PROMOTING SAFETY OF MEDICINES FOR CHILDREN

World Health Organization

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Promoting safety of medicines for children

1. INTRODUCTION

Monitoring the safety of medicine use in children is of paramount importance since, during the clinical development of medicines, only limited data on this aspect are generated through clinical trials. Use of medicines outside the specifications described in the licence (e.g. in terms of formulation, indications, contraindications or age) constitutes off-label and off-licence use and these are a major area of concern.

These guidelines are intended to improve awareness of medicine safety issues among everyone who has an interest in the safety of medicines in children and to provide guidance on effective systems for monitoring medicine safety in the paediatric populations. The document will be of interest to all health-care professionals, medicine regulatory authorities, pharmacovigilance centres, academia, the pharmaceutical industry and policy-makers.

Systems for monitoring medicine safety are described in Annex 1 - Pharmacovigilance methods and some examples of recent information on adverse reactions to marketed medicines are discussed in Annex 2.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems (1). For the purposes of this document, an adverse reaction to a medicine (ADR) includes not only reactions occurring during normal use of medicines, but also reactions due to errors in medicine administration, non-adherence, overdose, off-label use, drug abuse and adverse effects due to the use of traditional and complementary medicines. It does not address the paediatric use of vaccines. Separate WHO guidelines on safety monitoring of vaccine use in children will be developed in the future.

2. CURRENT SITUATION

2.1 Problems with medicine treatment in children and adolescents around the world

The following problems occur with the use of medicines in the treatment of children and adolescents.

- Often, medicines used are off-label and unlicenced.
- Over-the-counter, traditional and herbal medicines are readily available, but their use is generally not evidence-based and is often inappropriate.
- Counterfeit and substandard medicines are widespread.
- Abuse by teenagers occurs with non-medical prescription of legal medicines and illegal drugs.
- New and innovative medicines are available with a paediatric indication, but with no evidence of long-term benefit and risk, e.g. the biological agents used as disease modifying antirheumatic medicines, such as etanercept.

Additionally, in resource-poor countries the following may apply:

- No treatment may be available, particularly during times of war and civil strife.
- Medicines may be available through illegal street vendors.
- Medicines are used in public health driven programmes e.g. for the treatment of endemic infectious diseases such as HIV/AIDS, malaria, tuberculosis and for parasitic diseases.

In many low-income countries, much of the medicine supply is by-passing the official health care system. Consumers with limited buying power often acquire medicines from acquaintances, relatives and unregistered vendors who have little or no health-care training. In these countries, prescription medicines may often be acquired without a prescription from markets and chemist's shops. The resulting self-medication, unsupervised by any health professional, is also having a major effect on children. This situation is associated with high risks for adverse consequences because of the risk of poor-quality medicines being taken and the absence of information on how to use medicines in general. Even if serious adverse reactions occur as a result of self-medication with products acquired from street markets, they are often not reported to any health practitioner, since seeing a health professional is often not feasible or is considered too expensive. Civil society and non-governmental organizations need to be engaged in soliciting information from local communities about child health and possible medicine-related problems affecting children. Information about the actual extent of medicine-related problems in children in these settings can only be collected through systematic active surveillance. The affected children and their parents have a low likelihood of actively seeking help from a health-care system, even if one exists in the community.

2.2 Consequences of the current status of the use of medicines in children (environmental aspects)

The consequences of the current status of the use of medicines in children include the following:

- Wrong dosage causes short-term toxicity or treatment failure. For example, a standard dose of phenobarbital of 15 mg/kg daily will most likely be inappropriate for a newborn with seizures as often a loading dose of more than 20 mg/kg is needed and a maintenance dose of 5 mg/kg might already be more than enough.
- Non-availability of appropriate paediatric formulations forces health care providers to resort to administering crushed tablets, dissolving tablets in solvents or administering the powder contained inside the capsule. Consequently, these formulations are administered without any data regarding their bio-availability, efficacy and toxicity.
- Formulations of strengths suitable for administration to neonates, infants and young children are not always available. Adult formulations therefore need to be diluted or administered in miniscule volumes over a period of time. This leads to administration errors (intravenous drips running fast, errors in dosage calculation and dilution), especially in circumstances that require urgent action (as in emergency units, premature units and paediatric and neonatal intensive care units).
- Inappropriate packages and lack of awareness among parents and caregivers about the methods to be used for prevention of injuries, accidents and poisoning lead to accidental poisoning in infants and small children.
- Adolescents may ingest medicines with suicidal intent or may experience health problems from illicit drug abuse.
- Medicines can interact with traditional and herbal medicines.
- Medicines may have long-term safety problems. For example, etanercept may increase susceptibility to tuberculosis, or long-term use of inhaled corticosteroids in early infancy may increase the risk of growth retardation and/or osteoporosis.
- In public health programmes in resource-poor countries, co-morbidity or malnutrition may exacerbate the toxicity. Dehydration is frequently associated with ibuprofen-induced renal failure and malnutrition with paracetamol hepatotoxicity.
- Cultural differences can lead to misunderstanding of medicine instructions especially of package insert information and information on promoting rational use of medicines.
- A simple process of reconstitution of nonsterile oral powder can be a risk for stability or even safety. Some medicines for oral use need to be reconstituted with water before ingestion. It is important to remind health-care providers that the water must be clean and filtered, and that after reconstitution, the product has a strict expiration date. This recommendation is fundamental especially in developing countries.

Albendazole

Four children under 36 months died from choking on albendazole tablets during a deworming campaign in Ethiopia in 2007. Forcing very small children to swallow large tablets may cause choking and asphyxiation. Recommendations for the administration of such tablets are as follows: scored tablets should be broken into smaller pieces or crushed for administration to young children; older children should be encouraged to chew tablets of albendazole or mebendazole. It is strongly recommended that manufacturers of anthelminthics for public health programmes targeted at preschool children develop formulations that are appropriate for this age group. The formulation should be a safe single-dose formulation (e.g. granules or liquid for oral use) to replace the tablets currently in use.

2.3 General risk factors that predispose children to develop an adverse reaction to a medicine (medical aspects)

Risk factors that predispose children to develop an adverse reaction to a medicine can be physiological, indirect or iatrogenic.

Physiological causes for increased risk:

- young age, e.g. neonates and infants with the greatest physiological differences from adults;
- continuous changes of medicine dispositional parameters during maturation in all age classes.

Indirect causes for increased risk:

- greater prevalence of polypharmacotherapy, e.g. in the neonatal intensive care unit;
- greater length of hospital stay, e.g. children with congenital or chronic diseases;
- critically ill children, e.g. those who have neoplastic diseases.

Iatrogenic causes for increased risk:

- use of unlicenced and off-label medicines with very little information regarding appropriate dose, e.g. medicines used in orphan diseases such as cystic fibrosis;
- insufficient number of well-trained health-care professionals to treat seriously ill children.

2.4 Differences between paediatric populations and adults

The paediatric population represents a spectrum of different physiologies, and children should not be treated as "miniature men and women" (Abraham Jacobi, 1830-1919). The spectrum extends from the very small preterm newborn infant to the adolescent. The internationally agreed, and to some extent arbitrary, classification of the paediatric population is as follows (2):

- preterm newborn infants
- term newborn infants (0 to 28 days)
- infants and toddlers (> 28 days to 23 months)
- children (2 to 11 years)
- adolescents (12 to 16 to 18 years, depending on the region).
  (Ages are defined in complete days, months and years.)

Substantial changes in body proportions and composition accompany growth and development. This dynamic process of maturation is one of the differences between the paediatric and the adult populations. The developmental changes in physiology and, consequently, in pharmacology, influence the efficacy, toxicity and dosing regimens of medicines used in children. It is, therefore, important to review the relevant changes that take place from birth through to adolescence.

The proportions of body fat, protein and extracellular water content also change significantly during early childhood. For example, the body water decreases from about 80% in the newborn to 60% by five months of age. The percentage of body fat doubles by four to five months. The process continues throughout the second year of life until protein mass increases with a compensatory reduction in fat as the consequence of increased motor activity of the child. Moreover, liver and kidney size, relative to body weight, also changes during growth and development. Both these organs reach maximum relative weight in the one- and two-year-old child during the period of life when the capacity for drug metabolism and elimination is greatest. Likewise, body surface area relative to body mass is greater in infants and young children than in older children and young adults. In addition to these developmental changes in body composition and proportions, there are other specific changes in organ function during growth and maturation, which affect the pharmacokinetic characteristics of medicines at different ages.

