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Title: The PIPc Study: development of indicators of potentially inappropriate prescribing in children in primary care.

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ABSTRACT

Objective: There is limited evidence regarding the quality of prescribing for children in primary care. Several prescribing criteria (indicators) have been developed to assess the appropriateness of prescribing in older and middle aged adults but few are relevant to children. The objective of this study was to develop of a set of prescribing indicators that can be applied to prescribing or dispensing datasets to determine the prevalence of potentially inappropriate prescribing (PIP) in children (PIPc) in primary care settings.

Design: Two round Delphi consensus method

Setting: Irish and United Kingdom (UK) General Practice

Participants: A project steering group consisting of academic and clinical general practitioners (GPs) and pharmacists was formed to develop a list of indicators from literature review and clinical expertise. Fifteen experts consisting of general practitioners, pharmacists, paediatricians and clinical pharmacologists from the Republic of Ireland and the UK formed the Delphi panel.

Results: 47 indicators were reviewed by the project steering group and 16 were presented to the Delphi panel. In the first round of this exercise, consensus was achieved on nine of these indicators. Of the remaining seven indicators, two were removed following review of expert panel comments and discussion of the steering group. The second round of the Delphi process focused on the remaining five indicators, which were amended based on first round feedback. Three indicators were accepted following the second round of the Delphi process and the remaining two indicators were removed. The final list consisted of 12 indicators categorised by respiratory system (n=6), gastrointestinal system (n=2), neurological system (n=2) and dermatological system (n=2).

Conclusions: The PIPc indicators are the first set of prescribing criteria developed for use in children in primary care. The utility of these criteria will be tested in further studies using prescribing databases.

Strengths and limitations of this study

The members of Delphi panel in this study were heterogenous in experience and setting, and represented the professions involved in prescribing and dispensing to children.

The Delphi process used in the study followed pre-defined methodology in line with best practice.

The dispensing database does not contain clinical information limiting the application of indicators that require such information for interpretation.

The reliability of the Delphi technique as a method for achieving consensus has been debated but its potential limitations are similar to other consensus techniques.

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BACKGROUND

Quality of prescribing for children has been identified as an area of concern since the late 1970's, when it was reported that 60% of children under 14 years received at least one prescription a year from their family practitioner(1). Currently children represent over 25% of the population and receive an average of three prescription medications before five years of age(2). There are ongoing concerns over the quality of prescribing for children, but there is a lack of studies in this area(3). Potential consequences for children may be adverse drug events leading to unplanned hospital admissions and preventable deaths(4).

Medicines are generally considered appropriate in an adult population when they have a clear evidence-based indication, are well tolerated in the majority of patients and are cost-effective(5). Medicines or prescribing patterns that do not fit this description can be considered inappropriate; this term includes mis-prescribing, under- prescribing and over-prescribing. The term "potentially inappropriate prescribing" acknowledges the reality of prescribing in clinical practice whereby the prescription of an inappropriate medication may be justified by the individual needs of a particular patient(6). For example, sedating antihistamines may be considered inappropriate for young children, however they may in some instances, be useful in the treatment of insomnia relating to itch caused by eczema.

Research into potentially inappropriate prescribing in adults has focused on the development of indicators or explicit criteria of prescribing, which are measurable criteria against which quality standards can be set and audited. Explicit indicators such as the Screening Tool to Alert doctors to the Right Treatment/ Screening Tool of Older Peoples potentially inappropriate Prescriptions (START/STOPP) criteria used in older populations have been found to be valid, reliable and generalisable across international primary care settings(7).

To date, many quality indicators of care of children in primary care relate to specific diseases or conditions such as mental health or diabetes(8, 9). More recent work in France has led to the development of the first set of indicators of inappropriate prescribing in

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children for use in hospital and community settings(10). Researchers in the United Kingdom have also developed primary care quality indicators for children which include some prescribing indicators but focus on broader issues such as the management and assessment of clinical conditions, child development and child protection(11). Other criteria have been developed for use in the out-of-hours setting and in paediatric emergency departments(12, 13).

Ideally a prescribing indicator would be based on a thorough review of patient records with access to the full clinical and treatment history of the patient, but this is time-consuming and can be extremely complex(14, 15). A more realistic option is the development of indicators that can be applied to automated databases containing information on dispensed drugs. These databases are available in most developed countries; they generally lack detailed information about the patient or indication for the prescription but they allow process-based prescribing indicators to be applied and to assess aspects of prescribing patterns, safety and cost. This study aims to create indicators that are based on commonly prescribed medications to children in primary care and are supported by international best practice guidelines.

METHOD

Study design

A Delphi consensus technique was used to develop these prescribing criteria. This technique allows an estimate of an overall group opinion to be reached by improving agreement between a panel of experts through rounds of questionnaires(16). Ethical approval for this study was obtained from the Royal College of Surgeons in Ireland (RCSI) Research Ethics Committee, Dublin, Ireland in April 2014.

Compilation of initial criteria

We undertook a comprehensive literature search using PubMed to identify any previously developed indicators relating to potentially inappropriate prescribing in children. Supplementary file 1 shows the search string used. As very few indicators from lists devised for adults or older adults are applicable to children, the search strategy was limited to include only those articles involving infants, children or adolescents. The search was performed initially in April 2014 and updated in August 2015.

Clinical guidelines, the references of relevant papers and additional web sources were also used to identify potential indicators. Supplementary file 2 details a full list of information sources used. The British National Formulary for Children (BNFc) (17) and the Irish Medicines Formulary (IMF) (18) were used as reference resources for indication, dosages and licensing information.

Inclusion criteria: Indicators had to:

- describe a pattern of prescribing that was potentially hazardous or known to be ineffective
- describe a pattern of prescribing that was not in keeping with best practice or current guidelines
- apply to the population of interest; children < 16 years.

Exclusion criteria

- medications currently unavailable in the study setting
- criteria which could not be applied in the absence of clinical information
- criteria containing medications with a low prevalence of use (to define uncommon use, a cut-off of less than 0.5% was agreed by the Project Steering Group)

The prevalence of individual drug use in children in 2011 was determined using dispensing data from the Health Service Executive-Primary Care Reimbursement Service (HSE-PCRS). The PCRS is a national dispensing database in Ireland; it stores information on all medications, and other health services, provided without charge to people eligible for free medical services in Ireland under the General Medical Scheme (GMS). Eligibility for free medical care is established via means testing and therefore the data collected by the PCRS is not fully representative of the entire population of Ireland. Approximately 39% (414,856) of the total population (1,072,220) of children <16 years in the Republic of Ireland were eligible for the scheme in 2014. The PCRS contains data on prescriptions originating in both primary and secondary care for all children who are eligible for free medical services. Children who receive a prescription from a hospital specialist will have their prescription transcribed to a GMS prescription by their general practitioner (GP) in order to avail of free medication. The PCRS does not record data on whether a prescription has originated in primary or secondary care. An Anatomical Therapeutic Chemical Classification System (ATC) code was assigned to each indicator to allow for extraction from the dispensing database.

The initial criteria were compiled following the literature review and screened by all members of the Project Steering Group. Members applied the exclusion criteria and examined the evidence supporting each indicator, removing those which did not fulfil the inclusion criteria. For example, the criterion 'Fluoxetine is the most appropriate antidepressant for children, other SSRI's should

not be prescribed” was removed by the Steering Group during this screening stage as the criterion related specifically to patients with depression and could only be successfully applied to a dataset with clinical information. Some criteria identified from literature were modified by the Steering Group to make them applicable to dispensing data, for example, “Children with eczema should be prescribed an emollient” was altered to “Children prescribed greater than one topical corticosteroid in a year should also be prescribed an emollient.” Supplementary file 3 details the indicators removed and the reasons for exclusion by the Steering Group.

Selection of the Delphi Panel

Thirty specialists from the United Kingdom and Republic of Ireland, recognised as experts in their fields (academic and clinical general practitioners (GPs), clinical and academic paediatricians, academic and clinical pharmacists and clinical pharmacologists) identified by the Steering Group were invited a priori (via e-mail) to participate in a Delphi panel to develop these criteria. Eighteen agreed to participate, and were representative of all specialties invited to participate in terms of location and expertise. Written consent was received before commencing the process.

Data collection and analysis

The consensus process involved two rounds of web-based questionnaires. The Steering Group and GP members of the Department of General Practice, Royal College of Surgeons in Ireland (RCSI) piloted the questionnaire and it was modified accordingly. The first and second rounds of this development process took place between January 2015 and May 2015, and between June 2015 and July 2015, respectively. For each round, panel members were emailed a link to a questionnaire which was maintained on an online survey software tool (SurveyGizmo®). Panellists were presented with indicators and accompanying rationales, categorised by physiological systems (gastro-intestinal system, respiratory system, central nervous system) along with a hyperlink to a supporting evidence resource e.g. Cochrane systematic review where available, the BNFc or national or international guidelines. Panellists were asked to indicate their level of agreement with each indicator using a five-point Likert scale(19), (where

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1 was strongly disagree and 5 was strongly agree) and to provide comments within a free text box. Using this scale, the median response and the interquartile range were calculated. The level required for consensus between the panel members was decided prior to commencing the study. When the upper quartile was ≤ 2 , this indicated there was consensus on rejection of the criterion. When the lower quartile was ≥ 4 , this indicated there was general agreement with the criterion between the panel members and the criterion was accepted. When the interquartile range included 3, this indicated there was a lack of agreement between the panel members and a need for further review of the particular criterion. These criteria were reviewed by Steering Group (via discussion) and were either revised and included in the second questionnaire or rejected based on the additional comments received from the panel members. Panellists did not receive feedback from the first questionnaire. The second questionnaire was presented in the same format as the first. Again, the median response and the interquartile range were calculated, and the Steering Group reviewed these measures of agreement along with any additional comments. If consensus was not reached following the second round, the criterion was rejected.

RESULTS

Figure 1 summarises the development of the indicators. Literature searches identified 47 potential indicators. Thirty-one indicators were removed following the application of the inclusion and exclusion criteria along with a detailed examination of the evidence by the Steering Group. Sixteen indicators were presented to the Delphi panel in the first round. Fifteen of the 18 experts who consented to participate completed each round of the questionnaire. Three experts did not complete either round. Consensus was reached for nine indicators on the first round with no indicators being rejected; consensus was not reached on seven indicators. From these seven indicators, two were rejected by the Steering Group on the basis of the clinical comments of the Delphi panel. Five indicators were then presented to the Delphi panel in round 2. Consensus was reached on three indicators and none was rejected outright. Consensus was not reached on the remaining two indicators which were then removed by the Steering group following review of the comments of the Delphi panel. Table 1 summarises the progression of the indicators through the Delphi process and Table 2 provides an example of some of the comments of the Delphi panel.

