When to Report Adverse Drug Reactions in Children?

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The use of medicines can never be 100% safe, or 100% effective, and therefore each prescription is a balance of the intended benefits from using the medication versus the risks associated with it. Any patient using medicines may experience only the positive effects, only the negative effects, a combination of both positive and negative effects, or no effects at all. The negative effects of medicines are referred to as “Adverse Drug Reactions” (ADRs), and are officially defined as “A response to a medicinal product which is noxious and unintended” [[1](#_ENREF_1)]. A negative symptom or effect of a medicine may be categorised as an ADR regardless of how a drug has been used, and so includes abuse, overdose, industrial exposure, medication errors, and unlicensed and/or off-label use.

To generate data on ADRs, including identification of previously unsuspected ADRs, the UK set up one of the world’s first spontaneous reporting schemes for collecting **SUSPECTED** ADRs in 1964. These data were initially collected by doctors who would complete a yellow coloured card found at the back of the British National Formulary. Fifty years later, although the range of potential reporters and means of completion have evolved, the “Yellow Card” Scheme continues to be a vitally important mechanism to collect these data. To identify the rarest ADRs, national data may not be sufficient, and so the World Health Organization (WHO) Programme for International Drug Monitoring was established in 1968, and has been coordinated by the Uppsala Monitoring Centre (UMC) in Sweden since 1978. The UMC is a WHO collaborating centre currently collecting, assessing and communicating information and data from the pharmacovigilance programs collaborating Member State countries own national ADR reporting schemes (e.g. UK’s Yellow Card Scheme). The main focus and source of data is individual case safety reports, with a common reporting form, common terminologies and classifications. A centrally maintained database (including these core data sets) exists at the UMC, with agreed guidelines for entering the information formulated. Research currently includes data-driven statistical analysis, interaction detection, safety surveillance, drug signalling (including paediatric prescribing) and risk-benefit analysis, based on data from over 10 million reports of suspected ADRs.

There are well recognised barriers to reporting using spontaneous reporting schemes. These include service pressures and time constraints, difficulty recognising ADRs (especially in intensive care environments), reluctance to report mild ADRs and tendency to report only ADRs associated with new drugs, or serious reactions, a lack of education over the implications of ADR for patients and health care services or a belief that as an ADR can be anticipated, or has previously been recognised that it need not be reported. All spontaneous reporting schemes used around the world, suffer from massive under-reporting, with estimates that up to 95% of all ADRs are not reported. This appears to be as true in paediatrics as the rest of medicine. Within the UK, children receive 5% of the approximately 1 billion prescriptions. If only 0.01% of all prescriptions in children caused an ADR, and all ADRs were reported, we would estimate that the Yellow card scheme would receive 1300 reports per day, but the Yellow Card Scheme only received 6 reports of a suspected ADR per day between 2000-2009 [[2](#_ENREF_2)]. Closer analysis of the UK paediatric Yellow Card reports received over this time period has also shown that:

* The rate of reporting is different depending of the class of drug. For example vaccines are reported more frequently than other medications, comprising 69% of all suspected ADR reports [[2](#_ENREF_2)]
* For non-vaccines, despite the advice at the time being to report **all suspected ADRs**, mild clinically insignificant symptoms were not commonly reported, while clinically severe symptoms were amongst the most common. For example, “aggression” and “convulsion” were the fifth and sixth most commonly reported suspected ADRs in this group [[2](#_ENREF_2)].

The small number of spontaneous reports of ADRs received associated with paediatric patients does not mean that there is not a clinical problem to address. Prospective data on ADR occurrence has helped to establish the extent of the problem in paediatric patients, showing that 3% of paediatric hospital admissions are directly attributable to ADRs [[3](#_ENREF_3)], while 18% of paediatric hospital inpatient stays were complicated by an ADR [[4](#_ENREF_4)].

These ADRs will not necessarily be the same as those seen in adults as there are key differences in children including i) altered pharmacokinetics (especially in the very young), ii) increased use of medicines as either ‘off-label’ or as unlicensed products (which may be associated with higher rates of ADRs in children [[5](#_ENREF_5)], iii) paediatric specific ADRs (for example growth suppression, Grey Baby Syndrome, Reye’s Syndrome) iv) use of different formulations and/or sensitivity to excipients, and v) different diseases being treated.

Spontaneous reports about ADRs in children have resulted in changes in the prescribing of many medicines in children and neonates. In terms of lives saved, it is likely that the spontaneous reports and other scientific evidence that led to the advice not to prescribe aspirin to children in 1986 has probably had the greatest effect, virtually eliminating Reyes syndrome in the UK, and probably preventing more than a 1000 cases in the last 30 years (based on the incidence in the 1980’s). There are many other changes based on spontaneous ADR reports that affect children. Review of the MHRA publication “Drug Safety Update” (<https://www.gov.uk/drug-safety-update>), used by the agency to inform medical professionals about new and important issues in pharmacovigilance, shows that 33% of the alerts have relevance to children.

Recently the advice from the Medicines and Healthcare products Regulatory Agency (MHRA) for when to submit a Yellow Card in children within the UK has changed. Until August 2014, the MHRA asked for all suspected ADRs in patients age under 18 years to be reported. The rationale for the previous advice was to maximise the number of reports received, as children were historically excluded from the standard drug development process, leading to a lack of safety information on ADRs in this population. However it has been recognised that this was impractical, and may even have deterred reporting.

The updated advice from the MHRA for which suspected reactions in children they would now like to be reported is:

* All suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.
* All suspected ADRs associated with new drugs and vaccines identified by the black triangle symbol (▼). Black triangle drugs are either new to the market, or the UK/European regulators have requested additional post marketing surveillance.

This includes suspected ADRs associated with misuse, overdose, medication errors or from use of unlicensed and off-label medicines.

This brings the advice for children into line with that for adults. A Yellow Card report may be completed by anyone (clinician, nurse, allied health professional, parent, patient) who **SUSPECTS** that a medicine has caused an ADR. This report can be completed online ([mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)), using a Yellow Card (available in BNF/BNFc or MIMS Companion), or forms can be obtained by emailing (yellowcard@mhra.gsi.gov.uk). An up to date list of the black triangle drugs (▼) can be obtained either from the European Medicines Agency website, the MHRA website (mhra.gov.uk/blacktriangle), an up to date BNF/BNFc, or by looking at the summary of product characteristics online for the medicine.

This is a very positive change, that is likely to improve the quality and quantity of the spontaneous reports received by the MHRA in the UK.

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**2. Hawcutt, D.B., et al., *Reported paediatric adverse drug reactions in the UK 2000–2009.* British journal of clinical pharmacology, 2012. 73(3): p. 437-446.**

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**4. Thiesen, S., et al., *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(1): p. 237.**

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