.5-2.3]	< 0.0001
12 - 18 years	1		1	
Service				
Hospital	1			
Community	5.1 [4.5-5.8]	< 0.001	5.4 [4.8-6.2]	< 0.0001

OR: Odds ratio, CI: Confidence intervals.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	p5
Methods			
Study design	4	Present key elements of study design early in the paper	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P6 NA
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p6-7-14
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p15-16
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P16+figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	p17

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Appendix1
Discussion			
Key results	18	Summarise key results with reference to study objectives	p18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p22 to 24
Generalisability	21	Discuss the generalisability (external validity) of the study results	p24-25
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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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.

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	General practice / Family practice
Keywords:	inappropriate prescription, omission, tool, detection

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.

A. Berthe-Aucejo[1,2], H.P.K Nguyen[1], F. Angoulvant[2,3], X. Bellettre[4], P. Albaret[5,6], T. Weil[1], R. Boulkedid[2,7,8], O. Bourdon[1,6,9,10], S.Prot-Labarthe[1,2,10]

[1] Department of Pharmacy, Robert-Debré Hospital, Paris, France

[2] UMR-S1123, ECEVE; Inserm U1123, Paris, France

[3] Emergency unit, Necker Hospital, Paris, France

[4] Emergency unit AP-HP, Robert-Debré Hospital, Paris, France

[5] Albaret Pharmacy, Cesson, France

[6] Clinical Pharmacy, Paris Descartes University, Paris, France

[7] Assistance publique-Hôpitaux de Paris, Hôpital Robert Debré, Clinical Epidemiology Unit, 75 019 Paris, France

[8] CIC-EC 1426, 75019 Paris, France

[9] Laboratoire Educations et Pratiques de Santé, Paris XIII University, Bobigny, France

[10] Groupe Pédiatrie de la Société Française de Pharmacie Clinique, Paris, France

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Corresponding author

Dr Aurore Berthe-Aucejo, Service Pharmacie, AP-HP Hôpital Robert-Debré, 48 Boulevard Sérurier, 75019 Paris, Fax: 01-40-03-24-81, Tel: 01-40-03-57-41, Email: aurore.berthe@aphp.fr

Keywords

Inappropriate prescription, omission, tool, detection

ABSTRACT

Background and Objective: POPI **(**Pediatrics: Omission of Prescription and Inappropriate prescription) is the first detection tool for potentially inappropriate medicines (PIM) and potentially prescribing omissions (PPO) in pediatrics. The aim of this study was to evaluate the prevalence of PIM and PPO detected by POPI regarding issuing of prescription in hospital and outpatients . The second objective is to determine the risk factors related to PIM and PPO.

Design: A retrospective, descriptive study was conducted in the emergency department (ED) and community pharmacy (CP) during 6 months. POPI was used to identify PIM and PPO.

Setting: Robert-Debré Hospital (France) and Albaret community pharmacy (Seine and Marne).

Participants: Patients who were under 18 years old and who had one or more medicine prescription were included. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients.

Primary and secondary outcome measures: PIM and PPO rate and risk factors

Results: At ED, 18,562 prescriptions for 15,973 patients and 4,780 prescriptions for 2,225 patients at the CP were analyzed. The PIM rate and PPO rate were respectively 3.3% and 2.6% at the ED and 26.4% and 13.2% at the CP. Respiratory and digestive diseases had the highest rate of PIM.

Conclusion: This is the first study to assess the prevalence of PIM and PPO detecting by POPI in a pediatric population. This study allowed to describe PIMs or PPOs within a hospital and a community pharmacy. POPI could be used to improve medication use and patient care and to limit hospitalization and adverse drug reaction. A prospective and multicenter study should be conducted to evaluate the impact and benefit of implementing POPI in clinical practice.

Strengths and limitations of this study

- This study is the first to observe the prevalence of PIM and PPO in a pediatric population.

- It is a retrospective and monocentric study. The prevalence of PIM and PPO may be underestimated (large number of prescriptions, absence of specific pathology). Some criteria could be analyzed only in a prospective study. A lack of clinical information is the main limitation in detection in a community setting.

- Many omissions and inappropriate prescriptions can be easily detected with POPI despite limited clinical information.

INTRODUCTION

Inappropriate prescribing is a known preventable cause of adverse drug events (ADE) and has an important impact on public health and cost of care. [1,2] In the literature, ADE is defined by "an injury resulting from medical intervention related to a drug" (dose error, adverse drug reaction (ADR), misuse of medication such as antibiotics).[3–5] In the pediatric population, ADR during hospitalization was estimated between 0.6% and 33.7% and between 1% and 1.5% for outpatients.[6–9] Incidence of ADR leading to admission was evaluated between 1.8% and 17.7%.[6,7,10] Many drugs were concerned in commonly used medication.[11–13]

The World Health Organization estimated that 50% of medications are prescribed and used inappropriately.[14] The most recent definition of inappropriate prescription (IP) encompasses potentially inappropriate medicines (PIM) and prescribing omissions (PPO).[15] In a report from the French National Authority for Health, PIMs are defined as "drugs being used in a situation in which the risks involved in treatment potentially outweigh the benefits, lack of demonstrated indication, high risk of ADE, and an unfavorable cost-effect or risk-benefit ratio exists". PPO or underuse of appropriate medication is defined as the absence of initiation of an effective treatment in subjects with a condition for which one or several drug classes have demonstrated their efficacy. In an elderly population, which presents with age-related physiological changes and high prevalence of polypharmacy, various measures have been developed to detect PIM such as: Beers' criteria, the Inappropriate Prescribing in the Elderly Tool, The Medication Appropriate Index, and STOPP/START (Screening Tool of Older Person's prescriptions/Screening Tool to Alert doctor to Right Treatment).[16–21]

Only the STOPP/START enables us to detect under-prescribing.[15] Using these tools, many studies have been carried out which have detected that inappropriate prescriptions are issued to between 35% and 51% of this population.[22–26]

Omission prescriptions in geriatric population detected by START tool concerned between 58%-61% of patients.[27,28] Negative outcomes related to an IP such as side effects, hospitalization, mortality and utilization of resources were also demonstrated.[21,29–31]

Prescribing in a pediatric population is always a challenge for physician. It is often empirical and primarily based on safety and pharmacology information obtained in adults.[32] This is a worry not only in a hospital or general practitioner setting but also for the community pharmacists. They may only be able to check information and resources or even dispense infrequently for this vulnerable population.[33] ADRs were three time higher in the pediatric population. This frequency was explained by the vulnerability of young people, pharmacokinetic changes during childhood and pediatric off-label drug used.[4,34] Large differences relating to treatment were seen within and between the countries.[6,35] Question about rational of prescription could be asked.[36] Optimizing children's care is based on rational prescribing and allowing a decrease in side effects.[35,36] In order to improve the correct drug use and optimize practice, the first tool of detection for PIM and PPO was created by Prot-Labarthe *et al.* in 2013. The tool was named POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions) (Table 1).[37,38] Presently, the complete tool has not been tested in actual practice and the prevalence of PIM and OP is not known.

Our aim is to assess the prevalence of PIM and PPO detected using POPI in hospital and outpatient care. This was its first application, regarding issuing of prescriptions in the emergency department and the community pharmacy. The second objective is to determine the risk factors related to PIM.

METHODS

Population

A retrospective and descriptive study was conducted in the emergency department (ED) of AP-HP Robert-Debré hospital (Paris) - the largest French pediatric hospital - and the Albaret community pharmacy (CP) (Seine and Marne). Inclusion criteria included patients who were under 18 years old and who had one or more medicine prescriptions between 1st October 2014 and 31st March 2015. Prescription was defined as one or more lines of drugs prescribed by a physician. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients. POPI contains 102 criteria (76 PIMs, 25 PPO). 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). Criteria were validated by 2-round-Delphi consensus technique.[38]

Data collection

The prescriptions given on leaving the hospital emergency department were extracted from the Urqual software V5® (*) (McKesson Corp, Paris, France). Urqual® is an emergency prescription software which is used in many French hospitals. Patient information including age, sex, weight, medicine prescription and current diagnosis was collected. Medical histories and clinical examinations were consulted individually when necessary. Due to the significant amount of data, clinical files of ED were analyzed, based on primary diagnosis. For this study, 82/102 criteria were analyzed (Table 1). Some criteria could not be used for a hospital setting.

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.

Table 1. POPI - Pediatrics: Omission of Prescriptions & Inappropriate prescriptions

DIVERSE ILLNESSES	**A- PAIN AND FEVER**	
	Inappropriate prescriptions	**Omissions**
	AI-1. Prescription of two alternating antipyretics as a first-line treatment. **AI-2.** Prescription of a medication other than paracetamol as a first line treatment (except in the case of migraine). **AI-3.** Rectal administration of paracetamol as a first-line treatment. **AI-4.** The combined use of two NSAIDs. * ° **AI-5.** Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (other than Advil ®). ° **AI-6.** Opiates to treat migraine attacks. *	**A0-1.** Failure to give sugar solution to new-born babies and infants under four months old two minutes prior to venipuncture. **A0-2.** Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours.
	B- URINARY INFECTIONS	
	Inappropriate prescriptions	
	BI-1. Nitrofurantoin used as a prophylactic. * **BI-2.** Nitrofurantoin used as a curative agent in children under six years of age, or indeed any other antibiotic if avoidable. * **BI-3.** Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy). * **BI-4.** Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy). *	
	C- VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS	

	Inappropriate prescriptions	Omissions
	CI-1. Fluoride supplements prior to six months of age. ◦*	CO-1. Insufficient intake of vitamin D. Minimum vitamin D intake: ▪ Breastfed baby = 1,000 to 1,200 IU/day ▪ Infant < 18 months of age (milk enriched with vitamin D) = 600 to 800 IU/day ▪ Child aged between 18 months and five years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80,000 to 100,000 IU/day in winter (adolescents can take this as one dose). CO-2. Antibiotic prophylaxis with phenoxymethylpenicillin (Oracilline) starting from two months of age and lasting until five years of age for children with sickle-cell anemia: 100,000 IU/kg/day (in two doses) for children weighing 10kg or less and 50,000 IU/kg/day for children weighing over 10kg (also in two doses). *
	D- MOSQUITOS	
	Inappropriate prescriptions	**Omissions**
	DI-1. The use of skin repellents in infants less than six months old and picardin in children less than 24 months old. DI-2. Citronella (lemon grass) oil (essential oil). DI-3. Anti-insect bracelets to protect against mosquitos and ticks. DI-4. Ultrasonic pest control devices, vitamin B1, homeopathy, electric bug zappers, sticky tapes without insecticide.	DO-1. **DEET** ‘‘30%’’ (max) before 12 years old ‘‘50%’’ (max) after 12 years old. DO-2. **IR3535** ‘‘20%’’ (max) before 24 months old ‘‘35%’’ (max) after 24 months old. DO-3. Mosquito nets and clothes treated with pyrethroids.
PROBLEMS	**E- NAUSEA, VOMITTING, OR GASTROESOPHAGEAL REFLUX**	
	Inappropriate prescriptions	**Omissions**
	EI-1. Metoclopramide. * ◦ EI-2. Domperidone. * ◦ EI-3. Gastric antisecretory drugs to treat gastroesophageal reflux, dyspepsia, the crying of new-born babies (in the absence of	EO-1. Oral rehydration solution in the event of vomiting.*

any other signs or symptoms), as well as faintness in infants. *

EI-4. The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors. *

EI-5. Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube). *

EI-6. The use of type H2 antihistamines for long periods of treatment. * ◦

EI-7. Erythromycin as a prokinetic agent. *

EI-8. The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting. *

F- DIARRHEA

Inappropriate prescriptions	Omissions
FI-1. Loperamide before 3 years of age.*°	**FO-1.** Oral rehydration solution in the event of diarrhea.*
FI-2. Loperamide in the case of invasive diarrhea.*	
FI-3. The use of Diosmectite (Smecta®) in combination with another medication.*°	
FI-4. The use of Saccharomyces boulardii (Ultralevure) in powder form, or in a capsule that has to be opened prior to ingestion, to treat patients with a central venous catheter or an immunodeficiency.*	
FI-5. Intestinal antiseptics.*°	