Gastrointestinal tract and oral absorption: Clinically important developmental changes in the gastrointestinal tract that may affect oral absorption of medicines occur predominantly during the newborn period, infancy and early childhood. These changes affect gastric acidity, gastric emptying time, gut motility, gut surface area, gastrointestinal medicine-metabolizing enzymes and transporters, secretion of bile acids and pancreatic lipases, first-pass metabolism, enterohepatic recirculation, bacterial colonization of the gut, diet at different ages and diurnal variations. For example, preterm and term infants have greatly reduced gastric acid secretion. Neonates also show prolonged

gastric emptying. Thus during the neonatal period, acid-labile medicines like benzylpenicillin and ampicillin are well-absorbed, while the absorption of medicines like phenytoin, phenobarbital and rifampicin is low. Moreover reflux of gastric contents retrograde into the oesophagus is very common during the first year of life (3). Excessive gastro-oesophageal reflux may result in regurgitation of medication, particularly when associated with delayed gastric emptying, which results in variable and unpredictable loss of orally administered medicines. The gastric acid levels reach adult values by two years of age. Sustained-release preparations are not readily absorbed in children due to rapid intestinal transit times. Likewise, medicines with a high hepatic clearance and first-pass metabolism such as propranolol have a variable absorption in children. In contrast, intact protein and high-molecular-weight medicines such as immunoglobulins, which are hardly absorbed by older children and adults, are more easily taken up in the gut of infants as it is more permeable to large molecules (4, 5). The administration of medicines with meals needs to be appropriately tailored, although most medications, except medicines like rifampicin, are best given with food to improve adherence.

Medicine distribution: Newborn infants have a much higher extracellular fluid volume than any other paediatric population or adults. Preterm babies have a higher extra-cellular fluid volume than full-term infants, older infants or adults. Total body water is also much greater in neonates. On the other hand, fat content is lower in premature babies than in full-term neonates and infants. As medicines are distributed between extracellular water and depot fat based on their lipid/ water partition coefficient, these changes in body composition can influence the distribution of a medicine in various compartments of the body. For water-soluble medicines such as aminoglycoside and cefalosporin antibiotics, larger initial doses, on a mg/kg body weight basis, need to be given to achieve plasma concentrations similar to those obtained in adults. Highly lipid-soluble compounds such as inhalation anaesthetic agents and lipophilic sedative/hypnotic agents (see phenobarbital) exhibit relatively larger distribution volumes in infants. This is related to the increase in proportion of body fat that occurs during the first year of life. In addition, the volume of distribution of many medicines may be increased as plasma protein binding in neonates and especially in premature babies is less than that in adults resulting in increased concentrations of unbound "free" medicine. The blood-brain barrier is also functionally incomplete in neonates.

Hepatic and renal function and the elimination process: Total-body clearance of many medicines is primarily dependent on hepatic metabolism followed by excretion of parent compound and metabolites by the liver and kidneys. Nonpolar, lipid-soluble medicines are typically metabolized to more polar and water-soluble compounds prior to excretion (e.g. theophylline, diazepam and paracetamol), whereas water-soluble drugs are usually excreted unchanged by glomerular filtration and/or tubular secretion in the kidney (e.g. aminoglycosides, penicillins and diuretics). Phase I metabolic processes involve oxidative, reductive or hydrolytic reactions. Mixed-function oxidase enzymes

are generally more important than reductive or hydrolytic reactions. Phase II, or synthetic, metabolism involves conjugation of the substrate to polar compounds such as glucuronic acid, sulfate or glycine. This usually results in a polar, water-soluble compound that is readily excreted. There are significant differences in the eliminating capacities of neonates, infants and children. In general, the more premature the infant the poorer the hepatic metabolizing and renal excreting capacity. For medicines that are cleared by the liver, this leads to a longer plasma half-life and thus a longer time to reach steady-state. Similarly, for medicines that are entirely eliminated renally, the greater the prematurity, the less able are the kidneys to excrete them and therefore the longer their half-life. Hence, compared to older children and adults, newborns require lower maintenance doses to avoid toxicity. Examples for this kind of dosage regimen are methylxanthines, phenobarbital, indomethacin, aminoglycoside and furosemide. Maturation of the various hepatic and renal functions occurs with some variation during the first year of life.

In young children, the hepatic and renal elimination capacity for many drugs may even exceed that in adults, which often makes administration of a higher maintenance dose necessary. The differentiation between loading and maintenance dose is no longer appropriate.

Besides these quantitative differences in the disposition of medicines, there are also various qualitative differences in the metabolic pathways in infants and children. For example, N7-methylation of theophylline to produce pharmacologically active caffeine is well developed in newborn infants, whereas oxidative demethylation and inactivation is highly inefficient (6). A similar example is that of paracetamol (acetaminophen). In infants and children, the major pathway of paracetamol metabolism is sulfate conjugation whereas glucuronidation is the primary pathway in adolescents and adults (7).

Pharmacodynamics during development: Although a great deal is known about pharmacokinetic changes during development, information regarding developmental changes in pharmacodynamics (medicine action and toxicity) is limited. There are few examples that provide evidence for changes in the response to medicines during development independent of pharmacokinetic changes. Medicine targets, such as receptors, transporters and channels, are certainly also subjected to developmental processes (as are metabolizing enzymes). For example, earlier development of opioid receptors specifically in the medulla and pons, where respiratory and cardiovascular centres are located, than in other parts of the brain, is consistent with a clinically observed higher incidence of opioid-related respiratory depression and bradycardia associated with insufficient analgesia in newborns who receive opioids (8, 9).

Another clinically relevant example of pharmacodynamic differences during development is the greater immunosuppressive response to ciclosporin seen in infants. The concentration in infants at which 50% inhibition occurs in peripheral blood monocytes is only half that in older children and adults (10). The exact molecular mechanism needs to be investigated.

Experimental studies have observed developmental changes at the receptor level for prostanoids, angiotensin II, catecholamines including dopamine, serotonin or GABA-A receptor complex with significant functional changes in a variety of organ systems such as the cardiovascular, renal and neuronal system (11, 12).

In genetic studies of patients with inherited salt-losing tubulopathies, indirect evidence was found that channels and transporters involved in trans-epithelial electrolyte transport are in a dynamic process during early postnatal renal maturation, which—in contrast to that of loop diuretics—leads to blunted diuretic response to thiazide diuretics in preterm and term newborn infants (13).

There are several well-documented examples of increased drug sensitivity or toxicity in young children as well. For example, acute dystonic reactions or seizures in young children have been reported after exposure to the dopamine 2-antagonists metoclopramide and prochlorperazine as antiemetics (14); hyperpyrexic reactions to anticholinergic drugs such as atropine and scopolamine in infants and young children have been documented since 1939; and an increased risk of sudden cardiac arrest has been noted in infants with supraventricular tachyarrhythmias treated with verapamil (15).

Finally, it should be noted that specific diseases occur in the growing and maturing organism, which are not seen in adults. Examples include disorders in the postnatal adaptation period of the newborn, such as wet lung syndrome with respiratory stress and persistent fetal circulation with pulmonary hypertension or hormonal imbalances of the adolescent during puberty.

2.5 The need for additional, independent studies on the development of paediatric medicines

Ignorance or lack of knowledge of these differences in paediatric pharmacotherapy has led to various medicine-related tragedies in the past. Most of them occurred in early life, during the neonatal period: e.g. sulfonamides causing kernicterus (severe brain damage related to neonatal hyperbilirubinaemia) and chloramphenicol causing grey baby syndrome (cardiovascular collapse) in the newborn. Another well-known example is that of in utero exposure to thalidomide leading to the birth of congenitally deformed infants (phocomelia).

As a consequence of these tragedies, the medicines agencies asked the medicine manufactures for much more extensive and thorough pre-marketing medicine investigations. Efficacy and safety of the medicine was required to be investigated in the population for which it is aimed and marketed. Special medicine development strategies for children are therefore needed. However, there are a variety of obstacles to be overcome in this special field of medicine development:

- ethical hurdles, including the difficulties of obtaining informed consent;
- need for non-invasiveness;
- need for microassays, as volumes of samples (e.g. blood) that are available are mostly smaller;
- stratification of patient population into at least five categories: preterm neonates, full-term neonates, infants and toddlers, older children and adolescents;
- difficulty in predicting long-term effects during the maturation process;
- rare diseases (making patient recruitment difficult and small market size providing lower return on investment);
- necessity for training of paediatricians to assess protocols for research;
- high regulatory requirements.

Further information on research involving children is contained in Guideline 14 of the International ethical guidelines for biomedical research (16).

2.6 Current legal and regulatory framework

European Union

Legislation came into force in January 2007, which is applicable across the EU with respect to medicinal products for paediatric use (Regulation (EC) 1902/2006 of the European Parliament and of the Council (17), amending Regulation (EC) 1901/2006 on medicinal products for paediatric use (18)). This legislation aims to enhance the safety of medicines for children by increasing research, development and authorization of medicines based on specific paediatric experience, without subjecting the paediatric population to unnecessary clinical trials. In addition, this legislation creates requirements for the pharmaceutical industry regarding the development of medicines for paediatric use, as well as providing incentives to the industry for undertaking such developments. A framework to manage the operation of the legislation, including the development of a paediatric committee is also addressed.

The EU has issued guidance relating to the above legislation. This guidance addresses the conduct of pharmacovigilance for medicines used by the paediatric population and is aimed at both the pharmaceutical industry and national competent authorities (19). A further draft guideline (20) (Commission Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies) has been issued by the European Commission for a period of consultation.

North America

In 2002, the Best Pharmaceuticals for Children Act (BPCA) was signed into law, providing an incentive of six months of marketing exclusivity for products studied in response to a written request for paediatric studies from the United States Food and Drug Administration (US FDA). The BPCA required a special safety review for adverse events reported for the year after a product has received its paediatric exclusivity. The adverse event reports are to be referred to the newly mandated Office of Pediatric Therapeutics (OPT), at which time the OPT can provide the report for review and recommendation by the Pediatrics Advisory Committee. The review of products assessed under this programme, the presentations to the paediatric advisory committee and the transcripts of the meeting are available on the US FDA web site (www.fda.gov).

