to children under the age of 5 from at-risk communities.

Taken together, the two papers published in this issue of *Archives* indicate a widespread insufficiency of vitamin D in children. Worryingly, from the perspective of current UK strategies to prevent vitamin D deficiency, virtually all of the vitamin D metabolite measured in the serum of the Manchester cohort was sunlight derived. Taken together with the earlier data from Sheffield, there may be a need to revise our current approaches to the prevention of vitamin D deficiency and insufficiency.

For now, however, we need to take simple, practical measures to reduce the burden of early bone disease and other later problems. These measures need to be part of our routine practice and recommendations, particularly in the at-risk groups of infants and young children from non-white backgrounds.

Education is a major part of this. Paediatricians, obstetricians, midwives, health visitors, and GPs all need to remind patients that there is virtually no vitamin D in breast milk, and that totally breast fed babies should be supplemented (irrespective of the colour of their skin) until receiving a full mixed diet. The other recommendations from the CMO are clear and simple and should now be applied universally in respect of infants and young children. We do still need to decide how best to meet the needs of older children and adolescents in a culture that covers up, either with clothing or with sunscreen. Perhaps more exercise outdoors would help deal with this problem.

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REFERENCES

1 **Robinson PD**, Högler W, Craig ME, *et al*. The re-emerging burden of rickets: a decade of experience from Sydney. *Arch Dis Child* 2006;**91**:564–8.
2 **Hypponen E**, Laara E, Reunanen A, *et al*. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001;**358**:1500–3.
3 **Das G**, Crocombe S, McGrath M, *et al*. Hypovitaminosis D among healthy adolescent girls attending an inner city school. *Arch Dis Child* 2006;**91**:569–72.
4 **Grant WB**, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. *Alternative Medicine Review* 2005;**10**:94–111.
5 **Sullivan SS**, Rosen CJ, Halteman WA, *et al*. Adolescent girls in Maine are at risk for vitamin D insufficiency. *J Am Diet Assoc* 2005;**106**:971–4.
6 **Lawson M**, Thomas M. Vitamin D concentrations in Asian children aged 2 years living in England: a population survey. *BMJ* 1999;**318**:28.
7 **Pawley N**, Bishop NJ. Prenatal and infant predictors of bone health; the influence of vitamin D. *Am J Clin Nutr* 2004;**80** (suppl 6):1748–51.

Children's medicines

Improving children's medicines

I Choonara

Perspective on the paper by McLay *et al* (see page 584)

It is reassuring that the majority of Scottish paediatricians are aware of the concept of off label prescribing (***p XXX***).[1] The term off label relates to the use of a medicine in a manner different from that recommended by the manufacturers in their product licence.[2] A formal classification system for the different types of off label and unlicensed drug use was described in 1997. In a period of a few years, several studies confirmed that off label drug prescribing was a significant problem in children in hospital,[3] in neonates,[4] and in primary care.[5]

The main reason for carrying out these epidemiological studies was to highlight the fact that medicines used in children have not been scientifically evaluated to the same extent as those used in adults.[6 7] Groups such as the European Network for Drug Investigation in Children have highlighted that this is a problem in different European countries[8] and subsequent studies have shown that it is a worldwide problem.[9] Off label prescribing is associated with a greater risk of drug toxicity.[10] This is to be expected as the licensing process is carried out to ensure the efficacy and safety of medicines.

EUROPEAN LEGISLATION

The political response to the problem of off label prescribing in children has been discussed both nationally and at a European level. Legislation is currently being proposed that would hopefully improve the scientific study of medicines in children.[11] This proposed legislation will offer a financial incentive to the pharmaceutical industry as it is accepted that the cost of studying medicines in children is greater than in adults. Legislation in the USA has been successful in ensuring that more medicines are licensed for paediatric use.[12] Concerns have been raised, however, that the types of medicines studied are those that generate the greatest profits rather than address the clinical needs of children.[13]

The proposed European legislation recognises this point and suggests the establishment of a paediatric committee.[11] It is essential that the members of the paediatric committee are advocates of children and ensure that the medicines studied are those that will improve patient care. The majority of Scottish paediatricians are prepared to participate in clinical trials.[1] A weakness of the Aberdeen study, however, is that it did not try to differentiate between clinical trials of medicines for conditions where treatment is currently unsatisfactory and clinical trials of ''me-too'' medicines.

A major weakness in the proposed European legislation is the lack of funding for Medicines Investigation for the Children of Europe (MICE). This was in the original proposal but was unfortunately dropped owing to differences over who should fund it. The creation of a fund to ensure research and development of off patent medicines would significantly benefit children.

DEVELOPMENTS IN THE UNITED KINGDOM

There have been three major developments within the UK over the last few years. The publication of the BNF for Children following on the success of Medicines for Children will hopefully result in safer prescribing of medicines. The establishment of a Medicines for Children Research Network should facilitate the performance of clinical trials. The UK is unique in that it now has a formally recognised training programme in paediatric clinical pharmacology.[14] The first fully accredited trainee has recently completed her training. Paediatric clinical pharmacologists working alongside other paediatric health professionals have helped to

ensure that medicines are used more safely and effectively in children.