ENT-PULMONARY PROBLEMS

G- COUGH

Inappropriate prescriptions	Omissions
GI-1. Pholcodine. * ◦	**GO-1.** Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family of expectant parents and those in contact with them (parents, grand-parents, nannies/child minders).
GI-2. Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age. * ◦	
GI-3. Alimemazine (Theralene®), oxomemazine (Toplexil®), promethazine (Phenergan®), and other types. * ◦	
GI-4. Terpene-based suppositories. * ◦	

H- BRONCHIOLITIS IN INFANTS

Inappropriate prescriptions	Omissions
HI-1. Beta2 agonists, corticosteroids to treat an infant's first case of bronchiolitis. *	**HO-1.** 0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer). *
HI-2. H1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis. *	**HO-2.** Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities.
HI-3. Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.). *	

I- ENT INFECTIONS

Inappropriate prescriptions	Omissions
II-1. An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for an pneumococcal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day.*	**IO-1.** Doses in mg for drinkable (solutions of) amoxicillin or josamycin. *◦
II-2. Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children more than three years old.*	**IO-2.** Paracetamol combined with antibiotic treatment for ear infections to relieve pain. *
II-3. Antibiotics for nasopharyngitis, congestive otitis, sore throat before three years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, after two years of age.*	
II-4. Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months.*	
II-5. Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat.*	
II-6. Nasal or oral decongestant (oxymetazoline	

(Aturgyl®), pseudoephedrine (Sudafed®), naphazoline (Derinox®), ephedrine (Rhinamide®), tuaminoheptane (Rhinofluimicil®), phenylephrine (Humoxal®)).*◦

II-7. H1-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor; inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age.* ◦

II-8. Ethanolamine tenoate (Rhinotrophyl®) and other nasal antiseptics.* °

II-9. Ear drops in the case of acute otitis media.*

J- ASTHMA

Inappropriate prescriptions	Omissions
JI-1. Ketotifen and other H1-antagonists, sodium cromoglycate. *	**JO-1.** Asthma inhaler appropriate for the child's age.
JI-2. Cough suppressants. *	**JO-2.** Preventative treatment (inhaled corticosteroids) in the case of persistent asthma. *

DERMATOLOGICAL PROBLEMS

K-ACNE VULGARIS

Inappropriate prescriptions	Omissions
KI-1. Minocycline.* °	**KO-1.** Contraception (provided with a logbook/diary) for menstruating girls taking isotretinoin.
KI-2. Isotretinoin in combination with a member of the tetracycline family of antibiotics.* °	**KO-2.** Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy. *
KI-3. The combined use of an oral and a local antibiotic.*	
KI-4. Oral or local antibiotics as a monotherapy (not in combination with another drug).*	
KI-5. Cyproterone+ethinylestradiol (Diane 35®) as a contraceptive to allow isotretinoin per os.* °	
KI-6. Androgenic progestins (levonorgestrel, norgestrel, norethisterone, lynestrenol, dienogest, contraceptive implants or vaginal rings).*	

L- SCABIES

Omissions
LO-1. A second dose of ivermectin two weeks after the first. *
LO-2. Decontamination of household linen and clothes and treatment for other family members.

M- LICE

Inappropriate prescriptions
MI-1. The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnea.

N- RINGWORM	
Inappropriate prescriptions	**Omissions**
NI-1. Treatment other than griseofulvin for Microsporum. *	**NO-1.** Topical treatment combined with an orally-administered treatment. * **NO-2.** Griseofulvin taken during a meal containing a moderate amount of fat. * ◦

O-IMPETIGO

Inappropriate prescriptions
OI-1. The combination of locally applied and orally administered antibiotics.* **OI-2.** Fewer than two applications per day for topical antibiotics.* **OI-3.** Any antibiotic other than mupirocin as a first-line treatment (except in cases of hypersensitivity to mupirocin).*

P- HERPES SIMPLEX	
Inappropriate prescriptions	**Omissions**
PI-1. Topical agents containing corticosteroids. * **PI-2.** Topical agents containing acyclovir before six years of age. * ◦	**PO-1.** Paracetamol during an outbreak of herpes. * **PO-2.** Orally administered acyclovir to treat primary herpetic gingivostomatitis. *

NEUROPSYCHIATRIC DISORDERS

Q-ATOPIC DERMATITIS

Inappropriate prescriptions

QI-1. A strong topic steroid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate Diprosone) applied to the face, armpits or groin, and to the backside of babies or young children. *
More than one application per day of a topical steroid, except in cases of severe lichenification. *
QI-2. Local or systemic antihistamine during the treatment of outbreaks. *
QI-3. Topically applied 0.03% tacrolimus before two years of age. *◦
Topically applied 0.1% tacrolimus before 16 years of age.
QI-4. Oral corticosteroids to treat outbreaks. *

R- EPILEPSY

Inappropriate prescriptions

RI-1. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy. *
RI-2. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabaline, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy). *
RI-3. Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL. * ◦

S-DEPRESSION

Inappropriate prescriptions

SI-1. An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy). *
SI-2. Tricyclic antidepressants to treat depression. *

T- NOCTURNAL ENURESIS

Inappropriate prescriptions

TI-1. Desmopressin administered by a nasal spray. * ◦

Desmopressin in the case of daytime symptoms.

TI-2. An anticholinergic agent used as a monotherapy in the absence of daytime symptoms. *
TI-3. Tricyclic agents in combination with anticholinergic agents. * ◦
TI-4. Tricyclic agents as a first-line treatment. *

U- ANOREXIA

Inappropriate prescriptions

UI-1. Cyproheptadine (Periactin®), clonidine * ◦

V- ATTENTION DEFICIT DISORDER WITH OR WITHOUT HYPERACTIVITY

Inappropriate prescriptions	Omissions
VI-1. Pharmacological treatment before age six (before school), except in severe cases. *	VO-1. Recording a growth chart (height and weight) if the patient is taking methylphenidate. *
VI-2. Antipsychotic drugs to treat attention deficit disorder without hyperactivity. *	
VI-3. Slow release methylphenidate as two doses per day, rather than only one dose. *◦	

* Criteria analyzed in emergency department

◦ Criteria analyzed in community pharmacy

Data from the community pharmacy were obtained from the pharmacy management software OPUS® (Computer PG, France). Patient's age and drugs prescribed were collected. Current diagnosis and sex were not available, in the OPUS software, so the number of patients per pathology and the number of prescriptions per pathology were missed. Only drugs that did not require assessment of diagnosis (for example domperidone, metoclopramide etc.) were analyzed (Table 1) (28 criteria/102).

Among the 5 criteria including analgesics and antipyretics, only three were evaluated due to a large number of prescriptions and their association with many diseases. Pathologies analyzed by POPI were the same in emergency department and in community. Summary of data and inclusion criteria are detailed in Appendix 1.

Statistical analysis

Data were presented as continuous variables (age, number of prescriptions by patient, number of medications per prescription) and were presented as median and interquartile range (25th-75th percentiles) or mean (standard deviation), minimum and maximum depending on normal distribution.

Mixed effects logistic regression modelling for repeated measurements was applied to identify factors associated with PIM and PPO (yes/no) in the hospital and community settings. Unit of analysis was "the prescription".

Univariate models were performed using different candidate factors as:

- For model performed with hospital data: sex and age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years);
- For model performed with community data: age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years) and number of medications (drugs) per prescription;

The model was constructed using the parameters of the univariate analysis, which showed at least a trend toward significance, with a cut-off of p=0.2. Odds ratios (OR) with 95% confidence intervals (CI) were estimated. Statistical significance was established at $p<0.05$. SPSS-22® software (SPSS Inc., Chicago, IL, USA) and SAS 9.4 were used for analysis.

This project was approved by the local research ethics committee (n°2015/218).

Patient and Public Involvement

No Patient and Public involvement

RESULTS

In the emergency department, 18,562 prescriptions for 15,973 patients consulted were analyzed. Among them, 29% had at least two visits in 6 months. In the community pharmacy, 4,780 prescriptions for 2,225 patients were evaluated (Figure 1). In ED and CP, 53% of patients had been issued with one prescription, 21% with two and 26% with three or more prescriptions. The population's characteristics and the frequency of pathologies were presented in Table 2. Distribution of number of prescriptions by age category was described in the Figure 2.

Table 2. Characteristics of the study population

Population characteristics	Hospital (N=15,973)	Community (N=2,225)
Age (years) mean (SD) Min, Max	4.9 (4.5) 0-18	7.9 (5.3) 0-18
Female gender N(%)	8,769 (54.9)	NA
Number of prescriptions/patient mean (SD) Min, Max	1.4 (0.9) 1-12	2.2 (1.9) 1-16
Number of drugs per prescription mean (SD) Min, Max	NA	2.4 (1.6) 1-22

Number of prescriptions by pathology N(%)		
Digestive disorders	2,728 (14.7)	NA
ENT-Pulmonary disorders	8,397 (45.2)	NA
Dermatological disorders	604 (3.3)	NA
Neuropsychiatric disorders	242 (1.3)	NA
Other illnesses[#]	6,591 (35.5)	NA

NA: Not available; ENT: ear, nose and throat
[#] *For example, traumatic injury, pain, sickle cell disease*

In hospital, POPI tools identified 541 PIMs in 2.9% of the prescriptions analyzed. They were detected in 3.3% of the patients (n=530). PPOs were detected in 0.1% of prescriptions for 0.1% of patients. In the community, PIMs and PPOs represented 12.3% and 0.9% of all prescriptions, affecting 26.4% and 1.9% patients respectively (Table 3).

Table 3. Potentially Inappropriate Medications (PIMs) and Potential Prescription Omission (PPOs) identified by POPI

	Hospital N (%)	**Community N (%)**
Number of prescriptions (N)	**18,562**	**4,780**
PIMs identified per prescription		
1	519 (2.8%)	551 (11.5%)
2	11 (0.1%)	37 (0.8%)
Prescriptions with at least one PIM	530 (2.9%)	588 (12.3%)
PPOs identified per prescription		
1	0 (0%)	0 (0%)

2	20 (0.1%)	44 (0.9%)
3	1 (0.01%)	1 (0.02%)
Prescriptions with at least one PPO	21 (0.1%)	45 (0.9%)
Number of patients (N)	**15,793**	**2,225**
Patients with at least one PIM °	530 (3.3%)	588 (26.4%)
Patients with at least one PPO	21 (0.1%)	43 (1.9%)

Table 4 presents the prevalence of PIMs (or PPOs) in the ED in patients with the targeted disorders. Patients with the targeted disorders represent the individuals who were at risk of each PIM/PPO. Table 5, however, presents the PIMs (or PPOs) as a proportion of the total number of PIMs (or PPOs) in the community pharmacy. Respiratory and digestive diseases had the highest rate of PIM in hospital and community pharmacy. For various illnesses, we removed one criterion involving medicines containing codeine because of their new contraindication in children under 12 years old.[39] However, the prescription of codeine was observed in 18 cases. According to our comparison of PIMs detectable in both settings, out-of-hospital medication always presents with a higher prevalence of PIMs (Figure 3).

