CURRENT OPINION

Drug Safety 2003; 26 (8): 529-537
0114-5916/03/0008-0529/$30.00/0

Paediatric Medicines Research in the UK

How to Move Forward?

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Abstract

There have been numerous studies to show that many of the medicines used in children are used off-label or are unlicensed for use in children. When children are prescribed unlicensed and off-label medications, some people may see them as unknowing participants in informal and uncontrolled experiments. However, the licensing status of a drug can be seen as a by-product of the real issues: the safety, efficacy and quality of these medicines in the current licensing system. It is important to conduct research in order to provide high quality data regarding safety and efficacy to support evidence-based paediatric prescribing. Clinical trials will always be an invaluable means of acquiring vital information about a drug; but when it comes to children, we may find that these trials are not always practical for technical, ethical and financial reasons; therefore, it is important to explore other methodologies in paediatric medicines research. Pharmaco-epidemiological and prospective cohort studies could provide vital safety and efficacy data on paediatric medicines; however, resources need to be invested in the methodological research. Paediatric drug formulation research is under-resourced and under-valued, and, unfortunately, fatal and serious adverse reactions due to inappropriate formulations have been reported in many instances. Paediatric medication is a complex problem; we need to use all available tools for research on safety, efficacy and formulation. The reason for lack of progress in paediatric drug research is most likely due to lack of resources and research capacity. The industry and government should work together and invest more money in paediatric drug research. Finally, regulatory authorities, healthcare professionals and academics need to rethink the research strategy in order to provide better medicines for children.

'Let the little children come to me and do not stop them, because the Kingdom of God belongs to them.' Luke's Gospel 18:16.[1]

In the days of Jesus, society did not have much consideration for children. However, Jesus told his followers that children deserved special attention. In many aspects, the developed countries have taken on board this attitude, investing increasing resources in children's welfare. In a personal example; when the corresponding author recently bought a Barbie doll for his 4-year-old daughter, he made certain that

the toy had a CE logo[1] as assurance that this doll was suitable for a child of her age, i.e. it has been tested according to a recognised standard for a 4-year-old child. Similarly, when he took his 8-year-old son to see 'Jungle Book 2' with a G[2] certificate, he knew his child would not see inappropriate scenes in the film. Ironically, when it comes to medicines administered to children, there is a lot of uncertainty, as a large proportion of medicines are not licensed or have not been tested in children. We have found it difficult to accept toys and films unless they are 'tested' for children in our modern society, whilst medicines that have a direct effect on a child's health are often given based on educated guesses and extrapolations. Although the above analogies may be 'unscientific', it seemed to be the most appropriate way to describe the current situation in children's medicines, which, similarly, does not always adhere to the rigid 'scientific' agenda known to other areas of the medical profession.

In the UK, the publication of the first module of the National Service Framework for Children is imminent; furthermore, the Medical Research Council, Royal College of Paediatric and Child Health and the Association of British Pharmaceutical Industry are currently conducting a review on the paediatric clinical pharmacology research in the UK; we wish to take this opportunity to share our thoughts in the research of paediatric medicines and stimulate further discussion.

1. Do We Really Need a Product Licence?

There have been numerous studies to show that many of the medicines used in children are used off-label or are unlicensed for use in children.[3-7] When children are prescribed unlicensed and off-label medications they are being placed at a considerable disadvantage where specialists have to rely on educated guesses about doses, safety, and effectiveness.[8] Some even go as far as considering children 'potential guinea-pigs without their knowledge or the knowledge of their parents' as suggested by Mr Andrew Love (MP) in the British House of Commons.[9] Limited evidence shows that use of medicines in children in this way may result in a higher risk of adverse drug reactions, particularly when the number of different medications given to children is increased.[10] The US was one of the first countries to officially tackle this problem in 1998 by introducing the 'paediatric exclusivity' rule, a regulation that specifies circumstances where pharmaceutical manufacturers are required to test their products to determine whether they are safe and effective in children,[11] and subsequently establishing the 'Best Pharmaceuticals for Children Act' in 2002.[12] More recently, the European Union (EU) issued a document providing regulatory initiatives to ensure better use of medicines in children. This document stated that the primary objective is to 'increase availability of authorised medicinal products for use in children'.[13]

