Involvement of Children and Young People in reporting Suspected adverse drug reactions: past and future

Nikita Bhoombla1, Jennifer Preston, 2,3, Jenny Ainsworth3 , Helena Bird4, Mitul Jadeja4, Charlotte King1, Daniel B Hawcutt2,3

1: University of Liverpool Medical School, Liverpool, UK

2: Department of Women’s and Children’s Health, Institute of Translational Medicine, University of Liverpool, UK

3: NIHR Alder Hey Clinical Research Facility, Alder Hey Children’s Hospital, Liverpool, UK

4: Medicines and Healthcare Products Regulatory Agency, London, UK

There are no competing interests to declare

Word count: 1723

Tables: 4

Figures: 2

Keywords: Adverse Drug Reaction; Spontaneous Reporting; Paediatrics; Patient Involvement

Abstract

**Objectives**

To determine children’s and young people’s (CYPs) contribution to the Medicines and Healthcare Products Regulatory Agency (MHRA) Yellow Card scheme (YCS), and develop age appropriate information with CYP to aid their reporting.

**Methods**

Reports for suspected ADRs received by the MHRA YCS from 01/01/2008 to 29/11/2018 were examined. Consultation activities with CYP from regional, national and international groups were undertaken to develop CYP appropriate information about reporting ADRs to the YCS.

**Results**

CYP contributed 2.3% of YCS reports for patients <19 years. Patients from age 10 years old contributed YCS reports, and CYP reports are increasing annually. Reports from CYP contain different suspected medications and reactions compared to YCS about patients age <19 years. The most reported medicines on CYP generated YCS were adolescent vaccinations (Human papilloma virus, n=69), oral contraceptives, acne medication, anti-infectives, and antidepressants. The most commonly reported suspected ADRs from CYP were headache (n=107), nausea and fatigue. CYP generated reports additional suspected ADRs compared to adult reports about CYP, including depression, anxiety and suicidal ideation. Phase I of the consultation with CYP identified divergent information needs for <11 and 12-18 year olds. Phase II-VI updated and improved the information for both age groups. Overall, more than 300 CYP contributed to the development of the information.

**Conculsion**

CYPs contribution to the YCS is limited, but increasing, and demonstrated distinct patterns of suspected medications and reactions. Age appropriate information for CYP to aid reporting of suspected ADRs has been developed.

Word count = 241/250

Introduction

The Medicines and Healthcare Regulatory Agency’s (MHRA) Yellow Card scheme (YCS) collects spontaneous reports about suspected adverse drug reactions (ADRs) from a range of stakeholders in the UK, including healthcare professionals, patients, parents, and carers. Patient and carer reports have increased since their introduction in 2005, and have increased to constitute approximately 20% of all YCS reports received annually [1]. The quality of patient reports is similar to physician generated reports [2], and identifies additional information beyond that contained within physician reports [3]. The inclusion of patient and carer reports in spontaneous reporting schemes has increased worldwide [4]. However, despite increasing the range of possible reporters for suspected ADRs, under reporting remains a problem for all spontaneous reporting schemes [5].

ADRs affect children and young people (CYP) who use medicines, are responsible for approximately 3% of paediatric admissions, and complicate 18% of paediatric inpatient stays [6, 7]. There are key differences between CYP and older adults, including physiological differences (different diseases experienced, altered body composition, vertical growth, varied renal and hepatic function at younger ages, and psychological development) as well differences in the medications used (alternate formulations, doses, more common off label and unlicensed use), and hence CYP experience different ADRs to adults [6, 7]. There are multiple publications assessing the type of reports submitted to various spontaneous reporting schemes worldwide about the ADRs suspected in CYP [8-13], but it is not clear whether the reports contained within these publications were completed by health professionals, parents/carers, or CYP themselves. To date, there has not been any evaluation of reports of suspected ADRs specifically received from CYP [14].

Across the teenage years, a transition from dependence on parents/carers, to full independence with regard to health matters occurs. This has historically focussed on aspects of disease management, such as adherence to treatment, and attendance at appointments, but should include all aspects of healthcare including the identification and reporting of suspected ADRs. There is therefore a need for specific guidance aimed at CYP to inform, educate and empower them to report their suspected ADRs, however no such information has been previously published.