Table 4. Prevalence of PIMs and PPOs identified by POPI in hospital

Criteria		**No. of PIMs**	**No. of patients with the targeted disorders**	**% of PIMs in patients with the targeted disorders**
Potentially inappropriate medications (PIMs)		**541**	**7,304**	**7.4%**
Various illnesses		**3**	**64**	**4.6%**
AI-6	Opiates to treat migraine attacks	3	64	4.6%
Digestive disorders		**56**	**1,956**	**2.8%**
EI-2	Domperidone	28	1,956	1.4%
FI-3	The use of Diosmectite (Smecta®) in	27	1,956	1.4%

	combination with another medication			
EI-1	Metoclopramide	1	1,956	0.05%
ENT-Pulmonary disorders		**472**	**5,163**	**9.1%**
II-4	Antibiotics to treat acute suppurative otitis media etc.	2	7	28.6%
II-2	Antibiotic treatment for a sore throat, without a positive RDT.	23	160	14.4%
II-9	Ear drops in the event of acute otitis media	86	1,083	7.9%
HI-1	Beta2 agonist, corticosteroids to treat an infant's first case of bronchiolitis	25	386	6.4%
II-5	Corticosteroids to treat acute suppurative otitis media etc.	190	3,616	5.2%
II-1	An antibiotic other than amoxicillin as a first-line treatment.	59	1,259	4.7%
JI-1	H1-antagonist to treat asthma	9	802	1.1%
II-8	Tenoate Etanolamine (Rhinotrophyl®) and other nasal antiseptics	21	2,455	0.8%
II-3	Antibiotics for nasopharyngitis	26	3,444	0.7%
GI-3	Alimemazine (Theralene®), oxomemezine (Toplexil®) etc.	18	2,585	0.7%
JI-2	Cough suppressants to treat asthma	5	802	0.6%
HI-2	H1-antagonists, cough suppressants etc. to treat bronchiolitis	2	386	0.5%
II-7	H1-antagonists with sedative or atropine-like effects.	4	2,585	0.2%
GI-2	Mucolytics drugs, mucokinetics drugs or helicidine before 2 years of age	1	2,585	< 0.1%
II-6	Nasal or oral decongestant etc.	1	2,455	< 0.1%
Dermatological disorders		**10**	**100**	**10%**
OI-1	A combination of locally applied and orally administered antibiotics	9	32	28.1%
PI-2	Topical agents containing acyclovir administered to a child under six years of age	1	68	1.5%
		No. of PPO	**No. of patients with the targeted disorders**	**% of PIMs in patients with the targeted disorders**
Potentially Prescribing Omissions (PPO)		**425**	**4,508**	**9.4%**
Digestive disorders		**372**	**1,956**	**19.0%**
EO-1	Oral rehydration solution in the event of vomiting	135	313	43.1%
FO-1	Oral rehydration solution in the event of diarrhea	237	1,643	14.4%
ENT-Pulmonary disorders		**52**	**1,469**	**3.5%**
HO-1	0.9% NaCl to relieve nasal congestion etc.	38	386	9.8%
IO-2	Acetaminophen combined with antibiotic	14	1,083	1.3%

	treatment for ear infections etc.			
Dermatological disorders		**1**	**3**	**33.3%**
NO-2	Griseofulvin taken during a meal containing a moderate amount of fat	1	3	33.3%

ENT: ear, nose and throat; No: Number; RDT: Rapid diagnostic test.
% Percentage calculated by the number of PIMs or PPO detected from the total number of analyzable cases
**the number of patients with the targeted disorder corresponds to patients with clinical situations at risk of PIM or PPO*

Table 5. Most frequently occurring PIMs and PPOs identified by POPI in community setting

Criteria	Proportion of PIMs per disorder according to total number of PIMs N(%)
Total number of Potentially Inappropriate Medications (PIMs) N= 591	
Various illnesses	**15 (2.5)**
AI-5 Oral solutions of ibuprofen administered in more than 3 doses etc.	7 (1.2)
CI-1 Fluoride supplements prescribed to infants under six months of age	5 (0.8)
AI-4 The combined use of two NSAIDs	3 (0.5)
Digestive disorders	**201 (34)**
EI-2 Domperidone	152 (25.7)
FI-3 The use of Diosmectite (Smecta®) in combination with another medication	35 (5.9)
FI-5 Intestinal antiseptics	9 (1.5)
EI-1 Metoclopramide	2 (0.3)
EI-6 The use of type H2 antihistamines for long periods of treatment	2 (0.3)
FI-1 Loperamide before 3 years of age	1 (0.2)
ENT-Pulmonary disorders	**369 (62.4)**
GI-3 Alimemazine (Theralene®), oxomemazine (Toplexil®), etc.	202 (34.2)
GI-1 Pholcodine	81 (13.7)
II-8 Etanolamine tenoate (Rhinotrophyl®) and other nasal antiseptics	62(10.5)
II-6 Nasal or oral decongestant etc.	20 (3.4)
GI-2 Mucolytic drugs, mucokinetic drugs or helicidine prescribed to a child under 2 years of age	3(0.5)
GI-4 Terpene-based suppositories	1(0.2)
Dermatological disorders	**1(0.2)**

PI-2 Topical agents containing acyclovir prescribed to a child under six years of age	1(0.2)
Neuropsychiatric disorders	**5 (0.8)**
RI-3 Levetiracetam in mL or in mg prescribed without systematically indicating XX mg per Y mL	5(0.8)
	Proportion of PIM per disorder according to total number of PIM N(%)
Potential Prescribing Omissions (PPOs) N= 293	
IO-1 Dose in mg for oral (solution of) amoxicillin etc. N (%)	293 (100%)

NSAIDs: Non-steroidal anti-inflammatory drugs; ENT: ear, nose and throat
% Percentage of PIMs or PPOs calculated from the total number of PIMs or PPO detected

The criterion on prescribing amoxicillin in mg (IO-1) was not analyzable due to the fact that this drug is prescribed in great quantity. Among 100 prescriptions randomly assessed in hospital extractions, 97 prescriptions were inappropriate. Nonetheless, one analysis on acute otitis media alone identified a rate of 99.5% (807/811) of prescriptions issued without specification of the doses in mg for oral amoxicillin. In community care, this was observed in 97% of prescriptions, in 13.2% of patients (Table 5).

PIMs classed by age were presented in the figure 4. Potential factors associated with PIM or PPO are presented in Appendix 2a, b. On univariate analysis, only different age categories were associated with risk of PIM or PPO in hospital setting. In community setting, the number of medications (drugs) per prescription and different age categories were found to be significantly associated with risk of PIM or PPO on univariate analysis. In the multivariable logistic regression model, the same results were obtained.

DISCUSSION

This is the first study to observe the prevalence of PIMs and PPOs in a pediatric population. In the literature, the tool detected PIMs/PPOs in a geriatric population. [22,40–42] The two

populations are not comparable. Respiratory and digestive pathologies are typical in children and not so in a geriatric population, which is concerned by cardiovascular and nervous central system diseases.[22,40,43].

Domperidone was frequently prescribed in a community setting, yet this drug is responsible for cardiac adverse effects such as QT prolongation. This side effect is described in the literature in adult populations and pediatric populations. Detecting of this prescription will enable us to avoid cardiac risks. [44–49]

Prevalence of beta2 agonists or corticosteroids in an infant's first case of bronchiolitis is 6.4% (25/386 cases), lower than that observed in a study of another French area in 2012 (41%).[50–52] Use of beta2 agonists in a first case of bronchiolitis has no impact on oxygen saturation, length of hospitalization or length of illness. They concurrently cause side effects as tachycardia, oxygen saturation, and tremors. [53] Implementation of guidelines has permitted to decrease beta2 agonist and corticosteroid use in a French hospital without increase morbidity. [54]

Unnecessary exposure to cough suppressants, pholcodine, nasal or oral decongestants was also observed frequently in this sector.[55] In Norway, all drugs containing pholcodine have been refused marketing authorization for March 2007. As of this date, a decrease in sensitization to suxamethonium used in anesthesia and a decrease of 30-40% cases of anaphylaxis were identified. [56]

Our tool enabled us to detect rare PIMs but with a major impact, such as opioid use for migraines. The use of opioids for this disease induces a transition from episodic to chronic headaches and an increase of sensitivity to pain.[57–59]

Overuse of medication overuse, in particular opioids, could contribute to the chronicity of headaches in 20–30% of children and adolescents with chronic daily headaches.[59]

In the management of diarrhea caused by gastroenteritis, in hospital, our study found that it was common to omit prescription of an oral rehydration solution (ORS): 14% (237/1643 case). Even so, this rate is lower than that found in another national study in 2007 (29%).[60] However, ORSs prevent hospitalization in cases of acute gastroenteritis. In the United Kingdom, the use of ORSs has enabled a decrease from 300 deaths/year in 1970s to 25 deaths/year in 1980s.[61,62]. The need for ORS prescriptions was confirmed by the recommendation of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in 2014.[63]

As estimated, the child aged between 0 and 12 years has the highest risk of presenting with a PIM, according to a multivariate analysis. No inappropriate prescriptions or omissions were detected for patients aged less than 28 days. As we know, they are also affected by off-label drug prescriptions, which is consistent with reports from other sources.[64,65] As with geriatrics, an increase in numbers of medications can be associated with PIM.[40] Prescriptions issued from hospitals elicit fewer PIMs than those issued by the community. The main reason for this is that many drugs are not available in this hospital, such as cough suppressants, Rhinotrophyl® (tenoate ethanolamine), domperidone, etc. This shows that many PIM are preventable in a hospital setting. An efficient method for prevention of PIM could be to focus on the prescribing habits of physicians and thus have an impact on the selection of drugs, thereby reducing the rate of PIM.

Our study has several limitations. Firstly, it is a retrospective and monocentric study. Our result in the hospital could be underestimated. In addition, several criteria could not be analyzed due to the large number of prescriptions (for example, those for fever or pain which

are associated with many diseases) or absence of a specific pathology (mosquitos, lice, hyperactivity etc.). Antibiotic prophylaxis, vitamin supplements, proposition of vaccination etc. can be analyzed in prospective studies. A lack of clinical information is the main limitation in detection in a community setting. This also constitutes a challenge for pharmaceutical care review in elderly patients.[66] However, a certain amount of PIM was identified using POPI. Our study showed that there are many criteria which could be detected without access to clinical information and are easy to identify. Moreover, community pharmacists, in their practice, can extrapolate diagnoses from their experience, from common indications or by interviewing their patient. The study presents a limitation regarding the URQUAL software, from which the number of medications per prescription could not be extracted.

This is the first study which permits to evaluate prevalence of PIM and PPO in pediatrics prescription. Detecting of PIMs/PPOs would improve patient care, and prevent hospitalization and adverse drug reactions. A stepped wedge randomized cluster multicenter study will be conducted to prove if POPI decreases number of PIM and PPO. It is also necessary to evaluate the impact of this tool on reducing adverse drugs events, both in consultation or upon hospitalization. The impact of pharmacists in providing appropriate prescriptions should be also evaluated. Subsequently, this tool may be proposed to several professional societies such as the French Society for Pediatricians and the French Society of Clinical Pharmacy to make its use more widespread. The tool should be regularly updated to reflect recent events and to specify certain criteria.

To facilitate its use, this tool can be presented as a mobile app, a small handbook or be installed into prescription software. In summary, we hope that POPI could be a practical option used to reduce medication errors and to improve the suitability of prescriptions. It

provides rapid detection of PIM and PPO and can also open up a discussion on the relationship between the doctor and the pharmacist to remedy the issue at hand.[67]

CONCLUSION

Our study was carried out in in two sectors, hospital and community, and provides a global view of PIM and PPO in pediatric patients. POPI has a clinical impact and plays a role in improving prescription quality in various sectors and patient care. POPI should be applied in different services to deepen and reinforce its utilization. A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice.

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ETHICS

This project was approved by the local research ethics committee (n°2015/218).

DISCLOSURE OF INTEREST

None Declared

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AUTHOR'S CONTRIBUTION

Sonia Prot-Labarthe, Aurore Berthe-Aucejo conceptualised and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Rym Boulkedid and HPK Nguyen carried out analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Xavier Bellettre, Thomas Weil, Olivier Bourdon reviewed and revised the manuscript and approved the final manuscript as submitted.

François Angoulvant and Patrick Albaret supplied data from hospital and community pharmacy and reviewed and revised the manuscript and approved the final manuscript as submitted.

