

PAEDIATRIC CLINICAL PHARMACOLOGY

Spontaneous adverse drug reaction reports for neonates and infants in the UK 2001–2010: content and utility analysis

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AIMS

The UK Medicines and Healthcare products Regulatory Agency (MHRA) runs a national spontaneous reporting system (Yellow Card [YC] Scheme) to collect 'suspected' adverse drug reaction (ADR) data. We aim to describe the content and utility of YC reports received for patients aged <2 years.

METHODS

Data on all ADRs reported using YC in infants aged <2 years from the years 2001–10 were supplied by the MHRA.

RESULTS

For infants age <2 years, 3496 suspected ADRs were reported using YC (paternal medication pre-conception $n = 3$, transplacental $n = 246$, transmammary $n = 30$, neonates $n = 97$, infant $n = 477$, and vaccinations $n = 2673$), averaging 0.96 YC per day. There was a male preponderance (male 49.1%, female 44.4%, unknown 6.5%), and only 34 (1.0%) of YC reports stated a gestational age. The medications most frequently reported were: transplacental and transmammary (fluoxetine, $n = 21$ and $n = 4$ respectively), neonate (swine flu vaccine, $n = 8$) infant (oseltamivir, $n = 37$) and vaccines (meningococcal vaccine, $n = 693$). Paternal, transmammary, neonatal and infant YC did not reflect clinical concerns raised by the UK regulator. Transplacental and vaccination reports did correlate with some of the changes in practice and clinical alerts received.

CONCLUSIONS

The frequency of YC reports for those <2 years is low, neonates are poorly represented, and recording of gestational age is poor. With the exception of vaccinations, spontaneous reports alone are not currently generating the data required, and important safety messages from the regulator do not match reporting patterns. Additional reporting strategies are required to improve the quantity and quality of suspected ADR data in young children.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Neonates and infants have different adverse drug reaction (ADR) profiles compared to adults and older children

WHAT THIS STUDY ADDS

- The overall frequency of ADR reporting for those aged <2 years is low, and safety messages from the regulator do not match reporting patterns
- Gestation is poorly recorded in spontaneous ADRs
- The frequency of reporting for transplacental, transmammary and paternal suspected ADRs is extremely low
- New systems of generating data regarding ADRs from specific groups such as sentinel sites may be required to improve the quality and quantity of reports

Table of Links

LIGANDS		
Acyclovir	Fluoxetine	Ranitidine
Azathioprine	Ibuprofen	Sertraline
Caffeine	Indomethacin	Sulfasalazine
Citalopram	Lamotrigine	Valproate
Desogestrel	Methotrexate	Venlafaxine
Domperidone	Montelukast	Vitamin K
Erythromycin	Olanzapine	
Etanercept	Paroxetine	

This Table lists key ligands in this article, which are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

Introduction

The World Health Organization defines an adverse drug reaction (ADR) as ‘a response to a drug which is noxious, and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function’ [2]. ADRs are responsible for 2% of paediatric hospital admissions (compared to 4–7% of adult admissions) [3–6], but there is considerable variation depending on the paediatric specialty involved (0.2% of neonatal admissions compared to 22% of paediatric oncology admissions). Paediatric inpatient stays are complicated by an ADR in 15–18% of cases [7, 8], with 28% of these inpatient ADRs classified as severe [9]. Medication is also required in 22% of pregnant women, and fathers may be on medication at the time of conception, so many infants are born following medication exposure [10]. Furthermore, within the UK in 2010, 73.7% of new mothers initiated breastfeeding [10, 11], generating another potential route of exposure. All these medications are prescribed to achieve therapeutic benefit, but it is important to ensure that consideration is given to any potential ADRs exhibited by the baby.

Neonates have a very high rate of use of unlicensed and off-label medications [12], the use of which may increase the risk of an ADR [13]. Profound changes in development and rapid maturation of organ and enzyme systems in both premature babies and new-borns mean that prescribing in this group poses different risks compared to older children and adults with respect to drug action and toxicity [14].

Fifty years after thalidomide, a transplacental ADR that led to the creation of the UK Yellow Card (YC) Scheme, post-marketing surveillance through spontaneous reporting remains the major means of obtaining ADR data in this population. During the period this study was conducted, the YC scheme applied to all ADRs in children. The Medicines and Healthcare Regulatory Agency (MHRA) recently altered guidance for paediatric YC reporting to match the reporting guidelines to that of adult patients [15].

Previous work describing spontaneous ADR reports amongst children indicated the highest number of reports to be in those <1 year of age [16], and that maternal use of medications may cause ADRs [17]. Previous work has not specifically addressed the youngest children [16, 18], focused on individual medicines [19] or ADRs [20], been unable to stratify by source of exposure, or used unlinked data (therefore unable to determine outcomes of individual ADRs [16]).