The aim of this project was therefore to examine the YCS reports supplied by CYP, and work with regional, national and international groups of CYP to adapt existing, adult orientated, information about reporting suspected ADRs into a form that would be useful and acceptable to CYP of various ages.

# Methods

YCS reports supplied to the MHRA between 01/01/2008 and 29/11/2018 were examined.

For information development, existing information produced by the MHRA to inform adult patients about reporting suspected ADRs was used initially. The review process used four different groups of children and young people to adapt this into text that the CYP in the final group judged acceptable. Details of each group of CYP who participated are shown in Table 1. The questionnaires used to facilitate the group discussions with CYP are in the supplementary data section.

# Results

Between 01/01/2008 and 29/11/2018, the MHRA received 41630 reported ADR reports in patients <19 years of age. Of these, only 948 (2.3%) were identified as being self reported by CYP. The medications reported by CYP differ markedly from those reported in CYP generally (Table 2). Of the 25 most commonly reported medications in patients <19 years, seven are immunisations given to very young children only. Of the remaining 18 most commonly reported medications, only six (33.3%) were present in the 25 most commonly reported by CYP. Human Pappiloma Virus was the most commonly suspected medication for both reports in patients <19 years, and by CYP.

The reactions reported by CYP also differ from those reported about CYP. The 25 most common reactions for each group are shown in table 3. Sixteen of the twenty-five suspected reactions are included in both the reports by CYP, and those about CYP. CYP generated included reactions related to mental health (depression [n=60], anxiety [n=31], and suicidal ideation [n=26]) that were not present in the common reports about CYP.

The youngest CYP to provide reports to the YCS were age 10, although most were older teenagers (Table 4). Reports from CYP have increased in frequency since reporting was introduced, (Table 4), and in the current year to date shows a 3% increase, despite overall YCS reports decreasing by 4% (MHRA, personal communication).

For the development of CYP specific information about how to report a suspected ADR, details of the CYP groups attended, ages, and number of participants is shown in Table 1. A summary of each phase of information development is presented below. Full details of the discussions that occurred in each session are in the supplementary data section.

### Phase I

The CYP were clear that a single source of information would not be sufficient. They suggested that there should be two versions of the information, one for older children (approximately 12 and older) and one for younger (less than twelve). Additionally, when reviewing existing adult orientated information, it was stated that these contained too much information, and re-working them into ‘bite sized’ chunks for CYP was requested. Specific information the CYP requested be part of both the older and younger CYP information included: The ways you can make a yellow card report; what to report; protection of personal information; where to get more information; what are the potential benefits to reporting?

### Phase II

Phase II refined the language used, and topics covered in the two versions of the information under development. This session also strongly supported the concept that this information should enable CYP to report their own ADRs. This was incorporated into the older CYP information sheet.

### Phase III-VI

Phase IV through to VI consisted of iterative improvements to both the information for older and younger CYP. Updates to the information included the format, language and structure. At the final review (Phase VI), there were no substantive changes suggested by the groups of CYP who reviewed the information. The final text is shown in Figures 1 & 2.

# Discussion

This is first time the contribution of CYP to a national spontaneous reporting scheme for suspected ADRs has been examined. CYP only complete a small percentage of the total YCS reports for patients <19 years of age, but the medications they included were distinct from those reported in patients <19 years in general, and appear well aligned with commonly used medications in the teenage population. Many of the suspected reactions were similar between reports from CYP, and those about CYP, but reports related to concerns about mental health (depression, anxiety and suicidal ideation) were more common in the reports from CYP themselves. Mental health was identified as a priority in the 2017 State of Child Health report [15], so it is particularly pleasing that supporting and empowering CYP to report suspected ADRs may also help improve the reporting of suspected ADRs in this area.