DATA SHARING STATEMENT

We have no additional unpublished data

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Figure 1. Flow chart indicating the course of the study

* Prescriptions with only one medical device, dietary supplement or hygiene product, ED: Emergency department

Figure 2. Distribution of number of prescriptions according to age category in hospital and community settings

Figure 3. Comparison of PIMs detected in hospital and in outpatient care

Figure 4. Total prescription and PIMs in both hospital and outpatient care: Percentage distribution by age group

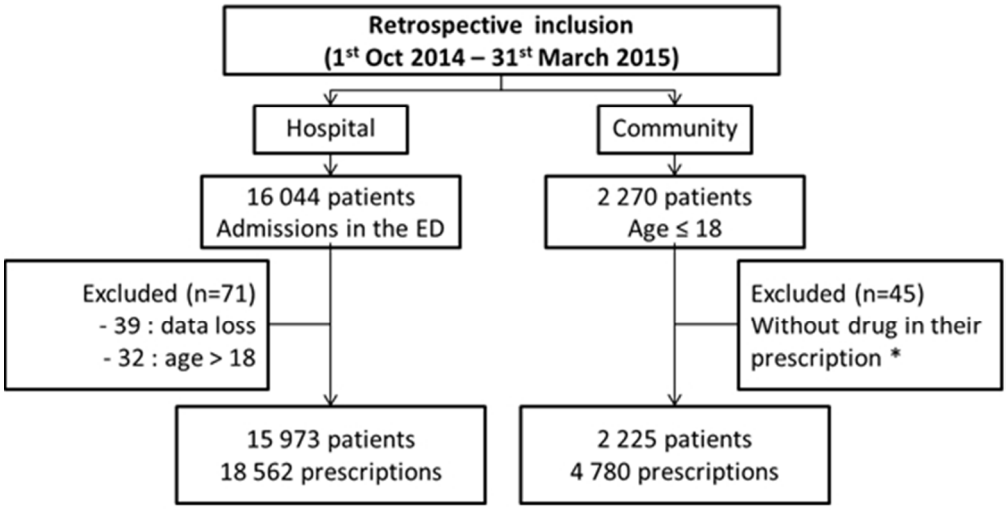

Figure 1. Flow chart indicating the course of the study† * Prescriptions with only one medical device, dietary supplement or hygiene product, ED: Emergency department

51x27mm (300 x 300 DPI)

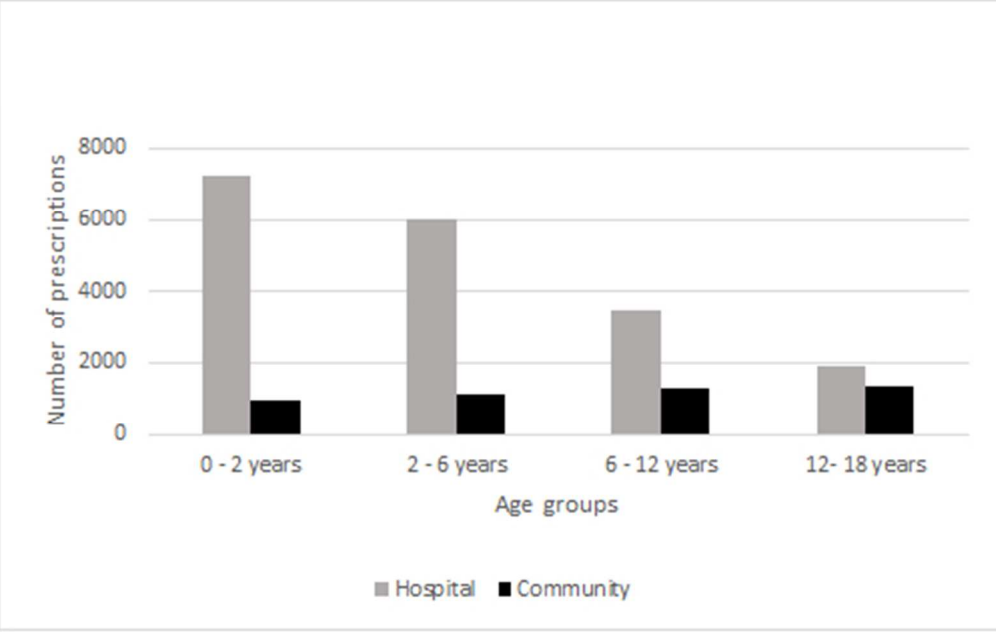

Figure 2. Distribution of number of prescriptions according to age category in hospital and community settings

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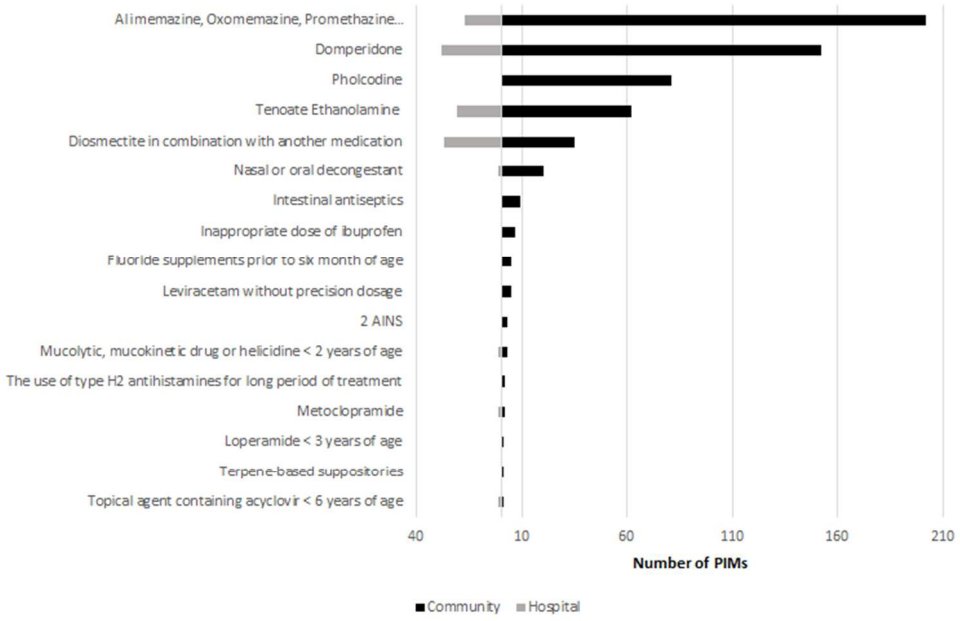

Figure 3. Comparison of PIMs detected in hospital and in outpatient care

254x190mm (300 x 300 DPI)

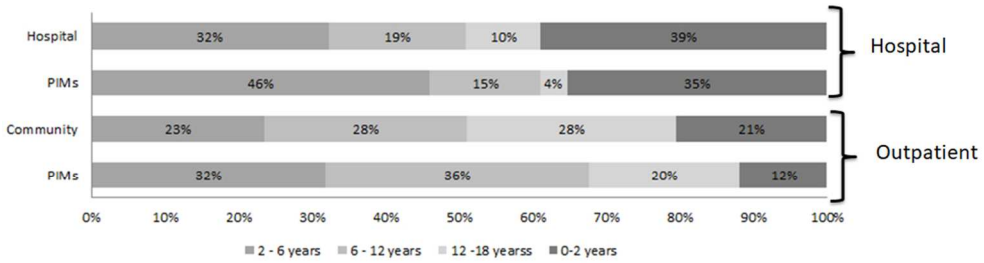

Figure 4. Total prescription and PIMs in both hospital and outpatient care: Percentage distribution by age group

90x23mm (300 x 300 DPI)

Appendix 1. Description of inclusion/exclusion criteria, data collected and POPI criteria analyzed among the two cohorts

	Hospital	Community
Inclusion criteria	Patient under 18 years old Patient with one or more medicine prescriptions	Patient under 18 years old Patient with one or more medicine prescriptions
Exclusion criterion	Inaccessible medical records for patients	Prescription without any drug prescribed
Software extracted	Urqual®	Opus®
Data collected	Age Sex Weight Current diagnosis Number of prescriptions	Age Number of prescriptions Number of drugs per prescription
Number of POPI items analyzed (among the 102 criteria)	82	28 (items usable for retrospective analysis if no diagnostic available)

Appendix 2a. Univariate and multivariate analysis to determine factors associated with PIM according to POPI criteria

Variable	Univariate analysis		Multivariate analysis	
Model 1: Hospital prescription	*OR* [CI 95%]*	*p-value*	*OR* [CI 95%]*	*p-value*
Sex				
Male	1			
Female	1.1 [0.9-1.3]	0.3		
Age category				
0 - 2 years	2.5 [1.6-3.9]	0.0001	2.5 [1.6-3.9]	< 0.001
2 - 6 years	4.0 [2.5-6.3]	< 0.0001	4.0 [2.5-6.3]	< 0.0001
6 - 12 years	2.2 [1.4-3.6]	0.0016	2.2 [1.4-3.6]	0.0016
12 - 18 years	1		1	
Model 2: Community prescription				
Age category				
0 - 2 years	0.8 [0.6-1.1]	0.1	0.7 [0.5-1.0]	0.06
2 - 6 years	2.0 [1.5-2.6]	< 0.0001	1.9 [1.4-2.4]	< 0.0001
6 - 12 years	1.9 [1.5-2.4]	< 0.0001	1.9 [1.5-2.5]	< 0.0001
12 - 18 years	1		1	
Number of medications per prescription	1.4 [1.3-1.6]	< 0.001	1.4 [1.3-1.6]	< 0.0001

OR: Odds ratio, CI: Confidence intervals.

Appendix 2b. Univariate and multivariate analysis to determine factors associated with PPO according to POPI criteria

Variable	Univariate analysis p		Multivariate analysis	
Model 1: Hospital prescription	*OR* [CI 95%]*	*p-value*	*OR* [CI 95%]*	*p-value*
Sex				
Male	1			
Female	1.1 [0.9 ; 1.3]	0.3053		
Age category				
0 - 2 years	1.1 [0.7 ; 1.6]	0.7703	1.1 [0.7 ; 1.6]	0.7703
2 - 6 years	1.4 [0.9 ; 2.1]	0.0761	1.4 [0.9 ; 2.1]	0.0761
6 - 12 years	1.9 [1.3 ; 2.8]	0.0015	1.9 [1.3 ; 2.8]	0.0015
12 - 18 years	1		1	
Model 2: Community prescription				
Age category				
0 - 2 years	6.1 [2.9 ; 12.7]	<0.0001	6.1 [2.9 ; 12.9]	<0.0001
2 - 6 years	22.4 [11.4 ; 44.1]	<0.0001	22.4 [11.3 ; 44.3]	<0.0001
6 - 12 years	9.8 [4.9 ; 19.6]	<0.0001	10.2 [5.1; 20.7]	<0.0001
12 - 18 years	1			
Number of medications per prescription	1.2 [1.1 ; 1.3]	<.0001	1.2 [1.2 ; 1.4]	<0.0001

OR: Odds ratio, CI: Confidence intervals.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	p5
Methods			
Study design	4	Present key elements of study design early in the paper	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P6 NA
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p6-7-14
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p15-16
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P16+figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	p17

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Appendix2
Discussion			
Key results	18	Summarise key results with reference to study objectives	p18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p22 to 24
Generalisability	21	Discuss the generalisability (external validity) of the study results	p24-25
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

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.

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Secondary Subject Heading:	General practice / Family practice
Keywords:	inappropriate prescription, omission, tool, detection

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.

A. Berthe-Aucejo[1,2], H.P.K Nguyen[1], F. Angoulvant[2,3], X. Bellettre[4], P. Albaret[5,6], T. Weil[1], R. Boulkedid[2,7,8], O. Bourdon[1,6,9,10], S.Prot-Labarthe[1,2,10]

[1] Department of Pharmacy, Robert-Debré Hospital, Paris, France

[2] UMR-S1123, ECEVE; Inserm U1123, Paris, France

[3] Emergency unit, Necker Hospital, Paris, France

[4] Emergency unit AP-HP, Robert-Debré Hospital, Paris, France

[5] Albaret Pharmacy, Cesson, France

[6] Clinical Pharmacy, Paris Descartes University, Paris, France

[7] Assistance publique-Hôpitaux de Paris, Hôpital Robert Debré, Clinical Epidemiology Unit, 75 019 Paris, France

[8] CIC-EC 1426, 75019 Paris, France

[9] Laboratoire Educations et Pratiques de Santé, Paris XIII University, Bobigny, France

[10] Groupe Pédiatrie de la Société Française de Pharmacie Clinique, Paris, France

Word count: 2639

Corresponding author

Dr Aurore Berthe-Aucejo, Service Pharmacie, AP-HP Hôpital Robert-Debré, 48 Boulevard Sérurier, 75019 Paris, Fax: 01-40-03-24-81, Tel: 01-40-03-57-41, Email: aurore.berthe84@gmail.com

Keywords

Inappropriate prescription, omission, tool, detection

ABSTRACT

Background and Objective: POPI **(**Pediatrics: Omission of Prescription and Inappropriate prescription) is the first detection tool for potentially inappropriate medicines (PIM) and potentially prescribing omissions (PPO) in pediatrics. The aim of this study was to evaluate the prevalence of PIM and PPO detected by POPI regarding prescriptions in hospital and for outpatients. The second objective is to determine the risk factors related to PIM and PPO.