Other spontaneous reporting schemes aid identification of significant ADRs in neonates [21, 22], but significant under-reporting is recognized (up to 95% of all ADRs are not reported) [23, 24]. While spontaneous reporting is unlikely to be complete, we speculated that the YC Scheme would have useful functionality in neonates and infants. We postulated that functional spontaneous ADR reporting would: (1) reflect uncertainties about medicines (e.g. more reactions when new medications or formulations are introduced (as exemplified by the increased reporting after the introduction of a new brand of BCG in 2001 [16]) and (2) contribute to the recognition of new signals so that

information about ADRs to professionals would reflect YC reports.

The objectives of the study were therefore to describe the content of YC reports in those <2 years (drug suspected, age, source, type and outcome of ADR) in key groups (neonates, infants, vaccinations, transplacental exposure, transmammary exposure and paternal exposure) and assess the utility of these reports by comparing them with information received from the regulator by healthcare professionals.

Methods

Yellow Card data

Data were requested from the UK national medicines regulator MHRA. Data were supplied to the researchers in anonymized format. Approval was prospectively obtained from the Independent Scientific Advisory Committee for MHRA database research (ISAC) (Reference AYCD031), and all data received by the research team were anonymized.

Data on all YC reports submitted from 2001–2010, on which the age of the patient was listed as being <2 years of age, from all sources (health professionals, parents, patients, industry and other reporters), were supplied by the MHRA.

Compared to our previous study of childhood ADRs reported via the YC Scheme [16], these data were different in the following ways:

- All YC data for the population were included (previous data published were limited to the most common drugs and reactions)
- Complete linked data (including suspected drug, age, and outcomes for each YC received in the target population)
- Different 10-year timeframe
- Specific focus on the youngest children (<2 years of age)

Reporting via the YC reporting scheme was initially restricted to doctors. Hospital pharmacists were introduced to the scheme in 1997, and in 1999 all community pharmacists were included. As part of the National Meningococcal C vaccine immunization campaign in 2000, nurses were also able to report ADRs via the YC Scheme, and from October 2002 the scheme was extended generally to all nurses, midwives and health visitors. Parents, carers and patients have been able to report ADRs since 2003, initially through the telephone helpline NHS direct. Following an independent review of access to the YC Scheme, a nationwide pilot scheme was launched for parents, carers and patients to report ADRs directly to the MHRA in January 2005, with formal implementation in February 2008, although uptake has been low [16]. The final analysis therefore consists of reports from all of these groups.

Population definitions

The term 'neonates' can refer to more than one group of babies. The internationally accepted epidemiological definition of a neonate, and International Conference on Harmonization suggestion for this age group, is a baby within 28 days

of birth. However, this definition ignores the impact of prematurity. We have therefore used the more clinically relevant definition of a baby within 28 days of expected date of delivery. Prematurity was defined as birth before 37 completed weeks of gestation. Stillbirth was defined as delivery of a dead fetus ≥ 24 weeks gestation and intrauterine death < 24 weeks.

YC are classified according to exposure to the medication as follows:

- Paternal: The suspected medication was taken at the time of conception by the father
- Transplacental: The suspected medication was taken by the mother during pregnancy
- Transmammary: The suspected medication was taken by a breastfeeding mother after delivery
- Neonatal: Suspected medication taken by patient with a corrected gestational age of less than 28 days, or labelled 'neonate' on the YC (includes vaccinations)
- Infant: Suspected medication taken by patients older than 28 days corrected gestational age (excludes vaccinations)
- Vaccination: All ADRs where a vaccine was listed as a suspected medication

Comparator data

Birth rates were obtained from UK national maternity statistics [25]. Rates of adverse events related to individual medications were obtained from Summary of Product Characteristics, recognized formularies (e.g. British National Formulary for Children), or from the medical literature. Frequency of HIV infection was obtained from UK government data (Health Protection Agency) [26]. The number of deliveries and number of women taking antiepileptic medications were retrieved from hospital computerized records system. Drug alerts were collated from 'Drug Safety Update' (DSU), a monthly update for healthcare professionals produced by the MHRA [27].

Statistics

Data were described as frequencies, percentages, medians, or means with 95% confidence intervals. Statistical analysis was undertaken using Excel 2007 (Microsoft Corporation, USA).