Table 1 Progression of indicators through the Delphi process

	Indicator	Round 1 Median IQR	Outcome	Revised indicator	Round 2 Median IQR	Outcome
1	Systemic antihistamines should not be prescribed to children under 1 year.	3 (2.5 to 4)	Revision required	Sedating anti histamines should not be prescribed to children under 2 years	4 (4 to 4)	Accepted
2	Intranasal Beclometasone should not be prescribed to children under 6 years	4 (4 to 4)	Accepted	n/a	n/a	Accepted
3	Mucolytics should not be prescribed to children under 2 years	4 (3.5 to 5)	Revision required	Carbocysteine should not be prescribed to children under 2 years	4 (4 to 5)	Accepted
4	An inhaled short acting beta-2 agonist (SABA) should be prescribed to all children who are prescribed two or more inhaled corticosteroids for presumed asthma	5 (4 to 5)	Accepted	n/a	n/a	Accepted
5	An inhaled SABA should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist for presumed asthma.	5 (4 to 5)	Accepted	n/a	n/a	Accepted
6	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA)	5 (4 to 5)	Accepted	n/a	n/a	Accepted

7	LABAs should not be prescribed to children under 5 years.	4 (3.5 to 4)	Revision required	LABA's (either in combination or on their own) should not be prescribed to children under 5 years. New evidence presented	4 (3.5 to 4)	Rejected based on lack of consensus of Delphi panel
8	Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months.	4 (4 to 5)	Accepted	n/a		Accepted
9	Loperamide should not be used in the treatment of diarrhoea in children under 4 years.	4 (3.5 to 5)	Revision required	Loperamide should not be used in the treatment of diarrhoea in children under 4 years. New evidence presented.	4 (4 to 5)	Accepted

Table 2 Progression of indicators through the Delphi process (contd.)

	Indicator	Round 1 Median IQR (to)	Outcome	Revised indicator	Round 2 Median IQR (to)	Outcome
10	Domperidone should not be prescribed to children under 1 year and for children over 1 year, it should not be prescribed for greater than 7 days.	<1 year 5 (3.25 to 5) <7 days 4.6 (3.25 to 5)	Revision required	Rejected based on comments of panel. Lack of evidence to support.	n/a	Rejected
11	Domperidone should not be prescribed concomitantly with erythromycin.	4 (4 to 5)	Accepted	n/a	n/a	Accepted

12	Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
13	Systemic corticosteroids should not be prescribed to children aged 5-15years without evidence of asthma.	3 (2.5 to 4)	Revision required	Other than in children with asthma , systemic corticosteroids should not be prescribed to children aged 5-15years.	4 (2 to 4)	Rejected-lack of consensus of Delphi panel.
14	Children prescribed greater than one topical corticosteroid in a year should also be prescribed an emollient.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
15	Very potent or potent topical corticosteroids e.g. Clobetasol propionate should not be prescribed to children under 1 year.	4 (3 to 4)	Revision required	Rejected by Steering Group on the basis that clinical information is required	n/a	Rejected
16	Tetracyclines should not be prescribed to children under 12 years.	5 (4 to 5)	Accepted	n/a	n/a	Accepted

Following a two-round Delphi process, the final list of indicators consisted of 12 indicators by system: respiratory n=6, gastrointestinal n=2, dermatological n=2, neurological n=2. Table 3 summarises the accepted indicators.

Table 2 Exemplar comments received from the Delphi panel on rejected indicators

Rejected following Round 1	
Indicator	Comments
Rationale	
Domperidone should not be prescribed to children under one year and for children over 1 year it should not be prescribed for more than 7 days.	<p><i>"domperidone is not evidence based for little ones"</i></p> <p><i>"would not prescribe ...because of risk of extrapyramidal side effects"</i></p> <p><i>"have used this longer term in many cases with no adverse effects But am aware of recent questions"</i></p> <p><i>"efficacy of this drug is unproven, any drug which may mask symptoms or disease progression should never be prescribed for apparent gastroenteritis"</i></p>
Efficacy in Gastro-oesophageal reflux disease (GORD) and gastroenteritis is uncertain in this age group. Extrapyramidal side effects occur in young children. Can be used for short term treatment of nausea and vomiting, max duration of use should not normally exceed 1 week.	
Very potent or potent topical corticosteroids should not be prescribed to children under 1year	<p><i>"occasional use necessary- if a child can't sleep won't grow..."</i></p> <p><i>"very rare situations this might be appropriate"</i></p> <p><i>"agree unless prescribed by a consultant"</i></p> <p><i>"if child has severe eczema they may be needed for a short period of time"</i></p> <p><i>"possibly under dermatology guidance for rare severe eczema"</i></p>
Topical corticosteroids can cause adrenal suppression and Cushing's syndrome.	

Table 2. Exemplar comments received from the Delphi panel on rejected indicators (contd)

Rejected following Round 2	
Indicator	Comments
Rationale	
Other than in children with asthma, systemic corticosteroids should not be prescribed to children aged 5-15years.	<i>"Agree unless there is a clinical indication such as flare of juvenile rheumatoid arthritis"</i>
Systemic corticosteroids can cause serious side effects including adrenal suppression, immunosuppression and mood disturbances. In the general paediatric population there are few indications for systemic corticosteroids apart from asthma and croup. Croup commonly affects children under 5 years	<i>"Exceptions being serious diseases where specialists might prescribe. e.g. glomerulonephritis"</i>
	<i>"there are relatively rare indications for systemic steroids in children- they would always be initiated by a specialist"</i>
Long acting beta agonists (LABAs) should not be prescribed to children under 5 years.	<i>"Not recommended by the British thoracic guidelines in under 5's"</i>
Use of LABAs is associated with increased risk of asthma exacerbations, hospitalisations and asthma related deaths in children and adults. It is not known if combination use with inhaled corticosteroids reduces this risk.	<i>"Lack of fear of their pernicious side effects plus a lack of understanding of the definition of asthma is to blame"</i>
	<i>"The Cochrane review summary that is attached says that LABA does not significantly decrease exacerbations or hospitalisations as opposed to your statement of increasing the risk based on the SMART trial"</i>
	<i>"I have seen evidence of poor response to short acting bronchodilators in those on long acting bronchodilators"</i>

Table 3 Accepted indicators

Respiratory System	
1	Intranasal beclometasone should not be prescribed to children under 6 years.
2	Carbocisteine should not be prescribed to children under 2 years.
3	An inhaled short acting beta-2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids for presumed asthma
4	An inhaled short acting beta-2 agonist should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist for presumed asthma.
5	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA)
6	Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months
Gastrointestinal System	
7	Loperamide should not be used in the treatment of diarrhoea in children under 4 years.
8	Domperidone should not be prescribed concomitantly with erythromycin.
Dermatological System	
9	Children prescribed greater than one topical corticosteroid in a year should also be prescribed an emollient.
10	Tetracyclines should not be prescribed to children under 12 years.
Neurological System	
11	Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.
12	Sedating antihistamines should not be prescribed to children under 2 years.

DISCUSSION

We have developed a set of twelve indicators of potentially inappropriate prescribing for use in children in primary care through a consensus Delphi method. These twelve indicators can be easily and quickly applied to large prescribing or dispensing datasets in the absence of clinical information. The indicators developed in this study were not designed as an exhaustive list of PIP in children, but rather represent a list of commonly prescribed medications in Ireland and the UK, which may be used to explore the prevalence of PIP in children. The utility and validity of these indicators will be investigated in future studies using national prescription-based databases.

Comparison with existing literature

Concerns about the quality of care received by children in the USA were highlighted in a large study in 2007, which examined the management of common medical conditions in primary care using 175 quality indicators applied to the medical records of 1536 children(3). A screening tool consisting of 104 explicit criteria for identifying the omission of prescriptions and inappropriate prescriptions (POPI) in children has recently been developed in France using a Delphi process(10). The POPI tool includes propositions or indicators of inappropriate prescribing including omissions of prescribing in the treatment of commonly encountered paediatric health problems for example, management of pain and fever. Although intended for community and hospital settings, this tool was developed without the input of general practitioners and has not yet been validated(10). A set of 35 primary care quality indicators for children were also developed in the UK in 2014 using a multi-step consensus methodology(11). These quality indicators are based on routine and chronic care in addition to child development and child protection and include six prescribing indicators of a total number of 35 indicators overall. There is an overlap between two of these prescribing indicators and the indicators developed in this study. “Children with asthma should be prescribed a spacer” and “Children with atopic eczema should be prescribed emollients” overlap in both studies. However, in the UK study clinical and diagnostic information is required to implement the indicators, which were designed for auditing computerised primary care records, which contain codes for clinical conditions and have yet to be validated(11). A cross-sectional study performed in the Netherlands in 2007 examined prescribing and referral in a single

out-of-hours setting using 24 indicators developed from national guidelines and a GP expert panel(12). These indicators focused on drug choice, primarily antibiotics in the management of infections. In our study indicators relating to antibiotic prescribing were excluded as clinical information is required to determine the appropriateness of choice of antibiotic. Nonetheless, our indicators remain relevant to general practice as they relate to commonly prescribed medications such as antiasthmatics. The largest cohort study to date of drug use in children found that antifectives, respiratory drugs and dermatological agents had the highest prevalence of use across all age groups of children(20).

Strengths and limitations

This study followed a well-defined process that has been refined by others in the development of similar criteria in populations other than children e.g. The START/STOPP criteria for detection of PIP in older adults and the Prescribing optimally in Middle aged People's Treatment (PROMPT) criteria for detection of PIP in middle aged adults(7, 21). The PIPc criteria were constructed from two sources –a literature search and the expertise of the Project Steering group whose members had experience in both clinical medicine in primary care settings and in the development of quality indicators of prescribing in other population groups. A second strength was the broad and representative sample of medical professionals involved in paediatric prescribing on the Delphi panel. The panel members were distributed across academic and clinical experience in specialities such as paediatrics, general practice and pharmacy providing a high level of (face) validity to the process and were representative of geographically diverse areas of Ireland and the UK. All members who participated in the panel completed both rounds of the process. The number of rounds and consensus method was decided in advance of questionnaire distribution with pre-defined limits for the acceptance, revision or rejection of indicators. Feedback was not provided to the panellists between rounds in order to remove any potential bias of panellists altering their responses to fit those of the groups. The Delphi consensus method allowed the expert panel members to inform the development of these criteria through their level of agreement and additional comments. Some criteria were rejected by the panellists due to the difficulty in determining the appropriateness of a prescribed medication without knowledge of whether a treatment had been initiated by a specialist. Medications which were

considered to be appropriate “under specialist supervision only” were therefore removed. Finally, to ensure relevance to clinical general practice each indicator was presented with a clear rationale that described either a lack of clinical effectiveness or the potential serious side effects of the relevant medication. The rationale for the indicator was supported by the highest level of evidence available, provided to the panel in an easily accessible format to facilitate informed decision making.