Since 2002, the US FDA has conducted postmarketing reviews of adverse events for 65 drug products studied under BPCA. Safety concerns warranting new labelling or further study were expressed for some products. The adverse events reported in connection with these products included deaths and serious events associated with the inappropriate use of opioid transdermal system medicines; neonatal syndrome with the ingestion of selective serotonin reuptake inhibitor (SSRI) antidepressants during pregnancy; suicidality with the

use of antidepressants; cardiovascular and psychiatric events with the use of attention-deficit hyperactivity disorder (ADHD) medicines; and, finally, neuropsychiatric adverse events (delirium, self-harm, confusion) with the use of oseltamivir (Tamiflu). These reviews are in addition to the routine pharmacovigilance activities for all products in all populations and have helped to focus on safety issues that may present in paediatric patients.

In Canada, paediatric associations take the initiative to report ADRs resulting from the use of off-label products, in order to make data on medicine safety in children available. These data are also shared with the national centre.

Other areas

There appears to be an absence of formal frameworks in other areas, highlighting the need for developments.

2.7 Consequences of the lack of studies of medicines development in children and authorization of paediatric medicines

Medicines of major clinical importance, even essential medicines, are not readily tested and not officially approved for use, especially in the very young. This led Harry Shirkey in 1963 to state that children constitute therapeutic orphans.

Among the 340 medicines in the WHO Model List of Essential Medicines 2007 (21) those that have relevance for paediatric populations should be the top priority for documenting paediatric experiences, wherever these medicines are being used.

However, children have therapeutic needs which probably cannot be met if medicines representing major therapeutic advances in adults are not tested and labelled for paediatric use. Once a medicine becomes available on the market for adults, it is possible to use it in children in an off-label way. Thus use of unlicenced and off-label medicines for children has been common practice for decades; this does not offer children the same quality, safety and efficacy of medicines as adults. This situation is not consistent with the UN Convention on the Rights of the Child (22).

From the practical point of view this means that for the physician:

- No information is available on effective and safe dosing regimens (dose range, frequency of administration and duration of therapy).
- An ethical dilemma exists as to the choice between using off-label medications when little or no information is available about their safety and efficacy or depriving the child of a possibly effective medicine, just because it happens to be off-label.
- It may be necessary to deal with parents and guardians, who after reading the prescribing information, are apprehensive that a medicine not tested in children, or not cleared for use in children, is being used to treat their child.
- It is necessary to take greater responsibility for using a medicine that is off-label or unlicenced in case something goes wrong and to depend upon professional bodies, guidelines issued and information about general professional practices for defence.
- There is frequently no age-appropriate medicine formulation or equipment/ devices for administration.
- Warnings of possible ADRs and adverse events are insufficient or lacking.
- Little or no information is available about possible medicine interactions.
- The marketing authorization holder (MAH) has no product liability for the medicine.
- Long-term surveillance is insufficient.

Therefore it is not surprising that paediatric patients are exposed to a rate of potentially dangerous medication errors three times higher than that for adult patients (23). However, only a small proportion of these medication errors will lead to ADRs and be recognized as such. For more information see chapter 4.

3. THE ESSENTIAL ROLE OF SAFETY MONITORING IN THE LIFE-CYCLE OF A MEDICINE

The benefit-risk assessment of any kind of medicine treatment is essential. No assessment of the treatment is, however, possible without safety data and knowledge. The "trial and error" principle is not acceptable in an extremely vulnerable population.

3.1 Pre-marketing assessment of medicine safety

The two major stakeholders responsible for medicine safety at the time of authorization are:

- marketing authorization holder (MAH/medicine manufacturer); and
- competent authorities/medicine regulatory agencies.

Preclinical investigations on reproductive toxicology, mutagenicity and carcinogenicity are mandatory. Special consideration must be given to the long-term follow-up on skeletal, neural, behavioural, sexual and immunological maturation and development in toxicology studies in juvenile animals. The predictive value of such studies in relation to effects in the paediatric population is however uncertain.

Clinical investigations include pharmacodynamic, pharmacokinetic and efficacy studies. Safety studies in the target population are required. Such studies may be performed using different methodological approaches, which are dependent on the type of safety parameters, and the practical, clinical and economic circumstances.

A new conceptual model has been developed, which calls for pharmacovigilance processes to be involved earlier in the life-cycle of a medicine (24). The European Medicines Agency (EMEA) and the FDA develop the policies for risk management strategies (proposed pharmacovigilance measures and if necessary risk minimization) to be applied in the future to the management of medicines throughout their life-cycle. Additionally, in 2004, the International Conference on Harmonisation (ICH) published a guideline *Pharmacovigilance planning* (25) that addressed the issue of the type of studies required for the marketing of a new medicine. The safety specification addresses the populations potentially at risk (where the product is likely to be used) such as children, and outstanding safety questions which warrant further investigation to further the understanding of the benefit-risk profile during the post-approval period. The pharmacovigilance plan provides details of planned pharmacoepidemiological studies. (For more details, see the EMEA *Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (19).)*

3.2 Post-marketing monitoring of medicine safety for medicines already on the market including those used "off-label"

Paediatric pharmacovigilance assessment may be rather limited before authorization due to difficulties and deficiencies in pre-authorization clinical trials of medicines for paediatric use. Sample sizes in phase I and II trials are usually small and, even in phase III trials, sample size is nearly always based on end-points for efficacy. Thus the sample size limits the ability to observe less-than-common reactions. Serious adverse events are often rare, and are generally not observed in a paediatric clinical trial programme, particularly if there is a lag period before onset or a trigger such as changes in growth and development. ADRs in children cannot be predicted on the basis of those observed in adults. Given these limitations every opportunity should be taken to increase the information available from ADR monitoring and to organize and communicate this information to the medical community and the public.

Additional reasons for monitoring post-marketing medicine safety in children include the following:

- The use of unlicenced and off-label medicines is highly prevalent in children (see above).
- Children may not voice complaints and ADRs may remain unnoticed.
- Long-term follow-up is essential in a population with a long lifespan/life-expectancy and medicines may have a specific impact on development and maturation of the skeletal, neural, behavioural, sexual and immune systems.
- Accidental ingestion in small children and suicidal ingestion in adolescents are not uncommon.
- Routinely available safety data may not adequately capture events arising in the paediatric population and only in exceptional circumstances can safety data in the paediatric population can be extrapolated from data obtained in adults. This is because certain ADRs may only be seen in the paediatric population, irrespective of effects on growth and development. Thus ADRs from specific ingredients/excipients may be expressed differently in adults and children. A good example for this kind of poisoning is the life-threatening gasping syndrome seen in infants exposed to benzyl alcohol (26).
- In the case of life-long treatment for chronic diseases, the total duration of treatment is longer if started in childhood. This may expose the patient to increased risk of medicine toxicity and adverse events, e.g. chronic use of amphetamines and methylphenidate to treat ADHD carries the possible risk for cardiovascular events such as myocardial infarction, stroke and sudden death later in life (27).

Benzyl alcohol

Benzyl alcohol is commonly used as the preservative in multidose injectable pharmaceutical preparations. For this purpose, concentrations in the range of 0.5-2% are used and the amount of benzyl alcohol injected is generally very well tolerated. Concentrations of 0.9% are used in bacteriostatic sodium chloride (USP) and bacteriostatic water for intravenous use (USP). It may be a component of water for hydration of medications (28). Benzyl alcohol is widely used as a preservative in allergenic extracts for scratch and intracutaneous testing, and can lead to false-positive results (29).

The content of benzyl alcohol in many injectable pharmaceutical preparations should be considered carefully. Unfortunately many countries still take the view that the identity of the additives and excipients in medicines is a trade secret, and this attitude must be deplored. The duty to declare the additives and excipients is only realized in some countries.

Deaths in neonates have been associated with administration of 99-234 mg/kg/day benzyl alcohol in large-volume parenteral solutions or endotracheal solutions. The toxic effects of benzyl alcohol, which include respiratory vasodilatation, hypertension, convulsions and paralysis, have been known for years. However, little is known about the toxic effects or levels of benzyl alcohol and the metabolic acidosis caused by accumulation of the metabolite, benzoic acid, in neonates, especially in sick premature infants. Its effect is mainly related to an excessive body burden relative to body weight, so that the load of this metabolite may exceed the detoxification capacity of the immature liver and kidneys.

The FDA has recommended that neither intramuscular flushing solutions containing benzyl alcohol nor dilutions with this preservative should be used in newborn infants.

3.3 Benefit-to-risk considerations in children

In the absence of clinical trials, neither efficacy nor safety are established for the indications for which the medicines may be used. It is therefore necessary to identify indications for which medicines are actually used in paediatrics, as well as the dosage forms. Effectiveness studies are necessary to determine the results in real-life clinical situations, and then to match evidence of harm to effectiveness, by age group.

Actual measurement of benefit-to-risk balances is not an easy task, and is the subject of much research, but as a minimum, there is a need to gather the information suggested above, wherever possible.