Results

Between 2001 and 2010, the MHRA received 3509 YC for children aged <2 years. Five YC were excluded as therapeutic failure or 'misclassified' adult data after review of the drug suspected and reaction(s) (e.g., Varenicline smoking cessation therapy), leaving 3504 YC (0.96 YC per day). Table 1 gives characteristics of these YC. Overall, there was a slight male preponderance with 1718 (49.0%) categorized as male, 1548 (44.2%) as female, and 238 (6.8%) not recorded.

There were 6663 suspected ADRs reported across the entire cohort, with a median of one reaction per YC (range 1–15). Details of the YC reactions reported, suspected medications, outcomes and reporter are shown in Table 1, and the most commonly reported medications per category are shown in Table 2.

Table 1

Demographics of patients aged <2 years for which a report of a suspected adverse drug reaction was received by the Yellow Card Scheme 2001–10 excluding misclassified adult yellow cards

	Total	Paternal	Transplacental	Transmammary	Neonates	Infant	Vaccines
Number of reports	3504	3	248	30	97 ^a	471	2673 ^a
Total number of drugs (can be >1 per card)	4587	4	304	33	108	514	3646
Total number of different medications	273	4	221	24	68	223	31
Median number of drugs per YC (range)	1 (1–15)	1 (1–2)	1 (1–14)	1 (1–3)	1 (1–5)	1 (1–3)	1 (1–15)
Total Number of Reactions (can be >1 per YC)	6663	6	486	88	184	837	5090
Median number of reactions (range) per YC	1 (1–15)	1	1 (1–14)	1 (1–5)	1 (1–5)	1 (1–12)	1 (1–15)
Gender							
Male	1718	1	89	12	52	254	1318
Female	1548	1	70	12	42	197	1236
Not recorded	238	1	89	6	3	20	119
Outcomes^b							
Fatal	65	0	28	2	3	13	19
Not recovered/Not resolved	507	0	75	2	16	65	350
Recovered/Resolved	2413	0	49	21	67	350	1939
Unknown	519	3	96	5	11	44	365
Reporter							
Doctor	1445	3	188	22	54	251	934
Nurse	1086	0	8	1	10	41	1033
Pharmacist	138	0	14	2	15	87	20
Parent/Carer	173	0	8	3	2	42	118
Other healthcare	652	0	30	2	16	47	563
Unknown	8	0	0	0	0	3	5

^aYC that contain vaccines given to those infants on the neonatal age range are included in both neonates and vaccinations data ($n = 18$).

^bOutcomes shows the worst recorded on each YC.

Paternal

Four drugs, all for the management of autoimmune conditions, were recorded on three YCs. The reactions listed on these YC were growth retardation, diarrhoea, developmental delay, hypotonia, fetal cardiac disorder and development of a birth mark. Gestation of the child was not documented in any of the cases and the ADR outcomes were all 'unknown'.

Transplacental

Reporting improved across the decade; during the first five years the mean YC received per year was 14.6, but for the latter five years it increased to a mean of 34.4 (Figure 1A). A total of 221 different medications were listed with 81 (36.6%) generating more than one report. The most commonly reported medication suspected of causing an ADR was fluoxetine ($n = 21$) and overall, 16 different psychotropic drugs were associated with 120 reported reactions. The most commonly reported medications are shown in Table 2; however, under-reporting appears widespread.

Most of the 11 000 HIV-positive women who became pregnant in the UK during this time period will have received

antiretroviral drugs [28]. Current evidence suggests no increase in congenital abnormalities reported with these drugs, either in the UK or internationally (2.8 birth defects per 100 live births) [29, 30]. We would therefore estimate, based on the standard frequency of congenital anomalies, that approximately 300 children within this population would be affected. Over the 10-year period, only seven reports associated with maternal antiretroviral drug use in pregnancy were reported via the YC Scheme, an under-reporting rate of 97.7%.

It has been known for some time that there are significant adverse effects of anti-epileptic medications in pregnancy, but use is continued as the benefits to the mother outweigh the risks to the child. Epidemiological estimates put the number of pregnancies exposed to anti-epileptic drugs (AEDs) at 0.3–0.4% [31, 32], while the frequency of major congenital malformations in pregnancies exposed to AEDs has been shown to be 4.2% overall (with some variation between different AEDs) [33]. Extrapolating from the average number of deliveries per year in the UK 2001–10 (659 551), we would expect 0.35% (2300) pregnancies per year to be to women using AEDs, with approximately 100 children per year with major

Table 2

The most common medications causing spontaneous reports of suspected adverse drug reactions received by the MHRA Yellow Card Scheme in children age < 2 years