The main limitation of this study relates to use of the Delphi technique. While it is a commonly used technique, the reliability of the Delphi method for achieving consensus has been debated in the literature. The information gathered using a Delphi method only represents the views of chosen experts about a specific practice at a given time and this may vary depending on the experts involved(22). In this study, a panel size of 15 experts with clinical and academic expertise in prescribing to children was used to mitigate this limitation. This is thought to be a sufficient panel size when the experts have a similar training and general understanding of the field of interest(24). Ideally, the level of expertise required to be a member of the Delphi panel would be clearly defined prior to the beginning of the study(23). Nonetheless, significant efforts were made to ensure that the Delphi panel were heterogeneous in experience and setting to limit this potential bias. There may be variation in knowledge underpinning panel members’ views but the Delphi panel was provided with the best available evidence to mitigate this effect. It may have been useful to provide the panel with a more objective rating of the evidence e.g. using the GRADE system to further aid decision-making, but this was beyond the scope of the current study(24).

Finally the database used in this study to determine the prevalence of the indicators is not fully representative of the entire population of children in Ireland. The PCRS database contains information on prescriptions dispensed under the means-tested GMS scheme for which approximately 39% of the population under 16 years were eligible in 2014. Poorer health has been reported in socioeconomically deprived areas (25) with an increased prevalence of prescribing, therefore the use of this database would have inflated the prevalence of prescribing thus mitigating against the effects of this potential source of bias(26). Unfortunately data on non-eligible patients is not routinely collected in the Republic of Ireland.

Implications for research and practice

The examination of individual clinical information to assess the appropriateness of prescribing can be time-consuming and difficult. These indicators can be applied quickly and easily to large population-based datasets in the absence of clinical information to identify PIP in children unexamined to date. A study to validate the indicators developed in this study is currently underway using the PCRS database. Changes and unwarranted variation in prescribing patterns can be identified across time and geographical area. Researchers in other countries outside of Ireland and the UK could use these indicators with translation and some modifications based on country specific guidelines, clinical practices and drug formularies(27). The indicators can be used to examine the impact of changes in guidelines on prescribing patterns on a population level e.g. asthma care. The cost of PIP in children can also be examined.

The indicators may be used as a screening tool at the level of individual clinical practices. Community pharmacists, who routinely dispense medications without clinical information, could also use these indicators as a resource for clinically checking prescriptions for children.

Identification and quantification of PIP in older populations has led to the development of interventions that improve prescribing. For example, a randomised controlled trial of a multi-faceted interventions which included pharmacist advice, web-based pharmaceutical treatment algorithms and tailored patient information leaflets had a positive effect on PIP in older populations(27). Integrating some of these supports into clinical decision support systems may prove to be a practical method of improving PIP in children.

CONCLUSION

Research into paediatric prescribing in primary care is lacking to date. This study offers a set of 12 evidence based explicit prescribing indicators to identify PIP in children in primary care. Application of the indicators to large population-based prescribing or dispensing databases will enable investigation of the prevalence of PIP in children and examine changes over time.

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COMPETING INTERESTS

The authors declare they have no competing interests.

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AUTHOR CONTRIBUTIONS

EB assisted in the compilation of the initial indicators, revised the indicators, developed the online survey, engaged the Delphi panel and drafted the manuscript. SMS conceived and supervised the study, KOB devised the initial indicators. KB extracted the prevalence data. FB provided statistical support. FM, JC, PR, CMH, TF and SMS formed the Project Steering group and reviewed the indicators throughout the study. All members of the Project Steering group revised the manuscript.

DATA SHARING

No additional data are available.

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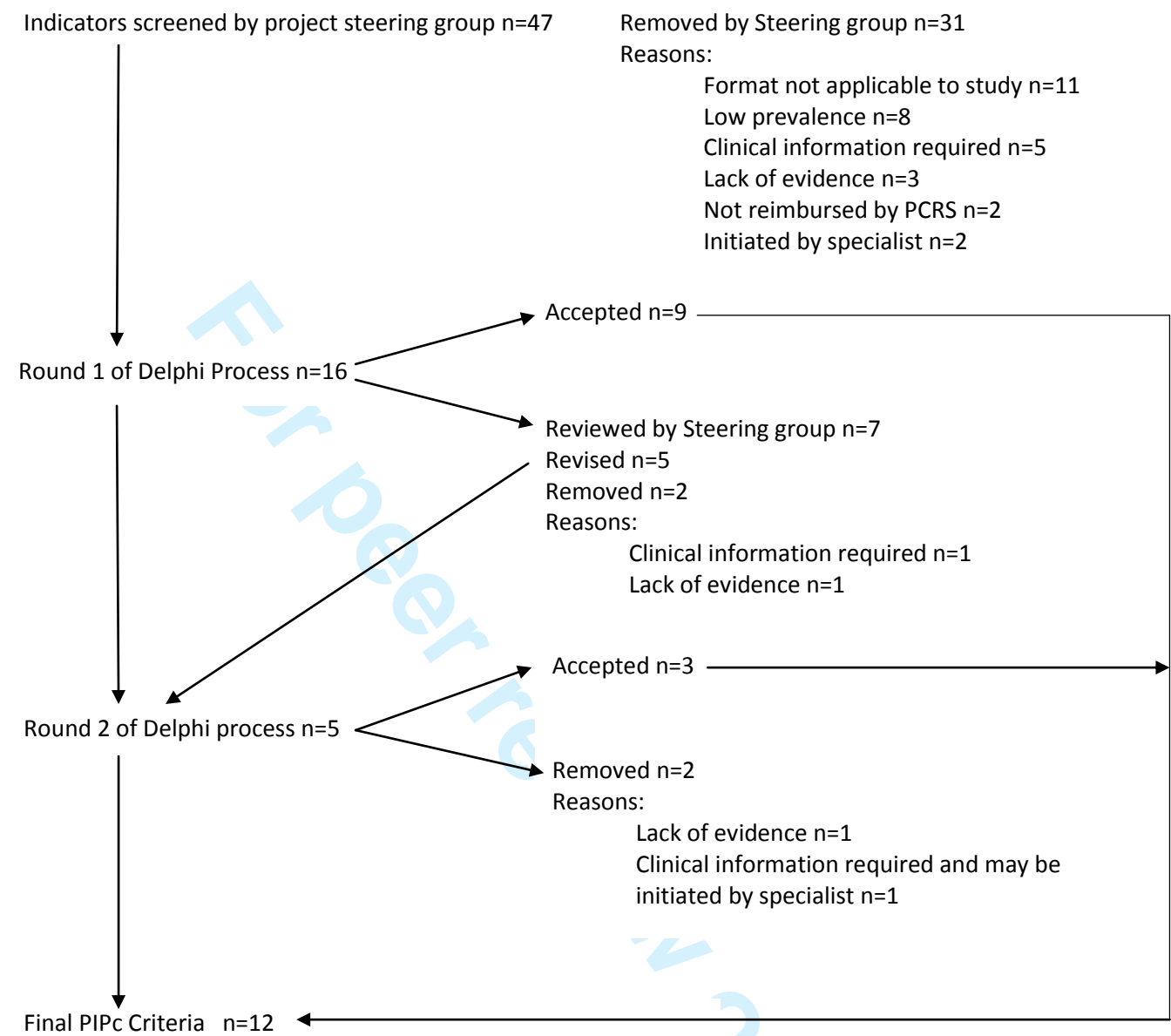
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FIGURE 1: The development of the PIPc Indicators



Appendix 1 Search string

Pubmed Search and Cochrane Database April 2014.No filters/limits applied

((inappropriate or appropriate or optimal or suboptimal or ineffective or unnecessary)
AND (medication or prescribing)) AND ((prescribing indicator or prescribing
indicators) OR (quality indicator) OR (guideline adherence) OR (prescribing tool or
prescribing tools))

Duplicates removed 31

Irrelevant 1171

Relevant 25

Search update: Pubmed and Cochrane Database August 2015.No filters/limits
applied

((inappropriate or appropriate or optimal or suboptimal or ineffective or unnecessary)
and (medication or prescribing)) AND ((prescribing indicator or prescribing
indicators) OR (quality indicator) OR (guideline adherence) OR (prescribing tool or
prescribing tools))

Results: 1545

Reviewed titles in terms of studies relating to children, primary care, drugs/conditions
likely to affect children: 115

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PIPC Study: Appendix 2 List of information sources used for development of indicators.

Pubmed Search 2014 and 2015

British National Formulary for Children online

Irish Medicines Formulary 14th Edition 2013 and 16th Edition 2014

Cochrane Database of Systematic reviews

British Medical Journal Clinical Evidence

Clinical Knowledge Summaries (pre 2014 when still available from ROI)

References of References

Medicines and Healthcare products Regulatory Agency website (MHRA)

European Medicines Agency website (EMA)

U.S Food and Drug Administration website (FDA)

St James Hospital National Medicines Information Centre Therapeutic Update Bulletins

Guidelines including those produced by

- National Institute for Health and Care Excellence (NICE)
- British Thoracic Society (BTS)
- Scottish Intercollegiate Guidelines Network (SIGN)
- European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
- British Society for Allergy and Clinical Immunology (BSACI)
- Royal College of Paediatrics and Child health (RCPCH)

PIPc Study: Appendix 3 Table of indicators excluded by the Steering Group during the screening process

Physiological system	
Indicator by system	Reason for exclusion
Rationale for inclusion	
A Gastro-intestinal system	
1 Metoclopramide should not be prescribed to children under the age of 1 year	Low prevalence
Metoclopramide can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises.	
2 Domperidone should not be prescribed concomitantly with Ketoconazole	Low prevalence
Ketoconazole inhibits Domperidone metabolism; Domperidone levels may be increased up to 3-fold. This resulted in a small mean increase in QT prolongation.	
3 Anti-obesity drugs are generally not recommended for children under the age of 16 years	Medications not reimbursed through PCRS from 2012.
Diet and exercise are the preferred methods of weight loss in children.	
4 Proton Pump Inhibitors (PPI's) should not be prescribed to children under the age of 2 years	May be initiated by specialist.
The efficacy of PPIs for children younger than 2 years of age with GORD is inconsistent and is insufficient to support the use of PPIs. In addition, evidence suggests that PPIs are associated with an increased risk of lower respiratory tract infections and gastroenteritis.	

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5 Histamine H2 antagonists should not be prescribed to children under the age of 2 years for gastro-oesophageal reflux disease (GORD)

Evidence is insufficient to support the use in primary care of histamine-2 receptor antagonists (H₂RAs) for children younger than 2 years of age with GORD. Limited evidence indicates that H₂RAs are associated with an increased risk of lower respiratory tract infections and gastroenteritis.

Lack of evidence.