4. MEDICATION ERRORS

Medical errors have received a great deal of attention in recent years. The phrase "medical error" is an umbrella term covering all errors that occur within the health-care system. Medication errors are probably one of the most common types of medical error, as medication is the most common health-care intervention. In the USA, it is estimated that medication errors kill 7000 patients (both adults and children) per year (30). In UK hospitals, the incidence and consequences of medication errors appear similar to those reported in the USA—with prescribing errors occurring in 1.5% of prescriptions (31). While the majority of all errors (61%) originated in medication order writing, most serious errors (58%) originated in the prescribing decision.

Several published reports confirm that medication errors are not uncommon in paediatrics; one significant study has shown that potentially harmful medication errors may be three times more common in the paediatric population than in adults (32). This in turn indicates that the epidemiological characteristics of medication errors may differ between adults and children.

4.1 Increased risk of medication errors in children

Paediatrics pose a unique set of risks of medication errors (33), predominantly because of the need to make dosage calculations, which are individually based on the patient's weight, age or body surface area, and their condition. This increases the likelihood of errors, particularly dosing errors (34). For potent drugs, when only a small fraction of the adult dose is required for children, it becomes very easy to cause dosing errors of 10-fold or greater because of miscalculation or misplacement of the decimal point. For example, Selbst et al. (35) reported a case of a 10-month-old baby who had received 10 times the correct dose of intravenous theophylline as a result of miscalculation of the drug dosage. Furthermore, incorrect recording of patients' weights and the difficulties health-care professionals have in making arithmetical calculations could also contribute to incorrect dosing (35).

As discussed above, many drugs used to treat children are either not licenced (unlicenced) or are being prescribed outside the terms of the product licence (off-label prescribing) (36). This poses an additional risk to children from medication errors as doses must be calculated on an individual patient basis, often in the absence of appropriate dosing information from the pharmaceutical manufacturer.

In addition, adult dosage formulations often have to be manipulated at ward level by nursing staff, or suitable products prepared extemporaneously in the pharmacy, to meet the need for small doses in paediatric patients. Such manipulations may involve, for example, cutting or grinding up tablets or dispersing or mixing drugs with such agents as food or drinks before administration. These practices are associated with a high risk of errors as the bioavailability of the drugs following such manipulations is often unknown and unpredictable. Compatibility and stability information is often lacking.

Furthermore, the lack of standardization has caused confusion in parents resulting in serious medication errors. An example is the case of a child who received his regular supplies of diazoxide suspension made as an extemporaneously prepared suspension at 10 mg/ml, from a local community pharmacy. He was given a 50 mg/ml solution on his visit to a paediatric hospital. His parents did not read the label and gave the same volume of the suspension resulting in a five times overdose. Consequently, the child required hospitalization (37).

4.2 Incidence of medication errors

The following tables contain information on the epidemiology of medication errors in children and the stage in medication use at which the error occurred.

Table 1: Epidemiology of medication errors in children

Author	Study design	Patients	ADE per 1000 pt-day	ADE per 100 admits	Near-miss 1000 pt-day[a]	Near-miss 100 admits	Med. error 1000 pt-day[a]	Med. error per 100 admits
Kaushal, 2001	Prospective chart review	Ward, NICU PICU	6.6	2.3	29	10	157	55
Holdsworth, 2003	Prospective chart review	Ward, NICU	7.5	6	9.3	8	—	—
Proctor, 2003	Prospective chart review Paediatric	surgical service	—	—	—	—	8.3	—
Ross, 2000	Incident report	Ward, NICU PICU	—	—	—	—	0.51	0.15
Raju, 1989	Incident report	NICU, PICU	—	—	—	—	8.8	14.7
Vincer, 1989	Incident report	NICU	—	—	—	—	13.4	—

ADE, adverse drug event; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.
[a] When available, the rate per 1000 patient-days is used to account for the effect of length of stay on number of errors.
Source (38).

Table 2: Stage in medication use at which error occurred

Author	Setting	MD ordering (%)	Transcribing (%)	Pharmacy dispensing (%)	Rn administering (%)
Kaushal, 2001	NICU, PICU wards	79	11	4	4
Ross, 2000	NICU, PICU wards	20	—	20	60
Raju, 1989	PICU	3	—	30	60
Vincer, 1989	NICU	16	8	8	27

NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.
Source (38).

5. PRIMARY RESPONSIBILITY OF STAKEHOLDERS

When a medicine is marketed, the health professionals (physicians, nurses, other health-care workers and in part the parents/caretakers) take the major responsibility for the assessment of medicine safety. This is also true for off-label use, which ranges between 50 and 90% in the paediatric population in most countries, as demonstrated by hospital-based surveys. The medicine regulatory agencies and the medicine manufacturers must take the responsibility whenever they receive feedback from the health professionals. These professionals—if they are trained adequately—are the ones who are able to observe reactions and events associated with a new medicine on the market, when it is introduced into a quite heterogeneous population with different ages, sex, co-morbidity and polypharmacotherapy. In addition, environmental, nutritional and social conditions are important modulators of the ADRs experienced.

It has been recognized that the current system of medicine regulation in western countries does have some serious drawbacks (39). As the medicine regulatory agency has been responsible for the authorization process at the beginning of the medicine life-cycle, there is a need for a reform of the system to reduce the influence of conflict of interest in the evaluation of the post-marketing events. It is important that drug manufacturers follow up on adverse reactions to their products once they are well-established on the market. A Guideline on conduct of pharmacovigilance for medicines used by the paediatric population has been prepared by EMEA (19).

Spontaneously reported ADRs remain one of the most important sources for detecting safety signals or other issues in the post-authorization period. However, spontaneous reporting is expected to be of only limited value in the safety monitoring of paediatric medicines, unless the notorious underreporting among health professionals including paediatricians can be overcome. It has been estimated that less than 10% of all serious, and 2-4% of all non-serious, ADRs are reported (40).

Reasons for underreporting in general medicine are as follows (41-43):

- lack of information and awareness among most stakeholders in our present health system (most likely a consequence of non-inclusion of pharmacovigilance as an important issue in the undergraduate (medical, pharmacy and nursing) curriculum;
- lack of training programmes for health-care professionals;
- absence of formal pharmacovigilance systems in many countries and, if present, limited efforts made to inform health-care professionals regarding the systems in place in a given country or region;
- problems with diagnosis of ADRs;
- problems with the clinical workload for most health-care professionals, especially in developing countries (i.e. no time to make reports);
- problems with the reporting procedure (too bureaucratic);
- problems related to potential conflicts (legal liability) and fear of punitive consequences including unfavourable media coverage;
- absence of a feedback system.

In addition, there are even more obstacles related to the reporting of ADRs in paediatric patients (44, 45):

- Children, particularly small children, may be unable to express their sensations and complaints.
- A high proportion medicines used are off-label and unlicenced (see above).
- Many poorly evaluated phytotherapeutic, ayurvedic, anthroposophic, traditional and homeopathic medications are popular because they are perceived as "soft" and less toxic medicines by many parents, caretakers and even health professionals.
- There is irrational use of medicines, e.g. antibiotics.
- Clinical trials are lacking and experience and skills in reporting ADRs and AEs are insufficient.
- A paediatric essential medicine list (pEML) has yet to be developed.
- Appropriate medicine formulations and administration devices for children are lacking.
- No paediatric list of laboratory values giving rise to a laboratory filter signal is available.
- There is incompatibility of some excipients in the medicine formulations and in poorly defined mixtures of traditional medicines for paediatric use, e.g. diethylene glycol.

Diethylene glycol

Diethylene glycol is a highly toxic organic solvent that causes acute renal failure and death when ingested. There have been repeated reports of fatalities caused by accidental contamination of medicines with this substance, most commonly in cough syrups used mainly by children (46).

Systematic and targeted local monitoring (if possible computerized) from medical records may soon become another important method of detecting safety signals (47). The advantages of this approach are that:

- One has the ability to focus on specific areas of importance for the real-life assessment of medicine safety, e.g. in a neonatal intensive care unit.
- The chances of detecting unrecognized medication errors and serious dose-related ADRs are much better; this is important as these are more frequent and theoretically more preventable than idiosyncratic reactions.
- The direct feedback at the local level is much more motivating and educational for all responsible health professionals and has a direct effect on quality of medicine use and patient care.

From various pharmacoepidemiological studies in paediatrics, it is well known that the risk of ADRs increases with the length of the patient's stay in hospital; the number of medicines she or he is receiving; the extent of off-label use; and the dynamics of physiological changes during early life. In addition, retrospective and prospective monitoring from computerized medical records, requiring a more or less passive role of the health professionals, is time-efficient compared with other intensive surveillance systems. It will probably improve spontaneous reporting of pharmacological, unpredictable and not dose-related reactions and the much more common, and in part preventable, dose-related reactions to a medicine.