Paternal Drug	Transplacental		Transmammary		Neonates		Infant		Vaccinations		Reports
	Reports	Drug	Reports	Drug	Reports	Drug	Reports	Drug	Reports	Drug	
Azathioprine	1	Fluoxetine	21	Fluoxetine	4	Swine Flu Vaccine	8	Oseltamivir	37	Meningococcal Vaccine	693
Sulphasalazine	1	Citalopram	20	Erythromycin	2	Caffeine	5	Tetracaine	22	DTaP/IPV /Hib vaccine	600
Methotrexate	1	Paroxetine	19	Sertraline	2	Acyclovir	3	Amoxicillin	17	DTwP/ Hib vaccine	540
Etanercept	1	Venlafaxine	18	Citalopram	2	Chlorhexidine	3	Ibuprofen	12	Pneumococcal vaccine	496
		Sertraline	11	Lamotrigine	2	DTPw Hib vaccine	3	Palivizumab	12	Bacillus Calmette Guerin Vaccine	309
		Olanzapine	7	Fluconazole	2	Ibuprofen	3	Domperidone	10	MMR vaccine	257
		Valproate	7	Desogestrel	2	Indomethacin	3	Cefotaxime	9	Haemophilus influenzae type b vaccine	190
		Lamotrigine	6			Trimethoprim	3	Montelukast	9	Poliomyelitis vaccine	174
						Vitamin K substances	3	Trimethoprim	9	DTwP vaccine	104
						Ranitidine	8			Hib/MEN C conjugate vaccine	87

For transmammary, transplacental and paternal all reported medications shown. For neonates, all drugs with $n > 2$ shown, vaccinations and infants, 10 most commonly reported shown. Vaccinations given to those in neonatal period are shown in both neonates and vaccination columns. DTaP, Diphtheria, tetanus and (acellular) Pertussis; DTPw, Diphtheria, Tetanus and (whole cell) Pertussis; Hib, Haemophilus influenzae type b; MEN C, Meningococcal group C; MMR, Measles/Mumps/Rubella. Full dataset for all groups in supplementary data section

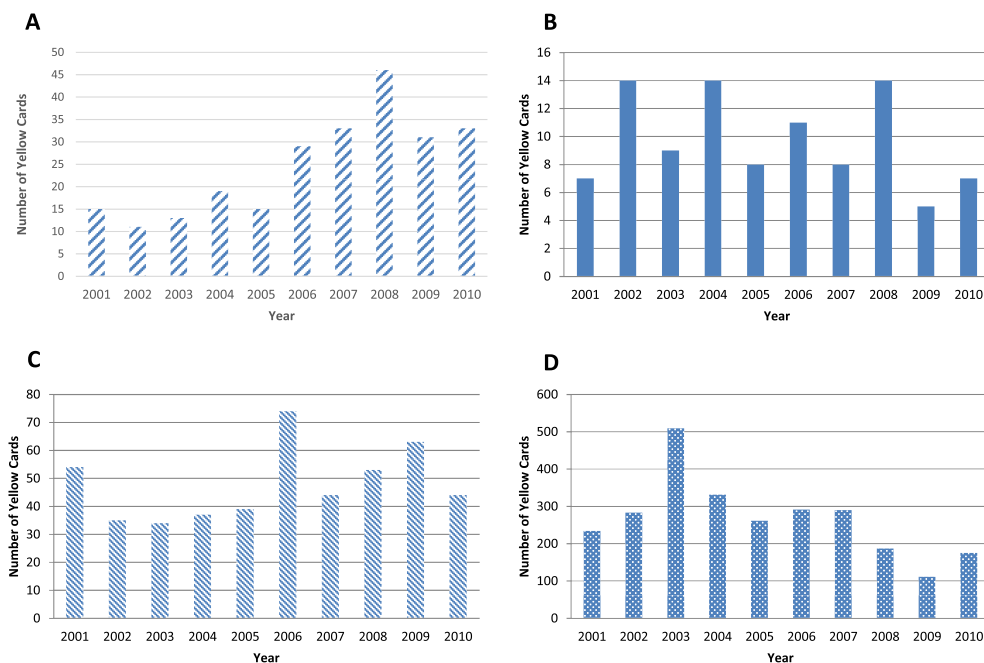


Figure 1

Number of Yellow Card reports of suspected adverse drug reactions received by the Medicines and Healthcare Regulatory Agency (MHRA) per year for (A) transplacental, (B) neonates, (C) infants and (D) vaccinations

congenital malformations. The YC system collected 29 reports of suspected ADRs to anti-epileptics over the 10-year period, suggesting under-reporting of approximately 98.8%.

The most commonly reported reactions (for all transplacental YC) were 'irritability/jittery/agitation' ($n = 21$), 'congenital abnormality' ($n = 17$), withdrawal syndrome ($n = 12$), cleft lip/palate ($n = 11$), death (stillbirth, intrauterine or neonatal) ($n = 11$), prematurity ($n = 11$) and cardiac septal defect ($n = 10$).