B	Respiratory system	Reason for exclusion
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6 Number of items for cough suppressants or nasal decongestants/patient

Known to be of limited effectiveness.

Format not appropriate to the aims of the study. Elements included in other indicators
Low prevalence

7 Children who have been prescribed Theophylline should not be prescribed Erythromycin, Ciprofloxacin or Azithromycin

Theophylline has a narrow margin between therapeutic and toxic dose. Plasma concentration increased by antibacterials mentioned.

8 Ratio of corticosteroid to bronchodilator as indicator of quality of asthma prescribing

A low ratio indicates poor prescribing.

Format not appropriate to the aims of the study. Elements included in other indicators

C Central Nervous system	Reason for exclusion
9 Children under the age of 16 yrs should not be prescribed systemic Aspirin Risk of Reye's syndrome.	Low prevalence
10 Children under the age of 16 yrs should not be prescribed topical oral pain relief products containing salicylate salts (e.g. teething gels) The CHM (2009) has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye's syndrome.	Not reimbursed by PCRS
11 Phenothiazines should not be prescribed to children under 1 yrs Extrapyramidal side effects and respiratory depression may occur in susceptible children.	Low prevalence
12 Children under 16 yrs should not be prescribed ≥ 2 stimulants (in a 90 day period) Identified as a clinically questionable prescribing in previous studies.	Low prevalence
13 Females taking enzyme inducing antiepileptic drugs (EIAED) including Phenobarbitone, Primidone, Phenytoin, Carbamazepine, Oxcarbazepine and Topiramate should not be prescribed a combined oral contraceptive (COC), patch or vaginal ring EIAEDs increase metabolism of estrogens and progesterone thereby affecting contraceptive efficacy.	Low prevalence
14 Tricyclic and tetracyclic antidepressants should not be prescribed to children under 16 years Lack of efficacy and can has serious side effects in some children.	Clinical information required.

- 15

Paroxetine and Venlafaxine should not be prescribed to children under 16 years

Clinical trials have failed to show efficacy and have shown an increase in harmful outcomes.

Low prevalence
- 16

Children under the age of 16 yrs should not be prescribed ≥ 2 antidepressants in a single subclass in a 90 day period.

Identified as a clinically questionable prescribing in previous studies

Low prevalence
- 17

Children under 16 years should not be prescribed ≥ 2 benzodiazepines (in a 90 day period)

Identified as a clinically questionable prescribing in previous studies. Risk of dependence

Low prevalence
- 18

Benzodiazepines should not be prescribed for greater than 30 days

Risk of dependence.

Clinical information required
- 19

Children under the age of 16 yrs should not be prescribed a high total number of psychotropics (≥ 3)

Higher risk of side effects.

Clinical information required
- 20

Ratio of the number of children under the age of 6 yrs prescribed any psychotropic medication divided by the number of youths under 18 yrs who were prescribed any medication.

There has been a drastic increase in recent years in the number of very young children being prescribed psychotropics.

Format not applicable to this study

E

Endocrine system

Reason for exclusion

- 21 In children aged 5-16 yrs who are on long term steroid tablets (eg longer than three months) or requiring frequent courses of steroid tablets (eg three to four per year) an inhaled corticosteroid should also be prescribed as well as a short acting beta 2 agonist, and a trial of a LABA.**

Patients on long term steroid tablets (eg longer than three months) or requiring frequent courses of steroid tablets (eg three to four per year) will be at risk of systemic side effects.

Clinical information needed. Some elements included in other indicators.

F Dermatological system

Reason for exclusion

- 22 Proportion of children prescribed more than one topical corticosteroid that have been prescribed Fucidin or prescribed a corticosteroid cream with Fusidic acid**

There are high rates of resistance to fusidic acid.

Lack of evidence

- 23 If Isotretinoin is prescribed there should be evidence of failure of previous acne therapy (within the last 12 months)**

Many side effects including changes in bone density and growth as well as suicidal ideation and depression

May be initiated by specialist.

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

30 Ratio of 2nd line (or broad spectrum?) antibiotic to the number of items for any antibiotic

Second line and broad spectrum antibiotics should be prescribed at a much lower level than narrow spectrum and first line antibiotics.

31 Ratio of the consumption of broad spectrum antibiotics to the consumption of narrow spectrum antibiotics

Second line and broad spectrum antibiotics should be prescribed at a much lower level than narrow spectrum and first line antibiotics.

32 Seasonal variation in the total antibiotic consumption

Marked variation in antibiotic use is likely to reflect poorer practice since it represents higher use of antibiotics for respiratory infections which has a poor evidence base.

33 Mefloquine should not be prescribed to children under 16 years with a history of convulsions

Mefloquine is an anti-infective agent for protection and treatment of malaria, there is an increased convulsion risk with epilepsy.

Format not applicable to the study.

Public health indicator.

Format not applicable to the study.

Public health indicator

Format not applicable to the study.

Public health indicator

Clinical information needed

BMJ Open

The PIPc Study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique.

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-012079.R1
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Paediatrics
Keywords:	prescribing indicators, potentially inappropriate prescribing, children, Delphi method, explicit criteria

SCHOLARONE™
Manuscripts

Title: The PIPc Study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi Technique.

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Key words: potentially inappropriate prescribing, quality indicators, explicit criteria, Delphi technique, children.

Word count: 3385

ABSTRACT

Objective: There is limited evidence regarding the quality of prescribing for children in primary care. Several prescribing criteria (indicators) have been developed to assess the appropriateness of prescribing in older and middle aged adults but few are relevant to children. The objective of this study was to develop of a set of prescribing indicators that can be applied to prescribing or dispensing datasets to determine the prevalence of potentially inappropriate prescribing in children (PIPC) in primary care settings.

Design: Two round modified Delphi consensus method

Setting: Irish and United Kingdom (UK) General Practice

Participants: A Project Steering Group consisting of academic and clinical general practitioners (GPs) and pharmacists was formed to develop a list of indicators from literature review and clinical expertise. Fifteen experts consisting of general practitioners, pharmacists and paediatricians from the Republic of Ireland and the UK formed the Delphi panel.

Results: 47 indicators were reviewed by the Project Steering Group and 16 were presented to the Delphi panel. In the first round of this exercise, consensus was achieved on nine of these indicators. Of the remaining seven indicators, two were removed following review of expert panel comments and discussion of the Project Steering Group. The second round of the Delphi process focused on the remaining five indicators, which were amended based on first round feedback. Three indicators were accepted following the second round of the Delphi process and the remaining two indicators were removed. The final list consisted of 12 indicators categorised by respiratory system (n=6), gastrointestinal system (n=2), neurological system (n=2) and dermatological system (n=2).

Conclusions: The PIPC indicators are a set of prescribing criteria developed for use in children in primary care in the absence of clinical information. The utility of these criteria will be tested in further studies using prescribing databases.

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Strengths and limitations of this study

The members of Delphi panel in this study were heterogeneous in experience and setting, and represented the professions involved in prescribing and dispensing to children.

The Delphi process used in the study followed pre-defined methodology in line with best practice.

Dispensing databases may not contain clinical information limiting the application of indicators that require such information for interpretation.

The reliability of the Delphi technique as a method for achieving consensus has been debated but its potential limitations are similar to other consensus techniques.

BACKGROUND

Quality of prescribing for children has been identified as an area of concern since the late 1970's, when it was reported that 60% of children under 14 years received at least one prescription a year from their family practitioner(1). Currently children represent over 25% of the population and receive an average of three prescription medications before five years of age(2). There are ongoing concerns over the quality of prescribing for children, but there is a lack of studies in this area(3). Potential consequences for children may be adverse drug events leading to unplanned hospital admissions and preventable deaths(4).

Medicines are generally considered appropriate in an adult population when they have a clear evidence-based indication, are well tolerated in the majority of patients and are cost-effective(5). Medicines or prescribing patterns that do not fit this description can be considered inappropriate; this term includes mis-prescribing, under-prescribing and over-prescribing(6). Mis-prescribing includes the incorrect prescription of an indicated medication and can be divided into drug choice, dosage, duration of therapy, duplication of drugs of the pharmacological class and drug - disease or drug-drug interactions or drug- food interactions. Under prescribing includes the omission of a prescription that is needed and overprescribing; the prescription of a medication that is unnecessary(7). The term "potentially inappropriate prescribing" acknowledges the reality of prescribing in clinical practice whereby the prescription of an inappropriate medication may be justified by the individual needs of a particular patient(8). For example, sedating antihistamines may be considered inappropriate for young children because of the risk of side effects such as sedation, paradoxical excitation and potential cardiac toxicity. However they may in some instances, be useful in the treatment of insomnia relating to itch caused by eczema.

Research into potentially inappropriate prescribing in adults has focused on the development of indicators or explicit criteria of prescribing, which are measurable criteria against which quality standards can be set and audited. Explicit indicators such as the Screening Tool to Alert doctors to the Right Treatment/ Screening Tool of Older Peoples potentially inappropriate Prescriptions (START/STOPP) criteria

were devised to identify PIP in older adults and have been found to be valid, reliable and generalisable across international primary care settings(9).

To date, many quality indicators of care of children in primary care relate to specific diseases or conditions such as mental health or diabetes(10,11). More recent work in France has led to the development of the first set of indicators of inappropriate prescribing in children for use in hospital and community settings(12). Researchers in the United Kingdom have also developed primary care quality indicators for children that include some prescribing indicators but focus on broader issues such as the management and assessment of clinical conditions, child development and child protection(13). Other criteria have been developed for use in the out-of-hours setting and in paediatric emergency departments(14,15).

Recent studies have highlighted that explicit prescribing indicators are not sufficient to assess whether prescribing is appropriate or not in the context of assessing daily prescribing practices(16). Ideally a prescribing indicator would be based on a thorough review of patient records with access to the full clinical and treatment history of the patient. Nonetheless this process is time-consuming and can be extremely complex(17,18). Although the evidence base for developing explicit prescribing indicators is limited, combining expert professional opinion with consensus methodology can create quality indicators in areas where it would not otherwise be possible(19). Explicit indicators can be useful in assessing the quality of prescribing using large national prescribing databases without clinical information(20).

This study aims to create indicators that are based on commonly prescribed medications to children in primary care and are supported by international best practice guidelines.

METHOD

Study design

A modified Delphi consensus technique was used to develop these prescribing criteria. This technique allows an estimate of an overall group opinion to be reached by improving agreement between a panel of experts through rounds of questionnaires(21). The Delphi panel was modified as direct feedback would not be provided to the Delphi panel members between rounds. Ethical approval for this study was obtained from the Royal College of Surgeons in Ireland (RCSI) Research Ethics Committee, Dublin, Ireland in April 2014.