TRANSPARENCY

As the number of paediatric clinical trials increases it is essential that the information from these trials is made readily available. The European Commission has already funded a European Paediatric Clinical Trials Register (www.dec-net.org).[15] This is the only paediatric clinical trials register worldwide.[16] There is no charge for investigators who wish to enter their trial onto the register. The European Paediatric Clinical Trials Register is freely accessible to both paediatric health professionals and the public. It is essential that information regarding paediatric clinical trials remains open and accessible to all. We have seen the problems associated with the lack of publication of important clinical information by the pharmaceutical industry,[17] and paediatric health professionals have a duty to children to ensure that this information remains in the public domain.

SAFETY

It is important to remember that the rationale for the European legislation and the establishment of research networks to perform clinical trials in children is to improve the evidence basis on which medicines are used in children. This should hopefully result in the safer and more effective use of medicines. One needs to be aware that adverse drug reactions (ADRs) may occur during the course of a trial.[18] If such ADRs do occur, then it is essential that consideration is given to stopping the trial. Many clinical trials incorporate the establishment of a data monitoring committee/independent safety monitoring board.[19] Such a committee has the responsibility to evaluate suspected ADRs and also to terminate the trial if this is felt appropriate. Every single clinical trial does not require such a committee but if there is any likelihood of significant toxicity then the creation of such a committee is essential. The responsibility for safe clinical trials in children rests primarily on paediatric health professionals rather than on the pharmaceutical industry or the regulatory authorities. These are exciting times in relation to the development of medicines for children but it is essential that the safety of children in clinical trials is paramount.

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REFERENCES

1 **McLay JS**, Tanaka M, Ekins-Daukes S, *et al.* A prospective questionnaire assessment of attitudes and experiences of off label prescribing amongst hospital based paediatricians. *Arch Dis Child* 2006;**91**:584–7.
2 **Turner S**, Nunn AJ, Choonara I. Unlicensed drug use in children in the UK. *Paediatr Perinat Drug Ther* 1997;**1**:52–5.
3 **Turner S**, Longworth A, Nunn AJ, *et al.* Unlicensed drug use on paediatric wards. *BMJ* 1998;**316**:343–5.
4 **Conroy S**, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F142–5.
5 **McIntyre J**, Conroy S, Avery A, *et al.* Unlicensed and off label prescribing of drugs in general practice. *Arch Dis Child* 2000;**83**:498–501.
6 **Bonati M**, Choonara I, Hoppu K, *et al.* Closing the gap in drug therapy. *Lancet* 1999;**353**:1625.
7 **Autret E**, Bonati M, Choonara I, *et al.* Medicines for children. *Paediatr Perinat Drug Ther* 2000;**4**:23.
8 **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.
9 **Turner S**. Unlicensed and off label drug use in Australia. *Paediatr Perinat Drug Ther* 2000;**4**:24–27.
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**:965–968.
11 **Saint-Raymond A**, Seigneuret N. Medicines for children: time for Europe to act. *Paediatr Perinat Drug Ther* 2005;**6**:142–6.
12 **Roberts R**, Rodriguez W, Murphy D, *et al.* Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA* 2003;**7**:905–11.
13 **Jong GW**, van den Anker J, Choonara I. FDAMA's written request list: medicines for children. *Lancet* 2001;**357**:398.
14 **Choonara I**, Dewit O, Harrop E, *et al.* Training in paediatric clinical pharmacology in the UK. *Br J Clin Pharmacol* 2004;**58**:217–18.
15 **Bonati M**, Pandolfini C, Rossi V, *et al.* Launch of a European paediatric clinical trials register. *Paediatr Perinat Drug Ther* 2004;**6**:38–9.
16 **Sammons HM**, Naylor C, Choonara I, *et al.* Should paediatricians support the European Paediatric Clinical Trials Register? *Arch Dis Child* 2005;**90**:559–60.
17 **Whittington CJ**, Kendall T, Fonagy P, *et al.* Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;**363**:1341–5.
18 **Choonara I**. Paediatric pharmacovigilance. *Paediatr Perinat Drug Ther*, (in press).
19 **van den Ouweland FA**, Brown E, Carr DJ. Data monitoring committees in paediatric research. *Paediatr Perinat Drug Ther* 2004;**6**:81–8.

Falling necropsy rates

Falling necropsy rates and risks to public health

W Squier, J Ironside

Perspective on the paper by Verity *et al* (see page 608)

Dr Verity and his colleagues publish the results of their continuing study of progressive intellectual and neurological deterioration (PIND) in childhood[1]. The most surprising aspect of this study is the low rate of necropsies in this carefully followed group of children; only four of the 46 deaths were examined after death. This is an obstacle to detection of variant CJD (vCJD). Although most of this group of children had undergone investigations in life that allow a ''probable'' diagnosis to be made in the adult population, detailed neuropathological study remains the only way to confirm this diagnosis. Although the annual incidence of new cases of variant CJD has declined overall since 1999, more onsets have been observed in 2004 than in 2003, suggesting that it is premature to assume that this disease will soon disappear.[2] Furthermore, the age specific incidence of variant CJD has remained essentially unchanged since the disorder was first described in 1996, reinforcing the need for continued paediatric surveillance.

While this low necropsy rate has serious implications for public health and for understanding of the epidemiology of vCJD, there are far wider implications. PIND is heterogeneous and 92 children (almost 10% of the study group) had no diagnosis; half of these died. They never will have a diagnosis. How will we begin to understand the nature of their disease? How can we prevent it?