For psychotropic drugs, the most commonly reported reactions were congenital hand malformation ($n = 7$), dextrocardia ($n = 4$), cardiac septal defect ($n = 2$), stillbirth/intrauterine death ($n = 16$), withdrawal syndrome ($n = 14$), spina bifida ($n = 4$) and neonatal agitation ($n = 11$) (full list in supplementary data).

Gestational age was recorded in 45 out of 246 (18%) cases with the highest proportion documented in 2004. Not all were specific, with 'premature' written in four cases and 'term' in one. The mean recorded gestational age was 32.8 weeks.

Transmammary

From the 30 transmammary reports, no discernible trend in reporting frequency was observed (range: 0 reports in 2003 to 10 reports in 2010). Twenty-four different medications were listed, with fluoxetine being the most frequently reported drug, featuring on four YCs. Seven drugs were reported more than once (Table 2, full list in the supplementary data section). The most commonly reported reactions were irritability/agitation ($n = 5$), sleep disorder/somnolence ($n = 4$), dyskinesias ($n = 4$), abdominal pain ($n = 3$), diarrhoea ($n = 3$) and failure to thrive ($n = 3$). One gestation was provided as 'full term' with another documented as 'premature' but no accurate gestational ages were given.

Neonates

No pattern was noted in the neonatal reporting rates over the time period (Figure 1B). The most commonly reported medication suspected of causing an ADR was swine flu vaccine ($n = 8$), followed by caffeine ($n = 5$). There were 68 different medications listed on neonatal YC as being suspected of causing an ADR (full list in supplementary data section), although only eight (11.7%) generated more than one report (Table 2, full list in the supplementary data section). There were 10 YC reports for antibiotics (trimethoprim [$n = 3$], benzylpenicillin [$n = 2$], gentamicin [$n = 2$], ceftazidime [$n = 2$], clindamycin, erythromycin and metronidazole [$n = 1$ for each]). Despite well publicized safety concerns, there were no reports for codeine, ceftriaxone or ritonavir-boosted lopinavir (Kaletra) [21] over the 10-year period.

Approximately 7% of neonates receive antibiotics to treat suspected early onset neonatal infection, so between 42 000 and 51 000 babies a year were exposed to antibiotics, totalling 450 000 babies exposed to antibiotics during the study period. This implies a reporting rate of one YC per 4500 babies receiving antibiotics. There were no reports relating to surfactant, but during the study period almost all live births born at 28 weeks gestation or less would have received at least one dose of surfactant [34]. This represents 1.4% of the total births (93 000 babies), and other babies born closer to term would have been eligible for, and received, surfactant. We therefore estimate that at least 100 000 babies received surfactant without prompting a YC report. Other medications with well-recognized ADRs that are commonly used on neonatal units were not commonly found among YC reports, e.g. corticosteroids.

The most commonly reported reactions for neonates were rashes ($n = 14$), erythema ($n = 7$), bradycardia ($n = 6$),

convulsion ($n = 5$), tachycardia ($n = 5$), local reaction ($n = 4$), cardiac arrest, dyspnoea, hypotension, necrotizing colitis, decreased oxygen saturations and pruritus ($n = 3$ for all).

Of the 97 YC that were categorized as neonatal, 88 were categorized on the basis of age since delivery as stated on the YC (6–24 hours, 0–27 days, or 1–3 weeks), five stated ‘neonate’ and gave clinical details that put the affected child in the neonatal period, and four gave an age >27 days but recorded gestation in the clinical details section enabling a calculation of corrected gestational age. Overall, only 25 (0.8%) YC reports stated a gestational age at birth for the affected neonate. Twenty-three provided an exact gestation, one stated ‘preterm’ and one ‘9 weeks premature’.

Infants

There was no discernible pattern to the reporting frequency in infants (Figure 1C). In 2006 there was an apparent ‘spike’ in reporting in the infant cohort, with 74 YC submitted. The most frequently reported medication that year was domperidone ($n = 5$), and of the 61 different medications reported in 2006, only 11 of them were reported on more than one occasion (for full list, see supplementary data section). Overall, the most common suspected drug was oseltamivir ($n = 37$). Overall, there were 223 different medications listed in this cohort. There was a single report for codeine in the infant category. Gestation was recorded in nine YC in this cohort (1.9%).