Compilation of initial indicators

We undertook a comprehensive literature search using PubMed to identify any previously developed indicators relating to potentially inappropriate prescribing in children. Supplementary file 1 shows the search string used. As very few indicators from lists devised for adults or older adults are applicable to children, the search strategy was limited to include only those articles involving infants, children or adolescents. The search was performed initially in April 2014 and updated in August 2015.

A set of initial indicators were identified from the literature search. Clinical guidelines, web sources and PubMed were used to identify the best available evidence to support each indicator. Supplementary file 2 details a full list of information sources used. The British National Formulary for Children (BNFc) (22) and the Irish Medicines Formulary (IMF) (23) were used as reference resources for indication, dosages and licensing information.

A Project Steering Group was formed to guide the development of the indicators using predefined inclusion and exclusion criteria. The Steering Group consisted of academic/clinical general practitioners, three academic/clinical pharmacists, a pharmacoepidemiologist/statistician and a postdoctoral researcher, all members of either the HRB Centre for Primary Care Research at the RCSI Dublin or the School of Pharmacy at Queen's University Belfast.

Inclusion criteria: Indicators had to:

- describe a pattern of prescribing that was potentially hazardous or known to be ineffective
- describe a pattern of prescribing that was not in keeping with best practice or current guidelines
- apply to the population of interest; children < 16 years.

Exclusion criteria

- medications currently unavailable in the study setting
- criteria which could not be applied in the absence of clinical information
- criteria containing medications with a low prevalence of use (to define uncommon use, a cut-off of less than 0.5/1000 GMS patients was agreed by the Project Steering Group)

Members of the Project Steering Group applied the inclusion and exclusion criteria and examined the evidence supporting each indicator. For example, the criterion ‘Fluoxetine is the most appropriate antidepressant for children, other SSRIs should not be prescribed’ was removed by the Project Steering Group during this screening stage as the criterion related specifically to patients with depression and could not be successfully applied in the absence of clinical information. Some criteria identified from literature were modified by the Project Steering Group to make them applicable to dispensing database without clinical information, for example, “Children with eczema should be prescribed an emollient” was altered to “An emollient should be prescribed to children who are prescribed greater than one topical corticosteroid in a year” where the prescription of greater than one topical corticosteroid in a year was considered a proxy for a diagnosis of eczema. Supplementary file 3 details the indicators removed and the reasons for exclusion by the Project Steering Group.

The Primary Care Reimbursement Service database (HSE-PCRS)

The prevalence of individual drug use in children in 2011 was determined using dispensing data from the Health Service Executive- Primary Care Reimbursement Service (HSE-PCRS). The PCRS is a national dispensing database in Ireland; it stores information on all medications, and other health services, provided without charge to people eligible for free medical services in Ireland under the General Medical Scheme (GMS). Eligibility for free medical care is established via means testing and therefore the data collected by the PCRS is not fully representative of the entire population of Ireland. Approximately 39% (414,856) of the total population (1,072,220) of children <16 years in the Republic of Ireland were eligible for the scheme in 2014. The PCRS contains data on prescriptions originating in both primary and secondary care for all children who are eligible for free medical services. Children who receive a prescription from a hospital specialist will have their prescription transcribed to a GMS prescription by their general practitioner (GP) in order to avail of free medication. The PCRS does not record data on whether a prescription has originated in primary or secondary care. An Anatomical Therapeutic Chemical Classification System (ATC) code was assigned to each indicator to allow for extraction from the dispensing database.

Selection of the Delphi Panel

Thirty specialists from the United Kingdom and Republic of Ireland were invited a priori (via e-mail) to participate in a Delphi panel to develop these criteria. Although no specific standard was applied to define an expert, the specialists invited to participate on the panel were peer recognised as experts in their fields by the Project Steering Group and consisted of academic and clinical general practitioners (GPs), paediatricians and pharmacists. Eighteen specialists agreed to participate. The panel consisted of 9 experts from the Republic of Ireland (3 GPs, 3 paediatricians, 3 pharmacists) 9 from the UK (3 GPs 3 paediatricians, 3 pharmacists). Written consent was received before commencing the process.

Data collection and analysis

The consensus process involved two rounds of web-based questionnaires. The questionnaire was piloted among the Project Steering Group and GP members of the Department of General Practice, Royal College of Surgeons in Ireland (RCSI) with minor modifications made subsequently. The first and second rounds of the

questionnaires were sent to the Delphi panel between January 2015 and May 2015, and between June 2015 and July 2015, respectively. For each round, panel members were emailed a link to a questionnaire which was maintained on an online survey software tool (SurveyGizmo®). Panellists were presented with each indicator and an accompanying rationale for the indicator, categorised by physiological systems (gastro-intestinal system, respiratory system, central nervous system, dermatological system) along with a hyperlink to a supporting evidence resource e.g. Cochrane systematic review, the BNFc or national or international guidelines. Panellists were asked to indicate their level of agreement with each indicator using a five-point Likert scale(24), (where 1 was strongly disagree and 5 was strongly agree) and to provide comments within a free text box.

Following completion of the first round of questionnaires, the median response and the interquartile range for each indicator were calculated from the Likert scale. The level required for consensus between the panel members was decided prior to commencing the study. When the upper quartile was ≤ 2 , this indicated there was consensus by the Delphi panel members on rejection of the indicator. When the lower quartile was ≥ 4 , this indicated there was consensus by the Delphi panel members on acceptance of the indicator. When the interquartile range included 3, this indicated there was a lack of agreement between the panel members and a need for further review of the particular indicator. These indicators were reviewed by Project Steering Group and were either revised and included in the second questionnaire or rejected based on the comments received from the Delphi panel. Panellists did not receive feedback from the first questionnaire. The second questionnaire was presented in the same format as the first. Again, the median response and the interquartile range were calculated, and the Project Steering Group reviewed these measures of agreement along with any additional comments. If consensus was not reached following the second round, the criterion was rejected.

RESULTS

Figure 1 summarises the development of the indicators. Literature searches identified 47 potential indicators. Thirty-one indicators were removed following the application of the inclusion and exclusion criteria along with a detailed examination of the evidence by the Project Steering Group. Sixteen indicators were presented to the Delphi panel in the first round. Fifteen of the eighteen experts who consented to participate completed each round of the questionnaire. Three experts did not complete either round. Consensus was reached for nine indicators on the first round with no indicators being rejected; consensus was not reached on seven indicators. From these seven indicators, two were rejected by the Project Steering Group on the basis of the clinical comments of the Delphi panel. Five indicators were then presented to the Delphi panel in round 2. Consensus was reached on three indicators and none was rejected outright. Consensus was not reached on the remaining two indicators which were then removed by the Project Steering group following review of the comments of the Delphi panel. Table 1 summarises the progression of the indicators through the Delphi process and Table 2 provides an example of some of the comments of the Delphi panel.

Table 1 Progression of indicators through the Delphi process

	Indicator	Round 1 Median IQR	Outcome	Revised indicator	Round 2 Median IQR	Outcome
1	Systemic antihistamines should not be prescribed to children under 1 year.	3 (2.5 to 4)	Revision required	Sedating anti histamines should not be prescribed to children under 2 years	4 (4 to 4)	Accepted
2	Intranasal Beclometasone should not be prescribed to children under 6 years	4 (4 to 4)	Accepted	n/a	n/a	Accepted
3	Mucolytics should not be prescribed to children under 2 years	4 (3.5 to 5)	Revision required	Carbocysteine should not be prescribed to children	4 (4 to 5)	Accepted
4	An inhaled short acting beta-2 agonist (SABA) should be prescribed to all children who are prescribed two or more inhaled corticosteroids for presumed asthma	5 (4 to 5)	Accepted	n/a	n/a	Accepted
5	An inhaled SABA should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist for presumed asthma.	5 (4 to 5)	Accepted	n/a	n/a	Accepted
6	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA)	5 (4 to 5)	Accepted	n/a	n/a	Accepted
7	LABAs should not be prescribed to children under 5 years.	4 (3.5 to 4)	Revision required	LABA's (either in combination or on their own) should not be prescribed to children under 5 years. New evidence presented	4 (3.5 to 4)	Rejected based on lack of consensus of Delphi panel
8	Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months.	4 (4 to 5)	Accepted	n/a		Accepted
9	Loperamide should not be used in the treatment of diarrhoea in children under 4 years.	4 (3.5 to 5)	Revision required	Loperamide should not be prescribed to children under 4 years. New evidence presented.	4 (4 to 5)	Accepted

Table 2 Progression of indicators through the Delphi process (contd.)

	Indicator	Round 1 Median IQR (to)	Outcome	Revised indicator	Round 2 Median IQR (to)	Outcome
10	Domperidone should not be prescribed to children under 1 year and for children over 1 year, it should not be prescribed for greater than 7 days.	<1 year 5 (3.25 to 5) <7 days 4.6 (3.25 to 5)	Revision required	Rejected based on comments of panel. Lack of evidence to support.	n/a	Rejected
11	Domperidone should not be prescribed concomitantly with erythromycin.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
12	Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
13	Systemic corticosteroids should not be prescribed to children aged 5-15years without evidence of asthma.	3 (2.5 to 4)	Revision required	Other than in children with asthma , systemic corticosteroids should not be prescribed to children aged 5-15years.	4 (2 to 4)	Rejected-lack of consensus of Delphi panel.
14	An emollient should be prescribed to children who are prescribed greater than one topical corticosteroid in a year.	4 (4 to 5)	Accepted	n/a	n/a	Accepted
15	Very potent or potent topical corticosteroids e.g. Clobetasol propionate should not be prescribed to children under 1 year.	4 (3 to 4)	Revision required	Rejected by Project Steering Group on the basis that clinical information is required	n/a	Rejected
16	Tetracyclines should not be prescribed to children under 12 years.	5 (4 to 5)	Accepted	n/a	n/a	Accepted

Following a two-round Delphi process, the final list of indicators consisted of 12 indicators by system: respiratory n=6, gastrointestinal n=2, dermatological n=2, neurological n=2. Table 3 summarises the accepted indicators. Supplementary file 4 details the PIPc indicators with supporting references.

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Table 2 Exemplar comments received from the Delphi panel on rejected indicators

<i>Rejected following Round 1</i>	
Indicator	Comments
Rationale	
Domperidone should not be prescribed to children under one year and for children over 1 year it should not be prescribed for more than 7 days.	<i>“domperidone is not evidence based for little ones”</i> <i>“would not prescribe ...because of risk of extrapyramidal side effects”</i> <i>“have used this longer term in many cases with no adverse effects But am aware of recent questions”</i> <i>“efficacy of this drug is unproven, any drug which may mask symptoms or disease progression should never be prescribed for apparent gastroenteritis”</i>
Efficacy in Gastro-oesophageal reflux disease (GORD) and gastroenteritis is uncertain in this age group. Extrapyramidal side effects occur in young children. Can be used for short term treatment of nausea and vomiting, max duration of use should not normally exceed 1 week.	
Very potent or potent topical corticosteroids should not be prescribed to children under 1year	<i>“occasional use necessary- if a child can’t sleep won’t grow...”</i> <i>“very rare situations this might be appropriate”</i> <i>“agree unless prescribed by a consultant”</i> <i>“if child has severe eczema they may be needed for a short period of time”</i> <i>“possibly under dermatology guidance for rare severe eczema”</i>
Topical corticosteroids can cause adrenal suppression and Cushing’s syndrome.	