What these regulatory documents have in common is the main aim of obtaining official approval for use in children of medicine currently unlicensed for this age group. This is based upon the concept that the use of a drug within its license specifications would ensure optimal outcome in patients, which is reflected in the UK Medicines and Healthcare products Control Agency's (MHRA) mission statement: 'To protect and promote public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely'. The MHRA further states that one of its key activities is 'licensing of medicines before marketing and subsequent variations'.[14] However, recent research is beginning to

1 CE stands for Conformité Européenne, which is French for 'European Conformity'. A product in one of the controlled product categories, which includes children's toys, cannot legally be sold in the European Union unless it has passed the tests to receive the CE marking.

2 G stands for 'General Audiences' all ages admitted, according to the Classification and Rating Administration (CARA). It suggests that the film contains nothing most parents will consider offensive for even their youngest children to see or hear.[2]

indicate that we may be losing sight of the objective that matters most to those involved. We are currently conducting a study to determine attitudes of professionals in various sectors of healthcare on the use of unlicensed and off-label medicines. Representatives were asked to contemplate a hypothetical situation of prioritising factors related to 'unapproved' medicines to determine which drugs required most urgent attention. Participants were to list and rank the factors that they would consider most relevant when prioritising these drugs. Preliminary results of overall ranking showed with statistical significance that licensing status of the drugs was rated amongst the least important within the participants (table I). In contrast, safety and efficacy were rated highest. This exercise demonstrates that in actual fact, greater interest is displayed towards determining that a drug is safe and effective, rather than application of regulatory action rendering a drug officially approved.[15] Licensing status of a drug can be seen as a by-product of the real issues: the safety, efficacy and quality of these medicines in the current licensing system.

There is little doubt that the expertise found within the regulatory authority is extremely valuable in obtaining, organising and assessing the information on safety, efficacy and quality of paediatric medicines, regardless of whether the information is in the public domain or a commercial confidential setting. Therefore, we believe all medicines used in children should be assessed by the licensing authority allowing a verdict to be given based on the existing evidence. However, it should be stressed that this 'verdict' need not take the form of an approved license, which is expensive and time-consuming, hence delaying the availability of essential information pertinent to these drugs. If there is an evidence gap in the safety, efficacy or quality of a drug used in children, the regulatory authority should attempt to encourage pharmaceutical companies or independent researchers to provide evidence in order to 'protect and promote public health' as suggested in the mission statement of the MHRA[14]

Table I. Factors considered by health professional to be most relevant when prioritising paediatric medications

Factors	Average ranking	Friedman's test
Safety	1	1.14
Efficacy	2	2.36
Characteristics of the disease	3	4.47
Exposure	4	5.33
Availability of literature	5	5.89
Quality of the drug	6	6.92
Patient acceptability	7	7.25
Availability of licensed alternative	8	7.69
Novelty	9	8.25
Licensing status	10	8.69
Extrapolation problems	11	9.75
Cost of the drug	12	10.25

2. Clinical Trials and Alternatives

Clinical trials will always be an invaluable means of acquiring vital information about a drug. From an evidence-based practice point of view, it would be greatly beneficial to conduct more clinical trials, particularly randomised controlled trials and meta-analyses. We fully agree with the EU commissioner[13] and the US National Institute of Health[16] that we need to build up the research capacity of clinical trials in children and establish centres of excellence and research networks. Furthermore, the idea of setting up a 'clinical trial register' is endorsed by the EU commissioner and has gained significant support by the respondents to the 'Better Medicines for Children Consultation'.[17] Such a register can help to avoid the possible repetition of studies that do not enhance the collective knowledge. In our opinion, the register can also act as a medium for researchers to seek information and possible partners for future studies.