As long as comprehensive, but at the same time, simple and clear clinical documentation in medical records—such as the problem-oriented medical record—is available, the same approach can be applied manually in less developed countries with simple protocols. Such surveys could be limited in time and only give a snapshot as a point of care observation (quality of medicine use approach) and can be repeated at regular intervals. These surveys could primarily be developed in close collaboration with a regional pharmacovigilance centre or the department of clinical pharmacology at a university clinic or hospital in a particular country. Surveys can be done manually as well with a couple of hundred patients observed retrospectively or prospectively and might focus on medicine-related problems including ADRs and medication errors. Each such survey should lead to a report and combining the information from such reports from many regional centres will provide a picture of the paediatric medicine problems in a specific country.

6. GUIDANCE: MEASURES TO BE TAKEN

Some developed countries have well-established systems for reporting, collecting and analysing medicine safety data. Such systems are also currently evolving in a few developing countries. However, the health administrators in developing countries cannot depend solely upon data generated in western countries for predicting ADRs and assessing medicine safety in their own paediatric population, as:

- Children in developing countries belong to a different ethnic group and hence their genetic composition is unlike that of children in developed countries. This could mean differences in medicine metabolism and variability in the frequency and severity of ADRs.
- Children in developing countries have different comorbidities and suffer from a dissimilar spectrum of disease. Malnutrition is rampant and worm infestations and infectious diseases are responsible for significant morbidity and mortality.
- Country-specific medicine handling circumstances and the series of steps from prescribing all the way to the patient receiving medication need to be considered.
- A large proportion of the population, particularly in developing countries, concomitantly uses traditional medicines and homemade remedies to treat illnesses. These medicines are often used for the treatment of upper respiratory tract infections, allergies and bronchial asthma, conditions with a high prevalence in children. It is possible that these medicines could have hitherto unnoticed interactions.
- In the past, newer medicines were introduced into resource-poor countries years after their launch in developed countries. The postmarketing data generated in developed countries was, therefore, available to regulators, medical professionals and consumers in developing countries, before new medicines were introduced to their local markets. In the present era of globalization, newer medicines are sometimes launched almost simultaneously in developed and developing countries. Hence, even preliminary post-marketing data from developed countries may not be available when a new medicine becomes available in developing countries.
- The situation regarding frequency and severity of ADRs varies among countries not only because of factors such as spectrum of disease, variable comorbidities and different genetic composition, but also owing to variations in medicine production, pharmaceutical quality and composition (excipients) of locally-produced pharmaceutical products and differences in medicine use (indications, dose, formulation, route of administration and availability).

Thus the importance of generating country-specific data on paediatric ADRs cannot be over-emphasized. Unless locally generated data are available, the health-care providers do not pay attention to it. It is commonly felt that data generated elsewhere may not be relevant because of different circumstances. It is not surprising then that even medicine regulators are less keen to act on data generated elsewhere.

6.1 Improvement of awareness among stakeholders

Improvement of awareness of the medicine safety issue and of the importance of post-marketing surveillance in children, among health professionals and the whole public health system appears to be an essential first step.

Identification of the responsible stakeholders: They need strong motivation and support. However, in addition, the spectrum of these stakeholders needs to be enlarged.

The stakeholders in post-marketing surveillance are:

- physicians, who are directly involved in treatment with paediatric medicines, e.g. general practitioners, paediatricians, child psychiatrists, anaesthesiologists, dentists and medical students;
- pharmacists, particularly those working at a children's hospital who are responsible for the medicine dispensary;
- nurses, e.g. those working on a neonatology ward, study nurses working in the paediatric networks and particularly nurses specialized in quality assurance and risk management;
- other health workers, particularly programme managers in public health programmes;
- regional and national pharmacovigilance centres in a country; they are the key institution in organizing and conducting local studies as part of the clinical quality work in the rational and safe use of medicines;
- clinical pharmacology departments, even if there is no pharmacovigilance unit;
- patients, parents and caretakers: they can be very helpful when provided with special forms together with the patient information leaflets to encourage detailed recording as a supplement to the physician's report;
- government agencies who formulate the laws, regulations, safety precautions and rules of reporting;
- poison and medicine information centres, which can play an important role in signal detection.

Potential additional stakeholders for post-marketing surveillance could include:

- patients' and parents' self-help groups and organizations;
- health insurance companies and health economists, who may have a great interest in the prevention of expensive hospital admissions related to ADRs;
- academic centres in teaching hospitals which could promote methods and activities related to pharmacovigilance, pharmacoepidemiology and pharmacoeconomy in the curricula of medical, nursing, pharmacy and other paramedical professions;
- learned societies in paediatrics, clinical pharmacology, pharmacy and biostatistics which can contribute to all the medicine safety investigations recommended (see below). They can also be asked to

identify and validate adequate biomarkers particularly for pharmacodynamic and pharmacogenomic studies;
- editors of scientific journals;
- health administrators and health department officials;
- programme directors of public media;
- politicians;
- civil society and nongovernmental organizations.

6.2 Methods, approaches and infrastructure for an effective system for medicine safety monitoring at the national level

Post-marketing medicine surveillance is particularly important for new paediatric medicines as they have often not been vigorously tested in the pre-marketing phase of medicine development (see above).

The spectrum of conventional methodological approaches for safety monitoring is presented in annex 1. They are also described in the ICH Guideline E2E pharmacovigilance planning (25). However, by analogy to the assessment of effectiveness and benefit of medicine treatment for orphan diseases, less conventional approaches might be required and be acceptable to evaluate potential medicine toxicity and to identify ADRs when there are few patients available to analyse. The pharmacovigilance situation becomes more complex when one considers the frequent use of off-label medicines in children, which is often associated with less standardized extemporaneous medicine formulations and a less harmonized dosage regimen. All of these circumstances add to the sum of avoidable "bio-noise", which can interfere with detection of relevant signals.

Three approaches to paediatric safety monitoring might be worth mentioning in this context:

- A detailed knowledge of the pathophysiology of the disease and the pharmacological profile and the toxic potential of a medicine will facilitate the selection of the most appropriate clinical and laboratory data for assessment of safety and benefit-risk analysis.
- Preclinical pharmacodynamic studies with juvenile animals may also provide important hints for a more focused search for possible ADRs in children.
- As true concurrent controls and comparator groups might be unavailable for studies of orphan diseases, disease or exposure registries might supply important information on the natural course of the disease in question. Such information may also be particularly helpful for the evaluation of long-term safety of medicines and might also be used as a base for a case-control study comparing the exposure to medicine of cases identified from the registry and controls selected from either patients within the registry with another condition and taking different medication, or from outside the registry.

Infrastructure

A suitable infrastructure would include the following:

- A full-time commissioner for medicine safety affairs should be enrolled or employed in children's hospitals and departments of paediatrics at medical schools, as suggested by the Canadian Paediatric Society, for a special programme for reporting on use and safety of medicines in children.
- Regional pharmacovigilance centres should be set up with the following functions:
  - making access and contact easier for health professionals;
  - definition of priorities for spontaneous reporting;
  - providing information and support activities for reporting ADRs;
  - feedback on pharmacovigilance activities;
  - and, last but not least, development of a local monitoring system that uses medical charts for the detection of serious ADRs and medication errors (see above).
- A national pharmacovigilance programme (NPP) with a bottom-up structure should be developed, paying attention to the local or national characteristics of culture, climate, resources, equipment, nutrition, comorbidity and genetics.
- A single address for reporting ADRs and AEs is essential. The reporting procedure must be kept as simple and clear as possible.

6.3 Implementation of methods and structural changes for effective monitoring of medicine safety at the national level

Legal measures

Desirable legal measures include:

- prevention of liability being a concern for practitioners when reporting ADRs, for example through the anonymity of professional societies, medical boards or local paediatric groups such as quality circles, and development of a blame-free and non-punitive reporting system of medication errors;
- building confidence via the regional centres in each country;
- introduction of the topic of medicine safety and medicine development into the curriculum of future generations of physicians, nurses and pharmacists;
- more academic credit given to the work of clinical trialists and for research in the field of pharmacovigilance and pharmacoepidemiology;
- legal balance between patient-protection and patent- or data-protection.

Regulatory measures

The regulatory measures to be taken are as follows:

- reinforcement of conduct of more clinical trials in children by the MAH through incentives and requests (see USA and European legislation - 17, 18);
- acceptance of reports about ADRs not only from physicians, but also from other stakeholders in the health systems, such as nurses and pharmacists;
- pharmacovigilance measures for a product in the postmarketing phase as suggested by the EMEA to include:
  - complete safety specification derived from the premarketing medicine development phase;
  - an active postmarketing surveillance programme;
  - periodic safety update reports (PSURs);
  - risk management plan;
  - standardized safety evaluations in clinical trials to facilitate the assessment of rare AEs and ADRs;
  - data management should allow reproducible data retrieval and analysis by indication and by exact age in the five paediatric subpopulations and, if possible, data presentation on the basis of sales statistics;
  - up-to-date information about paediatric efficacy and safety issues to be included and explained in the summary of the product characteristics (SPC) and in the patients'/parents' information leaflet.

6.4 Impact measurement and audit

All safety monitoring activities, and benefit versus risk experiences should be subject to follow-up, audit and review for their impact on public and individual health. It is essential to check that knowledge gained on safety of medicines in paediatrics is successfully communicated to and used by health-care professionals. This is more important even than in adult medicine in the absence of clinical trials to guide clinicians. Authoritative information should be made available on the Internet to counteract any misleading information which may find its way through the same channel.