Table 2. Exemplar comments received from the Delphi panel on rejected indicators (contd)

<i>Rejected following Round 2</i>	
Indicator	Comments
Rationale	
Other than in children with asthma, systemic corticosteroids should not be prescribed to children aged 5-15years.	<p><i>"Agree unless there is a clinical indication such as flare of juvenile rheumatoid arthritis"</i></p> <p><i>"Exceptions being serious diseases where specialists might prescribe. e.g. glomerulonephritis"</i></p>
Systemic corticosteroids can cause serious side effects including adrenal suppression, immunosuppression and mood disturbances. In the general paediatric population there are few indications for systemic corticosteroids apart from asthma and croup. Croup commonly affects children under 5 years	<i>"there are relatively rare indications for systemic steroids in children- they would always be initiated by a specialist"</i>
Long acting beta agonists (LABAs) should not be prescribed to children under 5 years.	<p><i>"Not recommended by the British thoracic guidelines in under 5's"</i></p> <p><i>"Lack of fear of their pernicious side effects plus a lack of understanding of the definition of asthma is to blame"</i></p> <p><i>"The Cochrane review summary that is attached says that LABA does not significantly decrease exacerbations or hospitalisations as opposed to your statement of increasing the risk based on the SMART trial"</i></p> <p><i>"I have seen evidence of poor response to short acting bronchodilators in those on long acting bronchodilators"</i></p>
Use of LABAs is associated with increased risk of asthma exacerbations, hospitalisations and asthma related deaths in children and adults. It is not known if combination use with inhaled corticosteroids reduces this risk.	

Table 3 Accepted indicators

Respiratory System	
1	Intranasal beclometasone should not be prescribed to children under 6 years.
2	Carbocisteine should not be prescribed to children
3	An inhaled short acting beta-2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids for presumed asthma
4	An inhaled short acting beta-2 agonist should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist for presumed asthma.
5	An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA)
6	Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months
Gastrointestinal System	
7	Loperamide should not be prescribed to children under 4 years.
8	Domperidone should not be prescribed concomitantly with erythromycin.
Dermatological System	
9	An emollient should be prescribed to children who are prescribed greater than one topical corticosteroid in a year.
10	Tetracyclines should not be prescribed to children under 12 years.
Neurological System	
11	Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.
12	Sedating antihistamines should not be prescribed to children under 2 years.

DISCUSSION

We have developed a set of twelve indicators of potentially inappropriate prescribing for use in children in primary care through a modified Delphi method. These twelve indicators can be easily and quickly applied to large prescribing or dispensing datasets in the absence of clinical information. The indicators developed in this study were not designed as an exhaustive list of PIP in children, but rather represent a list of commonly prescribed medications in Ireland and the UK, which may be used to explore the prevalence of PIP in children. The utility and validity of these indicators will be investigated in future studies using national prescription-based databases.

Comparison with existing literature

Concerns about the quality of care received by children in the USA were highlighted in a large study in 2007, which examined the management of common medical conditions in primary care using 175 quality indicators applied to the medical records of 1536 children(3). A screening tool consisting of 104 explicit criteria for identifying the omission of prescriptions and inappropriate prescriptions (POPI) in children has recently been developed in France using a Delphi process(12). The POPI tool includes propositions or indicators of inappropriate prescribing including omissions of prescribing in the treatment of commonly encountered paediatric health problems for example, management of pain and fever. Although intended for community and hospital settings, this tool was developed without the input of general practitioners and has not yet been validated(12). A set of 35 primary care quality indicators for children were also developed in the UK in 2014 using a multi-step consensus methodology(13). These quality indicators are based on routine and chronic care in addition to child development and child protection and include six prescribing indicators of a total number of 35 indicators overall. There is an overlap between two of these prescribing indicators and the indicators developed in this study. "Children with asthma should be prescribed a spacer" and "Children with atopic eczema should be prescribed emollients" overlap in both studies. However, in the UK study clinical and diagnostic information is required to implement the indicators, which were designed for auditing computerised primary care records, which contain codes for clinical conditions and have yet to be validated(13). A cross-sectional study performed in the Netherlands in 2007 examined prescribing and referral in a single

out-of-hours setting using 24 indicators developed from national guidelines and a GP expert panel(14). These indicators focused on drug choice, primarily antibiotics in the management of infections. In our study indicators relating to antibiotic prescribing were excluded as clinical information is required to determine the appropriateness of choice of antibiotic. Nonetheless, our indicators remain relevant to general practice as they relate to commonly prescribed medications such as antiasthmatics. The largest cohort study to date of drug use in children in Europe found that antifectives, respiratory drugs and dermatological agents had the highest prevalence of use across all age groups of children(25).

Strengths and limitations

This study followed a well-defined process that has been refined by others in the development of similar criteria in populations other than children e.g. The START/STOPP criteria for detection of PIP in older adults and the Prescribing optimally in Middle aged People’s Treatment (PROMPT) criteria for detection of PIP in middle aged adults(9, 26). The PIPc criteria were constructed from two sources –a literature search and the expertise of the Project Steering group whose members had experience in both clinical medicine in primary care settings and in the development of quality indicators of prescribing in other population groups. A second strength was the broad and representative sample of medical professionals involved in paediatric prescribing on the Delphi panel. The panel members were distributed across academic and clinical experience in specialities such as paediatrics, general practice and pharmacy providing a high level of (face) validity to the process and were representative of geographically diverse areas of Ireland and the UK. Fifteen of eighteen members who agreed to participate completed both rounds of the questionnaires. The number of rounds and consensus method was decided in advance of questionnaire distribution with pre-defined limits for the acceptance, revision or rejection of indicators. Feedback was not provided to the panellists between rounds in order to remove any potential bias of panellists altering their responses to fit those of the groups. The Delphi consensus method allowed the expert panel members to inform the development of these criteria through their level of agreement and additional comments. Some criteria were rejected by the panellists due to the difficulty in determining the appropriateness of a prescribed medication without knowledge of whether a treatment had been initiated by a specialist.

Medications which were considered to be appropriate “under specialist supervision only” were therefore removed. Finally, to ensure relevance to clinical general practice each indicator was presented with a clear rationale that described either a lack of clinical effectiveness or the potential serious side effects of the relevant medication. The rationale for the indicator was supported by the highest level of evidence available, provided to the panel in an easily accessible format to facilitate informed decision making.

The main limitation of this study relates to use of the Delphi technique. While it is a commonly used technique, the reliability of the Delphi method for achieving consensus has been debated in the literature. The information gathered using a Delphi method represents the views of chosen experts about a specific practice at a given time and this may vary depending on the experts involved(27). In this study, a panel size of 15 experts with clinical and academic expertise in prescribing to children was used to mitigate this limitation. This is thought to be a sufficient panel size when the experts have a similar training and general understanding of the field of interest(28). Ideally, the level of expertise required to be a member of the Delphi panel would be clearly defined prior to the beginning of the study(28). Nonetheless, significant efforts were made to ensure that the Delphi panel were heterogeneous in experience and setting to limit this potential bias. There may be variation in knowledge underpinning panel members’ views but the Delphi panel was provided with the best available evidence to mitigate this effect. It may have been useful to provide the panel with a more objective rating of the evidence e.g. using the GRADE system to further aid decision-making, but this was beyond the scope of the current study(29).

Explicit prescribing criteria are limited in that they do not address individual differences among patients or the complexity or appropriateness of entire medication regimens(30). Furthermore they need to be regularly updated in line with evidence and country specific adaptation are necessary where countries differ in their guidelines, standards and approved medications.

Finally the database used in this study to determine the prevalence of the indicators is not fully representative of the entire population of children in Ireland. The PCRS database contains information on prescriptions dispensed under the means-tested

GMS scheme for which approximately 39% of the population under 16 years were eligible in 2014. Poorer health has been reported in socioeconomically deprived areas (31) with an increased prevalence of prescribing, therefore the use of this database would have inflated the prevalence of prescribing thus mitigating against the effects of this potential source of bias. Unfortunately data on non-eligible patients is not routinely collected in the Republic of Ireland.

Implications for research and practice

The examination of individual clinical information to assess the appropriateness of prescribing can be time-consuming and difficult. These indicators can be applied quickly and easily to large population-based datasets in the absence of clinical information to identify PIP in children unexamined to date. A study to validate the indicators developed in this study is currently underway using the PCRS database. Changes and unwarranted variation in prescribing patterns can be identified across time and geographical area. Researchers in other countries outside of Ireland and the UK could use these indicators with translation and some modifications based on country specific guidelines, clinical practices and drug formularies(7). The indicators can be used to examine the impact of changes in guidelines on prescribing patterns on a population level e.g. asthma care. The cost of PIP in children can also be examined.

The indicators may be used as a screening tool at the level of individual clinical practices and could be used to support detailed medication review of individual patients. Community pharmacists, who routinely dispense medications without clinical information, could also use these indicators as a resource for clinically checking prescriptions for children.

Identification and quantification of PIP in older populations has led to the development of interventions that improve prescribing. For example, a randomised controlled trial of a multi-faceted intervention which included pharmacist advice, web-based pharmaceutical treatment algorithms and tailored patient information leaflets had a positive effect on PIP in older populations(32). Integrating some of these supports into clinical decision support systems may prove to be a practical method of improving PIP in children.

CONCLUSION

To date, research into paediatric prescribing in primary care is lacking. This study offers a set of 12 evidence-based explicit prescribing indicators to identify PIP in children in primary care. The application of these indicators will enable investigation of the prevalence of PIP in children and allow examination of changes in PIPc over time.

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DATA SHARING STATEMENT

Additional data including Delphi panel comments are available by request from the corresponding author.

COMPETING INTERESTS

The authors declare they have no competing interests.

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AUTHOR CONTRIBUTIONS

EB assisted in the compilation of the initial indicators, revised the indicators, developed the online survey, engaged the Delphi panel and drafted the manuscript. SMS conceived and supervised the study, KOB devised the initial indicators. KB extracted the prevalence data. FB provided statistical support. FM, JC, PR, CMH, TF and SMS formed the Project Steering group and reviewed the indicators throughout the study. All members of the Project Steering group revised the manuscript.