However, there are many additional considerations to be made regarding the design of experiments and ethics of testing drugs on children. Trials with children demand more skill, time and commitment to ensure that investigations are as painless and comfortable as possible, requiring trained staff with considerable experience in working with children. Other practical hindrances include availability of appropriate formulations, possible need for blood sampling, recruitment difficulties, and shortage of

paediatric clinical pharmacologists.[8,18,19] Another issue of particular significance to parents involves the ethical implications of testing drugs on children. Therefore, including children in clinical trials denotes that the study will be subjected to increased scrutiny from ethical review boards, to ensure that the child's best interest is fully considered. Investigators may face another ethical dilemma when obtaining informed consent from the parents. It has been argued that the amount of information revealed to parents can adversely affect recruitment rate,[20] leading to careful consideration of all relevant information that should be given to parents to maximise recruitment while ensuring that parents are given all the necessary information.

Furthermore, children are a heterogeneous group, encompassing wide differences, e.g. a child of 17 years (nearly fully grown) and one 2 years of age. Even greater differences are seen between a neonate and an 11-year-old. Of course ideally, we should study a drug in all different age groups, but in reality, this may not be very practical.

Also, even if the drug does not cause acute adverse drug reactions in a clinical trial, this does not guarantee the absence of long-term adverse effects, regardless of its use in either children or adults. However, there is an additional concern with respect to the effect of drugs on future development and maturity when used in young children. This leads to the implication that there should be long-term follow-up in paediatric clinical trials.[13]

Finally, several paediatric medical colleagues whom we encountered have expressed their concerns about the EU directive in conducting clinical trials. Conducting a clinical trial in accordance with the EU directive[21] is very complicated, and healthcare professionals are unlikely to have sufficient resources to comply with it. As a result, it is likely that only company-sponsored clinical trials will be conducted in the future. As we have already seen, pharmaceutical companies only fund drug studies that have a profitable market, leaving children at a further disadvantage. Therefore, funding agents should develop schemes to assists clinicians in conducting clinical trials that may not be of great commercial value.[8,18-20]

Currently, the licensing system relies heavily upon controlled trials to assess the safety and efficacy of medicines, resulting in very few medicines that obtain a license to be used in children. However, if our goal is to provide sound information on the safety, efficacy and quality of paediatric medicines to the health professionals and patients so that they can use these medicines appropriately,[22] then should we consider possible alternatives to controlled trials in the assessment of safety and efficacy of paediatric medicines? In 1995 the US FDA implemented a regulation that allows labelling of drugs for paediatric use based on appropriate studies in adults and additional pharmacokinetic, pharmacodynamic and safety studies in paediatric patients, if the course of their disease and drug effects in children and adults are similar. Furthermore, it specifically states that controlled clinical trials in the paediatric population may not be required.[23] The International Conference on Harmonisation (ICH) E11 document has already adopted this approach.[24] We agree with the FDA and ICH suggestions that controlled trials may not be required in some cases. We also believe that more research in alternative methods is urgently needed, such as prospective cohort studies and pharmacovigilance using automated databases.[25]

3. Pharmacoepidemiology

Pharmacoepidemiological studies have been used widely in drug safety monitoring;[26] however, applying pharmacoepidemiological techniques to paediatric medication use is relatively rare. We suspect there are two reasons for this under-use.

The first is methodological challenges. Most of the adverse drug reaction reports in literature are case reports and case series, very few cohorts and case control studies have been conducted. After being involved in two cohort studies, one in hospital and one using the General Practice Research Database, we found these studies to be much more difficult than in adults. One reason is that it is very difficult to recruit sufficient patients in children's

hospitals to attain a reasonable sample size. There are some successful studies that have been published, but they are likely to be multicentre studies[27,28] sometimes involving more than one country.[29] The organisation of multicentre and multinational studies is a methodological challenge and requires vast resources in building up and maintaining the research networks to support such research. Also, in many cases it is necessary to use parents as a liaison while gathering information, which may pose further complications in terms of co-operation and support, reducing the quality of data collected. Paediatric pharmacoepidemiology requires additional attention from the research community for methodological development.