Design: A retrospective, descriptive study was conducted in the emergency department (ED) and community pharmacy (CP) during 6 months. POPI was used to identify PIM and PPO.

Setting: Robert-Debré Hospital (France) and Albaret community pharmacy (Seine and Marne).

Participants: Patients who were under 18 years old and who had one or more drugs prescribed were included. Exclusion criteria consisted of inaccessible medical records for patients consulted in ED and prescription without drugs for outpatients.

Primary and secondary outcome measures: PIM and PPO rate and risk factors

Results: At the ED, 18,562 prescriptions of 15,973 patients and 4,780 prescriptions of 2,225 patients at the CP were analyzed. The PIM rate and PPO rate were respectively 2.9% and 2.3% at the ED and 12.3% and 6.1% at the CP. Respiratory and digestive diseases had the highest rate of PIM.

Conclusion: This is the first study to assess the prevalence of PIM and PPO detected by POPI in a pediatric population. This study assessed PIMs or PPOs within a hospital and a community pharmacy. POPI could be used to improve drug use and patient care, and to limit hospitalization and adverse drug reaction. A prospective multicentric study should be conducted to evaluate the impact and benefit of implementing POPI in clinical practice.

Strengths and limitations of this study

- This study is the first to observe the prevalence of PIM and PPO in a pediatric population.

- It is a retrospective and monocentric study. The prevalence of PIM and PPO may be underestimated (large number of prescriptions, absence of specific pathology). Some criteria could only be analyzed in a prospective study. The lack of clinical information is the main limit to detection in a community setting.

- Many omissions and inappropriate prescriptions can be easily detected with POPI despite limited clinical information.

INTRODUCTION

Inappropriate prescribing is a known preventable cause of adverse drug events (ADE) and has an important impact on public health and cost of care. [1,2] In the literature, ADE is defined by "an injury resulting from medical intervention related to a drug" (dose error, adverse drug reaction (ADR), misuse of medication such as antibiotics).[3–5] In the pediatric population, ADR during hospitalization was estimated between 0.6% and 33.7%, and between 1% and 1.5% for outpatients.[6–9] Incidence of ADR leading to admission was evaluated between 1.8% and 17.7%.[6,7,10] Many drugs were concerned in commonly used medication.[11–13]

The World Health Organization estimated that 50% of medications are prescribed and used inappropriately.[14] The most recent definition of inappropriate prescription (IP) encompasses potentially inappropriate medicines (PIM) and prescribing omissions (PPO).[15] In a report from the French National Authority for Health, PIMs are defined as "drugs being used in a situation in which the risks involved in treatment potentially outweigh the benefits, lack of demonstrated indication, high risk of ADE, or an unfavorable cost-effect or risk-benefit ratio exists". PPO or underuse of appropriate medication is defined as the absence of initiation of an effective treatment in subjects with a condition for which one or several drug classes have demonstrated their efficacy. In an elderly population, which presents with age-related physiological changes and high prevalence of polypharmacy, various measures have been developed to detect PIM such as: Beers' criteria, the Inappropriate Prescribing in the Elderly Tool, The Medication Appropriate Index, and STOPP/START (Screening Tool of Older Person's prescriptions/Screening Tool to Alert doctor to Right Treatment).[16–21]

Only the STOPP/START enables us to detect under-prescription.[15] Using these tools, many studies have been carried out which have detected that inappropriate prescriptions range from 35% to 51% in the above population.[22–26]

Omission of prescriptions in geriatric population detected by the START tool concerned 58%-61% of patients.[27,28] Negative outcomes related to an IP such as side effects, hospitalization, mortality and utilization of resources were also highlighted.[21,29–31]

Prescribing in a pediatric population is always challenging for physicians. It is often empirical and primarily based on safety and pharmacology information obtained in adults.[32] This is a worry not only in a hospital or general practitioner setting but also for the community pharmacists. With many off-label uses, they may be obligated to find alternative information sources , and might even dispense infrequently for this vulnerable population.[33] ADRs are three time higher in pediatric populations. This frequency is explained by the vulnerability of children, pharmacokinetic changes during childhood and pediatric off-label drug used.[4,34] Large differences relating to treatment were seen within and between countries.[6,35] Questions about the rationale of prescriptions could be asked.[36] Optimizing children's care is based on rational prescribing and aims for a decrease in side effects.[35,36] In order to improve the correct drug use and optimize practice, the first tool of detection for PIM and PPO was created by Prot-Labarthe *et al.* in 2013. The tool was named POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions) (Table 1).[37,38] Presently, the complete tool has yet to be tested in clinical practice and the prevalence of PIM and OP is not known.

Our first aim is to assess the prevalence of PIM and PPO detected using POPI in hospital and outpatient care. This is its first application, focusing on prescriptions extracted from the emergency department and the community pharmacy. Our second objective is to determine the risk factors related to PIM and PPO.

METHODS

Population

A retrospective and descriptive study was conducted in the emergency department (ED) of AP-HP Robert-Debré hospital (Paris) - the largest French pediatric hospital - and the Albaret community pharmacy (CP) (Seine and Marne). Inclusion criteria included patients who were under 18 years old and who had one or more drug prescriptions between 1st October 2014 and 31st March 2015. Prescription was defined as one or more lines of drugs prescribed by a physician. Exclusion criteria consisted of inaccessible medical records for ED patients and prescription without drugs for outpatients. POPI contains 101 criteria (76 PIMs, 25 PPO. A literature review was done to obtain criteria. Criteria were categorized according to physiological systems (gastroenterology, respiratory infections, pain, neurology, dermatology and miscellaneous). Criteria were validated by a 2-round-Delphi consensus technique.[38]

Data collection

The prescriptions given on leaving hospital emergency department were extracted from the Urqual software V5® (*) (McKesson Corp, Paris, France). Urqual® is an emergency prescription software which is used in many French hospitals. Patient information including age, sex, weight, medical prescription and current diagnosis was collected. Medical histories and clinical examinations were consulted individually when necessary. Due to the significant amount of data, clinical files of the ED were analyzed, based on primary diagnosis. Prescriptions for secondary diagnosis were not evaluated. For this study, 82/101 criteria were analyzed (Table 1). Some criteria could not be used for a hospital setting.

The data extracted from Urqual software give only the first drug per prescription for each diagnosis (impossibility to extract all drugs for all prescriptions). To have every medications concerning the primary diagnosis, the prescription was then manually analyzed for each diagnosis to evaluate presence of PIM/PPO. Consequently, the number of medications per prescription was not included. However, all prescriptions have been manually reviewed

directly from medical files by two authors. For each targeted disorder, the prescription was analyzed to detect PIMs or PPOs.

Table 1. POPI - Pediatrics: Omission of Prescriptions & Inappropriate prescriptions

DIVERSE ILLNESSES	**A- PAIN AND FEVER**	
	Inappropriate prescriptions	**Omissions**
	AI-1. Prescription of two alternating antipyretics as a first-line treatment. **AI-2.** Prescription of a medication other than paracetamol as a first line treatment (except in the case of migraine). **AI-3.** Rectal administration of paracetamol as a first-line treatment. **AI-4.** The combined use of two NSAIDs. * ◦ **AI-5.** Oral solutions of ibuprofen administered in more than three doses per day using a graduated pipette of 10mg/kg (other than Advil ®). ◦ **AI-6.** Opiates to treat migraine attacks. *	**A0-1.** Failure to give sugar solution to new-born babies and infants under four months old two minutes prior to venipuncture. **A0-2.** Failure to give an osmotic laxative to patients being treated with morphine for a period of more than 48 hours.
	B- URINARY INFECTIONS	
	Inappropriate prescriptions	
	BI-1. Nitrofurantoin used as a prophylactic. * **BI-2.** Nitrofurantoin used as a curative agent in children under six years of age, or indeed any other antibiotic if avoidable. * **BI-3.** Antibiotic prophylaxis following an initial infection without complications (except in the case of uropathy). * **BI-4.** Antibiotic prophylaxis in the case of asymptomatic bacterial infection (except in the case of uropathy). *	
	C- VITAMIN SUPPLEMENTS AND ANTIBIOTIC PROPHYLAXIS	

	Inappropriate prescriptions	Omissions
	CI-1. Fluoride supplements prior to six months of age. ◦*	CO-1. Insufficient intake of vitamin D. Minimum vitamin D intake: ▪ Breastfed baby = 1,000 to 1,200 IU/day ▪ Infant < 18 months of age (milk enriched with vitamin D) = 600 to 800 IU/day ▪ Child aged between 18 months and five years, and adolescents aged between 10 and 18 years: two quarterly loading doses of 80,000 to 100,000 IU/day in winter (adolescents can take this as one dose). CO-2. Antibiotic prophylaxis with phenoxymethylpenicillin (Oracilline) starting from two months of age and lasting until five years of age for children with sickle-cell anemia: 100,000 IU/kg/day (in two doses) for children weighing 10kg or less and 50,000 IU/kg/day for children weighing over 10kg (also in two doses). *
	D- MOSQUITOS	
	Inappropriate prescriptions	**Omissions**
	DI-1. The use of skin repellents in infants less than six months old and picardin in children less than 24 months old. DI-2. Citronella (lemon grass) oil (essential oil). DI-3. Anti-insect bracelets to protect against mosquitos and ticks. DI-4. Ultrasonic pest control devices, vitamin B1, homeopathy, electric bug zappers, sticky tapes without insecticide.	DO-1. **DEET** ‘‘30%’’ (max) before 12 years old ‘‘50%’’ (max) after 12 years old. DO-2. **IR3535** ‘‘20%’’ (max) before 24 months old ‘‘35%’’ (max) after 24 months old. DO-3. Mosquito nets and clothes treated with pyrethroids.
PROBLEMS	**E- NAUSEA, VOMITTING, OR GASTROESOPHAGEAL REFLUX**	
	Inappropriate prescriptions	**Omissions**
	EI-1. Metoclopramide. * ◦ EI-2. Domperidone. * ◦ EI-3. Gastric antisecretory drugs to treat gastroesophageal reflux, dyspepsia, the crying of new-born babies (in the absence of	EO-1. Oral rehydration solution in the event of vomiting.*

any other signs or symptoms), as well as faintness in infants. *

EI-4. The combined use of proton pump inhibitors and NSAIDs, for a short period of time, in patients without risk factors. *

EI-5. Oral administration of an intravenous proton pump inhibitor (notably by nasogastric tube). *

EI-6. The use of type H2 antihistamines for long periods of treatment. * ◦

EI-7. Erythromycin as a prokinetic agent. *

EI-8. The use of setrons (5-HT3 antagonists) for chemotherapy-associated nausea and vomiting. *

F- DIARRHEA

Inappropriate prescriptions	Omissions
FI-1. Loperamide before 3 years of age.*°	**FO-1.** Oral rehydration solution in the event of diarrhea.*
FI-2. Loperamide in the case of invasive diarrhea.*	
FI-3. The use of Diosmectite (Smecta®) in combination with another medication.*°	
FI-4. The use of Saccharomyces boulardii (Ultralevure) in powder form, or in a capsule that has to be opened prior to ingestion, to treat patients with a central venous catheter or an immunodeficiency.*	
FI-5. Intestinal antiseptics.*°	

ENT-PULMONARY PROBLEMS

G- COUGH

Inappropriate prescriptions	Omissions
GI-1. Pholcodine. * ◦	**GO-1.** Failure to propose a whooping cough booster vaccine for adults who are likely to become parents in the coming months or years (only applicable if the previous vaccination was more than 10 years ago). This booster vaccination should also be proposed to the family of expectant parents and those in contact with them (parents, grand-parents, nannies/child minders).
GI-2. Mucolytic drugs, mucokinetic drugs, or helicidine before two years of age. * ◦	
GI-3. Alimemazine (Theralene®), oxomemazine (Toplexil®), promethazine (Phenergan®), and other types. * ◦	
GI-4. Terpene-based suppositories. * ◦	