This study was not able to ascertain what the current barriers are to CYP reporting are, but assumed that a lack of specific information for CYP may be a potentially significant factor, and undertook a project to develop accessible, comprehensible information. The information development phases undertaken have created the the first information developed specifically by and for CYP, about how to report their own suspected ADRs. Taken together, this work represents the first steps in improving the quality and quantity of ADR reports to spontaneous reporting schemes from CYP themselves.

For the younger CYP, the groups who contributed to the development of information felt that the reporting would be carried out by a parent/guardian, and so the information focuses on informing about ADRs, and when to let a responsible adult know. However, the CYP developing the information also stated that even if the younger CYP were not going to report themselves, it was important for them to know the full process, and include the details of how to report.

For the older CYP, the groups who contributed to the information development deemed they had the understanding and capability to be able to report ADRs themselves, especially those with their own mobile phone. Therefore this information focuses on the CYP reporting themselves.

A strength of the information development work is the range of CYP involved. This included CYP with experience of healthcare, advocacy and paediatric health research design (Liverpool YPAG, ICAN) and without (School children), across a wide range of ages, including over 300 children overall. In addition, clinical oversight by a specialist in paediatric clinical pharmacology meant that the information remained accurate while being edited by the CYP for clarity and comprehensibility. The outputs of this project have the potential to be used nationally to positively influence CYPs behaviours with regard to healthcare.

Limitations of this work are that it focuses on a UK’s spontaneous reporting system, and it may need some additional work to meet the needs of other populations or spontaneous reporting schemes. However, there are many similarities between spontaneous reporting schemes worldwide, so this may provide a useful template to be adapted. Development of this information for CYP may also provide be a platform for other potential developments in CYP specific information, such as improving the communication about adverse events (AEs) and suspected ADRs in clinical trials.

Some of the CYP involved do have above average knowledge of healthcare, advocacy and paediatric health research design (Liverpool YPAG; iCAN). However, other groups who are naïve to healthcare (e.g. schoolchildren) were also included, and when combined with the large number of participants (>300), with varying ages and comprehension levels, we are confident that the information will be both comprehensible and useful to CYP across a broad range of ages and experience with healthcare.

The importance of parent and patient engagement (patient led innovation) is undervalued and plays a vital role in improving outcomes. However, it can be hard to measure improvements in outcomes as quantifying how parent and patient advice has improved the processes can be difficult [16]. However, the development of these information resources to improve reporting by CYP to the YCS represents an opportunity to measure impact in terms of quality and quantity of reports, providing evidence for the importance and positive impact involving CYP and their parents can make.

**Conclusion**

CYPs contribution to the YCS is limited, but increasing, and demonstrated distinct patterns of suspected medications and reactions. Age appropriate information for CYP to aid reporting of suspected ADRs has been developed.

# Acknowledgements

We would like to thank all of the young people who helped develop this information, from the Liverpool YPAG (<https://generationr.org.uk/liverpool/>), Steep Hill School, and the International Children’s Advisory Network (ICAN, <https://icanresearch.org/>) as this would not have been possible without their help.

This is a summary of independent research funded by University of Liverpool and carried out at the National Institute for Health Research (NIHR) Alder Hey Clinical Research Facility*.* The views expressed are those of the author(s) and not necessarily those of the University of Liverpool, NHS, the NIHR or the Department of Health

# References

1. McLernon DJ, Bond CM, Hannaford PC, Watson MC, Lee AJ, Hazell L, Avery A, Collaboration YC. Adverse Drug Reaction Reporting in the UK. Drug Safety 2010; 33: 775-88.

2. Blenkinsopp A, Wilkie P, Wang M, Routledge PA. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. British journal of clinical pharmacology 2007; 63: 148-56.

3. Avery AJ, Anderson C, Bond C, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee A, Mclernon DJ. Evaluation of patient reporting of adverse drug reactions to the UK ‘Yellow Card Scheme’: literature review, descriptive and qualitative analyses, and questionnaire surveys. Health Technology Assessment 2011.

4. Margraff F, Bertram D. Adverse Drug Reaction Reporting by Patients: An Overview of Fifty Countries. Drug Safety 2014; 37: 409-19.