The second reason is funding. Providing funding for drug safety studies should be the prime responsibility of the pharmaceutical industry. As the market for children is relatively small, in financial terms, it is not an attractive investment for most of the pharmaceutical companies, as a result, medicines for children is still a low priority for funding. Furthermore, funding should also be available from the regulatory authority and Department of Health; one suggestion would be that the regulatory authority could work with the pharmaceutical industry to develop a funding scheme allowing health professionals and academics to apply for funding in paediatric pharmacoepidemiology. To the credit of the then UK Medicines Control Agency, they partly funded the Trent Paediatric Adverse Drug Reaction monitoring Centre in England.[30] Unfortunately the funding ceased, and the scheme is no longer running; however, the scheme did help to advance paediatric adverse drug reaction monitoring and inform us of future research methodology. The need for pharmacovigilance systems specifically adapted for children was stressed by most parties who responded to the EU 'Better Medicines for Children' consultation.[17] Undoubtedly, it is important to develop both the methodology and reporting system in paediatric adverse drug reaction monitoring; once again emphasising that the regulatory authority work closely with the industry to provide sufficient resources for research and development.

4. Prospective Observational Cohort Study

It has been accepted that retrospective pharmacoepidemiological studies are not usually suitable to study the efficacy of medicines in children. In light of this, could we consider prospective observational cohort studies? The main objections to uncontrolled studies are bias and the placebo effect, which can distort the true efficacy and safety profile. On the other hand, the critics of controlled trials would also argue that a controlled trial does not give us the information obtained in a natural clinical setting,[31,32] i.e. effectiveness.

We have already established that it would be difficult to conduct a clinical trial in all different age and sex groups of children; therefore, a prospective cohort study could be an option in obtaining efficacy data in different groups in clinical practice. A high-quality clinical database has been used to assess the clinical effectiveness of medicines in typical clinical practice.[32] The Committee on Drugs of American Academy of Paediatrics' statement suggests that 'Physicians who choose to prescribe a medication with limited paediatric data have a public and professional responsibility to assist in the systematic development of the information about that drug for the benefit of other patients. Practitioners are encouraged to publish experiences that result from such off-label uses of drugs'.[33] It seems to be a logical step to develop a network of practitioners who collect such information. Indeed, the UK Department of Health Standing Medical Advisory Committee recommended that children's prescribing data should be collected prospectively for evaluation.[34] Further methodological research in using clinical databases in both hospital and community settings are urgently needed. However, we would like to point out that a prospective observational cohort study is not as simple as most people believe. Human resources required for a well-designed and well-conducted prospective observational study could be substantial. Furthermore, as the data are not as 'clean' as controlled trials, it is essential to have sufficient statistical and epidemiological input

throughout the whole study including planning, data collection and analysis.

5. Pharmaceutical Research Undervalued

Pharmaceutical research in paediatric medicine has received much less attention than it deserves. Pharmaceutical formulation issues are the cause of considerable problems in the development of medications for children. Modified delivery systems such as sustained-release formulations, for example, or inhalation therapies have generally been developed for an adult population, and there are many instances where special formulations are required for unique situations in paediatric practice. There is not much point in conducting expensive clinical trials if the drug cannot be delivered to the site of action. Unfortunately, fatal and serious adverse drug reactions caused by inappropriate formulations have been reported in many instances in the black market[35-37] as well as marketed products.[38-41] We are not aware of any funding initiative to improve the situation. Unfortunately, this type of research is not under the remit of research councils. On the other hand, pharmaceutical companies are not interested in funding a research project that generates minimal financial rewards. That may be the reason why no research unit has been set up in the UK to investigate paediatric drug delivery research. For this reason, the School of Pharmacy, University of London, The Institute of Child Health, University College London and Great Ormond Street Hospital for Children have prioritised the funding to set up the Centre for Paediatric Pharmacy Research.[42] As the first centre of it's kind, our collaboration and support has already been extended well beyond the London area, with particular interest from the UK Neonatal and Paediatric Pharmacy Group Executive Committee, which volunteered to collect information on the use of UK-imported unlicensed medication for the Centre, allowing us to prioritise the pharmaceutical research. It is very important for the funding bodies and pharmaceutical industry to recognise the significance of such research to children and support the new research initiative in paediatric drug delivery.