Vaccinations

Reporting of vaccination-related ADRs peaked in 2003 ($n = 506$) (Figure 1D). This year contained 256 reports (50.6%) for various preparations and combinations of primary immunizations containing diphtheria, pertussis and tetanus (DTP). Over the 10-year period, the percentage of reports in children <2 years of age related to vaccinations was 82.8%. There was a decrease in vaccine-related reports from 2006, likely related to the introduction of the acellular pertussis vaccine (associated with fewer ADRs than the previously used whole cell vaccines [35]). From the vaccination

cohort, the most commonly suspected drug on a YC was meningococcal C vaccine ($n = 693$). There were 31 different medications reported in the vaccination cohort, 29 of which were vaccinations (the remaining medications in addition were ketotifen and mesalazine, reported at the same time as swine flu vaccination). A complete list is contained in the supplementary data section. Most reports of ADRs after immunization were local or generalized reactions, including anaphylaxis ($n = 20$). However, there were a few reports of vaccine failure (Haemophilus influenzae type b 8, Meningococcal group C 1, Pneumococcal vaccine 1, Pertussis 1), vaccines not being given according to the schedule (e.g. single antigen measles, mumps or rubella) or hospitalization due to inter-current illness or ADR (upper respiratory tract infection, urinary tract infection, pneumonia, febrile convulsion).

Reporter

Overall, doctors reported the largest number of YC (1445), followed by nurses (1086), parents/carers (173), and pharmacists (138) (Table 1). Of note, the proportion of parent/carer reports was greater in the infant group (8.9%) than in any other group.

Outcome

There was a fatal outcome in 65 (1.9%) of YC submitted in this cohort. The drugs suspected of causing a fatal outcome are summarized in Table 3. The proportion of fatal reports for each category were: 0% paternal, 11.2% transplacental, 6.7% transmammary, 3.1% neonatal, 2.8% infant and 0.7% for vaccinations. Some ongoing issues remained in patients in 513 (14.5%) YC, while there was complete recovery reported in 2413 YC (68.8%). The outcome was unknown in 507 (14.5%) YC.

Review of drug safety update

Review and analysis of the monthly MHRA publication Drug Safety Update (DSU) between October 2007 and September 2014 has shown that alerts were provided on 405 drugs

Table 3

Most commonly reported medications listed on Yellow card reports from children age <2 years between 2001 and 2010 with fatal outcomes

Drug(s) listed on Yellow Card	Category	Reports
DTaP/IPV/Hib vaccine, pneumococcal vaccine	Vaccination	4
Palivizumab	Infant	4
Citalopram	Transplacental	4
DTaP/IPV/Hib vaccine, meningococcal vaccine	Vaccination	3
DTwP/Hib vaccine, meningococcal vaccine, polio vaccine	Vaccination	2
MMR vaccine	Vaccination	2
Olanzapine, Venlafaxine	Transplacental	2
Lamivudine and zidovudine, lopinavir with ritonavir	Transplacental	2

DTaP, diphtheria, tetanus and (acellular) pertussis; DTwP, diphtheria, tetanus and (whole cell) pertussis; Hib, haemophilus influenzae type b; IPV, inactivated polio vaccine; MMR, measles/mumps/rubella

(or classes of drug) over this period. Of these, 97 were medications with potential applicability to the population in whom YC reports were available (92 paternal, 96 transplacental, 90 transmammary, 50 neonates, 134 infant and 12 vaccinations [some applicable to more than one category]). Selected drugs for which DSU alerts were produced, and the number of YC reports for that medication during the study period are shown in Table 4 (the full table of drugs featured in DSU and relevance to this population are available from the authors on request). DSU alerts, while clinically important, were not well correlated with YC reports before or after the alert. There were two examples where some correlation was found: a single DSU report highlighting agitation in a baby following anti-psychotic use in pregnancy was preceded by a corresponding

YC; advice on avoiding sodium valproate in pregnancy unless no alternative was available was preceded by five YC reports for a range of suspected ADRs (Table 4).

Discussion

The MHRA spontaneous reporting scheme has been collecting data on suspected ADRs in the UK for 50 years. It originated following the devastating consequences of a transplacental ADR in newborn babies (phocomelia) secondary to *in utero* exposure to thalidomide. We present the most detailed examination of YC reports for children aged <2 years of age, covering a 10-year period from 2001 to 2010. Previous

Table 4

Comparison of selected drugs from Drug Safety Update alerts produced for the populations of interest and the YC reports received during the years 2001–10