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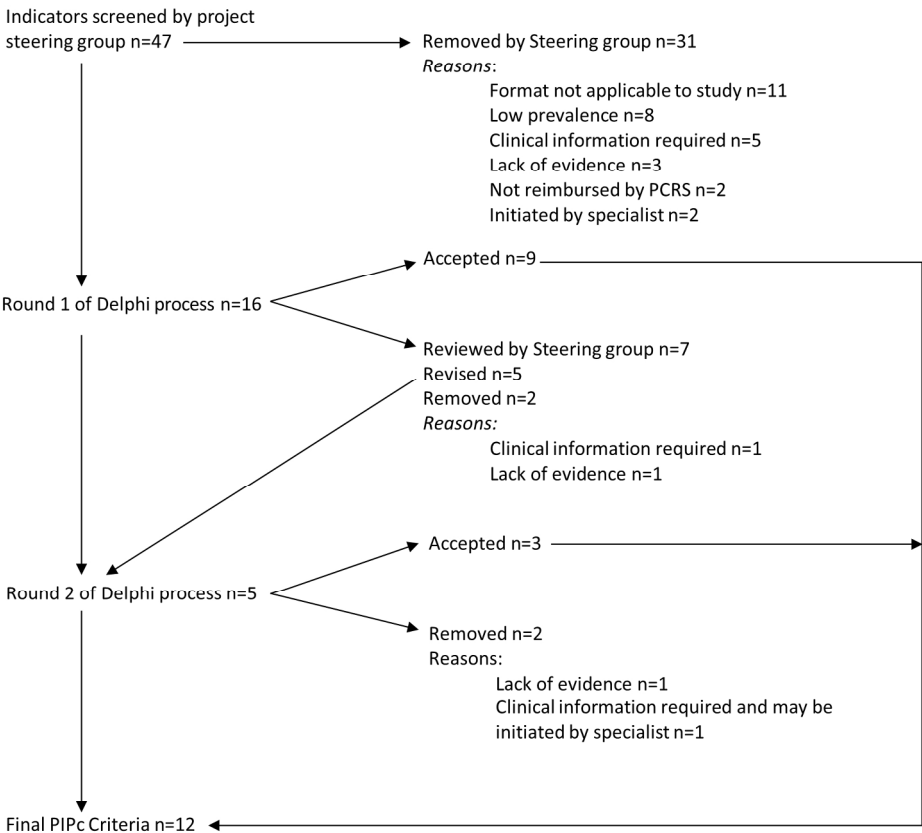


Figure 1: Flow diagram PIPc Study
189x180mm (300 x 300 DPI)

Appendix 1 Search string

Pubmed Search and Cochrane Database April 2014.No filters/limits applied

((inappropriate or appropriate or optimal or suboptimal or ineffective or unnecessary)
AND (medication or prescribing)) AND ((prescribing indicator or prescribing
indicators) OR (quality indicator) OR (guideline adherence) OR (prescribing tool or
prescribing tools))

Duplicates removed 31

Irrelevant 1171

Relevant 25

Search update: Pubmed and Cochrane Database August 2015.No filters/limits
applied

((inappropriate or appropriate or optimal or suboptimal or ineffective or unnecessary)
and (medication or prescribing)) AND ((prescribing indicator or prescribing
indicators) OR (quality indicator) OR (guideline adherence) OR (prescribing tool or
prescribing tools))

Results: 1545

Reviewed titles in terms of studies relating to children, primary care, drugs/conditions
likely to affect children: 115

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PIPc Study: Appendix 2 List of information sources used for development of indicators.

Pubmed Search 2014 and 2015

British National Formulary for Children online

Irish Medicines Formulary 14th Edition 2013 and 16th Edition 2014

Cochrane Database of Systematic reviews

British Medical Journal Clinical Evidence

Clinical Knowledge Summaries (pre 2014 when still available from ROI)

The reference lists of useful articles were also searched to identify any further relevant articles

Medicines and Healthcare products Regulatory Agency website (MHRA)

European Medicines Agency website (EMA)

U.S Food and Drug Administration website (FDA)

St James Hospital National Medicines Information Centre Therapeutic Update Bulletins

Guidelines including those produced by

- National Institute for Health and Care Excellence (NICE)
- British Thoracic Society (BTS)
- Scottish Intercollegiate Guidelines Network (SIGN)
- European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
- British Society for Allergy and Clinical Immunology (BSACI)
- Royal College of Paediatrics and Child health (RCPCH)

PIPc Study: Appendix 3 Table of indicators excluded by the Steering Group during the screening process

Physiological system

Indicator by system

Rationale for inclusion followed by reference

Reason for exclusion

A Gastro-intestinal system

1 Metoclopramide should not be prescribed to children under the age of 1 year

Low prevalence

Metoclopramide can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises. Reference: MHRA. Medicines Health Regulatory Authority Drug Safety Update: Metoclopramide: risk of neurological adverse effects. 2013 [cited 2015 April; Available from: <https://www.gov.uk/drug-safety-update/metoclopramide-risk-of-neurological-adverse-effects>

2 Domperidone should not be prescribed concomitantly with Ketoconazole

Low prevalence

Ketoconazole inhibits Domperidone metabolism; Domperidone levels may be increased up to 3-fold. This resulted in a small mean increase in QT prolongation. Reference: BNFC. British National Formulary for Children 2015 [cited 2015 June]; <https://www.medicinescomplete.com/mc/bnfc/2011/>.

3 Anti-obesity drugs are generally not recommended for children under the age of 16 years

Medications not reimbursed through PCRS from 2012.

Diet and exercise are the preferred methods of weight loss in children. BNFC. British National Formulary for Children 2011 <https://www.medicinescomplete.com/mc/bnfc/2011/>.

4 Proton Pump Inhibitors (PPI's) should not be prescribed to children under the age of 2 years

The efficacy of PPIs for children younger than 2 years of age with GORD is inconsistent and is insufficient to support the use of PPIs. In addition, evidence suggests that PPIs are associated with an increased risk of lower respiratory tract infections and gastroenteritis. Reference: Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. The Cochrane database of systematic reviews. 2014;11:CD008550.

5 Histamine H2 antagonists should not be prescribed to children under the age of 2 years for gastro-oesophageal reflux disease (GORD)

Evidence is insufficient to support the use in primary care of histamine-2 receptor antagonists (H₂RAs) for children younger than 2 years of age with GORD. Limited evidence indicates that H₂RAs are associated with an increased risk of lower respiratory tract infections and gastroenteritis. Reference: Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. The Cochrane database of systematic reviews. 2014;11:CD008550.

B Respiratory system

6 Number of items for cough suppressants or nasal decongestants/patient

Known to be of limited effectiveness.

7 Children who have been prescribed theophylline should not be prescribed

May be initiated by specialist.

Lack of evidence.

Reason for exclusion

Format not appropriate to the aims of the study. Elements included in other indicators
Low prevalence

erythromycin, ciprofloxacin or azithromycin

Theophylline has a narrow margin between therapeutic and toxic dose. Plasma concentration increased by antibacterials mentioned. Reference: BNFC. British National Formulary for Children 2015 <https://www.medicinescomplete.com/mc/bnfc/2011/>.

8 Ratio of corticosteroid to bronchodilator as indicator of quality of asthma prescribing

A low ratio indicates poor prescribing.

Format not appropriate to the aims of the study. Elements included in other indicators

C Central Nervous system		Reason for exclusion
9	Children under the age of 16 yrs should not be prescribed systemic Aspirin Risk of Reye's syndrome. BNFC. British National Formulary for Children 2015 [cited 2015 June]; https://www.medicinescomplete.com/mc/bnfc/2011/ .	Low prevalence
10	Children under the age of 16 yrs should not be prescribed topical oral pain relief products containing salicylate salts (e.g. teething gels) The CHM (2009) has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye's syndrome. Reference: MHRA. Medicines Human Regulatory Agency Drug Safety Update: Oral salicylate gels: not for use in those younger than age 16 years. 2009 [cited 2015 April]; Available from: https://www.gov.uk/drug-safety-update/oral-salicylate-gels-not-for-use-in-those-younger-than-age-16-years .	Not reimbursed by PCRS
11	Phenothiazines should not be prescribed to children under 1 yrs Extrapyramidal side effects and respiratory depression may occur in susceptible children. Reference: BNFC. British National Formulary for Children 2014 https://www.medicinescomplete.com/mc/bnfc/2011/ .	Low prevalence
12	Children under 16 yrs should not be prescribed ≥2 stimulants (in a 90 day period) Identified as a clinically questionable prescribing in previous studies. Reference: Catford JC. Quality of prescribing for children in general practice. British medical journal. 1980;280(6229):1435-7.	Low prevalence
13	Females taking enzyme inducing antiepileptic drugs (EIAED) including	Low prevalence

Phenobarbitone, Primidone, Phenytoin, Carbamazepine, Oxcarbazepine and Topiramate should not be prescribed a combined oral contraceptive (COC), patch or vaginal ring

EIAEDs increase metabolism of estrogens and progesterone thereby affecting contraceptive efficacy. Reference: BNFC. British National Formulary for Children 2015 [cited 2015 June]; <https://www.medicinescomplete.com/mc/bnfc/2011/>.

14 Tricyclic and tetracyclic antidepressants should not be prescribed to children under 16 years

Lack of efficacy and can has serious side effects in some children. Reference: BNFC. British National Formulary for Children 2015 [cited 2015 June]; <https://www.medicinescomplete.com/mc/bnfc/2011/>.

15 Paroxetine and Venlafaxine should not be prescribed to children under 16 years

Clinical trials have failed to show efficacy and have shown an increase in harmful outcomes. Reference: BNFC. British National Formulary for Children 2015; <https://www.medicinescomplete.com/mc/bnfc/2011/>. NICE. Depression in children and young people: identification and management. 2005 [cited 2015 January]; Available from: <https://www.nice.org.uk/guidance/cg28>.

16 Children under 16 years should not be prescribed ≥ 2 benzodiazepines (in a 90 day period)

Clinical information required.

Low prevalence

Low prevalence

Identified as a clinically questionable prescribing in previous studies. Risk of dependence
Reference: BNFC. British National Formulary for Children 2015;
<https://www.medicinescomplete.com/mc/bnfc/2011/>]. Essock SM, Covell NH, Leckman-
Westin E, Lieberman JA, Sederer LI, Kealey E, et al. Identifying clinically questionable
psychotropic prescribing practices for medicaid recipients in new york state. Psychiatric
services (Washington, DC). 2009;60(12):1595-602.

17 Benzodiazepines should not be prescribed for greater than 30 days

Risk of dependence. Reference: BNFC. British National Formulary for Children 2015;
<https://www.medicinescomplete.com/mc/bnfc/2011/>].