5. Hazell L, Shakir SA. Under-reporting of adverse drug reactions. Drug safety 2006; 29: 385-96.

6. Gallagher RM, Mason JR, Bird KA, Kirkham JJ, Peak M, Williamson PR, Nunn AJ, Turner MA, Pirmohamed M, Smyth RL. Adverse drug reactions causing admission to a paediatric hospital. PLoS One 2012; 7: e50127.

7. Thiesen S, Conroy EJ, Bellis JR, Bracken LE, Mannix HL, Bird KA, Duncan JC, Cresswell L, Kirkham JJ, Peak M. Incidence, characteristics and risk factors of adverse drug reactions in hospitalized children–a prospective observational cohort study of 6,601 admissions. BMC medicine 2013; 11: 237.

8. Hawcutt DB, Mainie P, Riordan A, Smyth RL, Pirmohamed M. Reported paediatric adverse drug reactions in the UK 2000–2009. British journal of clinical pharmacology 2012; 73: 437-46.

9. Kimland E, Rane A, Ufer M, Panagiotidis G. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. Pharmacoepidemiology and drug safety 2005; 14: 493-99.

10. Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over a 10-year period. Pediatrics 2006; 118: 555-62.

11. Aagaard L, Weber CB, Hansen EH. Adverse Drug Reactions in the paediatric population in Denmark. Drug safety 2010; 33: 327-39.

12. Morales-Olivas F, Martınez-Mir I, Ferrer J, Rubio E, Palop V. Adverse drug reactions in children reported by means of the yellow card in Spain. Journal of clinical epidemiology 2000; 53: 1076-80.

13. Priyadharsini R, Surendiran A, Adithan C, Sreenivasan S, Sahoo FK. A study of adverse drug reactions in pediatric patients. Journal of pharmacology & pharmacotherapeutics 2011; 2: 277.

14. Cliff-Eribo KO, Sammons H, Choonara I. Systematic review of paediatric studies of adverse drug reactions from pharmacovigilance databases. Expert opinion on drug safety 2016; 15: 1321-28.

15. Health RCoPaC. The State of Child Health. In, 2017.

16. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, Suleman R. Mapping the impact of patient and public involvement on health and social care research: a systematic review. Health Expectations 2014; 17: 637-50.

# Table 1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Phase** | **Reviewer** | **Number of CYP present** | **Age range (years)** | **Date of meeting** |
| I | Liverpool YPAG | 20 | 12-18 | 4th November 2017 |
| II | Royal College of Paediatrics and Child Health Quality Improvement (QI) group | 56 | 12-18 | 5th December 2017 |
| III | Steep Hill School | 40 | 9-11 | 5th February 2018 |
| IV | Liverpool YPAG | 21 | 12-18 | 22th February 2018 |
| V | Paediatric Pharmacology Physician | N/A | N/A | 8th June 2018 |
| VI | ICAN conference and workshop | 200 | 12-18 | 12th July 2018 |

### Table 1: Information on the phases of information development and children and young people (CYP) present.

Table 2

|  |  |  |  |
| --- | --- | --- | --- |
| Yellow Card Reports for patients <19 years (all reporters) | | Yellow Card Reports from patients age <19 years | |
| Suspect Drug | **Number of reports** | **Suspect Drug** | **Number of reports** |
| Human papilloma virus | 8703 | **Human papilloma virus** | 69 |
| Neisseria meningitidis | 2649 | Ethinyloestradiol and levonorgestrel | 50 |
| Live influenza virus | 1989 | Isotretinoin | 44 |
| Streptococcus pneumoniae | 1730 | **Meningococcal a,c,w135,y vaccine** | 41 |
| MMR vaccine | 1705 | Fluoxetine | 36 |
| Meningococcal a,c,w135,y vaccine | 1406 | Desogestrel | 33 |
| DT IPV vaccine | 1254 | Co-cyprindiol | 21 |
| DTPA IPV hib vaccine | 1158 | **Swine origin influenza virus** | 17 |
| Rotavirus | 956 | Clotrimazole | 17 |
| DTPA ipv vaccine | 735 | Sertraline | 16 |
| Amoxycillin | 723 | Flucloxacillin | 16 |
| Valproic acid | 646 | Levonorgestrel | 15 |
| Swine origin influenza virus | 619 | Citalopram | 14 |
| Methylphenidate | 616 | Etonogestrel | 13 |
| Phenoxymethylpenicillin | 573 | Co-amoxiclav | 12 |
| Paracetamol | 534 | Propranolol | 12 |
| Etonogestrel | 410 | Lymecycline | 12 |
| Oseltamivir | 405 | Doxycycline | 12 |
| Atomoxetine | 403 | **Amoxycillin** | 11 |
| Ibuprofen | 402 | Clarithromycin | 11 |
| HIB/MEN C conjugate vaccine | 394 | Trimethoprim | 11 |
| Montelukast | 362 | **Ibuprofen** | 11 |
| Methotrexate | 318 | **Phenoxymethylpenicillin** | 11 |
| Influenza virus | 308 | Erythromycin | 11 |
| Clozapine | 308 | Co-codamol | 10 |