6. Do We Have Sufficient Paediatric Clinical Pharmacology Research Capacity in the UK?

Modern paediatric pharmacology is a sophisticated clinical discipline capable of carrying out the studies necessary for the safe and ethical evaluation of drugs in children. Pursuit of such studies, however, is limited by the scarcity of available facilities with which to monitor children receiving drugs and to collect data in a systematic way. It is also limited by insufficient numbers of qualified clinical, scientific and pharmaceutical investigators interested in this problem. In fact, a training programme has been set up in London and Aberdeen to address to the lack of paediatric clinical pharmacologists in the UK. This programme takes 7 years to train two individuals.[18] In response to the need for appropriate drug therapy studies in paediatric patients, the US National Institute of Child Health and Human Development (NICHHD) established the 'Pediatric Pharmacology Research Unit' (PPRU) Network in 1994. The NICHHD has identified that the training of paediatric clinical pharmacologists and healthcare professionals involved in paediatric drug trials remains a priority because of the increased demand and scarcity of qualified individuals. Thirteen units have been subsequently established with the funding from the NICHHD. The 13 PPRUs form a network of research centres for federally sponsored paediatric pharmacology studies across the US. The network contains 160 000 paediatric inpatients per year and 2.3 million outpatient paediatric contacts per year. The NICHHD has just announced that they intend to continue to support PPRUs network and will commit $US4.8 million in 2004.[16]

Since the FDA and NICHHD took the lead in tackling paediatric medication problems, the EU has followed suit and, in a recent consultation document, similar proposals have been put forward by the EU commissioner for Health.[13] The Network for Drug Investigation in Children (ENDIC), a collaborative group in Europe, was established in 1998 to facilitate both clinical and scientific research into the medicines in children.[43] A survey of unlicensed

and off-label drug use in paediatric wards in European countries was conducted by this group.[4]

We are also glad to see that junior doctors can finally choose to take up paediatric clinical pharmacology training programmes. We wish to urge the UK Department of Health to make this a priority and establish more training posts for paediatric clinical pharmacology. Perhaps, the Department of Health could create a 'Paediatric Medicine Career Scientist Award Fellowship' to fast-track promising clinicians, pharmacists, nurses and other health professionals in a career of paediatric medicines research. Furthermore, hospitals should consider establishing more posts for consultant paediatric clinical pharmacologists. In the pharmacy profession, the Neonatal and Paediatric Pharmacist Group has been working with the College of Pharmacy Practice and academic institutions to develop competency and accreditation schemes[44] to improve the paediatric clinical pharmacy training. These encouraging initiatives will certainly enhance our clinical and research capacity. In due course, we hope that the new generation of paediatric clinical pharmacologists and clinical pharmacists will work together in both clinical and research settings to improve the use of medicines in children.

However, experience from the US suggests that it is necessary for funding agents to invest in resources and develop research units and networks in order to kick start research and build up a research capacity.

Given the size and complexity of paediatric medicine research and the grossly insufficient research capacity in the UK at the present time, we would like to propose the creation of a new research cooperative in children's medicine. Because of its interdisciplinary nature, a collaboration, bringing together experts in several universities and hospitals, is thought beneficial in the form of a single site unit. The School of Pharmacy London, The Institute of Child Health London, and University College London have decided to create a new initiative in Children's Medicine Co-operative along with several other universities and children's hospitals. This idea is also supported by other organisations and individuals who responded to the European Commissioner's consultation.[17] We do urge the Medical Research Council, Wellcome Trust and the Department of Health and European Commission to make such funding a priority.

7. National Service Framework for Children

The National Services Framework for Children – 'Standard for Hospital Services' has just been published.[45] In the use of medicines in children section, it specifies that: 'The use of medicines in children should be guided by the best available evidence of clinical effectiveness, cost effectiveness, and safety, ideally derived from clinical trials conducted with children. Good practice also includes using medicines for which there is a sound theoretical basis for believing that they are effective in children, for example, medicines that have been shown to work well for adults, but have not been formally researched for use in children. In practice, therefore, this means that many children receive medicines that are not licensed for their age group or for their particular health problem (use 'off-label'); or do not have a license at all ('unlicensed'). It is recognised that this is not ideal and a variety of steps are being taken, which over time should lead to an increased range of products and formulations that carry a license for use in children across the age ranges required.'