18 Children under the age of 16 yrs should not be prescribed a high total number of psychotropics (≥3)

Higher risk of side effects. Reference: BNFC. British National Formulary for Children
2015; <https://www.medicinescomplete.com/mc/bnfc/2011/>]. NICE. Psychosis and
schizophrenia in children and young people: recognition and management. 2013 [cited
2014 April]; Available from: <https://www.nice.org.uk/guidance/cg155>.

19 Ratio of the number of children under the age of 6 yrs prescribed any psychotropic medication divided by the number of youths under 18 yrs who were prescribed any medication.

There has been a drastic increase in recent years in the number of very young children
being prescribed psychotropics.

Clinical information required

Clinical information required

Format not applicable to this study

E Endocrine system	Reason for exclusion
<p>20 In children aged 5-16 yrs who are on long term steroid tablets (eg longer than three months) or requiring frequent courses of steroid tablets (eg three to four per year) an inhaled corticosteroid should also be prescribed as well as a short acting beta 2 agonist, and a trial of a LABA.</p> <p>Patients on long term steroid tablets (eg longer than three months) or requiring frequent courses of steroid tablets (eg three to four per year) will be at risk of systemic side effects. Reference: BTS/SIGN Asthma Guideline. 2014 [cited 2016 April]; Available from: https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline/.</p>	<p>Clinical information needed. Some elements included in other indicators.</p>
F Dermatological system	Reason for exclusion
<p>21 Proportion of children prescribed more than one topical corticosteroid that have been prescribed Fucidin or prescribed a corticosteroid cream with Fusidic acid</p> <p>There are high rates of resistance to fusidic acid. Reference: NICE. Atopic eczema in under 12s: diagnosis and management. 2007; Available from: https://www.nice.org.uk/guidance/cg57.</p>	<p>Lack of evidence</p>
<p>22 If Isotretinoin is prescribed there should be evidence of failure of previous acne therapy (within the last 12 months)</p> <p>Many side effects including changes in bone density and growth as well as suicidal ideation and depression. Reference: BNFC. British National Formulary for Children 2015; https://www.medicinescomplete.com/mc/bnfc/2011/].</p>	<p>May be initiated by specialist.</p>

G General	Reason for exclusion
<p>23 A high rate of generic prescribing</p> <p>A high rate of generic prescribing is considered to be a marker of cost consciousness. National medicines information centre .Generic prescribing 2009 [cited 2015 April]; Available from: http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/NMICBulletins.ie</p>	<p>Format not applicable to the study</p>
<p>24 Consumption of antibacterials for systemic use expressed in DID</p> <p>This is likely to best indicate the size of the pressure driving antibiotic resistance which is highly relevant for public health.</p> <p>Reference: Coenen S, Ferech M, Haaier-Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJ, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. Quality & safety in health care. 2007;16(6):440-5.</p>	<p>Format not applicable to the study.</p> <p>Public health indicator</p>
<p>25 Consumption of beta lactamase sensitive penicillins expressed as a percentage of the total consumption of antibacterials for systemic use</p> <p>Generally, narrow-spectrum antibacterials are preferred to broad-spectrum antibacterials unless there is a clear clinical indication e.g. life-threatening sepsis.</p> <p>Reference: Coenen S, Ferech M, Haaier-Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJ, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. Quality & safety in health care. 2007;16(6):440-5.</p>	<p>Format not applicable to the study.</p> <p>Public health indicator</p>

26 Consumption of 3rd and 4th generation of cephalosporins expressed as a % of the total consumption of antibiotics for systemic use.

Antibiotic-associated colitis may occur with the use of broad-spectrum cephalosporins, particularly second- and third-generation cephalosporins. Reference: Malo S, Bjerrum L, Feja C, Lallana MJ, Abad JM, Rabanaque-Hernandez MJ. The quality of outpatient antimicrobial prescribing: a comparison between two areas of northern and southern Europe. *European journal of clinical pharmacology*. 2014;70(3):347-53.

27 Ratio of number of items for Co-Amoxiclav to number of items for all antibiotics

Co-Amoxiclav is generally considered a second line antibiotic for most common conditions requiring antibiotic treatment and therefore the ratio of this antibiotic to all antibiotics prescribed should reflect this.

28 Ratio of number of items for quinolones to number of items for all antibiotics

Quinolones not generally recommended in children unless growth is complete, there is a risk of musculoskeletal damage. Reference: Coenen S, Ferech M, Haaijer-Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJ, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. *Quality & safety in health care*. 2007;16(6):440-5.

29 Ratio of 2nd line (or broad spectrum?) antibiotic to the number of items for any antibiotic

Second line and broad spectrum antibiotics should be prescribed at a much lower level than narrow spectrum and first line antibiotics. Reference: Coenen S, Ferech M, Haaijer-

Format not applicable to the study.

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Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJ, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. Quality & safety in health care. 2007;16(6):440-5.

30 Ratio of the consumption of broad spectrum antibiotics to the consumption of narrow spectrum antibiotics

Second line and broad spectrum antibiotics should be prescribed at a much lower level than narrow spectrum and first line antibiotics. Reference: Coenen S, Ferech M, Haaijer-Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJ, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. Quality & safety in health care. 2007;16(6):440-5.

31 Seasonal variation in the total antibiotic consumption

Marked variation in antibiotic use is likely to reflect poorer practice since it represents higher use of antibiotics for respiratory infections which has a poor evidence base. Reference: Coenen S, Ferech M, Haaijer-Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJ, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. Quality & safety in health care. 2007;16(6):440-5.

32 Mefloquine should not be prescribed to children under 16 years with a history of convulsions

Mefloquine is an anti-infective agent for protection and treatment of malaria, there is an increased convulsion risk with epilepsy. Reference: BNFc. British National Formulary for

Format not applicable to the study.
Public health indicator

Format not applicable to the study.
Public health indicator

Clinical information needed

Children 2015 [cited 2015 June]; <https://www.medicinescomplete.com/mc/bnfc/2011/>].

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PIPC Indicators

Respiratory System

1. Intranasal beclometasone should not be prescribed to children under 6 years. Rationale: Intranasal steroids can have an adverse effect on growth and hypothalamic-pituitary-adrenal axis function in children. Systemic absorption is high for beclometasone compared to other intranasal corticosteroids. Reference: Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2008; 38(1):19-42.

2. An inhaled short acting beta-2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids. Rationale: Inhaled corticosteroids are preventer therapy. Mild asthma symptoms can often be controlled with a short acting beta-2 agonist. Reference: BTS/SIGN Asthma Guideline. 2014 [cited 2016 April]; Available from: <https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline/>.

3. An inhaled short acting beta-2 agonist should be prescribed to children under 5 years who are also taking a leukotriene receptor antagonist. Rationale: Mild to moderate symptoms of asthma respond rapidly to the inhalation of a short acting beta-2 agonist. There is evidence that in children under 5 years, leukotriene receptor antagonists should be first choice for add on therapy. Reference: BTS/SIGN Asthma Guideline. 2014 [cited 2016 April]; Available from: <https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline/>.

4. An inhaled corticosteroid should be prescribed to children aged 5-15 years who are taking a long acting beta-2 agonist (LABA). Rationale: LABAs should only be prescribed as add-on therapy in asthma. Reference: BTS/SIGN Asthma Guideline. 2014 [cited 2016 April]; Available from: <https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline/>.

5. Children under 12 years who are prescribed a pressurised metered-dose inhaler (pMDI) should also be prescribed a spacer device at least every 12 months.

Rationale: Children find it difficult to correctly administer asthma medication via a pMDI without a spacer device. Wear and tear may adversely affect the integrity of the device after 6-12 months. Reference: BTS/SIGN Asthma Guideline. 2014 [cited 2016 April]; Available from: <https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline/>.

NICE. National Institute for Health and Care Excellence: Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma. 2000 [cited 2016 April]; Available from: <https://www.nice.org.uk/guidance/ta10>.

NICE. National Institute for Health and Care Excellence: Inhaler devices for routine treatment of chronic asthma in older children (aged 5–15 years). 2002 [cited 2016 April]; Available from: <https://www.nice.org.uk/guidance/ta38>.

6. Carbocysteine should not be prescribed to children

Rationale: There is a lack of evidence for its efficacy in the general paediatric population.

Reference: Chalumeau M, Duijvestijn YC. Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease. The Cochrane database of systematic reviews. 2013; 5:CD003124

Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. The Cochrane database of systematic reviews. 2014;11:CD001831.

Gastrointestinal System

7. Loperamide should not be used in children under 4 years.

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Rationale: Anti-diarrhoeal agents are rarely effective and have troublesome side effects including nausea, flatulence, headache and dizziness. Reference: National Institute Health and Care Excellence: Guideline CG84: Diarrhoea and vomiting caused by gastroenteritis in under 5s: diagnosis and management. 2009 [cited 2016 April]; Available from: <https://www.nice.org.uk/guidance/cg84>.

8. Domperidone should not be prescribed concomitantly with erythromycin.

Rationale: Erythromycin inhibits domperidone metabolism; domperidone levels may be increased up to 3 fold. This can result in a small mean increase in QT prolongation. Reference: BNFC. British National Formulary for Children 2015 [cited 2015 June]; <https://www.medicinescomplete.com/mc/bnfc/2011/>.

Dermatological System

9. Children prescribed greater than one topical corticosteroid in a year should also be prescribed an emollient.

Rationale: Regular use of emollients can reduce the need for topical corticosteroids. Reference: NICE. Atopic eczema in under 12s: diagnosis and management. 2007; Available from: <https://www.nice.org.uk/guidance/cg57>.

10. Tetracyclines should not be prescribed to children <12 years.

Rationale: Rationale: Tetracycline binds to calcium and is deposited in growing bone and teeth which can cause staining and dental hypoplasia. Reference: BNFC. British National Formulary for Children 2015 [cited 2015 June]; <https://www.medicinescomplete.com/mc/bnfc/2011/>.

Neurological System

11. Codeine/Dihydrocodeine medications should not be prescribed to children under 12 years.

Rationale: Children under 12 years may be at increased risk of serious side effects e.g. respiratory depression. There is limited data available on the effectiveness of codeine/dihydrocodeine in children. Reference: MHRA. Medicines and Healthcare Products Regulatory Agency: Codeine for cough and cold restricted use in children. 2015 [cited 2016 April]; Available from: <https://www.gov.uk/drug-safety-update/codeine-for-cough-and-cold-restricted-use-in-children>.

12. Sedating antihistamines should not be prescribed to children under 2 years

Rationale: Antihistamines often cause sedation. In some children, potentially life threatening side effects such as respiratory depression can occur. Reference: BNFC. British National Formulary for Children 2015 [cited 2015 June]; <https://www.medicinescomplete.com/mc/bnfc/2011/>.

MHRA. Medicines and Health Products Regulatory Agency: Over the counter cough and cold medicines for children drug safety update 2009 [cited 2016 April]; Available from: <https://www.gov.uk/drug-safety-update/over-the-counter-cough-and-cold-medicines-for-children>.