Table 2: Comparison of the 25 most reported drugs between patients <19 years of age, and reporters age <19 years of age. **Bold**: present in both columns. MMR: Measles mumps and rubella. DT: Diptheria and Tetanus. IPV: inactivated poliovirus. DTPA: DIptheria,Tetanus, acellular pertussis. HIB: Haemophilius Influenza B.

# Table 3

|  |  |  |  |
| --- | --- | --- | --- |
| **Yellow Card Reports for patients <19 years (all reporters)** | | **Yellow Card Reports from patients age <19 years** | |
| **Suspected reaction (PT)** | **Number of reports** | **Suspected reaction (PT)** | **Number of reports** |
| **Pyrexia** | 3772 | **Headache** | 107 |
| **Headache** | 3359 | **Nausea** | 100 |
| **Dizziness** | 3077 | **Fatigue** | 86 |
| **Vomiting** | 2992 | **Dizziness** | 81 |
| **Nausea** | 2631 | Depression | 60 |
| **Malaise** | 2414 | **Vomiting** | 53 |
| **Rash** | 2395 | **Diarrhoea** | 52 |
| **Pain in extremity** | 1655 | **Malaise** | 47 |
| **Erythema** | 1595 | Abdominal pain upper | 42 |
| **Fatigue** | 1396 | **Pyrexia** | 34 |
| Syncope | 1357 | **Pruritus** | 33 |
| **Diarrhoea** | 1283 | Dyspnoea | 32 |
| Urticaria | 1218 | Anxiety | 31 |
| Pallor | 989 | **Erythema** | 31 |
| Peripheral swelling | 945 | **Abdominal pain** | 28 |
| Foetal exposure during pregnancy | 854 | **Decreased appetite** | 28 |
| **Decreased appetite** | 830 | **Pain in extremity** | 26 |
| **Pruritus** | 809 | Myalgia | 26 |
| **Pain** | 793 | Vaginal haemorrhage | 26 |
| Seizure | 770 | Suicidal ideation | 26 |
| Dyspnoea | 767 | **Somnolence** | 26 |
| **Abdominal pain** | 741 | **Pain** | 25 |
| **Somnolence** | 723 | Arthralgia | 24 |
| Lethargy | 702 | Dry skin | 23 |
| Hypersensitivity | 659 | **Rash** | 22 |

Table 3: : Comparison of the 25 most reported reactions between patients <19 years of age, and reporters age <19 years of age. **Bold**: present in both columns.