7. MEASURES TO BE TAKEN BY WHO

Awareness

Methods to promote awareness include:

- workshops and training for health workers through special WHO programmes;
- publication of guidelines and lists, e.g. a paediatric essential medicine list (pEML);
- information about the need for pharmacovigilance initiatives directed to governments and appropriate governmental agencies;
- a paediatric list of laboratory values giving rise to a laboratory filter signal of a possible ADR.

Methods of monitoring

WHO should develop simple, standardized and internationally (WHO) accepted protocols for collecting data on ADRs from institutions, regions and the regional pharmacovigilance centres.

Infrastructure

The infrastructure should include the following:

- electronic networks;
- IT-based reporting and communication systems for prospective use;
- development of simple protocols for regional monitoring and ADR-detection from medical records;
- central coordination, e.g. the WHO Collaborating Centre for International Drug Monitoring (UMC) in Uppsala;
- harmonization of the national pharmacovigilance programmes (NPPs) by regular conferences;
- joint venture with the Global Consortium of Paediatric Pharmacology (GCPP);
- formation of regional collaborations and partnerships as suggested by Beggs, Cranswick and Reed (48):
  - North-South America
  - Europe-Africa
  - Japan-North Asia
  - Australia-Asia Pacific.

Charts with points of interest for local surveillance

Establishment of a national network between these centres and of affiliation with a relevant governmental agency would be desirable.

1. Establishment of national pharmacovigilance centres affiliated to larger health-care units

Admission/emergency room/outpatient clinics/intensive care unit/general wards

↓

Electronic medical records

↓

Reviewing team including the commissioner for medicine safety affairs in the hospital for all reported serious ADRs

↓

Reassurance by nurses/doctors specialized in quality and risk management

↓

Report to the regional pharmacovigilance centre

↓

Discussion at a local conference including the local pharmacist

↓

Report to the national pharmacovigilance centre and feedback to the house staff

2. Establishment of pharmacovigilance centres at minor health-care centres/hospitals

Emergency room/outpatient clinic/general ward

↓

Problem-oriented medical record

↓

Record review by house staff doctor and/or local pharmacist trained in pharmacovigilance

↓

Report to the local regulatory authority and/or to the national pharmacovigilance centre

↓

Feedback to the house staff

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ANNEX 1 - PHARMACOVIGILANCE METHODS

Passive surveillance

- Spontaneous reports

A spontaneous report is an unsolicited communication by health-care professionals or consumers to a company, regulatory authority or other organization (e.g., WHO, a regional centre or a poison control centre) that describes one or more adverse drug reactions (ADRs) in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme (1).

Spontaneous reports play a major role in the identification of safety signals once a medicine is marketed. In many instances, spontaneous reports can alert a company to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors and clinical features of known serious ADRs. Caution should, however, be exercised in evaluating spontaneous reports, especially when comparing medicines. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since the launch of the medicine, pharmacovigilance-related regulatory activity, media attention and the indication(s) for use of the medicine (2-5).

Systematic methods for the evaluation of spontaneous reports

More recently, systematic methods for the detection of safety signals from spontaneous reports have begun to be used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection (6-8). Data mining techniques have also been used to examine medicine-medicine interactions (9), but these techniques should always be used in conjunction with, and not in place of, analyses of single case-reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals that merit further evaluation. However, this tool does not quantify the magnitude of risk, and caution should be exercised when comparing medicines. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence reporting of spontaneous adverse events are not removed by data mining. The results of data mining should thus be interpreted in the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate for different medicines and the many potential biases inherent in spontaneous reporting. All signals should be evaluated while recognizing the possibility of false-positives. In addition, the absence of a signal does not mean that a problem does not exist.

- Case series

Series of case-reports can provide evidence of an association between a medicine and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between medicine exposure and outcome. There are certain distinct adverse events known to be associated more frequently with medicine therapy, such as anaphylaxis, aplastic anaemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome (10, 11). Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

Stimulated reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in hospital settings) for new products or for limited time periods (12). Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method. Although these methods have been shown to improve reporting, they are not immune to the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early post-marketing phase, companies might actively provide health professionals with safety information and, at the same time, encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by company representatives, by direct mailings or faxes). Stimulated adverse event reporting in the early postmarketing phase can lead companies to notify health care professionals of new therapies and provide safety information early on in their use by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan). This should be regarded as a form of spontaneous event reporting, and thus data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

Active surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain the exact number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular medicine through a risk management programme. Patients who fill a prescription for this medicine may be asked to complete a brief survey form and give permission for future contact (13). In general, it is more feasible to obtain comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

- Sentinel sites

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure that complete and accurate data on reported adverse events are collected from these sites. The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting system. Further, information on the use of a medicine, such as abuse, can be targeted at selected sentinel sites (14). The major weaknesses of sentinel sites include problems with selection bias, small numbers of patients and increased costs. Active surveillance with sentinel sites is most efficient for those medicines used mainly in institutional settings such as hospitals, nursing homes and haemodialysis centres. Institutional settings may use certain medicinal products more frequently and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan medicines.

- Medicine event monitoring

Medicine event monitoring is a method of active pharmacovigilance surveillance. Studies using this method are cohort-based and prospective and observational. For medicine event monitoring, patients can be identified from any source of prescription data including electronic or automated health insurance claims. The prescription data might represent the total population treated in a country, or in a region, depending on the source. A single prescription or a series might be collected over the period of monitoring. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Requests for information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, reasons for discontinuation and relevant past history can be included in the questionnaires (12, 15-19). The limitations of medicine event monitoring can include poor physician and patient response rates. However, the New Zealand Intensive Medicines Monitoring Programme (IMMP) has achieved consistently high physician response rates of at least 80% and patient response rates which are slightly higher. More detailed information on adverse events from a large number of physicians and/or patients could be collected. The unfocused nature of data collection, means that unexpected signals are less likely to be missed. Signal identification has proved highly effective in the IMMP.

Relationship assessment, using WHO causality definitions (20, 21), gives added value to the data by allowing the events to be sorted according to the strength of the relationship. Examining events with a strong relationship avoids the possible problem of signals or risk factors being masked by the presence of background noise. The events with no clear relationship to the medicine represent background morbidity in the cohort. When compared with likely reactions, these data are useful as within-medicine and between-medicine controls. Because incidence rates are available, risk factors can be calculated with accuracy.

The data can be stratified to look for subpopulations at increased risk. Events within the cohort can be further investigated using nested case-control studies. Further value might be gained by undertaking collaborative studies internationally.

Patient confidentiality is as secure as with spontaneous reporting.

The other forms of active surveillance, described below, are often inherent to medicine event monitoring e.g. cohort studies, comparator studies, pregnancy registries and drug utilization studies.

- Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (medicine registry). Both types of registry, which differ only by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help to collect data on medicine exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the medicine exposure of cases identified from the registry with controls selected either from patients with another condition within the registry, or from patients outside the registry.

Exposure (medicine) registries address populations exposed to the medicines of interest (e.g., a registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a medicine has a special impact on this group of patients. Some exposure (medicine) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan medicine indicated for a specific condition.

Comparative observational studies

Traditional epidemiological methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports, case series or medicine event monitoring. The most important of these designs are cross-sectional studies, case-control studies and cohort studies (both retrospective and prospective) (12, 15).

- Cross-sectional study (survey)

Data collected on a population of patients at a single point in time (or during a specified interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of study are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecological analyses. Cross-sectional studies are most useful when exposures do not change over time.

- Case-control study

In a case-control study, cases of disease (or events) are identified. Controls, or patients in whom the disease or event of interest has not occurred, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or using data collected specifically for the purpose of the study. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (e.g. the elderly, children, pregnant women). For rare adverse events, existing large population-based databases are a useful and efficient means of providing the necessary data on medicine exposure and medical outcome relatively quickly. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a medicine (or medicines) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions, such as renal and hepatic dysfunction, which might modify the relationship between the medicine exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

- Cohort study

In a cohort study, a population at risk for the disease (or event) is followed over time to record the occurrence of the disease (or event). Information on exposure status is available throughout the follow-up period for each patient. A patient might be exposed to a medicine at one time during follow-up, but not exposed at another time. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving medicine exposure, comparison cohorts of interest are selected on the basis of

medicine use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to the medicine of interest (such as an orphan medicine) or to study very rare outcomes. Like case-control studies, patients for cohort studies can be identified from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with comorbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients are included.

There are several automated databases available for pharmacoepidemiological studies (12, 15, 18). They include databases that contain automated medical records or automated accounting/billing systems. Databases that are created from accounting/billing systems might be linked to pharmacy claims and medical claims databases. These datasets may include millions of patients. Since they are created for administrative or billing purposes, they might not have all the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data. Although medical records can be used to ascertain and validate test results and medical diagnoses, one should be cognizant of the privacy and confidentiality regulations that apply to patient medical records.

Targeted clinical investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the medicine in general practice, conducting specific studies to investigate potential medicine-medicine interactions and food-medicine interactions might be called for. These studies can include population pharmacokinetics studies and medicine concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified at that time due to small sample sizes or the exclusion of subpopulations of patients from such studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Patients from these subpopulations might metabolize drugs differently from patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a medicine outside the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. In this type of trial, though, the event of interest will be focused to ensure a convenient and practical study. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the results of the trial. Large, simplified trials are also resource-intensive.