8. Conclusions

Paediatric medication is a complex problem; we need to use all available tools in research on safety, efficacy and drug delivery. The reason for lack of progress in paediatric drug research is most likely due to lack of resources and research capacity. The industry and government should work together and invest more money in paediatric drug research. Finally, regulatory authorities, healthcare professionals and academics need to rethink the research strategy in order to provide better medicines for children.

Acknowledgements

Ian Wong's post is funded by Department of Health Public Health Career Scientist Award to investigate safety of psychiatric medicines in children and adolescents.

Ian Wong and Alexander Florence both have received research grants from various pharmaceutical companies.

References

1. Gospel according to Luke. New Testament. Holy Bible
2. Parental Media Guide [online]. Available from URL: http://www.parentalguide.org/ [Accessed 2003 May 2]
3. Turner S, Longworth A, Nunn AJ, et al. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ 1998; 316: 343-5
4. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000; 320: 79-82
5. Bücheler R, Schwab M, Mörike K, et al. Off label prescribing to children in primary care in Germany: retrospective cohort study. BMJ 2002; 342: 1311-2
6. Schirm E, Tobi H, de Jong-van den Berg TW. Unlicensed and off label drug use by children in the community: cross sectional study. BMJ 2002; 324: 1312-3
7. t'Jong GW, Eland IA, Sturkenboom MCJM, et al. Unlicensed and off label prescription of drugs to children: population based cohort study. BMJ 2002; 324: 1313-4
8. Steinbrook R. Testing medications in children. N Engl J Med 2002; 347 (18): 1462-70
9. Parliament, U.K. Medicines (children), in House of Commons Hansard debates. Bound volume debates. Vol. 329, Column 669, April 19,1999
10. Turner S, Nunn AJ, Fielding K, et al. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr 1999; 88 (9): 965-8
11. Regulations Requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients: final rule. Federal Register 1998: 66631-66673
12. Best Pharmaceuticals for Children Act [online]. Available from URL:http://frwebgate.access.gpo.gov/cgibin/useftp.cgi [Accessed 2003 Mar 3]
13. Proposed regulatory actions on paediatric medicinal products, in better medicines for children. 2002: European Commission, Brussels [online]. Available from URL: http: //www.pharmacos.eudra.org/F2/pharmacos/medchild.htm [Accessed 2003 Mar 3]
14. Medicines and Healthcare Products Regulatory Agency [online]. Available from URL: http://www.mhra.gov.uk/aboutmhra/aboutmhra.htm [Accessed 2003 May 6]
15. Sweis D, Wong I. Electronic response: where do our interests lie? e-BMJ [online]. Available from URL: http://bmj.com/cgi/eletters/324/7349/1290#23972 [Accessed 2003 Mar 3]
16. Pediatric Pharmacology Research Unit Network. Release date: November 18, 2002 RFA: HD-03-001 [online]. Available from URL: http://www.grants1.nih.gov/grants/guide/rfa-files/RFA-HD-03-001.html [Access 2003 Mar 3]
17. Overview of comments on consultation paper "Better Medicines for Children" 2002: European Commission, Brussel. [online]. Available from URL: http: //pharmacos.eudra.org/F2/pharmacos/medchild.htm [Accessed 2003 Mar 3]
18. Choonara I. Clinical trials of medicines in children. BMJ 2000; 321 (7269): 1093-4
19. Conroy S, McIntyre J, Choonara I, et al. Drug trials in children: problems and the way forward. Br J Clin Pharmacol 2000; 49 (2): 93-7
20. Stephenson T, Walker DA. Telling parents all relevant details might reduce recruitment of children to trials. BMJ 1996; 313 (7053): 362-3
21. Clinical Trials. EU Directive on Good Clinical Practice in clinical trials [online]. Available from URL: http://www.mca.gov.uk/ourwork/licensingmeds/types/clintrialsconsult.htm [Accessed 2003 Mar 3]
22. Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group. Unlicensed medicines in paediatric practice. Medicines for Children. London; RCPCH Publications Ltd, 1999: xiii
23. Federal Register [online]. Available from URL: http://www.fda.gov/ohrms/dockets/98fr/120298c.txt [Accessed 2003 Mar 3]
24. Committee for Proprietary Medicinal Products (CPMP). ICH Efficacy Topics: E11. Clinical Investigation of medicinal products in the pediatric population. International Conference on Harmonisation; 2000 July 27: London. Available from URL: http://www.emea.eu.int/pdfs/human/ich/271199EN.pdf [Accessed 2003 Mar 3]
25. Wong ICK. Pharmacovigilance resources in the United Kingdom. Pharm J 1999; 263: 285-8
26. Wong ICK, Sweis D. Techniques in pharmacovigilance. Pharm J 2000; 264: 922-3
27. Baud O, Foix-L'Helias L, Kaminski M, et al. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. N Engl J Med 1999; 341 (16): 1190-6
28. Lesko SM, O'Brien KL, Schwartz B, et al. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001; 107 (5): 1108-15
29. de Vathaire F, Hawkins M, Campbell S, et al. Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. Br J Cancer 1999; 79 (11-12): 1884-93
30. Clarkson A, Ingleby E, Choonara I, et al. A novel scheme for the reporting of adverse drug reactions. Arch Dis Child 2001; 84 (4): 337-9
31. Britton A, McKee M, Black N, et al. Choosing between randomized and non-randomised studies: a systematic review. Health Technol Assess 1998; 2 (13): 1-124
32. Padkin A, Rowan K, Black N. Using high quality databases to complement the results of randomised controlled trials: the case of recombinant activated protein C. BMJ 2001; 323: 923-6
33. Committee on Drugs, American Academy of Pediatrics. Use of drug not described in the package insert (off-label uses). Pediatrics 2002; 110 (1): 181-3
34. Standing Medical Advisory Committee Advice. Licensing and prescribing of drugs in children (5/2001) [online]. Available from URL: http: //www.doh.gov.uk/smacdrugschildren.htm [Accessed 2003 Mar 3]
35. Okuonghae HO, Ighogboja IS, Lawson JO, et al. Diethylene glycol poisoning in Nigerian children. Ann Trop Paediatr 1992; 12 (3): 235-8