H- BRONCHIOLITIS IN INFANTS

Inappropriate prescriptions	Omissions
HI-1. Beta2 agonists, corticosteroids to treat an infant's first case of bronchiolitis. *	**HO-1.** 0.9% NaCl to relieve nasal congestion (not applicable if nasal congestion is already being treated with 3% NaCl delivered by a nebulizer). *
HI-2. H1-antagonists, cough suppressants, mucolytic drugs, or ribavirin to treat bronchiolitis. *	**HO-2.** Palivizumab in the following cases: (1) babies born both at less than 35 weeks of gestation and less than six months prior to the onset of a seasonal RSV epidemic; (2) children less than two years old who have received treatment for bronchopulmonary dysplasia in the past six months; (3) children less than two years old suffering from congenital heart disease with hemodynamic abnormalities.
HI-3. Antibiotics in the absence of signs indicating a bacterial infection (acute otitis media, fever, etc.). *	

I- ENT INFECTIONS

Inappropriate prescriptions	Omissions
II-1. An antibiotic other than amoxicillin as a first-line treatment for acute otitis media, strep throat, or sinusitis (provided that the patient is not allergic to amoxicillin). An effective dose of amoxicillin for an pneumococcal infection is 80–90 mg/kg/day and an effective dose for a streptococcal infection is 50 mg/kg/day.*	**IO-1.** Doses in mg for drinkable (solutions of) amoxicillin or josamycin. *◦
II-2. Antibiotic treatment for a sore throat, without a positive rapid diagnostic test result, in children more than three years old.*	**IO-2.** Paracetamol combined with antibiotic treatment for ear infections to relieve pain. *
II-3. Antibiotics for nasopharyngitis, congestive otitis, sore throat before three years of age, or laryngitis; antibiotics as a first-line treatment for acute otitis media showing few symptoms, after two years of age.*	
II-4. Antibiotics to treat otitis media with effusion (OME), except in the case of hearing loss or if OME lasts for more than three months.*	
II-5. Corticosteroids to treat acute suppurative otitis media, nasopharyngitis, or strep throat.*	
II-6. Nasal or oral decongestant (oxymetazoline	

(Aturgyl®), pseudoephedrine (Sudafed®), naphazoline (Derinox®), ephedrine (Rhinamide®), tuaminoheptane (Rhinofluimicil®), phenylephrine (Humoxal®)).*◦

II-7. H1-antagonists with sedative or atropine-like effects (pheniramine, chlorpheniramine), or camphor; inhalers, nasal sprays, or suppositories containing menthol (or any terpene derivatives) before 30 months of age.* ◦

II-8. Ethanolamine tenoate (Rhinotrophyl®) and other nasal antiseptics.* °

II-9. Ear drops in the case of acute otitis media.*

J- ASTHMA

Inappropriate prescriptions	Omissions
JI-1. Ketotifen and other H1-antagonists, sodium cromoglycate. *	**JO-1.** Asthma inhaler appropriate for the child's age.
JI-2. Cough suppressants. *	**JO-2.** Preventative treatment (inhaled corticosteroids) in the case of persistent asthma. *

DERMATOLOGICAL PROBLEMS

K-ACNE VULGARIS

Inappropriate prescriptions	Omissions
KI-1. Minocycline.* °	**KO-1.** Contraception (provided with a logbook/diary) for menstruating girls taking isotretinoin.
KI-2. Isotretinoin in combination with a member of the tetracycline family of antibiotics.* °	**KO-2.** Topical treatment (benzoyl peroxide, retinoids, or both) in combination with antibiotic therapy. *
KI-3. The combined use of an oral and a local antibiotic.*	
KI-4. Oral or local antibiotics as a monotherapy (not in combination with another drug).*	
KI-5. Cyproterone+ethinylestradiol (Diane 35®) as a contraceptive to allow isotretinoin per os.* °	
KI-6. Androgenic progestins (levonorgestrel, norgestrel, norethisterone, lynestrenol, dienogest, contraceptive implants or vaginal rings).*	

L- SCABIES

Omissions
LO-1. A second dose of ivermectin two weeks after the first. *
LO-2. Decontamination of household linen and clothes and treatment for other family members.

M- LICE

Inappropriate prescriptions
MI-1. The use of aerosols for infants, children with asthma, or children showing asthma-like symptoms such as dyspnea.

N- RINGWORM	
Inappropriate prescriptions	**Omissions**
NI-1. Treatment other than griseofulvin for Microsporum. *	**NO-1.** Topical treatment combined with an orally-administered treatment. * **NO-2.** Griseofulvin taken during a meal containing a moderate amount of fat. * ◦

O-IMPETIGO

Inappropriate prescriptions
OI-1. The combination of locally applied and orally administered antibiotics.* **OI-2.** Fewer than two applications per day for topical antibiotics.* **OI-3.** Any antibiotic other than mupirocin as a first-line treatment (except in cases of hypersensitivity to mupirocin).*

P- HERPES SIMPLEX	
Inappropriate prescriptions	**Omissions**
PI-1. Topical agents containing corticosteroids. * **PI-2.** Topical agents containing acyclovir before six years of age. * ◦	**PO-1.** Paracetamol during an outbreak of herpes. * **PO-2.** Orally administered acyclovir to treat primary herpetic gingivostomatitis. *

NEUROPSYCHIATRIC DISORDERS

Q-ATOPIC DERMATITIS

Inappropriate prescriptions

QI-1. A strong topic steroid (clobetasol propionate 0.05% Dermoval, betamethasone dipropionate Diprosone) applied to the face, armpits or groin, and to the backside of babies or young children. *
More than one application per day of a topical steroid, except in cases of severe lichenification. *
QI-2. Local or systemic antihistamine during the treatment of outbreaks. *
QI-3. Topically applied 0.03% tacrolimus before two years of age. *◦
Topically applied 0.1% tacrolimus before 16 years of age.
QI-4. Oral corticosteroids to treat outbreaks. *

R- EPILEPSY

Inappropriate prescriptions

RI-1. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin in the case of myoclonic epilepsy. *
RI-2. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabaline, tiagabine, or vigabatrin in the case of epilepsy with absence seizures (especially for childhood absence epilepsy or juvenile absence epilepsy). *
RI-3. Levetiracetam, oxcarbamazepine in mL or in mg without systematically writing XX mg per Y mL. * ◦

S-DEPRESSION

Inappropriate prescriptions

SI-1. An SSRI antidepressant other than fluoxetine as a first-line treatment (in the case of pharmacotherapy). *
SI-2. Tricyclic antidepressants to treat depression. *

T- NOCTURNAL ENURESIS

Inappropriate prescriptions

TI-1. Desmopressin administered by a nasal spray. * ◦

Desmopressin in the case of daytime symptoms.

TI-2. An anticholinergic agent used as a monotherapy in the absence of daytime symptoms. *
TI-3. Tricyclic agents in combination with anticholinergic agents. * ◦
TI-4. Tricyclic agents as a first-line treatment. *

U- ANOREXIA

Inappropriate prescriptions

UI-1. Cyproheptadine (Periactin®), clonidine * ◦

V- ATTENTION DEFICIT DISORDER WITH OR WITHOUT HYPERACTIVITY

Inappropriate prescriptions	Omissions
VI-1. Pharmacological treatment before age six (before school), except in severe cases. *	VO-1. Recording a growth chart (height and weight) if the patient is taking methylphenidate. *
VI-2. Antipsychotic drugs to treat attention deficit disorder without hyperactivity. *	
VI-3. Slow release methylphenidate as two doses per day, rather than only one dose. *◦	

* Criteria analyzed in emergency department

◦ Criteria analyzed in community pharmacy

Data from the community pharmacy were obtained from the pharmacy management software OPUS® (Computer PG, France). Patient's age and drugs prescribed were collected. Current diagnosis and sex are not available in the OPUS software, so the number of patients per pathology and the number of prescriptions per pathology were lacking. Only drugs that did not require an assessment of diagnosis (for example domperidone, metoclopramide etc.) were included (Table 1) (28 criteria/101).

Among the 5 criteria including analgesics and antipyretics, only three were evaluated due to an overwhelming number of prescriptions, and their association with many diseases. Pathologies analyzed by POPI were the same in emergency department and in community. Summary of data and inclusion criteria are detailed in Appendix 1.

Statistical analysis

Data were presented as continuous variables (age, number of prescriptions by patient, number of medications per prescription) and were presented as median and interquartile range (25th-75th percentiles) or mean (standard deviation), minimum and maximum depending on normal distribution.

Mixed effects logistic regression modelling for repeated measurements was applied to identify factors associated with PIM and PPO (yes/no) in the hospital and community settings. Unit of analysis was "the prescription".

Univariate models were performed using different candidate factors as:

- For model performed with hospital data: sex and age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years);
- For model performed with community data: age (0 days - 2 years, 2 - 6 years, 6 - 12 years, 12 - 18 years) and number of medications (drugs) per prescription;

The model was constructed using the parameters of the univariate analysis, which showed at least a trend toward significance, with a cut-off of p=0.2. Odds ratios (OR) with 95% confidence intervals (CI) were estimated. Statistical significance was established at $p<0.05$. SPSS-22® software (SPSS Inc., Chicago, IL, USA) and SAS 9.4 were used for analysis.

This project was approved by the local research ethics committee (n°2015/218).

Patient and Public Involvement

No Patient and Public involvement

RESULTS

In the emergency department, 18,562 prescriptions for 15,973 patients were analyzed. Around 11,500 prescriptions were reviewed manually that's 9500 patients. 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. Among the patients, 29% had at least two visits in 6 months. In the community pharmacy, 4,780 prescriptions for 2,225 patients were evaluated (Figure 1). In ED and CP, 53% of patients had been issued one prescription, 21% with two and 26% with three or more prescriptions. The population's characteristics and the frequency of pathologies were presented in Table 2. Distribution of number of prescriptions by age category was described in the Figure 2.

Table 2. Characteristics of the study population

Population characteristics	Hospital (N=15,973)	Community (N=2,225)
Age (years) mean (SD) Min, Max	4.9 (4.5) 0-18	7.9 (5.3) 0-18
Female gender N(%)	8,769 (54.9)	NA
Number of prescriptions/patient mean (SD) Min, Max	1.4 (0.9) 1-12	2.2 (1.9) 1-16

Number of drugs per prescription mean (SD) Min, Max	NA	2.4 (1.6) 1-22
Number of prescriptions by pathology N(%)		
Digestive disorders	2,728 (14.7)	NA
ENT-Pulmonary disorders	8,397 (45.2)	NA
Dermatological disorders	604 (3.3)	NA
Neuropsychiatric disorders	242 (1.3)	NA
Other illnesses[#]	6,591 (35.5)	NA

NA: Not available; ENT: ear, nose and throat
[#] *For example, traumatic injury, pain, sickle cell disease*

In the hospital, POPI identified 541 PIMs in 2.9% of the prescriptions analyzed. They were detected in 3.3% of the patients (n=530). PPOs were detected in 2.3% of prescriptions for 2.7% of patients. In the community, PIMs and PPOs represented 12.3% and 6.1% of all prescriptions, affecting 26.4% and 11.3% patients respectively (Table 3).

Table 3. Potentially Inappropriate Medications (PIMs) and Potential Prescription Omission (PPOs) identified by POPI

	Hospital N (%)	**Community N (%)**
Number of prescriptions (N)	**18,562**	**4,780**
PIMs identified per prescription		
1	519 (2.8%)	551 (11.5%)
2	11 (0.1%)	37 (0.8%)

Prescriptions with at least one PIM	530 (2.9%)	588 (12.3%)
PPOs identified per prescription		
1	424 (2.3 %)	293 (6.1%)
Number of patients (N)	**15,793**	**2,225**
Patients with at least one PIM °	530 (3.3%)	588 (26.4%)
Patients with at least one PPO	424 (2.7%)	251 (11.3%)

Table 4 presents the prevalence of PIMs (or PPOs) in the ED in patients with the targeted disorders. Patients with the targeted disorders represent the individuals who were at risk of each PIM/PPO. Table 5, however, presents the PIMs (or PPOs) as a proportion of the total number of PIMs (or PPOs) in the community pharmacy. Respiratory and digestive diseases had the highest rate of PIM in hospital and community pharmacy. For various illnesses, we removed one criterion involving medicines containing codeine because of their new contraindication in children under 12 years old.[39] However, the prescription of codeine was observed in 18 cases. According to our comparison of PIMs detectable in both settings, out-of-hospital medication always presents with higher prevalence of PIMs (Figure 3).