Medication	Cohort	Drug alert reason (date)	ADR (number and date) reported to YC from that cohort
Lopinavir and ritonavir	Neonate	Neonatal administration error (October 2007)	0
Codeine	Neonate and infant	Transplacental fatality (November 2007), Restricted use in children <12 years (June and July 2013)	0
Ceftriaxone	Neonate	Incompatible with calcium infusions (October 2009)	0
Domperidone	Neonate and infant	Cardiac side effects (May 2012, May and September 2014)	10 (2001 (diarrhoea), 2004 (dystonia) 2005 (irritability & gynaecomastia), 2006 × 5 (death out of hospital; trembling and muscle spasm; deranged LFTs; drowsiness with O ₂ requirement; worsening dystonia), 2010 × 2 (pruritis and increased instability))
Caffeine	Neonate	Check dose as two forms (August 2008, September 2008, June 2012), Single form now used (August 2013)	5 (2001 × 3 (all extravasations with tissue injury), 2007 (tachycardia and tachypnoea), 2010 (vasoconstriction))
Corticosteroids (including individual drug names)	Neonate	Psychiatric side effects (September 2007)	3 (2007 × 3 (Cushing's, Benign Intracranial Hypertension × 2))
Codeine	Transmammary	Neonatal death following maternal use (November 2007, October 2010, December 2012, June 2013, July 2013)	None
ACE inhibitors and angiotensin II receptor antagonists	Transmammary	Updated advice during breastfeeding – not recommended but not contraindicated (July 2009)	None
Antipsychotics	Transplacental	Increased extrapyramidal and/or withdrawal ADRs in infants if used in third trimester (September 2011)	9 (2004 (Lethargy [olanzapine]), 2005 (gastroschisis [haloperidol]), 2006 (agitation [olanzapine]), 2007 (macrosomia [olanzapine]), 2008 × 2 (both congenital anomalies [olanzapine]), 2009 × 2 (failure to thrive [quetiapine], congenital anomaly [quetiapine]), 2010 (congenital anomaly [quetiapine]))
Sodium Valproate	Transplacental	Avoid in pregnant women unless no alternative (November 2013)	2001 (congenital anomaly), (2005 × 2 (jittery, floppy with abnormal LFTs), 2006 (congenital anomaly), 2007 (fetal anticonvulsant syndrome))

studies of paediatric YC reports were unable to examine outcomes, and were limited to the most commonly reported medications within the entire paediatric population. To our knowledge there are no previous studies examining spontaneous ADR reports in neonates. These data show that the UK generates very few reports for paternal, transmammary and transplacental ADRs, and that key data (such as gestational age and outcome) are missing from many YC reports. The data used to create alerts from the regulator to clinicians is derived from many sources (including UK-specific and international data), but in this population, during the period studied, spontaneous YC generated in the UK do not appear to be a significant source of data.

Under-reporting is a problem for all spontaneous ADR reporting schemes, and estimates of the frequency of under-reporting are approximately 95% [36]. This may be an under-estimate of reporting frequency for some sections of our cohort, as evidenced by the lack of reports for HIV-positive and epileptic women. However, reporter fatigue and/or confusion may also have had a role (children previously having different reporting rules to adults, where all suspected ADRs were requested). Recently the MHRA have been actively promoting the reporting of suspected ADRs in children, and updated the paediatric reporting rules to align them with adults [15]. Future work will be required to see the response to these initiatives, and if they increase the quality and/or quantity of reports. Finally, these data only contain information on YC where the age was given by the reporter, and will omit YC submitted without ages provided.

Data from the British Paediatric Surveillance Unit found four infant deaths associated with ADRs in a single year (2002–3) [37], while equivalent ADRs (where the child received the medication postnatally) in this cohort are reported with a mean frequency of 3.7 per year, suggesting that clinicians are reporting these most serious of suspected ADRs to the YC Scheme.

Paternal

Given the paucity of reports of paternal adverse drug reactions, it is hard to draw any firm conclusions from these. The time delay between paternal use of the medication and the identification of the suspected ADR makes using a spontaneous reporting scheme for these ADRs difficult. Other mechanisms may therefore have to be considered to generate suspected ADR reports from this population.

Transplacental

The importance of ongoing active surveillance to reassure pregnant women that these immunizations are safe and beneficial for them and their babies [38–40] is highlighted by the very small number of reports of congenital anomalies in infants born to women given vaccines during pregnancy. These data contain nothing that would suggest the routinely recommended vaccines of pregnancy are unsafe for the fetus when given to healthy pregnant women.

More concerning is the report of fatally disseminated BCG following BCG vaccination in an infant whose mother received infliximab during pregnancy [41, 42]. TNF antagonists are known to increase the risk of tuberculosis [43] and are known to cross the placenta. It is recommended that infants

born to women given anti-TNF agents in pregnancy are not given live vaccines for up to 7 months. National guidance is now being updated to include this advice.

Despite the low frequency of YC reports, those related to transplacental ADRs were the best correlated with the clinical concerns of the UK regulatory agency.