# Table 4

|  |  |
| --- | --- |
| **Year of YCS report** | **Number of YCS reports** |
| 2008 | 15 |
| 2009 | 47 |
| 2010 | 28 |
| 2011 | 25 |
| 2012 | 38 |
| 2013 | 48 |
| 2014 | 72 |
| 2015 | 118 |
| 2016 | 175 |
| 2017 | 203 |
| 2018\* | 179 |
| **Age of reporter (years)** | **Number of YCS reports** |
| 10 | 2 |
| 11 | 1 |
| 12 | 9 |
| 13 | 39 |
| 14 | 49 |
| 15 | 87 |
| 16 | 16 |
| 17 | 236 |
| 18 | 369 |

Table 4: Number of reports per year, and age of CYP submitting YCS reports. \*2018 data complete to 29/11/2018.

|  |  |  |  |
| --- | --- | --- | --- |
| **What are Side Effects, and Yellow Card Reports?** | **What to Report?** | **When to Report?** | **How to Report?** |
| * Medicines may do more than just make you feel better. * They can sometimes cause other problems, which are called ‘Side Effects’ (see next page for examples). * It is important to find out which medicines are giving children side effects. * A **Yellow Card** report about a medicine is a **WARNING** that it might cause side effects! * If you think you may have a side effect, tell an adult you trust. * You, or an adult you trust, can help by filling out a **Yellow Card Report** about **ANY** medicine you think may have given you a side effect. | * There are lots of different side effects, including: * Diarrhoea * Constipation (difficult to poo) * Feeling/Being sick * Rash/Itching * Tummy pain * Pain in other parts of body * Headache * Sweating * Eating less or more than usual * Feel your own heartbeat * High temperature * More or less sleepy * Feeling very sad * Fainting * Bad dreams/nightmares * The side effect you are worried about may not be on the leaflet in the medicine box, that is ok, you can still report. | * If you use a medicine that you (or your family) think has given you ‘side effects’. * The medicine may have come from a doctor, pharmacy, or a shop, it doesn’t matter, all can be reported. * If you take more than one medicine, and are not sure which one caused the side effect, you can put the names of all the medicines on the report. * Reporting side effects can help doctors, by letting them know about new side effects. * Medicines that cause unwanted side effects may need to be checked again! | * You should get the help of an adult you trust, who knows a lot about you. They need to know about why you use medicines, which medicines you use, and what side effect you are worried about. * The Yellow Card report can be filled in a number of different ways:  1. Using a computer (with permission), go to   www.mhra.gov.uk/yellowcard   1. Using the Yellow card app on a mobile phone 2. By going to tell your doctor, nurse or pharmacist about it  * All Yellow Card Reports go to the Medicines and Healthcare Regulatory Agency (MHRA), who make sure medicines in the UK are safe. |

### Figure 1: Final text of information for children and young people age <11 years old

|  |  |  |  |
| --- | --- | --- | --- |
| **What are Side Effects, and Yellow Card Reports?** | **What to Report?** | **When to Report?** | **How to Report?** |
| * If a medicine causes you problems (symptoms) or makes you feel unwell, this may be a ‘Side Effect’. * Side effects that are already known are on the information sheet that comes with your medicine. * You can report **ANY** side effect, serious or not, from **ANY** medicine, using a Yellow Card report. By reporting a side effect, you help make medicines safer. * **Yellow Card r**eports help discover new, sometimes serious, side effects from medicines. * Some medicines are used differently, or not used anymore at all, because of Yellow Card Reports. | * **ANY** of your medicines that you think gives you a side effect. * It doesn’t matter what the side effect is, or how serious it is, it is ok complete a Yellow card. * It is especially important if the side effect you have is **not** already in the medicine’s information leaflet. * Side effects to medicines bought in shops, over the counter in pharmacies and to herbal remedies can be reported. * If you are taking more than one medication, or have more than one side effect, you can report them all on a single Yellow Card Report. | * The most important thing is to look after your health, so arrange to see a doctor, or phone 111 for advice, if you are worried you might have a side effect. * You can report a suspected side effect from a medicine you are taking now or after you have stopped it. * You can report the side effect you are worried about if you are responsible for that person, or any other person you are close to e.g. your sibling. | * Call: 0808 100 3352 * Online: www.mhra.gov.uk/yellowcard * Yellow Card app Download via apple app store/google play * Paper form (found in pharmacies). * **Always** contact a doctor if you are worried about symptoms. * Alternatively contact **NHS England 111.** * **It may help to talk to an adult you trust.** * More information on what/when/why to report found here: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) |

### Figure 2: Final text of information for children and young people age 12-18 years old