Table 4. Prevalence of PIMs and PPOs identified by POPI in hospital

Criteria		**No. of PIMs**	**No. of patients with the targeted disorders**	**% of PIMs in patients with the targeted disorders**
Potentially inappropriate medications (PIMs)		**541**	**7,304**	**7.4%**
Various illnesses		**3**	**64**	**4.6%**
AI-6	Opiates to treat migraine attacks	3	64	4.6%
Digestive disorders		**56**	**1,956**	**2.8%**
EI-2	Domperidone	28	1,956	1.4%
FI-3	The use of Diosmectite (Smecta®) in	27	1,956	1.4%

	combination with another medication			
EI-1	Metoclopramide	1	1,956	0.05%
ENT-Pulmonary disorders		**472**	**5,163**	**9.1%**
II-4	Antibiotics to treat acute suppurative otitis media etc.	2	7	28.6%
II-2	Antibiotic treatment for a sore throat, without a positive RDT.	23	160	14.4%
II-9	Ear drops in the event of acute otitis media	86	1,083	7.9%
HI-1	Beta2 agonist, corticosteroids to treat an infant's first case of bronchiolitis	25	386	6.4%
II-5	Corticosteroids to treat acute suppurative otitis media etc.	190	3,616	5.2%
II-1	An antibiotic other than amoxicillin as a first-line treatment.	59	1,259	4.7%
JI-1	H1-antagonist to treat asthma	9	802	1.1%
II-8	Tenoate Etanolamine (Rhinotrophyl®) and other nasal antiseptics	21	2,455	0.8%
II-3	Antibiotics for nasopharyngitis	26	3,444	0.7%
GI-3	Alimemazine (Theralene®), oxomemezine (Toplexil®) etc.	18	2,585	0.7%
JI-2	Cough suppressants to treat asthma	5	802	0.6%
HI-2	H1-antagonists, cough suppressants etc. to treat bronchiolitis	2	386	0.5%
II-7	H1-antagonists with sedative or atropine-like effects.	4	2,585	0.2%
GI-2	Mucolytics drugs, mucokinetics drugs or helicidine before 2 years of age	1	2,585	< 0.1%
II-6	Nasal or oral decongestant etc.	1	2,455	< 0.1%
Dermatological disorders		**10**	**100**	**10%**
OI-1	A combination of locally applied and orally administered antibiotics	9	32	28.1%
PI-2	Topical agents containing acyclovir administered to a child under six years of age	1	68	1.5%
		No. of PPO	**No. of patients with the targeted disorders**	**% of PIMs in patients with the targeted disorders**
Potentially Prescribing Omissions (PPO)		**424**	**4,508**	**9.4%**
Digestive disorders		**372**	**1,956**	**19.0%**
EO-1	Oral rehydration solution in the event of vomiting	135	313	43.1%
FO-1	Oral rehydration solution in the event of diarrhea	237	1,643	14.4%
ENT-Pulmonary disorders		**51**	**1,469**	**3.5%**
HO-1	0.9% NaCl to relieve nasal congestion etc.	38	386	9.8%
IO-2	Acetaminophen combined with antibiotic	13	1,083	1.3%

	treatment for ear infections etc.			
Dermatological disorders		**1**	**3**	**33.3%**
NO-2	Griseofulvin taken during a meal containing a moderate amount of fat	1	3	33.3%

ENT: ear, nose and throat; No: Number; RDT: Rapid diagnostic test.
% Percentage calculated by the number of PIMs or PPO detected from the total number of analyzable cases
**the number of patients with the targeted disorder corresponds to patients with clinical situations at risk of PIM or PPO*

Table 5. Most frequently occurring PIMs and PPOs identified by POPI in community setting

Criteria	Proportion of PIMs per disorder according to total number of PIMs N(%)
Total number of Potentially Inappropriate Medications (PIMs) N= 625	
Various illnesses	**15 (2.4)**
AI-5 Oral solutions of ibuprofen administered in more than 3 doses etc.	7 (1.1)
CI-1 Fluoride supplements prescribed to infants under six months of age	5 (0.8)
AI-4 The combined use of two NSAIDs	3 (0.5)
Digestive disorders	**201 (32.2)**
EI-2 Domperidone	152 (24.3)
FI-3 The use of Diosmectite (Smecta®) in combination with another medication	35 (5.6)
FI-5 Intestinal antiseptics	9 (1.5)
EI-1 Metoclopramide	2 (0.3)
EI-6 The use of type H2 antihistamines for long periods of treatment	2 (0.3)
FI-1 Loperamide before 3 years of age	1 (0.2)
ENT-Pulmonary disorders	**403 (64.4)**
GI-3 Alimemazine (Theralene®), oxomemazine (Toplexil®), etc.	202 (32.2)
GI-1 Pholcodine	81 (13.0)
II-8 Etanolamine tenoate (Rhinotrophyl®) and other nasal antiseptics	96(15.3)
II-6 Nasal or oral decongestant etc.	20 (3.2)
GI-2 Mucolytic drugs, mucokinetic drugs or helicidine prescribed to a child under 2 years of age	3(0.5)
GI-4 Terpene-based suppositories	1(0.2)
Dermatological disorders	**1(0.2)**

PI-2 Topical agents containing acyclovir prescribed to a child under six years of age	1(0.2)
Neuropsychiatric disorders	**5 (0.8)**
RI-3 Levetiracetam in mL or in mg prescribed without systematically indicating XX mg per Y mL	5(0.8)
	Proportion of PIM per disorder according to total number of PIM N(%)
Potential Prescribing Omissions (PPOs) N= 293	
IO-1 Dose in mg for oral (solution of) amoxicillin etc. N (%)	293 (100%)

NSAIDs: Non-steroidal anti-inflammatory drugs; ENT: ear, nose and throat
% Percentage of PIMs or PPOs calculated from the total number of PIMs or PPO detected

The analysis of criterion regarding the prescription of amoxicillin in mg (IO-1) was not possible due to the fact that this drug is prescribed in great quantity. Among 100 prescriptions randomly assessed in hospital extractions, 97 prescriptions were inappropriate. Nonetheless, one analysis on acute otitis media alone identified a rate of 99.5% (807/811) of prescriptions issued without specification of the doses in mg for oral amoxicillin. In community care, this was observed in 97% of prescriptions, in 13.2% of patients (Table 5).

PIMs classed by age are presented in the figure 4. Potential factors associated with PIM or PPO are presented in Appendix 2a, b. On univariate analysis, only age was associated with risk of PIM or PPO in hospital setting. In a community setting, the number of drugs per prescription and different age categories were found to be significantly associated with a higher risk of PIM or PPO on univariate analysis. With a multivariable logistic regression model, the same results were obtained.

DISCUSSION

This is the first study to observe the prevalence of PIMs and PPOs in a pediatric population. In the literature, such tools focused on detecting PIMs/PPOs in a geriatric population. [22,40–

42] The two populations are not comparable. Respiratory and digestive pathologies are typical in children and are not so in geriatric populations, which are more concerned by cardiovascular and nervous central system diseases.[22,40,43].

Domperidone was frequently prescribed in a community setting, yet this drug is responsible for cardiac adverse effects such as QT prolongation. This side effect is described in the literature in adult populations and pediatric populations. The detection of this prescription will enable us to avoid cardiac risks. [44–49]

Prevalence of beta2 agonists or corticosteroids in an infant's first case of bronchiolitis is 6.4% (25/386 cases), lower than that observed in a study of another French area in 2012 (41%).[50–52] The use of beta2 agonists in a first case of bronchiolitis has no impact on oxygen saturation, length of hospitalization or length of illness. They concurrently cause side effects as tachycardia, oxygen saturation, and tremors. [53] Implementation of guidelines has permitted to decrease beta2 agonist and corticosteroid use in a French hospital without increase morbidity. [54]

Unnecessary exposure to cough suppressants, pholcodine, nasal or oral decongestants was also observed frequently in this sector.[55] In Norway, all drugs containing pholcodine hwere refused marketing authorization in March 2007. As of this date, a decrease in sensitization to suxamethonium used in anesthesia and a decrease of 30-40% cases of anaphylaxis was? identified. [56]

Our tool enabled us to detect rare PIMs that carry heavy consequences, such as opioid use for migraines. The use of opioids for this disease induces a transition from episodic to chronic headaches and an increase of sensitivity to pain.[57–59]

Overuse of medication, in particular opioids, could contribute to the chronicity of headaches in 20–30% of children and adolescents with chronic daily headaches.[59]

In the management of diarrhea caused by gastroenteritis in hospitals, our study found that it was common to omit to prescribe oral rehydration solution (ORS):14% (237/1643 cases). Even so, this rate is lower than that found in another national study in 2007 (29%).[60] However, ORSs prevent hospitalization in cases of acute gastroenteritis. In the United Kingdom, the use of ORSs has enabled a decrease from 300 deaths/year in 1970s to 25 deaths/year in 1980s.[61,62]. The need for ORS prescriptions was confirmed by the recommendation of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in 2014.[63]

As estimated, children aged between 0 and 12 years have the highest risk of presenting with a PIM, according to a multivariate analysis. No inappropriate prescriptions or omissions were detected for patients aged less than 28 days. As we know, they are also affected by off-label drug prescriptions, which is consistent with reports from other sources.[64,65] As with geriatrics, an increase in the number of medications used can be associated with PIM.[40] Prescriptions issued from hospitals elicit fewer PIMs than those issued by the community. The main reason for this is that many drugs are not available in our hospital, such as cough suppressants, Rhinotrophyl® (tenoate ethanolamine), domperidone, etc. This shows that many PIM are preventable in a hospital settings. An efficient method for the prevention of PIM could be to focus on the prescribing habits of physicians and thus have an impact on the selection of drugs, thereby reducing the rate of PIM.

The data was extracted from a community pharmacy and the emergency department of a mother-child hospital during the winter months. The data focusses on winter epidemics. An analysis of the year in its entirety would have found other PMI / PPO concerning different

pathologies or events related to travel. While the Robert Debré hospital offers sub-specialized hospitalization services (cardiology, nephrology, hematology, etc.), the emergency department drains the more general activity. Likewise, the data coming from the community pharmacy provides a representative image of the pediatric prescriptions that could be found in other French pharmacies. Concerning a generalization of our data to other countries, a study is in progress to specify which POPI items could be applicable internationally.

Our study has several limitations. Firstly, it is a retrospective and monocentric study,the result in hospital could be underestimated. In addition, several criteria could not be analyzed due to the large number of prescriptions (for example, those for fever or pain which are associated with many diseases) or absence of certain pathologies (mosquitos, lice, hyperactivity etc.). All drugs were not evaluated. Antibiotic prophylaxis, vitamin supplements, propositions for vaccination etc. can only be analyzed in prospective studies. The lack of clinical information is the main limitation in detection in a community setting. This also constitutes a challenge for pharmaceutical care review in elderly patients.[66] However, a certain amount of PIM were identified using POPI. Our study showed that there are many criteria that are easily identifiable, and which could be detected without accessing clinical information. Moreover, community pharmacists, in their practice, can extrapolate diagnoses from their experience, from common indications or by interviewing their patients. The study presents a limitation regarding the URQUAL software, from which the number of medications per prescription could not be extracted.

This is the first study which permits an evaluation of the prevalence of PIM and PPO in pediatrics prescription. The detection of PIMs/PPOs would improve patient care, and prevent hospitalization and adverse drug reactions. A stepped wedge randomized cluster multicenter study will be conducted to prove if POPI decreases number of PIM and PPO. It is also

necessary to evaluate the impact of this tool on reducing adverse drugs events, both in consultation or hospitalization. The impact of pharmacists in providing appropriate prescriptions should be also evaluated. Subsequently, this tool may be offered to several professional societies such as the French Society for Pediatricians and the French Society of Clinical Pharmacy to make its use more widespread. The tool should be regularly updated to reflect recent events and to specify certain criteria.

To facilitate its use, this tool can be presented as a mobile app, a small handbook or installed into prescription software. In summary, we hope that POPI could be a practical option used to reduce medication errors and to improve the suitability of prescriptions. It provides rapid detection of PIM and PPO and can also open up discussion on the relationship between doctor and pharmacist to remedy the issues at hand.[67]

CONCLUSION

Our study was carried out in in two sectors, hospital and community, and provides a global view of PIM and PPO in pediatric patients. POPI has a clinical impact and plays a role in improving prescription quality in various sectors and patient care. POPI should be applied in different services to deepen and reinforce its utilization. A prospective and multicenter study should be conducted to evaluate its impact and benefit in clinical practice.