36. Hanif M, Mobarak MR, Ronan A, et al. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. BMJ 1995; 311: 88-91
37. O'Brien KL, Selanikio JD, Hecdivert C, et al. Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. JAMA 1998; 379: 1175-80
38. Gershanik J, Boecler B, Ensley H, et al. The gasping syndrome and benzyl alcohol poisoning. N Engl J Med 1982; 307: 1384-8
39. Phelps DL. E-Ferol: What happened and what now? Pediatr 1984; 74: 1114-6
40. Martin-Bouyer G, Lebreton R, Toga M, et al. Outbreak of accidental hexachlorophene poisoning in France. Lancet 1982; I (8623): 91-5
41. Powell H, Swarner O, Gluck L, et al. Hexachlorophene myelinopahty in premature infants. J Pediatr 1973; 82: 976-81
42. Wong ICK. Researching better medicines for children – a collaborative approach. Pharmaceutical Journal 2003; 270: 549-50. Available from URL: http://www. pharmj.com/pdf/agenda/pj_20030419_children.pdf [Accessed 2003 May 7]
43. Bonati M, Choonara I, Hoppu K, et al. Closing the gap in drug therapy [letter]. Lancet 1999; 353 (9164): 1625
44. General Paediatric Competencies [online]. Available from URL: http://www.collpharm.org.uk/FNPPCompetencies.PDF [Accessed 2003 Mar 3]
45. Department of Health. Getting the right start: National Service Framework for Children – Standard for Hospital Services. HMSO 2003 London. Available from URL: http://www.doh.gov.uk/nsf/children/standardhospserviceindex.htm [Accessed 2003 May 6]

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