Descriptive studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with medicine exposures. These studies are primarily used to obtain the background rate of outcome events and/or to establish the prevalence of the use of medicines in specified populations.

- Natural history of disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of, or risk factors for, the adverse event of interest, can assist in putting spontaneous reports into perspective (15). For example, an epidemiological study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

- Medicine utilization study

Medicine utilization studies (DUS) describe how a medicine is marketed, prescribed and used in a population, and how these factors influence outcomes, including clinical, social and economic outcomes (12). These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, sex, concomitant medication and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies, denominator data can be collected for use in determining rates of ADRs. DUS have been used to describe the effect of regulatory actions and media attention on the use of medicines, as well as to develop estimates of the economic burden of the cost of medicines. DUS can also be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a medicine has the potential for abuse by examining whether patients are taking escalating doses or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information on the indication for use of a product.

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ANNEX 2

Recent information on adverse reactions to marketed medicines in children

Medicines used for treating attention-deficit hyperactivity disorder
Attention deficit hyperactivity disorder (ADHD) is being increasingly diagnosed and treated in children. A recommended medicine, methylphenidate (MPH), is being increasingly used to treat this condition. Its side-effects increase linearly with dose, and include appetite suppression, insomnia, tachycardia, nervousness and headache (1); fixed medicine eruption induced by MPH is a rare adverse effect (2); and a small minority of ADHD children on MPH therapy is also at risk for serious growth decrement (3). In addition, preliminary data suggest a significant nocturnal dipping of blood pressure (BP) during sleeping hours and greater elevations in BP during waking hours (4). Paediatricians should, therefore, closely monitor the dose-related side-effects and aim for the lowest effective dose. They should also monitor heart rate, BP and growth in children on MPH therapy.

Pemoline is another medicine used to treat ADHD. There have been reports of serious hepatotoxicity (hepatic enzyme abnormalities, jaundice and even death) ascribed to its use. Limitations in post-marketing surveillance and public reporting in the United States of America, particularly in the 1980s, largely accounted for delays in initiating an appropriate response to pemoline hepatotoxicity (5).

Medicines used to treat nocturnal enuresis
Primary nocturnal enuresis is one of the most frequent complaints in paediatric practice. Either imipramine or desmopressin are routinely used to treat nocturnal enuresis in children. Although very rare, imipramine has been reported to cause sudden cardiac arrest. A number of case-reports have linked desmopressin use with hyponatraemic hypervolaemia associated with coma and seizures attributed to excess water intake before taking the medicine (6).

Inhaled corticosteroids for asthma
Inhaled corticosteroids (ICS) are now the first-line therapy for persistent asthma in children. Their benefits clearly outweigh any potential adverse effects and risks associated with poorly controlled asthma (7). Worldwide, diagnoses of asthma are increasing and children are receiving treatment with ICS to remain symptom-free. Although inhibition of growth has been seen following administration of the recommended dose during the early years of treatment with ICS (8), long-term studies suggest a negligible effect, if any, on final adult height (9). ICS use in children is not associated with an increased occurrence of posterior subcapsular cataract, tendency to bruise, voice change or any adverse effect on bone mineral density (9). However, the use of high doses of ICS (more than 400 micrograms per day) has been associated with a significant reduction in growth rate, when monitored in children aged 1-15 years, over a 4-year period (10). The dose of ICS should therefore be minimized to the lowest effective dose and growth velocity monitored (11). The paediatrician

should also ensure that the child is using the metered-dose inhaler properly. Wrong technique can result in increased swallowing of medicine and systemic availability of the medicine, defeating the purpose of inhaler therapy. In asthmatic children with concomitant allergic conditions (allergic rhinitis, atopic dermatitis) that require multiple forms of topical corticosteroids, the risk of high doses is compounded. The use of ICS where tuberculosis is rampant can present another risk. A report from India has documented that eight (1.4%) of 548 patients with asthma, including adults, developed active tuberculosis following the use of ICS (12).

Anti-pyretic and anti-inflammatory medicines

Nimesulide, a selective cyclo-oxygenase-2 inhibitor has become popular as a routine antipyretic and anti-inflammatory medicine in some countries such as India, Italy and Turkey. Its routine use after day-care surgery, due to its efficacy in pain relief, has been reported from India (13). Randomized controlled clinical trials carried out in Turkey (14) and in India (15) have documented that its antipyretic activity is better than that of paracetamol and ibuprofen in children. Better in this case means that the antipyretic activity is greater and more rapid. However, as for any medicine, it is not only its efficacy that is important, but also its safety. Such small studies, with only about 100 children each, cannot detect the rare adverse effects. Only post-marketing surveillance and spontaneous reporting can detect these effects. Nimesulide has also been used widely in children in Italy although there is no robust evidence on which to base its rational use (16). An analysis from Italy of its database of spontaneously reported adverse events has cautioned that use of nimesulide in patients at risk can be associated with hepatic and renal impairment (17). Paediatricians in India have also reported occurrence of gross haematuria, peri-orbital oedema and hypothermia associated with nimesulide use (18, 19). In response to the concern about hepatotoxicity, a pharmaceutical company that manufactures the medicine in India has analysed 4097 case-report forms gathered from 430 paediatricians who had prescribed nimesulide (20). This analysis revealed that no child had developed hepatotoxicity after nimesulide use. However, it is believed that nimesulide is associated with rare (0.1 per 100 000 patients treated), but serious and unpredictable, hepatotoxicity manifested as increases in serum aminotransferases, hepatocellular necrosis and intrahepatic cholestasis; this type and incidence of severe hepatic reaction, however, is comparable to that reported for other non-steroidal anti-inflammatory medicines (NSAIDs) (21). A recent meta-analysis has concluded that:

- Oral nimesulide is as safe or unsafe as other analgesics/antipyretics for short-term use (less than or equal to 10 days) in children.
- It is best avoided in children known or suspected to have liver disease.
- Caution is warranted while prescribing nimesulide concomitantly with other hepatotoxic medicines.
- There are limited data for drawing concrete inferences about its safety in infants below the age of six months (22).

The issue of hypersensitivity to NSAIDs in childhood has yet to be settled due

to lack of sufficient data. There have been recent reports of significant ADRs to ibuprofen in children primarily as a result of its availability as an over-the-counter preparation (23, 24). The predominant reactions were rash (acute urticaria, fixed medicine eruption), gastrointestinal and respiratory side-effects, and even haematemesis.

Cisapride for gastro-oesophageal reflux
Gastro-oesophageal reflux (GOR) is an extremely common and usually self-limiting condition in infants. Cisapride, a pro-kinetic agent, is commonly prescribed for the symptomatic management of GOR in infants and to reduce feed intolerance in premature neonates. Adverse cardiac events (serious ventricular arrhythmias, QTc interval prolongation, syncope and sudden death) have been reported in adult patients treated with cisapride, especially with the concomitant ingestion of antifungal medicines (fluconazole, miconazole) and macrolides (clarithromycin). A study from the United States of America has reported that 15 (30%) of 50 infants receiving cisapride developed QTc interval prolongation three days after starting to take the medicine, and in the majority the QTc interval had normalized by day 14 of cisapride therapy (25). This study suggested that documenting a prolongation of the QTc interval, three days following initiation of cisapride administration, would identify infants at risk for adverse cardiac events. Such a finding would mandate omitting cisapride and help reduce cardiac morbidity in hospitalized infants receiving cisapride. However a Cochrane Review has recently stated that there is no clear evidence that cisapride reduces symptoms of GOR (26). Studies done in Australia and India have also found no benefit of cisapride in reducing feed intolerance in premature neonates (27, 28).

Anti-epileptic medicines
A recent survey in the UK looking for fatal suspected ADRs has reported that anticonvulsants were associated with the greatest number of reports of fatalities and hepatotoxicity in particular. The individual medicine most frequently mentioned was sodium valproate (29).

Antiepileptic medicine hypersensitivity syndrome (AHS) is a rare idiosyncratic reaction that is known to occur in response to the first-line aromatic antiepileptics (carbamazepine, phenobarbital and phenytoin) within three months of starting therapy (30, 31). Its incidence in children is not known, but it is believed to be grossly underdiagnosed (32). A classic triad of fever, skin rash and internal organ involvement, especially hepatic dysfunction should serve as a presumptive diagnosis of AHS, and the offending antiepileptic should be promptly discontinued. AHS can easily be mistaken for a variety of infectious conditions and can be fatal if not promptly recognized. Since there is a high rate of cross-sensitivity (40 to 80%) between the aromatic antiepileptics, the child should henceforth receive benzodiazepines, valproic acid or topiramate for future seizure control. Recently an occurrence of AHS has been reported in a premature newborn infant who developed fever, skin reactions and oedema in response to phenytoin (33). AHS has also been

reported in a child treated with lamotrigine, a nonaromatic anti-epileptic (34). Also, cross-reactivity between aromatic antiepileptics and lamotrigine has been documented by doing the in vitro lymphocyte toxicity assay in an 11-year-old girl who developed AHS following administration of phenobarbital (35).