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ETHICS

This project was approved by the local research ethics committee (n°2015/218).

DISCLOSURE OF INTEREST

None Declared

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AUTHOR'S CONTRIBUTION

Sonia Prot-Labarthe, Aurore Berthe-Aucejo conceptualised and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Rym Boulkedid and HPK Nguyen carried out analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Xavier Bellettre, Thomas Weil, Olivier Bourdon reviewed and revised the manuscript and approved the final manuscript as submitted.

François Angoulvant and Patrick Albaret supplied data from hospital and community pharmacy and reviewed and revised the manuscript and approved the final manuscript as submitted.

DATA SHARING STATEMENT

We have no additional unpublished data

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Figure 1. Flow chart indicating the course of the study

* Prescriptions with only one medical device, dietary supplement or hygiene product, ED: Emergency department

Figure 2. Distribution of number of prescriptions according to age category in hospital and community settings

Figure 3. Comparison of PIMs detected in hospital and in outpatient care

Figure 4. Total prescription and PIMs in both hospital and outpatient care: Percentage distribution by age group

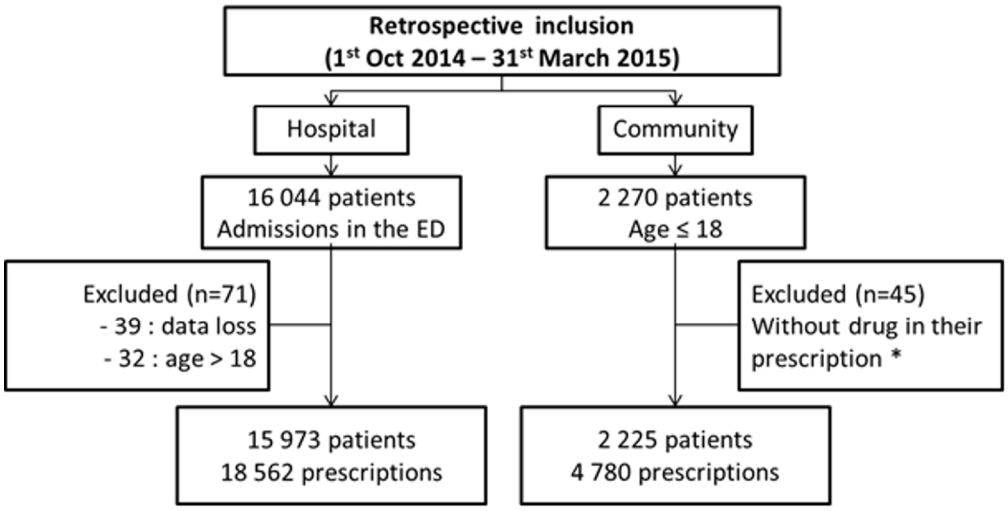

Figure 1. Flow chart indicating the course of the study┬ * Prescriptions with only one medical device, dietary supplement or hygiene product, ED: Emergency department

168x90mm (300 x 300 DPI)

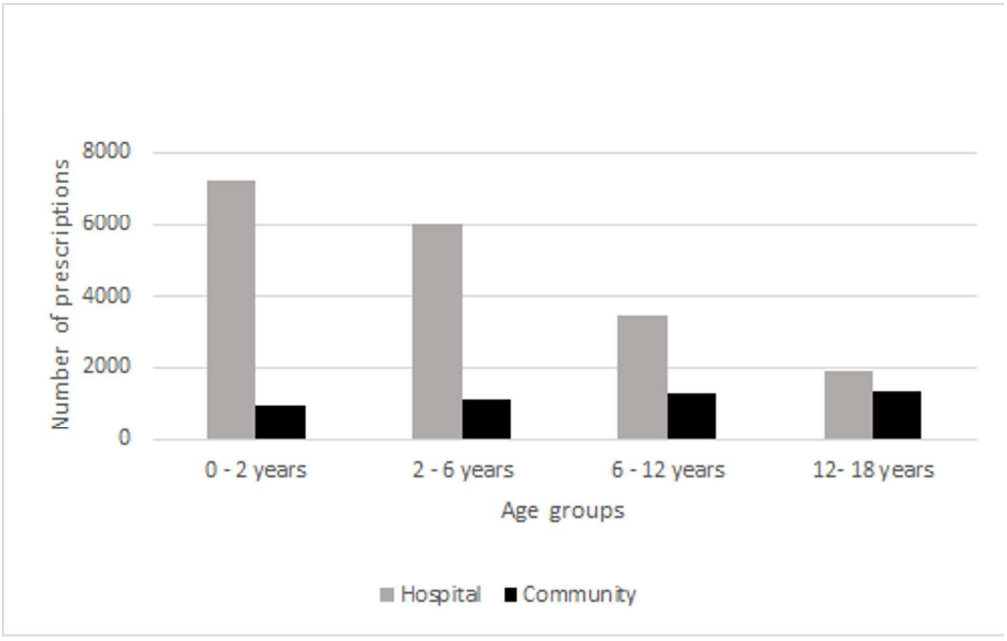

Figure 2. Distribution of number of prescriptions according to age category in hospital and community settings

141x90mm (300 x 300 DPI)

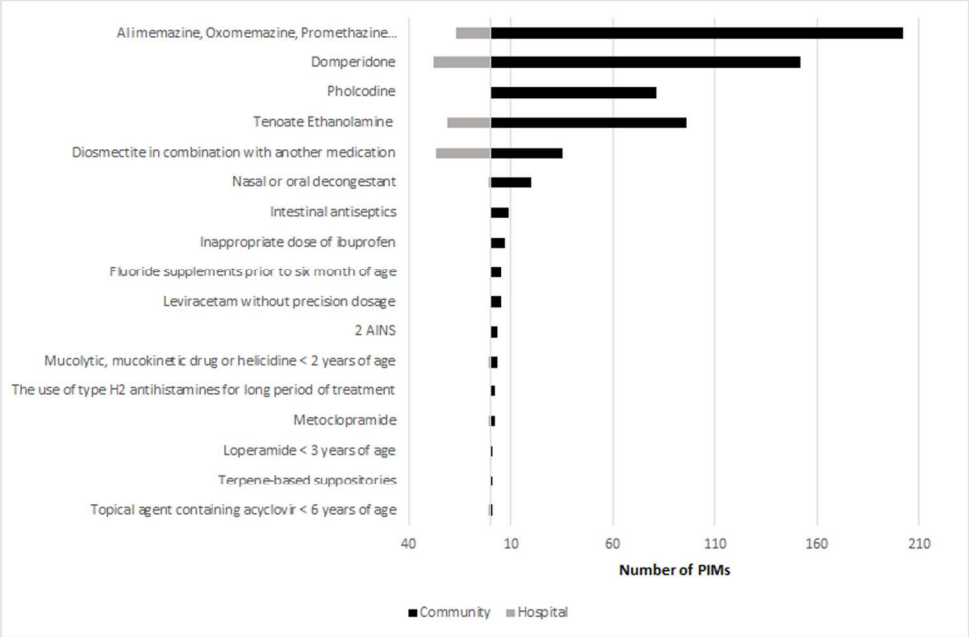

Figure 3. Comparison of PIMs detected in hospital and in outpatient care

119x90mm (300 x 300 DPI)

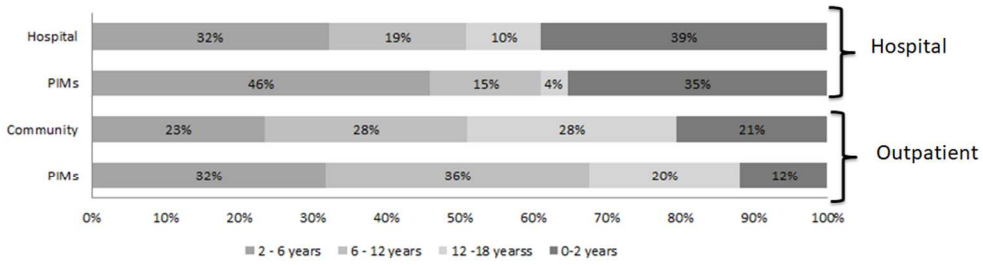

Figure 4. Total prescription and PIMs in both hospital and outpatient care: Percentage distribution by age group

344x90mm (300 x 300 DPI)

Appendix 1. Description of inclusion/exclusion criteria, data collected and POPI criteria analyzed among the two cohorts

	Hospital	Community
Inclusion criteria	Patient under 18 years old Patient with one or more medicine prescriptions	Patient under 18 years old Patient with one or more medicine prescriptions
Exclusion criterion	Inaccessible medical records for patients	Prescription without any drug prescribed
Software extracted	Urqual®	Opus®
Data collected	Age Sex Weight Current diagnosis Number of prescriptions	Age Number of prescriptions Number of drugs per prescription
Number of POPI items analyzed (among the 102 criteria)	82	28 (items usable for retrospective analysis if no diagnostic available)

Appendix 2a. Univariate and multivariate analysis to determine factors associated with PIM according to POPI criteria

Variable	Univariate analysis		Multivariate analysis	
Model 1: Hospital prescription	*OR* [CI 95%]*	*p-value*	*OR* [CI 95%]*	*p-value*
Sex				
Male	1			
Female	1.1 [0.9-1.3]	0.3		
Age category				
0 - 2 years	2.5 [1.6-3.9]	0.0001	2.5 [1.6-3.9]	< 0.001
2 - 6 years	4.0 [2.5-6.3]	< 0.0001	4.0 [2.5-6.3]	< 0.0001
6 - 12 years	2.2 [1.4-3.6]	0.0016	2.2 [1.4-3.6]	0.0016
12 - 18 years	1		1	
Model 2: Community prescription				
Age category				
0 - 2 years	0.8 [0.6-1.1]	0.1	0.7 [0.5-1.0]	0.06
2 - 6 years	2.0 [1.5-2.6]	< 0.0001	1.9 [1.4-2.4]	< 0.0001
6 - 12 years	1.9 [1.5-2.4]	< 0.0001	1.9 [1.5-2.5]	< 0.0001
12 - 18 years	1		1	
Number of medications per prescription	1.4 [1.3-1.6]	< 0.001	1.4 [1.3-1.6]	< 0.0001

OR: Odds ratio, CI: Confidence intervals.

Appendix 2b. Univariate and multivariate analysis to determine factors associated with PPO according to POPI criteria

Variable	Univariate analysis p		Multivariate analysis	
Model 1: Hospital prescription	*OR* [CI 95%]*	*p-value*	*OR* [CI 95%]*	*p-value*
Sex				
Male	1			
Female	1.1 [0.9 ; 1.3]	0.3053		
Age category				
0 - 2 years	1.1 [0.7 ; 1.6]	0.7703	1.1 [0.7 ; 1.6]	0.7703
2 - 6 years	1.4 [0.9 ; 2.1]	0.0761	1.4 [0.9 ; 2.1]	0.0761
6 - 12 years	1.9 [1.3 ; 2.8]	0.0015	1.9 [1.3 ; 2.8]	0.0015
12 - 18 years	1		1	
Model 2: Community prescription				
Age category				
0 - 2 years	6.1 [2.9 ; 12.7]	<0.0001	6.1 [2.9 ; 12.9]	<0.0001
2 - 6 years	22.4 [11.4 ; 44.1]	<0.0001	22.4 [11.3 ; 44.3]	<0.0001
6 - 12 years	9.8 [4.9 ; 19.6]	<0.0001	10.2 [5.1; 20.7]	<0.0001
12 - 18 years	1			
Number of medications per prescription	1.2 [1.1 ; 1.3]	<.0001	1.2 [1.2 ; 1.4]	<0.0001

OR: Odds ratio, CI: Confidence intervals.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	p5
Methods			
Study design	4	Present key elements of study design early in the paper	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P6 NA
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p6-7-14
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p15-16
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P16+figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	p17

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Appendix2
Discussion			
Key results	18	Summarise key results with reference to study objectives	p18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p22 to 24
Generalisability	21	Discuss the generalisability (external validity) of the study results	p24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p26

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.