Transmammary

The data received over 10 years for transmammary suspected ADRs is limited, and while there were several alerts from the regulatory agency regarding transmammary ADRs, none of the reports received reflected this. New strategies will be needed to improve this neglected area of reporting to the YC Scheme.

Neonates

The classification of infants as neonates requires either an accurate age at the time of the reaction accompanied by the gestational age at birth, or a corrected gestational age at the time of the reaction. Very few YC reports contained a gestational age at birth (0.8%). If more infants had accurate gestational ages included in the YC then it is probable that some infant ADRs would have been reclassified as neonatal, increasing interpretable reports in this neglected group.

It is disappointing that despite the regulatory agency producing many different clinical warnings about potential ADRs for various neonatal medications via the DSU (and other routes), there were no relevant reports from the UK preceding these reports. This suggests that the current rate or quality of YC reports (or both) needs to improve in order to ensure that the UK contributes meaningfully to international efforts to identify ADRs from spontaneous reports.

Infants

The infant cohort is the most heterogeneous, encompassing those 28 days old, to those 1 year 11 months old as the YC reports only give an age in years, so if the reporter gives an accurate age in years only, the child may still be nearly 2. An improvement to the YC system in the UK would therefore be to request reporters provide an age in completed months until the age of two years. The first two years after birth represent the most dynamic stage of *ex utero* ontogeny [44].

Vaccinations

Vaccine reports varied by year, and are associated with the introduction, or removal, of various vaccines from the national programme. As in our previous study of YC data in all children, meningococcal C vaccine was the most frequently reported vaccine. Reports for BCG vaccine were less than our previous paper, because older children were given BCG until 2005. However, the same 'spike' in reports was seen when the SSI BCG was introduced into the UK in November 2002 [16]. These data suggest that YC reports for vaccinations were responsive to the underlying pattern of medicine use. Vaccination therefore represents an area of success for the YC system for patients <2 years of age.

Most reports associated with a vaccine described local or generalized reactions. However, reporters also used the YC Scheme to report vaccine failures (especially the Hib vaccine

failures that occurred in 2003 [45]). Reports also described inadvertent use of the wrong vaccine in some infants (such as giving the diphtheria, tetanus, pertussis and polio vaccine without Hib, instead of the vaccine with Hib included (Pediaceel)).

Improving reporting

The value of the YC Scheme has been demonstrated many times, and it has helped to identify numerous important safety issues (including in this population), many of which were not previously recognized [46]. However, the shortcomings identified in the UK's spontaneous ADR reporting system for this population currently suggest that both improvements in the YC system, and consideration of alternative approaches, are needed. Since obtaining these data, we do note the active promotion of reporting in children, the amendments to the reports required to align with adults, and the updates to the online YC form (requesting gestational age, and improving the capture of pregnancy-related data). Additional simple measures to improve the quality of YC reports would include making the gestational age of children <1 year a mandatory field on the online YC reporting, as well as asking for all ages <2 years in completed months.

We believe that there is also a place for additional systems in parallel with YC reports, including some or all of the following: sentinel sites (undertaking active surveillance of ADRs); changed recommendations about reporting; increased professional education about reporting ADRs; a focus on specific questions (e.g., a couple of medicines a year, such as a neonatal black triangle, etc.). Internationally, there is an example of active surveillance in Canada [47]. Given the issues with causality, polypharmacy and multiple inter-current illnesses, spontaneous reporting may not be appropriate and registry-based data may be more useful. This does not only apply to non-intensive care situations: a large number of 'healthy' neonates receive medicines [47].

We further speculate that the paucity of reporting we found is not limited to the UK. Recent legislative changes will stimulate the development of medicines for neonates [48]. Post-marketing surveillance will become increasingly important, so that reporting by clinicians needs to be strengthened. Our findings may be informative for other jurisdictions.

Conclusions

Analysis of the content of YC reports suggests that gaps in reporting are not random: the YC Scheme is used more effectively in some therapeutic areas than others. Medications suspected of causing ADRs in those <2 years are reported to the MHRA through the YC Scheme, but the frequency of reports is low, with less than one per day overall. Paternal, transplacental, transmammary and neonatal ADRs are particularly poorly represented, and recording of gestational age is poor. The regulator draws attention to serious ADRs in the neonatal and infant populations, but these ADRs are not represented in YCs before regulatory action is taken. Action is required to stimulate ADR reporting for the youngest patients

to improve the quality and quantity of YC reports, including the consideration of additional systems to run in parallel with YC reporting.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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Table S1 Complete list of drugs reported as causing suspected ADRs for children of age <2 years between 2001 and 2010.