Newer antiepileptics (lamotrigine, oxcarbazepine and topiramate) are being marketed for paediatric use. There is a worldwide lack of systematic pharmacoepidemiological studies investigating ADRs to the newer antiepileptics, making it difficult to assess their incidence accurately (36). As with the older antiepileptics, the majority of ADRs to the newer antiepileptics are related to the central nervous system. The ADRs identified include hypersensitivity reactions ranging from simple morbilliform rashes to multi-organ failure; psychiatric ADRs and deterioration of seizure control in response to lamotrigine; hyponatraemia and skin rash in response to oxcarbazepine; and, cognitive deficits, word-finding difficulties, renal calculi and weight loss in response to topiramate (37). Vigabatrin, which is effective in controlling seizures in children with tuberous sclerosis, has been reported to cause aphasia, encephalopathy, motor disturbances and late-onset visual field constriction.

Cefaclor-induced serum sickness-like reaction
Cefaclor, an oral second-generation cefhalosporin, is commonly used to treat respiratory and skin infections in children. Recently a unique ADR, cefaclor-induced serum sickness-like reaction (SSLR), in which the child develops urticaria, arthralgia and facial oedema on receiving a second or third course of cefaclor, has been identified. It occurs in 0.055% of children and its tendency to develop is probably genetically (maternally) inherited (38). A report from India described a four-year old boy who developed SSLR (39). This child had received multiple courses of cefaclor (self-medication given by his parents). After his clinical condition improved with antihistamines and steroids, the parents were advised to ensure that the child never receives cefaclor in the future.

Multiple antibiotic sensitivity syndrome (MASS)
Multiple antibiotic sensitivity syndrome (MASS) is a rare but distinct ADR which manifests as urticaria or pruritis, skin rash, serum sickness-like reaction, angioedema or anaphylaxis, and erythema multiforme or Stevens-Johnson syndrome in response to antibiotics of multiple classes (penicillin, cephalosporins, sulfonamides, macrolides). Although its incidence in children is unknown, it is believed to occur after repeated use of these antibiotics (40).

Benzodiazepines
Midazolam, a benzodiazepine, is used as a sedative in mechanically ventilated neonates and children. The plasma clearance of midazolam is impaired in infants and children younger than three years of age, who therefore have increased susceptibility to its toxicity (41). It should also be administered cautiously in very low-birth-weight (VLBW) babies because it can cause hypotension and adverse neurological events such as grade III-IV intra-ventricular haemorrhage (42, 43). In a neonatal intensive care unit in New

Delhi, moderate hypotension was reported in six (19%) of 32 VLBW babies who received midazolam sedation during mechanical ventilation, but there was no increase in any adverse neurological event (44). Midazolam has also been reported to cause adverse effects (delayed time to become fully alert/abnormal behaviour) on withdrawal in critically ill children (45).

About 3.4% of children scheduled for elective surgery have been reported to develop paradoxical reactions following premedication with intravenous midazolam. These reactions may occur at variable times after administration and include restlessness, violent behaviour, physical assault, acts of self-injury and need for restraints (46). Ketamine has been reported to be an effective medicine for the treatment of these paradoxical reactions. The exact mechanisms of these reactions and how they are resolved by ketamine are not clear (46).

Intranasal midazolam is being increasingly used as a sedative and anxiolytic before painful procedures in children. An acute allergic reaction has recently been reported in a healthy 5-year-old boy, after receiving midazolam by intranasal atomizer for sedation purposes in a dental clinic (47). Shortly after the midazolam was given, the child developed urticaria in his ankles, which rapidly progressed to the lower extremities, stomach, back, arms, neck and face. The periorbital skin also became oedematous. The reaction required treatment with intramuscular diphenylhydramine in the emergency department.

Medicines for opportunistic infections and antiretrovirals in HIV/AIDS patients
Trimethoprim-sulfamethoxazole (TMP-SMZ) is being routinely prescribed in HIV-infected children for the treatment and *Pneumocystis carinii* pneumonia. Both life-threatening and treatment-limiting adverse events due to suspected delayed hypersensitivity are known to occur after 7-21 days of starting TMP-SMZ (48, 49). These include cardiorespiratory arrest, seizures, toxic epidermal necrolysis, hypotension, respiratory distress, liver function abnormalities, azotaemia, neutropenia, anaemia and gastrointestinal disturbances.

Adverse effects associated with antiretroviral medicines have been reported to occur in up to 30% of HIV-infected children on antiretroviral therapy. In one study thirteen patients (30%) had adverse effects related to the ART. Seven patients (16%) had hepatotoxicity, five patients (12%) had raised serum amylase without symptomatic pancreatitis, five patients (12%) had zidovudine- (AZT-) induced anaemia, four patients (9%) had nevirapine- (NVP-) induced rash, one patient (2%) had didanosine- (ddI-) induced pain in the abdomen, one patient (2%) had stavudine- (d4T-) induced angioedema and one patient (2%) had hepatic steatosis. Hepatotoxicity, especially at higher viral loads, is the commonest adverse effect noted, followed by elevated serum amylase (50). Most of the adverse effects are reversible by modifying the dosage or omitting the offending medicine.

The lamivudine-zidovudine combination for the prevention of mother-to-child transmission of HIV has been reported to result in neutropenia and anaemia in the infants, which at times is severe enough to require blood transfusion or even premature discontinuation of treatment (51). Reversible granulocytopenia has been reported to occur in all infants between 1.5 and 3 months of age who had received short-term antiretroviral prophylaxis with nevirapine alone or in combination with zidovudine to prevent mother-to-child transmission (52).

Newer adverse reactions to medicines in neonates

With improved neonatal care, many preterm newborn infants are now routinely surviving. This has resulted in an increasing occurrence of retinopathy of prematurity (ROP) which needs early specialized intervention to limit the visual disability. Recently, a preterm newborn infant has been reported to have developed renal failure after undergoing a mydriatic test with phenylephrine drops, which were instilled several times. The blood concentration of phenylephrine was elevated sufficiently to contract the renal vessels, ultimately inducing renal failure (53).

Imidazole nasal drops are widely used as a nasal decongestant. Special formulations with reduced drug concentration are available for children, and most preparations are available over-the-counter. Three cases have now been reported of neonates who developed apnoea and coma, two of whom needed short-term mechanical ventilation (54). After the exclusion of infectious and metabolic causes of these episodes, there remained at least a temporal relation to the treatment with oxymethazoline- and xylometazoline-based nose drops in all three infants. Similar cases have been reported previously (55, 56). It is speculated that these compounds can easily cross the blood-brain barrier in neonates and cause hypotensive and sedative effects by binding receptors of a specific group in the rostral ventrolateral medulla, to which clonidine also belongs (54, 57).

Another more recently reported ADR in neonates is that the use of selective serotonin reuptake inhibitors (paroxetine, fluoxetine, sertraline and citalopram) in pregnant women being treated for depression has been documented to cause neonatal convulsions and neonatal withdrawal syndrome (58).

In the literature, however, the most intensively discussed ARDs in neonatology remain those that might be causally related to the prostaglandin synthesis inhibitors or NSAIDs. When indomethacin treatment for ductal closure in preterm infants with symptomatic persistent ductus arteriosus (PDA) was introduced in the 1970s, the initial enthusiasm concerning "pharmacological closure" of the ductus arteriosus was soon followed by disillusionment. Many severe health problems in very preterm newborn infants, such as necrotizing enterocolitis (NEC), retinopathy of the preterm infant (ROP), intraventricular haemorrhage (IVH), and irreversible renal failure were thought to be associated with indomethacin treatment (59). Today we know that indomethacin treatment, like that with all potent prostaglandin synthesis inhibitors, can be associated with a further reduction of blood flow to the brain, gut and kidneys

under conditions with a restricted effective circulatory volume (60, 61). However, these problems are avoidable, if the infants have an adequate fluid balance (62, 63). Moreover, the transient vasoconstrictive effect of indomethacin on the cerebrovascular may even have a protective effect on the brain (64). The alternative to indomethacin, ibuprofen, was initially thought to have fewer adverse effects than indomethacin (65). However, this treatment was later found to be associated with an increased risk of chronic lung disease, pulmonary hypertension (66) and kernicterus (67). Ibuprofen interferes with bilirubin-albumin and increases the unbound bilirubin in pooled newborn plasma. Besides these safety concerns, ibuprofen has been shown to induce qualitative negative effects on renal function similar to those induced by any other nonselective NSAID (68). Further well-controlled head-to-head comparative studies with particular emphasis on short- and long-term safety aspects are needed to answer one of the most urgent pharmacotherapeutic issues in neonatology, namely, whether ibuprofen is really superior to indomethacin. For the time being indomethacin remains the medicine of choice (66).

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PROMOTING SAFETY OF MEDICINES FOR CHILDREN

Pharmacovigilance and medicine safety issues in children are relevant to everyone who has an interest in and cares about the health of children. The purpose of this guideline is **I)** to present a case for the importance of the improving safety monitoring of medicines for children, **II)** to describe possible ways of achieving it and **III)** to provide an outline for national pharmacovigilance programmes to make them more sensitive and open to adverse reactions to medicines in children.

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